Antonio M. Esquinas *Editor*

Noninvasive Mechanical Ventilation

Theory, Equipment, and Clinical Applications

Springer

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Abbreviations

ACPE	Acute cardiogenic pulmonary edema
AHI	Apnea hypopnea index
AHRF	Acute hypercapnic respiratory failure
ALI	Acute lung injury
ALS	Amyotrophic lateral sclerosis
ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
ASV	Adaptive servo-ventilation
BiPAP	Bi-level positive airway pressure
BNP	Brain natriuretic peptide
BPD	Bronchopulmonary dysplasia
CAD	Coronary artery disease
CCHS	Congenital central hypoventilation syndrome
CF	Cystic fibrosis
CHF	Congestive heart failure
CHRF	Chronic hypercapnic respiratory failure
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CPE	Cardiogenic pulmonary edema
CPF	Cough peak flows
CRF	Chronic respiratory failure
CSA	Central sleep apnea
CSR	Cheyne stokes respiration
CSR-CSA	Cheyne-stokes respiration with central sleep apnea
DMD	Duchenne muscular dystrophy
DR	Delivery room
ED	Emergency department
EELV	End expiratory lung volume
EPAP	Expiratory positive airway pressure
$ETCO_2$	CO_2 at the end of expiration

ETI	Endotracheal intubation
ETO_2	End-tidal O_2
EV	Exhaust vent
f	Respiratory rate
f/V_t	Respiratory frequency / tidal volume
FAO_2	Alveolar fraction of oxygen
$FiCO_2$	CO_2 inspired fraction
FiO_2	Inspirated fraction of oxygen
FRC	Functional residual capacity
F_{tot}	Total gas flow passing through the helmet
FVC	Forced vital capacity
GPB	Glossopharyngeal breathing
hCO_2	Mean carbon dioxide concentration inside the helmet
HTN	Hypertension
HVC	Home ventilation circuits
ICU	Intensive care unit
IMT	Intima media thickness
IPAP	Inspiratory positive airway pressure
IPPV	Intermittent positive pressure ventilation
ITE	Inspiratory triggering efforts
$Leak_i$	Different definitions of air leakage (i=1,2,3)
LVEF	Left ventricular ejection fraction
MAC	Mechanically assisted coughing
MEP	Maximal expiratory pressure
MIC	Maximum insufflation capacity
MIP	Maximal inspiratory pressure
MMRC	Modified medical research concil
MRSA	Methicillin resistant *Staphylococcus aureus*
MV	Mechanical ventilation
MWD	6-minute walking distance
N	Nasal
NIMV	Noninvasive mechanical ventilation
NIPPV	Noninvasive positive pressure ventilation
NIPSV	Noninvasive pressure support ventilation
NIV	Noninvasive ventilation
NMD	Neuromuscular weakness
NNPV	Noninvasive positive pressure
NO	Nasal oral
NPPV	Noninvasive positive pressure ventilation
NPSV	Noninvasive pressure support ventilation
ON	Oronasal
OLTx	Liver transplantation
OSA	Obstructive sleep apnea
$P[A = a]O_2$	Arterial oxygen pressure gradient

$PaCO_2$	Carbon dioxide tension
PaO_2	Arterial pressure of oxygen
PAP	Positive airway pressure
PAV	Proportional assist ventilation
PCV	Pressure controlled ventilation
PEEP	Positive end expiratory pressure
PPO	Potentially pathogenic organism
PSV	Pressure support ventilation
PTP	Di pressure time product
RASS Score	Richmond agitation sedation scale score
R_{CPAP}	Resistance of the CPAP interface
RCTs	Randomized controlled trials
RDI	Respiratory disturbance index
RDS	Respiratory distress syndrome
REM	Rapid eye movement
R_{Leak}	Air leakage resistance
RR	Respiratory rate
SBT	Spontaneous breathing trial
SCI	Spinal cord injury
SDB	Sleep disordered breathing
SGRQ	St. George's respiratory questionnaire
SINP	Sniff nasal inspiratory pressure
SMA1	Spinal muscular atrophy type 1
SMT	Standard medical treatment
SNIPPV	Synchronized nasal intermittent positive pressure ventilation
SpO_2	Oxygen hemoglobin saturation
T_{exp}	Expiratory time
TFM	Total face mask
T_i	Inspiratory time
T_i/T_{tot}	Inspiratory time / total time
T_i	Inspiratory time
T_{insp}	Inspiratory time
TNI	Treatment with nasal insufflation
TPPV	Tracheostomy positive pressure ventilation
TV	Tidal volume
V_{insp}	Inspired volume
VAP	Ventilation-associated pneumonia
V/CO_2	Patient's carbon dioxide metabolic production
V/Q	Ventilation / perfusion ratio
VC	Vital capacity
VD/V_T	Vital volume ratio
V_{exp}	Expired volume
VFBA	Ventilator-free breathing ability
VFBT	Ventilator free breathing time
V_T	Tidal volume

$\dot{V}_{Pat}$	Airflow of the patient
$\dot{V}_{meas}$	Flow measured by the flow sensor
$\dot{V}_{Leak}$	Leakage flow
$\dot{V}_E$	Minute ventilation
$\delta\dot{V}_{exp}$	Volume error of the displayed expiratory volume
$\max\dot{V}_{CPAP}$	Maximal CPAP flow
$\dot{V}_{Pat, means}$	Measured patient flow
QOL	Quality of life
WOB	Work of breathing

Section I

Interface Technology in Critical Care Settings

Full Mask Ventilation

1

Francis Cordova and Manuel Jimenez

1.1
Introduction

Noninvasive positive pressure ventilation (NPPV) has become an integral part of ventilator support in patients with either acute or chronic respiratory failure. NPPV has been shown to avoid the need for invasive mechanical ventilation, it's associated complications and facilitate successful extubation in patients with chronic obstructive pulmonary disease (COPD) who have marginal weaning parameters. In addition, some studies [1–3] have shown that NPPV improves survival compared with invasive mechanical ventilation in patients with acute respiratory failure. Moreover, NPPV has been shown to be an effective modality for the treatment of chronic respiratory failure in patients with restrictive ventilatory disorders [4–6] and in selected patients with COPD [7, 8]. Compared with invasive ventilation, NPPV decreased the risk of ventilator-associated pneumonia and optimized comfort. Because of its design, success depends largely on patient cooperation and acceptance. Some factors that may limit the use of NPPV are mask- (or interface-) related problems such as air leaks, mask intolerance due to claustrophobia and anxiety, and poorly fitting mask. Approximately 10–15% of patients fail to tolerate NPPV due to problems associated with the mask interface despite adjustments in strap tension, repositioning, and trial of different types of masks. Other mask-related problems include facial skin breakdown, aerophagia, inability to handle copious secretions, and mask placement instability. The most commonly used interfaces in both acute and long-term settings are nasal and nasal-oral (NO) masks. The following reviews the applications of full-face mask in patients who are unable to tolerate a conventional mask during NPPV.

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1.2
Total-Face Mask During NPPV

A wide variety of mask interfaces has become available to deliver NPPV. The most common in use are nasal and NO (or full-face) masks. A larger version of the NO mask, the total-face mask (TFM; Fig. 1.1) could be used as an option to improve patient acceptance and possibly improve gas exchange and avoid intubation and mechanical ventilation. This mask covers the whole anterior surface of the face and delivers effective ventilation via the nasal and oral routes. Criner and colleagues [9] compared the efficacy of NPPV via TFM mask versus nasal or NO masks in patients with chronic respiratory failure. Their study showed that NPPV via TFM in selected patients with chronic respiratory failure may improve comfort, minimize air leak from the mask interface, and improve alveolar ventilation. They also suggested that this form of mask may be effective in patients suffering from acute respiratory failure who are candidates for noninvasive mechanical ventilation in a controlled environment such as the intensive care unit (ICU). We [10] also reviewed retrospectively 13 cases of acute respiratory failure; this analysis showed that NPPV was successfully accomplished via TFM in patients who were previously unable to tolerate NPPV via conventional nasal or NO masks. NPPV via TFM improved gas exchange with increased pH, improved gas oxygenation levels, and decreased hypercapnia. In the majority of the patients, NPPV was well tolerated without dislodgement of the mask or significant need for readjustment. Complications from treatment were minimal and generally did not lead to an interruption in therapy. This type of mask was also rated by patients as more comfortable than the standard full-face mask in a preliminary report [11].

Because the TFM covers the entire face, one would think that this would worsen feelings of claustrophobia rather than improve them. However, Criner and colleagues [9] observed that this sensation was avoided with the use of TFM in some of the patients who were not able to tolerate an NO mask. Potential explanations for this include unobstructed field of vision for the patient; the ability to communicate verbally; and the sensation of air flowing over the entire face while using the mask.
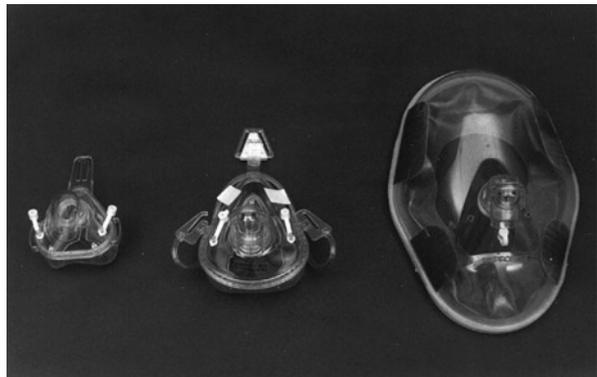
Fig. 1.1 Different types of mask available for the NPPV interface. Note the larger size of the TFM

Concerns have been raised about the TFM. Since this form of face mask has much larger volume, it has a significantly greater amount of dead space compared with other commercially available forms of nasal and NO masks, but streaming of airflow directly from the inlet to the patient's nose and mouth appears to minimize this problem.

Other complications, such as eye irritation and gastric distention, would be expected to be more common during NPPV with a TFM. However, an increase in these problems has not been reported in any of the studies.

The efficacy of nasal and NO masks has been compared in a controlled trial of 26 patients with COPD and restrictive thoracic disease. The NO masks were more effective in lowering Pa_{CO_2}, perhaps because of the greater air leak associated with the nasal mask [12]. This supports the belief that, in the acute setting, nasal-oral masks are preferable to nasal masks because dyspneic patient tend to be mouth breathers, predisposing to greater air leakage.

1.3
Discussion

Full-face masks have been used mainly on patients with acute respiratory failure but may also be useful for chronic ventilatory support. Full-face masks may be preferred for patients with copious air leaking through the mouth during nasal mask ventilation. As noted, the TFM is an option for patients who fail NPPV via more conventional nasal or NO masks. Patient traits or preferences may still favor the selection of one particular device over another. Regardless of the mask selected, proper fit is of paramount importance in optimizing the comfort and success of NPPV. Practitioners must be prepared to try different mask sizes and types in an effort to enhance patient comfort.

In summary, NPPV via a TFM in selected patients with acute or chronic respiratory failure may improve comfort, minimize air leaking from the mask–face interface, and improve alveolar ventilation in patients who fail NPPV with conventional oral or NO interface.

Key Recommendations

> Air leakage and claustrophobia associated with NPPV may be overcome by using a full-face mask.
> TFM is an interface option to provide NPPV in patients who fail the use of conventional types of masks (nasal or nasal-oral).
> Practitioners must be prepared to try different mask types and sizes in an effort to enhance the comfort and success of NPPV.

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Helmet Continuous Positive Airway Pressure: Theory and Technology

2

Giacomo Bellani, Stefano Isgrò, and Roberto Fumagalli

2.1
Introduction

Continuous positive airway pressure (CPAP) is administered to patients to maintain the airway at a selected pressure (usually named the positive end-expiratory pressure, PEEP) higher than that of the atmosphere one. PEEP application has several well-known effects on the respiratory system and hemodynamics, whose description is not among the aims of this chapter. The applied pressure is kept constant throughout the whole respiratory cycle so that intrapulmonary pressure swings around the set level. Patients can breath spontaneously at the selected pressure without any active support of inspiration; it follows that CPAP cannot be strictly considered a form of "ventilation."

2.2
Helmet Technology

The helmet interface [1] was conceived to deliver high oxygen concentrations during hyperbaric therapy. Since the nineties it has been increasingly used, particularly in the southern European countries, to deliver noninvasive ventilation. The helmet consists of a soft transparent plastic hood built on a hard plastic ring. A silicon/polyvinyl chloride soft collar built on the ring provides a pneumatic seal at the neck, while the hood contains the patient's entire head. The presence of two or more inlets and outlets enables connection of standard ventilator tubing for the expiratory and inspiratory ports of the circuit and the insertion of nasogastric tubes and straws. The collar provides a good seal without major compression at contact points. The lack of pressure points on the

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face avoids skin necrosis and pain, reduces discomfort, and improves patient tolerance. The seal around the neck allows the use of the helmet also in patients with difficult anatomical situations that commonly do not allow the use of a face mask, such as in edentulous patients, patients with a full beard, or patients with facial trauma. The helmet allows the patients to see, read, talk, and interact more easily than with other devices.

Different companies produce various adult, pediatric, and neonatal types and sizes of helmets, each provided with various fixing and safety features. Adult helmets are easily held in place by two straps positioned under the axillae. Codazzi et al. [2] introduced an interesting technique to provide helmet CPAP to preschool children by employing a "baby-body" worn under the pubic region as a diaper and fixed to the plastic ring. In a single-center prospective study, this system was effective in delivering CPAP and was well tolerated. A modified helmet has been developed to deliver CPAP to preterm infants [3]; the sealed hood is mounted on the upper part of the bed, to which the inspiratory line of the circuit is connected. Another port is provided for expiratory exit; a threshold valve is mounted here to generate PEEP. In addition, in the upper part of the hood there is a pressure release valve that prevents excessive pressure in the system. Pressure, inspiratory fraction of oxygen, and temperature in the chamber are continuously monitored. The pressure chamber is kept separate from the rest of the bed by a transparent, latex-free, polyurethane membrane. The cone-shaped membrane has a hole in the middle to allow the patient's head to pass through. Due to the pressure in the chamber, the soft membrane becomes a loose collar around the neck, adhering to the shoulders of the patient with a sealing and nontraumatic effect.

2.2.1
Helmet to Deliver Noninvasive CPAP

While a helmet has been used to deliver pressure support ventilation by connecting the inspiratory and expiratory line of the helmet to a ventilator, the efficacy of such a system in delivering pressure support is questionable [4]. The analysis of the patient–ventilator interaction becomes quite complicated and is not the subject of this chapter, which focuses on CPAP.

A typical circuit setup to deliver noninvasive CPAP by a helmet consists of an "inspiratory branch" that supplies a constant flow of fresh gas to the helmet. Gas flow (typically 30–60 l/min) is provided typically through an O_2/air flowmeter with an analog scale that allows the clinician to regulate oxygen and air flow separately and accordingly F_{IO_2}. The flowmeter is interposed between the source of fresh gases (wall, tanks) and the gas inlet of the helmet. The "expiratory branch" disposes the gas through a threshold spring-loaded or water-seal valve (see Fig. 2.1), which keeps the system under pressure. The helmet has been successfully used to deliver CPAP in several clinical studies (see chapter 3).

Patroniti et al. [5] compared the efficacy of the helmet versus the face mask in delivering CPAP to eight healthy volunteers. A combination of three PEEP levels (5, 10, and 15 cmH$_2$O) and three gas flows was tested in random order; the increase in end-expiratory
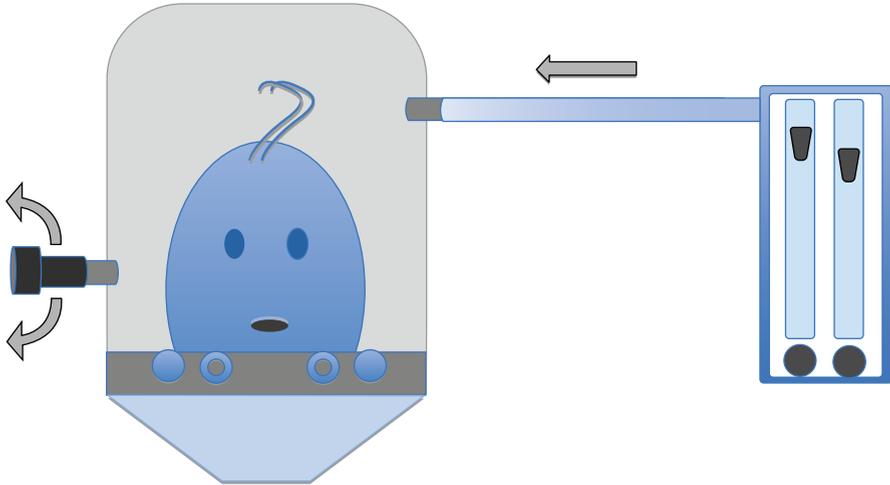
Fig. 2.1 Continuous flow CPAP system with threshold spring-loaded PEEP; see text for details

lung volume, the swings in airway pressure during the breathing cycle, and the work of breathing were similar at each PEEP level between the two interfaces, thus demonstrating that CPAP delivered by helmet is at least as effective as CPAP by face mask. It should be noted that due to its extremely high compliance, helmets act as a reservoir; even if the peak inspiratory flow rate of the patient exceeds the fresh gas flow rate, the pressure will remain almost constant. This is not the case when using a face mask CPAP, which requires either the presence of a reservoir able to dump the pressure swing or the presence of a mechanical ventilator able to generate as much flow as the patient demands.

The helmet CPAP system is effective, cheap, and easy to set up also outside the intensive care units (ICUs), such as in the hospital setting [6], in the emergency department, in the postanesthesia care unit [7], and even in the ward. The main disadvantages of this system are the inability to provide ventilatory assistance or lung recruitment if needed and the absence of an acoustic alarm system for inadvertent pressure/gas drop.

2.3
Limitations of the Technique

2.3.1
Carbon Dioxide Rebreathing

One of the main concerns when the head of the patient is in a closed system is the potential for CO_2 rebreathing, which is obviously avoided by providing an adequate fresh gas flow rate. Indeed, in comparison with face mask CPAP, the use of the helmet was associated

with higher inspiratory concentration of CO_2, which decreased at increasing flow rates [5]. Similar findings were reported in a bench and healthy volunteers study with an increase in inspired concentration of CO_2 when the gas flow rate was reduced below 30 l/min. It is noteworthy that the study also showed the inadequacy of delivering CPAP via helmet employing a mechanical ventilator, which, because it is only aimed at keeping the airway pressure "constant," lacks continuous delivery of gas flow to the helmet and provides a fresh gas flow to the helmet equal to or slightly superior than the patient's minute ventilation and well below the limit of 30 l/min suggested as effective in maintaining the inspiratory concentration of CO_2 in a reasonable range [8].

For this reason, we highly discourage connecting the helmet to a mechanical ventilator to provide CPAP. This result has been confirmed by Racca and coworkers, who also showed that elevated CO_2 rebreathing occurs if the PEEP valve is mounted on the inspiratory branch as opposed to the expiratory one [9].

Furthermore, a study [10] by Patroniti et al. addressed the issue of the potential danger deriving from the discontinuation of fresh gas flow. The study tested three different helmet models; one of the helmets bore an antisuffocation valve. After just 4 min from the disconnection of the fresh gas flow, the F_{IO_2} dropped, and the inspiratory CO_2 rose to extremely high levels (up to 70 mmHg), with a fourfold increase in the minute ventilation. These effects were greatly diminished in the presence of an antisuffocation valve. The authors concluded that some features of the helmet design (a high-volume, low-resistance inlet port and the adjunct of a safety valve) can effectively limit and delay the consequences of fresh gas supply interruption and that, when delivering helmet CPAP, there is a clear need to include a monitoring and alarm system along with a clinical control, even in ICU settings.

2.3.2
Noise

Cavaliere et al. [11] addressed the issue of the noise (arising from the turbulent flow at the gas inlet during helmet CPAP) as a possible source of discomfort for patients. The reported noise levels in the helmet during noninvasive ventilation equal 100 dB, and the noise perceived by the subjects (assessed by a visual analog scale) was significantly greater with the helmet than with a face mask; nonetheless, the helmet was overall better tolerated than the face mask. Finally, the presence of a simple filter for heat and moisture exchange on the inlet line significantly decreased the subjective noise perception. The same authors reported, after 1 h of pressure support ventilation delivered by helmet to healthy volunteers, a reversible increase in acoustic compliance (indicating a less-stiff tympanic membrane) that could predispose the middle and inner ear to mechanical damage. Although the clinical relevance of these data is unknown, particularly after prolonged treatment, the authors suggested the use of protective devices such as earplugs.

2.3.3
Pressure Monitoring and Generators

As an important factor affecting the pressure generated into the helmet is the flow rate passing through the PEEP valve generator, special attention must be reserved for providing adequate gas flow and avoiding major leaks. A simple way to assess if the pressure inside the helmet does not drop below the PEEP is to ascertain that gas is flowing through the expiratory valve throughout the respiratory cycle: If during inspiration the gas flow stops, this indicates that pressure in the helmet is below the PEEP and that a higher fresh gas flow rate is necessary. Moreover, it could be recommended to frequently measure pressure inside the helmet, especially when helmet CPAP is performed in a highly technological environment (such as ICUs).

Some companies employ pressure relief valve pressure, which opens when the pressure rises above a safety level (e.g., if the patients coughs).

Furthermore, to generate PEEP a threshold (or plateau) valve is usually employed. This valve is designed to open at a threshold pressure and above this level to generate a constant pressure independently from variations of flow. The most employed are spring-loaded and water-seal valves. Several different technologies have been developed to grant the first kind of valves a constant resistance in the wider range of gas flow, but depending on the manufacturer, when flow is high they could show some degree of flow dependency, thus increasing the pressure generated inside the helmet. The second kind is easy to provide also in a nontechnological enviroment and cheap; it needs a ventilator tube to connect the helmet and the water repository.

Key Recommendations

> Due to its low invasiveness and simplicity of use, a helmet should be taken into consideration when considering application of noninvasive CPAP.

> Adequate fresh gas flow (certainly not lower than 30 l/min, but higher might be necessary) must be provided to avoid rebreathing and pressure drop below PEEP. Mechanical ventilators set in CPAP modality should *not* be connected to helmets as fresh gas flow rate is inadequate.

> A filter for heat and moisture exchange and earplugs might be useful tools to reduce noise and discomfort.

> Pressure measurement inside the helmet is recommended to titrate the PEEP at the correct therapeutic level. A pressure/flow/CO_2 alarming system is still desirable to improve safety.

> The presence of a safety valve avoids the risk of choking due to fresh gas flow supply interruption.

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Helmet Continuous Positive Airway Pressure: Clinical Applications

3

Alberto Zanella, Alessandro Terrani, and Nicolò Patroniti

3.1
Introduction

During noninvasive continuous positive airway pressure (CPAP) the patient's respiratory system is maintained throughout the whole respiratory cycle at a constant pressure higher than the atmospheric pressure, usually termed the positive end-expiratory pressure (PEEP). Noninvasive CPAP is void of any active support for the patient's work of breathing and therefore cannot be considered a form of "ventilation."

Noninvasive CPAP is frequently used to improve gas exchange and respiratory mechanics in cooperative patients with an intact neuromuscular function with acute respiratory failure (ARF), including acute cardiogenic pulmonary edema (ACPE) [1]. If on one hand the use of techniques with an active support to inspiration, like pressure support ventilation, might determine further benefits to patients with ARF, on the other hand CPAP is easily delivered by simple continuous flow systems without the need for a mechanical ventilator, even outside intensive care units (ICUs).

In the past, noninvasive CPAP has been mostly delivered by a face mask, combined either with a "traditional" CPAP circuit, equipped with a large reservoir bag on the inspiratory limb (with the purpose of minimizing the pressure swings) and a PEEP valve, or combined with a "Boussignac valve." When using a face mask, to avoid leaks (thus maintaining a constant airway pressure), a tight seal between the patient's face and the device is crucial but often is difficult to obtain, especially with patients with peculiar characteristics (e.g., in an edentulous patient or in those with a beard); moreover, the elevated pressure exerted by the mask on the patient's face can potentially lead to patient discomfort and skin lesions, usually limiting the application of this device to short-term treatments or periodic applications. The correct application of the

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face mask is therefore somehow difficult and requires an experienced team and a collaborative patient.

The head helmet has been introduced with success as a tool to deliver noninvasive CPAP. It seems to offer some significant advantages compared to a face mask, mainly higher tolerability by the patient, prevention of pressure sores, and superior efficiency in keeping the PEEP level constant throughout the respiratory cycle.

3.1.1
Acute Cardiogenic Pulmonary Edema

During ACPE, the application of a CPAP improves the arterial oxygenation and the respiratory mechanics and may reduce the patient's respiratory drive and effort. Since the inspiratory effort decreases the intrathoracic pressure, the afterload of the left ventricle increases; for example, if the arterial systolic pressure is 120 mmHg and the intrathoracic pressure (surrounding the heart) is −20 mmHg, the ventricle has to generate a pressure of 140 mmHg. For this reason, a decrease in the inspiratory effort implies a reduction of the left ventricle afterload. Moreover, CPAP reduces the venous return and the ventricle size, diminishing the wall tension and myocardial oxygen consumption. Probably because of these multiple mechanisms CPAP is effective in reducing the need for intubation and the death of patients with ACPE. In a clinical study [2], a cohort of patients with ARF following ACPE was successfully treated with helmet CPAP, with a mean duration of treatment of 13 h; a significant reduction in respiratory and pulse rate and an improvement in gas exchange were observed after 1 h from instauration of treatment.

Helmet CPAP has been successfully used as a prehospital therapy in patients with presumed ACPE. In our experience [3], prehospital application of helmet CPAP was extremely effective in improving the respiratory function and decreased intrahospital mortality in patients with ACPE. Prehospital helmet CPAP was feasible, safe, and effective as an addition to standard medical therapy or as a stand-alone treatment. A similar approach to patients with ACPE has been described by Plaisance and coworkers [4].

3.1.2
Acute Noncardiogenic Respiratory Failure

In patients with acute noncardiogenic respiratory failure, CPAP, increasing the end-expiratory lung volume (EELV) and preventing alveolar collapse, can improve the gas exchange and respiratory mechanics, decreasing the work of breathing. In Fig. 3.1, curve A represents a normal respiratory system pressure–volume relationship, and P1 is the pressure needed to inspire a tidal volume (TV). A rightward shift of the pressure–volume curve B, which may occur with a reduction in respiratory system compliance, resulted in a decrease in functional residual capacity (FRC) and an increase in work of breathing because, to inspire the same TV, a higher pressure (P2) is required. An application of

Fig. 3.1 Curve A represents a normal respiratory system pressure–volume relationship, and *P1* is the pressure needed to inspire a tidal volume (*TV*). A rightward shift of the pressure–volume curve B results in a decrease in functional residual capacity and increases the work of breathing since, to inspire the same *TV*, a higher pressure (*P2*) is required. An application of 10 cmH$_2$O of CPAP reestablishes the normal end-expiratory lung volume and reduces the work of breathing (*P3 = P1*)
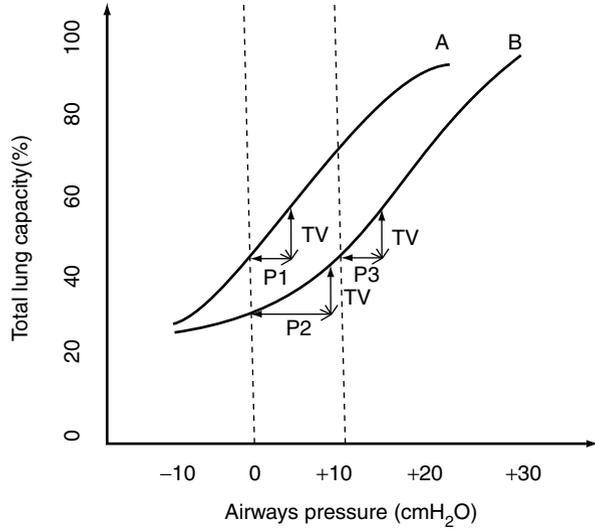
CPAP (in the figure, 10 cmH$_2$O), reestablished the normal EELV and the reduced the work of breathing (P3 = P1).

The effectiveness of CPAP in patients with ARF has been proven in many studies [5], especially in ARF complicating hematological malignancy, given the importance in those patients of avoiding endotracheal intubation. Principi et al. [6] compared a cohort of patients with hematological malignancy with ARF treated with CPAP delivered by helmet with a cohort of historical controls treated by face mask CPAP. Despite a similar improvement in oxygenation at 2 and 6 h from the initiation of the treatment, in the helmet group the mean duration of continuous application of CPAP without disconnection and the total duration of CPAP were longer than in the face mask group (28.4 ± 0.2 vs 7.5 ± 0.4 h and 34.1 ± 0.1 vs 28.1 ± 0.3 h, respectively), with better patient tolerance. The authors also reported statistically significant lower rates of death and intubation between the two groups, which can hardly be explained by a greater efficacy of the helmet (as the initial improvement in oxygenation was similar); rather, these could be attributable to a more continuative therapy. Despite its limitations, this study provided a strong suggestion that the head helmet, allowing treatment of patients for a longer period of time, might bear a substantial advantage in comparison to the face mask, at least in the subset of patients requiring long-term (days rather than hours) intervention, like those affected by hematologic malignancies. The capability of delivering noninvasive ventilation for a more prolonged period with better patient tolerance has been reported also in subsequent studies [7].

A head helmet has been successfully applied to deliver CPAP during hypoxic respiratory failure following major abdominal surgery [8]. Patients with a PaO$_2$/FiO$_2$ lower than 300 mmHg while breathing oxygen through a Venturi mask at an inspiratory fraction of 0.3, were randomly assigned to be treated for 6 h with oxygen through a Venturi

mask at an FiO_2 of 0.5 (control patients) or with oxygen at an FiO_2 of 0.5 plus a CPAP of 7.5 cmH_2O, delivered by the head helmet. The patients treated with head helmet CPAP showed a lower intubation rate (1% vs 10%) and a shorter duration of ICU stay. In this study, the helmet was not compared to other CPAP devices; however, the rate of intolerance of the helmet CPAP reported by the authors (4%) was lower than what has been reported for the face mask in other studies (14%).

Finally, in patients with chronic obstructive pulmonary disease (COPD), CPAP is able to substantially decrease the work of breathing by compensation for the patient's intrinsic PEEP.

3.2
Experience with Helmet CPAP at Our Institution

For several years at our institution, the number of available ICU beds was noticeably undersized in proportion to the total number of beds of the hospital. To reduce the requirement to transfer patients to other hospital ICUs and to prevent the ICU admission of certain patients categories (e.g., patients affected by hematological malignancies), the use of the head helmet in the general wards (medical and surgical) was implemented. The outreach team for intrahospital urgencies and emergencies, including one staff intensivist and one resident, is alerted by the ward physician when a patient might require the application of noninvasive CPAP (nCPAP). If this is considered to be the case, a treatment with helmet CPAP is instituted and managed by the ward nurses, who are specifically trained for the use of the system. Decisions on the titration of the therapy as well as its discontinuation or the need for a more aggressive therapy are made by the ward physician and the outreach team, who evaluate the patients twice a day. In the last 15 years, hundreds of patients have been managed in this way at our institution. We report data from a cohort of 39 consecutive patients with ARF (26 ARF and 13 ACPE) managed by helmet CPAP in general wards [9]. We included patients with hypoxia refractory to administration of oxygen by reservoir mask and with infiltrates on chest X-rays. Patients needing immediate intubation, with a history of COPD, and with more than two new organ failures were excluded. The average length of CPAP treatment was 2.9 ± 2.3 days with PEEP levels between 8 and 12 cmH_2O. Nine patients (23%) were subsequently intubated, and six (15%) ultimately died. In all patients, Pao_2/Fio_2 improved after 1 h of CPAP administration (from 113 ± 36 to 200 ± 83 mmHg). Patients who recovered from ARF without intubation showed, from 1 to 24 h of treatment, a significant improvement in Pao_2/Fio_2 (from 205 ± 84 to 249 ± 98 mmHg, $p < 0.05$) and a significant decrease in respiratory rate from 29.2 ± 7.3 to 26.2 ± 6.5 breaths per minute, $p < 0.05$. On the contrary, patients who needed intubation did not show any further improvement in Pao_2/Fio_2 and respiratory rate.

Again, we did not report any intolerance for the helmet, and we were able to easily obtain a good air seal in all patients, while patient discomfort, face mask intolerance, and

inability to obtain a sufficient seal are the most important causes of failure of noninvasive CPAP as well as of noninvasive positive pressure ventilation (NPPV). By avoiding these two major problems, the use of the helmet may extend the use of CPAP to a much larger patient population. Second, to limit patient discomfort and possible skin lesions, face mask NPPV cannot be administered continuously for long periods. In a study by Delclaux et al. [10] that did not show any benefit of face mask CPAP compared to standard oxygen therapy, the length of CPAP application required by protocol was only 6 h per day. The short duration of CPAP treatment may have greatly affected its efficacy, accounting at least in part for the lack of efficiency shown in this study. These results corroborate the findings of Principi et al. [6] and suggest that the possibility of applying CPAP treatment without disconnection for longer periods is the most promising advantage of the helmet.

3.3
Conclusion

The application of CPAP by helmet appears to be easy, efficient, and cheap. Some essential monitoring should be provided to warrant safety standards. Despite a similar pneumatic performance, helmet CPAP might be superior to face mask, at least in patients requiring long-term treatments, given the possibility of delivering CPAP more easily and for more prolonged periods with greater patient tolerance and with less harm for the patients. A large proportion of hypoxic patients, including those with ACPE, CAP, postsurgical respiratory failure, ARF in immunocompromised patients, and so on may potentially benefit from early application of CPAP.

Key Recommendations

> The head helmet is an efficient tool to deliver noninvasive CPAP, and it seems to offer some significant advantages compared to a face mask.
> CPAP is very effective in reducing the need for intubation and the death of patients with ACPE.
> Prehospital application of helmet CPAP improves the respiratory function and decreases intrahospital mortality in patients with ACPE.
> In patients with acute noncardiogenic respiratory failure, CPAP improves oxygenation by increasing the EELF and preventing alveolar collapse.

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Section II

Ventilatory Modes and Ventilators: Theory, Technology, and Equipment

Pressure Support Ventilation

4

Enrica Bertella and Michele Vitacca

4.1
Introduction

Noninvasive ventilation (NIV) refers to the provision of mechanical ventilation (MV) through the patient's upper airway by means of a mask without the use of an invasive artificial airway (endotracheal tube or tracheostomy) [1].

NIV has long been used as the standard method to treat patients with chronic respiratory failure (CRF) related to chest wall diseases, neuromuscular disorders, or central hypoventilation. It has been shown to be effective in treatment of different forms of acute respiratory failure (ARF) [2, 3].

Respiratory failure depends on two main processes: lung failure, which leads mainly to hypoxemia, and pump failure, which leads mainly to hypercapnia. Causes of hypoxemic respiratory failure can be airway collapse, alveolar filling, low ventilation/perfusion ratio (V/Q), and shunt. Causes of hypercapnic respiratory failure can be depression of central inspiratory drive (central alveolar hypoventilation, decreased chemosensitivity, hypothyroidism, use of diuretics, metabolic alkalosis, narcotics abuse); increased inspiratory load (increased airway resistance, reduced chest wall or lung compliance, dynamic hyperinflation); or inspiratory muscle impairment (static or dynamic hyperinflation, muscle weakness).

Carbon dioxide (CO_2) retention is mainly related to alveolar hypoventilation; thus, hypercapnia suggests that alveolar ventilation is inadequate to counterbalance CO_2 production. Usually, patients with CO_2 retention have a higher respiratory rate, shorter inspiratory time (Ti), and smaller tidal volume (Vt) than patients with normal CO_2 levels.

The main goals of MV are

1. Improvement of arterial blood gases
2. Improvement of minute ventilation

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3. Unloading of inspiratory muscles
4. Achieving optimal ventilator–patient interaction with maximal comfort

Different modes of MV exist to achieve these goals; among the assisted modalities, the most used is pressure support ventilation (PSV), a mode of partial ventilator support that during spontaneous inspiratory efforts imposes a set level of positive pressure in a patient with intact respiratory drive [4].

4.2
Mechanisms of Action

PSV is pressure limited and patient triggered, and its use assumes that the patient is able to initiate an inspiratory effort [5]. Expiration is passive.

PSV allows patients to control inspiratory and expiratory times while the ventilator provides a set pressure. This mechanism, in conjunction with patient effort and respiratory mechanics, determines the inspiratory flow and Vt [6].

The inspiratory effort is detected by a pressure or flow sensor with adjustable trigger sensitivity. The pressure trigger requires a decrease in airway pressure from end-expiratory level to a set threshold. The flow trigger requires a flow change sufficient to reach a predetermined threshold [5].

Flow-triggered ventilators have been shown to be more sensitive than pressure-triggered ventilators. Trigger sensitivity should be optimized according to patient need; a too sensitive trigger causes autotriggering; an insensitive trigger increases the work of breathing [6].

PSV is generally flow cycled, meaning that the expiratory trigger is determined by a decrease in inspiratory flow and when flow falls below a ventilator-determined threshold level, the exhalation starts [5]. Some ventilators have the possibility to set a time limit for inspiration, at which time the device will cycle into expiration regardless of the flow [6].

PSV has the major target of assisting respiratory muscles, improving the efficacy of inspiratory effort and reducing workload.

In patients with ARF, PSV reduces the work of breathing by increasing transpulmonary pressure, the inflation of the lungs, the increase of Vt, and the reduction of inspiratory muscle workload. PSV improves gas exchange firstly by increasing alveolar ventilation and increases functional residual capacity (FRC), opening collapsed alveoli, reducing shunt, and improving the V/Q ratio (Fig. 4.1).

Pressure delivery can be improved and the work of breathing decreased by increasing inspiratory pressure support and reducing the pressure rise time (the time set to reach the preset inspiratory level that can be individually adjusted) [6].

Patients with severe chronic obstructive pulmonary disease (COPD) must overcome the presence of intrinsic positive end-expiratory pressure (PEEP) to trigger the ventilator; thus, the work of breathing is further reduced by the addition of applied PEEP that counterbalances the intrinsic PEEP [5]. The results are the improvement of dyspnoea

Fig. 4.1 From *top* to *bottom*: effects of PSV on flow, airway pressure (*Pao*), esophageal pressure (*Pes*), transdiaphragmatic pressure (*Pdi*), and tidal volume (*Vt*). *Left panel*: patient breathing spontaneously (*SB*); *right panel*: under pressure support ventilation (*PSV*)
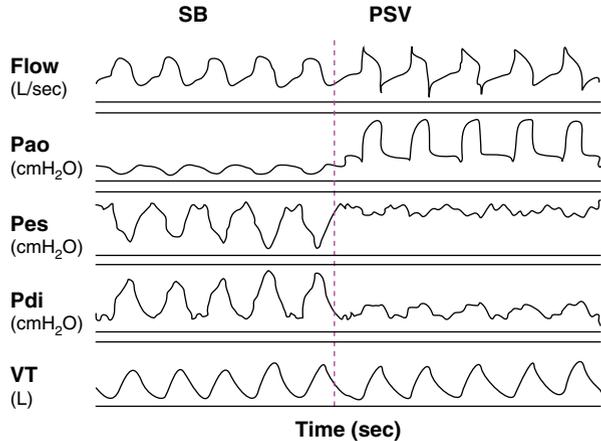
and the reduction of the respiratory rate, CO_2 retention, and sternocleidomastoid muscle activity [2].

Success with assisted ventilation is critically related to the adaptation of MV to the patient's needs. This is particularly true for NIV because the patient is conscious, and ventilation is ineffective or uncomfortable when the patient rejects it.

The variability in response to PSV appears to be particularly pronounced in patients with COPD during ARF. These patients usually show wide ranges of airway resistance, elastance, and intrinsic PEEP.

Quite few studies have been performed to compare different ventilatory modes applied noninvasively in COPD patients with hypercapnic ARF [7, 8]. Assist control ventilation seems to lower respiratory workload better than PSV, but it causes greater patient discomfort, more frequent loss of breathing control, and less possibility to compensate for mask leaks.

Pressure-targeted ventilators have several advantages compared to volume-targeted ventilators and are the preferred NIV devices in the treatment of ARF.

4.3
Patient–Ventilator Interaction

Patient–ventilator synchrony is paramount for the success of the ventilation. The presence of asynchrony determines the patient's discomfort and unnecessarily increases the work of breathing.

Patient–ventilator interaction has been described [9] as an expression of two controllers: the ventilator (controlled by the physician) and the patient's respiratory muscle pump. These controllers should be in harmony to obtain ventilation appropriate for the patient.

Vignaux et al. [10] studied the prevalence of patient–ventilator asynchrony in patients receiving noninvasive PSV for ARF. Autotriggering was present in 13% of patients, double triggering in 15%, ineffective breaths in 13%, premature cycling in 12%, and late cycling in 23%.

Autotriggering occurs when a respiratory cycle is falsely triggered by a signal not produced by the patient effort. The more frequent causes of autotriggering during PSV are expiratory leaks from the mask, setting too sensitive a trigger, patient movement, or motion of water in the circuit [4, 5, 10].

Autotriggering can be difficult to detect on ventilator curves. It is suggested by a sudden increase or a persistently high respiratory rate [4].

Double triggering occurs when patient demand or effort exceeds the flow delivery setting on the ventilator. If the level of pressure support is not sufficient, one pronounced inspiratory effort retriggers the ventilator after the termination of pressurization. This happens if the ventilator setting has not been adjusted to meet the patient's need or if the patient's demand suddenly increases, exceeding the ventilator setting [10, 11].

Ineffective triggering (or wasted effort) (Fig. 4.2) is likely in patients with COPD and is most often due to the additional inspiratory threshold load associated with intrinsic PEEP [10]. The presence of intrinsic PEEP creates a greater pressure gradient between lung pressure and ventilator circuit pressure. If the patient's effort is not sufficient to overcome this gradient, it cannot be transmitted to the sensor to trigger the ventilator [11]. As explained, this asynchrony can be reduced by applying an external PEEP.

Ineffective triggering can be detected on airway pressure or flow curves as irregularities during the expiratory phase.

Premature cycling (or short cycling) is mainly related to restrictive pulmonary mechanics. It is characterized by Ti lasting less than Ti during spontaneous breathing (ventilator cycles off before the end of the neural activity of the expiratory muscles) [4, 11].

Prolonged cycling (or delayed cycling) occurs when there is a difference between patient neural Ti and ventilator set breath termination (ventilator cycles off only after the activity of the expiratory muscles is initiated) [11]. During PSV, leaks have been shown to be the main causes of delayed cycling, while in contrast obstructive mechanics are likely to be a contributing factor for intubated patients [10].

Fig. 4.2 Representative tracing of ineffective triggering (IT) during PSV (*arrow*). *Upper panel*: patient under PSV presenting IT; *lower panel*: the same patient after PSV resetting. *Pao* = pressure at airway opening, and *Pes* = esophageal pressure
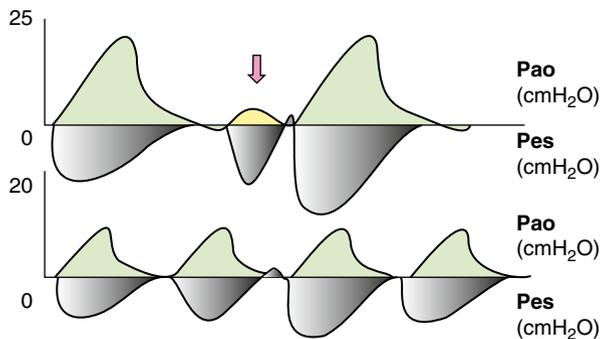
Table 4.1 More frequent problems observed during PSV (Modified from [6])

Problems	Mechanism involved and possible solution
Ineffective triggering	Air leaks (control circuit and interfaces)
	Insensitive trigger (adjust trigger sensitivity)
	High work of breathing (add PEEP, change to flow trigger if pressure trigger is used)
Autotriggering	Too sensitive trigger (reduce sensitivity)
	Air leaks (control circuit and interfaces)
	Water in the circuit (check circuit)
Inappropriate pressurization	Too long rise time (reduce rise time)
	Insufficient pressure support (increase support)
Delayed cycle to exhalation	Air leaks (check interfaces and change to facial mask if nasal is used)
	High end inspiratory flow (increase flow-cycling threshold or set time limit for inspiration)
CO_2 rebreathing	Ventilator with single circuit (change to a two-lines circuit)
	No true exhalation valve (use nonrebreather valve)
	Absence of PEEP (add PEEP)
	Large dead space in the mask (reduce dead space or change mask)
	High respiratory rate (look for causes of tachypnoea)

Pressure-targeted ventilators can compensate for air leaks, but this capability differs markedly between different ventilators [6].

CO_2 rebreathing is another problem observed with some home bilevel ventilators that have a single gas delivery circuit and do not contain a true exhalation valve. High respiratory rate and low external PEEP that shorten expiratory time and lower CO_2 lavage from the circuit increase the risk of CO_2 rebreathing [6].

Table 4.1 reports the more frequent problems observed during PSV.

4.4
Conclusions

PSV is able to reduce the workload of the inspiratory muscles and improve the breathing pattern.

PSV is a widely used method of NIV.

> **Key Recommendations**
>
> ❯ To avoid patients discomfort and ineffective efforts PSV should be used appropriately and by expert people.
> ❯ Monitoring and readjustment of PSV setting are needed to have success.

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Ventilators for Noninvasive Mechanical Ventilation

5

Raffaele Scala

5.1
Introduction

The use of noninvasive positive pressure ventilation (NPPV) to treat both acute respiratory failure (ARF) and chronic respiratory failure (CRF) has been tremendously expanded in the last two decades in terms of spectrum of diseases to be successfully managed, settings of application/adaptation, and achievable goals [1–3].

The choice of a ventilator may be crucial for the outcome of NPPV in the acute and chronic setting as poor tolerance and excessive air leaks are significantly correlated with the failure of this ventilatory technique [4]. Patient–ventilator dyssynchrony and discomfort may occur when the clinician fails to adequately set NPPV in response to the patient's ventilatory demands both during wakefulness and during sleep [5, 6]. This objective may be more easily achieved if the technical peculiarities of the applied ventilator (i.e., efficiency of trigger and cycling systems, speed of pressurization, air leak compensation, CO_2 rebreathing, reliable inspiratory fraction of O_2, monitoring accuracy) are fully understood.

With the growing implementation of NPPV, a wide range of ventilators has been produced to deliver a noninvasive support both in randomized controlled trials and in "real-life scenarios." This chapter examines the key points concerning the technology of ventilators for NPPV and their main impact in clinical practice. Due to constraints in space, ventilators for negative pressure ventilation (i.e., iron lung, cuirass, poncho-wrap) are not covered.

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5.2
Classification of Ventilators

Even if any ventilator can be theoretically used to start NPPV in both ARF and CRF, success is more likely if the ventilator is able to (a) adequately compensate for leaks; (b) let the clinician continuously monitor patient–ventilator synchrony and ventilatory parameters due to a display of pressure–flow–volume waveforms and a double-limb circuit; (c) adjust the fraction of inspired oxygen (F_{IO_2}) with a blender to ensure stable oxygenation; and (d) adjust inspiratory trigger sensitivity and expiratory cycling as an aid to manage patient–ventilator asynchronies [4].

Ventilators may be classified in four categories, whose features are summarized [4] in Table 5.1.

1. *Volume-controlled home ventilators* were the first machines used to deliver NPPV mostly for domiciliary care; even if well equipped with alarms, monitoring system, and inner battery, their usefulness for applying NPPV is largely limited by their inability to compensate for air leaks. Consequently, their application is today restricted to home-based noninvasive support of selected cases of neuromuscular disorders and to invasive support of ventilatory-dependent tracheostomized patients.

2. *Bilevel ventilators* are the evolution of home-based continuous positive airway pressure (CPAP) devices and derive their name from their capability to support spontaneous breathing with two different pressures: an inspiratory positive airway pressure (IPAP) and a lower expiratory positive airway pressure (EPAP) or positive end-expiratory pressure (PEEP). These machines were specifically designed to deliver NPPV thanks to their efficiency in compensating for air leaks. Due to their easy handling, transportability, lack of alarms and monitoring system, and low costs, the first generation of bilevel ventilators matched the needs for nocturnal NPPV in chronic patients with a large ventilatory autonomy. However, traditional bilevel ventilators showed important technical limitations (risk of CO_2 rebreathing due to their single-limb circuit in nonvented masks; inadequate monitoring; lack of alarms and O_2 blending, limited generating pressures; poor performance to face the increase in respiratory system load; lack of battery), which have been largely overcome by more sophisticated machines. The newer generations of bilevel ventilators have gained popularity in clinical practice for application of acute NPPV especially in settings with higher levels of care as well as to invasively support ventilatory-dependent chronic patients at home.

3. *Intensive care unit (ICU) ventilators* were initially designed to deliver invasive ventilation via a cuffed endotracheal tube or tracheal cannula either to sick patients in the ICU or to the theatre room to allow surgery procedures. Despite good monitoring of ventilatory parameters and of flow–pressure–volume waves as well as a fine setting of F_{IO_2} and of ventilation, performance of conventional ICU ventilators to deliver NPPV is poor as they are not able to cope with leaks. So, a new generation of ICU ventilators has been developed to efficiently assist acute patients with NPPV thanks to the option of leak compensation (i.e., "NPPV mode"), which allows partial or total correction of patient–ventilator asynchrony induced by air leaks, even if with a large intermachine variability.

Table 5.1 Characteristics of the four categories of ventilators for NPPV

	CO_2–rebreathing	Blender O_2	Adjustment of trigger and cycling	Modality of NPPV	Monitoring	Air leak compensation	Alarms	Battery	Transportability	Costs
Volume-target ventilators	–	No	+	Volumetric	+	–	++	Yes	++	++
First-generation bilevel ventilators	+++	No	–	Pressometric	–	+++	–	No	+++	+
Second-generation bilevel ventilators	+/–	No	+++	Pressometric and volumetric	++	+++	++	Yes	+++	++
Intermediate ventilators	+/–	Some	++	Pressometric and volumetric	++	++	+++	Yes	++	++
Conventional ICU ventilators	–	Yes	++	Pressometric and volumetric	+++	–	+++	Yes	+/–	+++
New ICU ventilators	–	Yes	+++	Pressometric and volumetric	+++	+++	+++	Yes	+/–	+++

– Absent; +/– low/absent; + low; ++ moderate; +++ high

4. *Intermediate ventilators* combine some features of bilevel, volume-cycled, and ICU ventilators (dual-limb circuit; sophisticated alarm and monitoring systems; inner battery; both volumetric and pressometric modes; wide setting of inspiratory and expiratory parameters). These new machines are studied to meet the patient's needs both in the home and in the hospital care context as well as to safely transport critically ill patients.

5.3
Technologic Issues

5.3.1
Source of Gas and Oxygen Supply

ICU ventilators are equipped with high-pressure air sources and with a blender where O_2 from high-pressure sources and room air are variably mixed, making the FIO_2 controlled and stable. Conversely, bilevel and several intermediate ventilators are provided with either a compressor or an electrically supplied turbine pump to pressurize the room air, which may not ensure a constantly stable pressurization; moreover, these machines do not have a blender, so O_2 is delivered from low-pressure sources, and the FIO_2 during NPPV is not easily predictable because it is dependent on several variables: site of O_2 enrichment, type of exhalation port, ventilator setting, O_2 flow, breathing pattern, and amount of leaks [4]. It was calculated that the highest FIO_2 is achieved with the leak port in the circuit and O_2 added into the mask by using low IPAP levels [7] (Table 5.2).

5.3.2
Circuit

Respironics BiPAP, like most of the first-generation bilevel ventilators, is provided with a single-limb circuit, and the exhalation of the expired air occurs through the whisper swivel, a fixed-resistance, variable-flow, leak port situated in the circuit proximally with respect to the interface. This equipment exposes the patient to the risk of CO_2 rebreathing, which may be detrimental when treating hypercapnic patients [8]. The options that the clinician has to prevent this risk are (a) keep the conventional whisper swivel and apply high EPAP levels, such as 8 cmH_2O, which therefore may be poorly tolerated; (b) use the *plateau exhalation valve* which, thanks to its diaphragm, limits air leaks during inspiration and allows unidirectional airflow during expiration; (c) apply a *nonrebreathing valve* ("mushroom," "diaphragm," "balloon" valve), which works like a "true valve" as during the inspiration the diaphragm or its balloon is inflated with a full occlusion of the expiratory circuit limb, while during the expiration, as the valve is deflated, the air is allowed to be exhaled throughout. However, even with a large variability, these valves may interfere with the resistance and the expiratory work and therefore may increase lung hyperinflation (i.e., intrinsic PEEP) [4].

The CO_2 rebreathing is also influenced by the site of the exhalation port, being significantly lower when using a facial mask with the exhalation port inside compared to a facial

Table 5.2 Key points of the performance of ventilators for NPPV [4]

• Source of gases
Compressed medical gases
Compressor or electrically supplied turbine pump
• Oxygen supply
High-pressure sources with a blender
Low-pressure sources with connection at the ventilator, circuit, mask
• Circuit
Single-limb circuit with nonrebreathing valve, plateau exhalation valve, or whisper
Double-limb circuit
• Inspiratory trigger with sensitivity changeable or not
Flow, pressure, volume, mixed
• Expiratory cycle
Flow dependent (with threshold changeable or not), time dependent, autofunction
• Inspiratory flow changeable or not
• Backup respiratory rate
• Air leak compensation
• Humidification
Heated humidifiers, heat–moisture exchangers
• Battery
Internal, additional external
• Alarms
Lack or minimal
Sophisticated
• Monitoring systems
Only some inspiratory parameters
Inspiratory and expiratory parameters
Flow, volume, pressure curves
• Mode of ventilation
Only spontaneous modes without (PSV, PAV) or with a guaranteed V_{T} (VAPS)
Both spontaneous (PSV, PAV) and mandatory modes (VCV, PCV)
• Interface
Nasal mask, full-face mask, total-face mask, helmet, mouthpiece

PSV pressure support ventilation, *PAV* proportional assist ventilation, *VAPS* volume-assured pressure support ventilation, *VCV* volume-controlled ventilation, *PCV* pressure-controlled ventilation

mask with the exhalation port in the circuit and a total-face mask with the exhalation port inside [9].

With ventilators that have a dual-limb circuit in which a complete separation exists between inspiratory and expiratory lines (i.e., ICU, last-generation bilevel, and intermediate ventilators), there is no risk of rebreathing.

5.3.3
Inspiratory Trigger and Expiratory Cycle

The optimization of patient–ventilator interaction during NPPV is essentially based on the technological efficiency of the machine in detecting the patient's minimum inspiratory effort as quickly as possible (i.e., *inspiratory trigger*) and in ending the delivery of mechanical support as close as possible to the beginning of the patient's expiration (i.e., *expiratory cycling*) independently from the respiratory system impedance and from the air leaks [4]. Ideally, the inspiratory trigger should be set at the higher sensitivity capable of reducing the patient's effort needed to activate the mechanical support. Bilevel ventilators equipped with flow triggers are associated with lower work of breathing and shorter triggering delay time with respect to those equipped with pressure triggers [10]. However, a too sensitive trigger, especially if flow based, may induce auto-triggering during NPPV with substantial air leaks and, consequently, patient–ventilator dyssynchrony with "wasted efforts." Inspiratory trigger function may significantly differ not only among the different categories of ventilators but also within the same category due to the structural features of the circuit (i.e., single-limb circuit with high resistive valves; "incomplete dual-limb circuit"; and a PEEP valve in the short expiratory limb) and the heterogeneity in their performance (pressure–time and flow–time waveforms, trigger delay, leak-induced autotriggering during NPPV with flow-triggered ventilators).

The cycling to expiration optimizes the synchrony between the inspiratory time (Ti) of the patient and that of the machine. During pressure support ventilation (PSV), cycling to expiration is flow dependent and occurs at a threshold, which is the decrease in flow either to a default or changeable percentage (usually 25%) of inspiratory peak flow or to an absolute flow [5]. Patient–ventilator dyssynchrony with expiratory muscle activation and wasted efforts due to incomplete lung emptying may happen under NPPV in case of excessive air leaks, which delay or avoid the inspiratory flow to reach the threshold (i.e., "inspiratory hang-up") [5]. Successful strategies in preventing the inspiratory hang-up may be applied with some ventilators: (a) set a suitable threshold or a maximum Ti; (b) use special algorithms (i.e., "autotrack system"); (c) switch to pressure-controlled ventilation (PCV) mode, in which expiratory cycling is time dependent. The chance of finely setting the threshold for expiratory cycling thanks to the display of mechanics waveforms available in some newer ventilators may be helpful clinically to improve patient–ventilator synchrony during NPPV as well as comfort and the possibilities of success [4]. As observed with the inspiratory trigger, the behavior of different ventilators varies in terms of cycling to expiration, and a marked heterogeneity is reported for a given ventilator in response to various conditions of respiratory mechanics and air leaks. Generally, most of

the bilevel ventilators use a cutoff at a higher fraction of inspiratory flow than most of the ICU ventilators to avoid the mask leak-induced deleterious prolongation of Ti. As a matter of a fact, newer bilevel ventilators tend to cycle prematurely to expiration under normal respiratory system mechanics, and this tendency is exaggerated in restrictive conditions. Conversely, under obstructive conditions, most of the bilevel ventilators show delayed cycling, and this behavior is greatly exaggerated by the presence of air leaks. Consequently, at their default setting, bilevel ventilators seem to be better adapted for supporting obstructed patients [4]. Opposite to bilevel ventilators, in the absence of leaks and at their default setting, newer ICU ventilators present some degree of delay in cycling to expiration that is worsened by obstructive conditions, while restrictive mechanics lead to premature cycling. The addition of leaks increases the delayed cycling in normal and obstructive conditions and partially corrects premature cycling in restrictive status. This dyssynchrony in expiratory cycling may be prevented by using NPPV modes in normal and obstructive mechanics [4].

5.3.4
Inspiratory Flow

It is known that severely dyspneic patients with chronic obstructive pulmonary disease (COPD) cope better with higher inspiratory flow and patients with neuromuscular problems do better with lower inspiratory flow (i.e., pressure rise time of 0.05–0.1 s and 0.3–0.4 s, respectively) [4]. In most of the bilevel ventilators, this parameter is unchangeable; conversely, in more advanced bilevel ventilators, as well as in most of the intermediate and ICU ventilators, the rise time may be set with a potential profound effect on unloading of respiratory muscles, tolerance, and leaks. In a physiologic study, the highest pressurization rate was associated with increased air leakage and poorer NPPV tolerance even though the diaphragmatic effort was increasingly reduced compared to lower speeds without significant differences in blood gases or breathing pattern. As the patient's comfort was not different at the lower pressurization speeds, the authors suggested that the individual titration should be targeted to achieve good tolerance and to minimize air leaks, keeping a relatively high pressurization rate [11].

5.3.5
Backup Respiratory Rate

Some bilevel ventilators do not have the option of setting a backup respiratory rate f, which therefore raises the costs. Conversely, the great majority of newer bilevel ventilators and all intermediate and ICU ventilators are equipped with a backup f. This option is particularly advantageous in sicker patients with instability of their respiratory drive as it prevents the phenomena of apnea and of periodic breathing, such as Cheyne–Stokes in chronic heart failure. Backup f may also be useful when cautious sedation is administered to improve patient compliance to NPPV [4].

5.3.6
Air Leak Compensation

Due to the kind of interface used, air leaks are almost a constant feature of NPPV and may interfere with the patient's comfort, patient–ventilator synchrony, and, eventually, the likelihood of success in both acute and chronic patients [1–6]. "Unintended leaks" may occur through the mouth during nasal ventilation or between the interface and the skin with both nasal and oronasal masks. On the other hand, the attempt of tightly fitting the straps of headgear to reduce air leaks should be avoided because this may reduce the patient's tolerance and predispose to skin damage. Consequently, it is important to have a ventilator capable of well compensating air leaks during NPPV. Air leak compensation is greater when using bilevel rather than volume-target home ventilators, with the fall in tidal volume V_T more than 50% with the latter (Fig. 5.1). Conversely, the fall in V_T is less than 10% and in IPAP less than 8% with bilevel ventilators in case of leaks thanks to an adequate increase in the inspiratory flow and in the Ti. However, the effects of air leaks during NPPV are more complex than the simple fall in IPAP and V_T due to the role played by further variables, such as Ti, expiratory cycling, and inspiratory trigger sensitivity. Mathematical models that
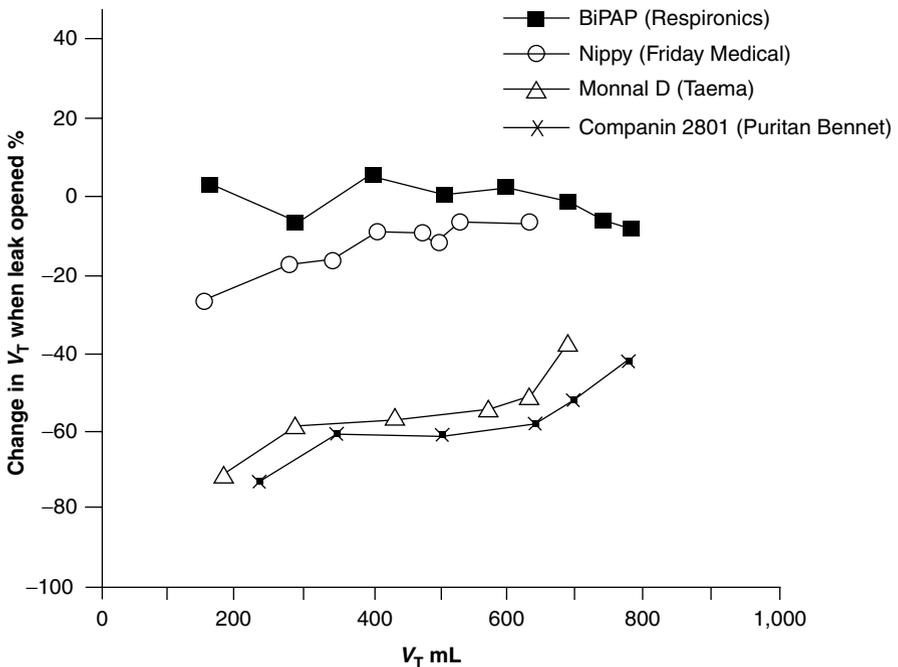
Fig. 5.1 Effect of an additional leak on the tidal volume V_T delivered by four home ventilators tested in a lung model. The relationship between the percentage changes in V_T with leak opened and the V_T delivered in the absence of a leak showed that pressure-target (BiPAP, Nippy) and not volume-target home ventilators (Monnal D, Companion 2801) well compensated for the leak [4]

analyze the complex interaction between air leaks and PSV in the obstructive conditions and their potential clinical implication have been recently implemented. Even though all bilevel ventilators and most intermediate and newer ICU ventilators equipped with NPPV modes were able to compensate for air leaks, their performance was not uniform [4].

5.3.7
Battery

For both acute and chronic patients with a high level of dependency on NPPV, a battery power source is mandatory in case of electricity supply failure at home and in case of need to transport the patient within the same hospital or to another hospital. However, the clinician must be aware that battery duration may differ greatly among the different portable ventilators and may be shorter than that reported in the operator's manual. Moreover, portable ventilator battery duration is affected by the setting, the lung impedance characteristics, and the ventilator features [4].

As an alternative or in addition to internal batteries for NPPV ventilators, it is also possible to use external batteries that guarantee prolonged autonomy of the ventilator in case of electricity blackout. It has to be considered that external batteries may make the ventilator too heavy if it needs to be transported.

5.3.8
Alarm and Monitoring System

The need for sophisticated alarms and monitoring systems during NPPV is essentially based on clinical practice as until now there is no scientific evidence for their clinical utility. This is especially true for patients with home ventilation, so care must be taken when setting the alarms on the ventilator to ensure that they will only function when a genuine need arises as frequent, often spurious, alarms can significantly disturb the sleep of the patient. The prototype of the Respironics BiPAP has neither alarm nor monitoring features, with an advantage in cost and transportability for home care. In the acute setting, the availability of newer bilevel, intermediate, and ICU ventilators with more sophisticated alarms (i.e., low and high pressure, V_T, f, F_{IO_2}, leaks) and monitoring graph (i.e., flow, V_T, and pressure curves) may be useful in terms of safety and in improving patient–ventilator interaction [4,5]. Conversely, too elaborate alarms may be counterproductive in clinical practice since they frequently indicate very minor air leaks during NPPV.

The key parameter to be monitored is the expiratory V_T as excessive air leaks may cause a significant discrepancy between inspiratory and expiratory V_T. Single-limb circuit bilevel ventilators allow monitoring only the inspiratory V_T, which corresponds to the sum of the patient's V_T and the air leaks; as the inspiratory V_T increases for air leak compensation, it does not reflect directly the minute ventilation of the patient. Moreover, the expiratory V_T estimated by some bilevel ventilators has not been validated. Dual-limb circuit bilevel ventilators, as well as most of the intermediate and all the ICU ventilators, allow close monitoring of expiratory V_T, whose value is more reliable with machines that make the

measurement at the level of the expiratory branch of the "Y-tube" than with those that measure it at the inlet of the expiratory tube into the ventilator [4].

5.4
Controversial Issues

Due to the huge gap between the commercially available increasing number of newer ventilators and their physiologic and clinical careful evaluation, unfortunately we still have not published data about several sophisticated ventilators routinely used in clinical practice. Because there are few in vivo investigations, the majority of data about the performance of the different available ventilators comes from in vitro studies conducted on a lung model. Therefore, some doubts remain about the real clinical significance of the technical differences observed in the bench studies among the various types of ventilators. Consequently, every extrapolation of these experimental data to clinical practice must be done cautiously since no lung model can simulate the ventilatory variability observed in patients. This is particularly true when the findings of in vitro studies have to be applied to acute patients under NPPV in the presence of leaks.

Based on the published data, despite a wide heterogeneity found in each category of machines, several bilevel ventilators demonstrated better performance compared to some conventional ICU ventilators (Fig. 5.2) [4]. However, no study has shown greater NPPV clinical success for one type of ventilator than another in both acute and chronic settings. Nevertheless, some points should be clear when the clinician has to choose a ventilator [4].
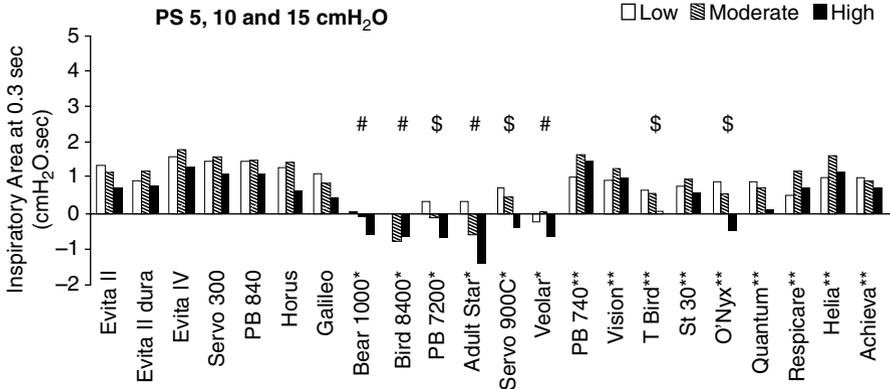
Fig. 5.2 Pressurization rate in the early inspiratory phase evaluated in a lung model as the inspiratory area in the first 0.3 s of inspiration according to three levels of pressure support (PS 5, 10, 15 cmH$_2$O) and three simulated levels of inspiratory effort (low, moderate, high) for 22 ventilators (*from left to right*: seven new-generation ICU ventilators, six old-generation ICU ventilators, and nine piston- or turbine-driven home ventilators). All new-generation ICU ventilators, but also most home devices, outperformed old-generation ICU ventilators. * Old-generation ICU ventilators; ** Piston- or turbine-driven home ventilators; # $p < 0.05$ vs all new-generation ICU ventilators; $ $p < 0.05$ vs at least one of the new-generation ICU ventilators [4]

Key Recommendations

> As excessive air leaks are correlated with treatment failure, the clinician should choose *ventilators designed for NPPV with leak compensation capability* (i.e., bilevel, some intermediate, and new ICU ventilators); moreover, the chance of *setting several parameters and looking at flow–volume–pressure waveforms* with newer ventilators may be helpful in improving patient–ventilator synchrony, comfort and, it is hoped, clinical outcome.

> The choice of ventilator should be tailored to the *pathophysiology and the severity of ARF and CFR*. In the acute setting, for hypoxemic patients, ventilators with an O_2 blender are recommended, while in those with hypercapnia, ventilators with a dual-limb circuit have an advantage in lowering Pa_{CO_2}. In patients with mild COPD exacerbation, the use of home ventilators may be appropriate, particularly if the patient is already on home NPPV; by contrast, patients with life-threatening ARF at risk of intubation should be treated with more sophisticated machines. In the chronic setting, conditions for which respiratory drive is good (i.e., COPD) could use a simple ventilator that works in a spontaneous mode, whereas those for whom respiratory drive is absent must have a mandatory backup rate; conversely, in the case of fast-progressing neuromuscular diseases, more sophisticated ventilators with adequate monitoring equipment and an inner battery are recommended.

> The selection of a ventilator should also take into account *costs and staff experience*. The more sophisticated a ventilator is, the longer is the required training for clinicians. Due to the tremendous growth of the ventilator market in terms of complexity, some of the new bilevel ventilators are not user friendly even for trained ICU clinicians. The smaller the variety of devices used, the greater the likelihood that all team members will acquire enough experience in NPPV setup with positive repercussions in costs and workload.

> The clinician should be aware of the *multiple interferences of the accessories for NPPV* (interfaces, exhalation systems, pressure settings, and humidification devices) with the performance of the different categories of ventilators. For example, concerning humidification during NPPV, heated humidifiers show great clinical and physiological advantages compared to heat–moisture exchangers, even though the former is more time consuming.

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Noninvasive Positive Pressure Ventilation Using Continuous Positive Airway Pressure

6

Pedro Caruso

6.1 Introduction

Continuous positive airway pressure (CPAP) is a technique of respiratory therapy, in either invasive mechanically or noninvasive mechanically ventilated patients, in which airway pressure is maintained above atmospheric pressure at a constant value throughout the inspiration and expiration by pressurization of the ventilator circuit. This chapter discusses the equipment and technology available to deliver CPAP in noninvasive positive pressure ventilation (NPPV) in the hospital scenario and does not discuss the equipment to deliver CPAP to patients with obstructive sleep apnea-hypopnea or at home care services. The interfaces to deliver CPAP are not discussed.

CPAP efficacy has been confirmed in common clinical conditions such as cardiogenic pulmonary edema, chronic obstructive pulmonary disease, and chest wall trauma [1]. CPAP can be provided with continuous flow generators, intensive care unit (ICU) ventilators (high-pressure-driven ventilators), ventilators designed to administer noninvasive positive pressure ventilation (NPPV ventilator) with or without NPPV modes and other medical devices, such as the bubble or Boussignac CPAP.

6.2 Equipments

6.2.1 Continuous Positive Pressure Flow Generators

Continuous positive pressure flow generators are electricity-independent devices that utilize an oxygen-driven venturi to entrain atmospheric air, producing high fresh gas flows. The resultant oxygen–air mixture enters a single-limb breathing circuit and exits through

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a threshold resistor (the CPAP valve) in the mask or helmet (acting as a double-limb circuit). CPAP valves have a spring-loaded variable orifice design that open at a set pressure and should maintain constant upstream pressure as flow varies (flow independence). The gas flow rate and O_2 inspiratory fraction generated by the continuous flow generator are adjustable using uncalibrated dials. The manufacturers allege a flow up to 140 l/min, but higher flows are described [2]. To mitigate the decrease of pressure during inspiration, a continuous positive pressure flow generator uses an inspiratory reservoir (CF 800, Dräger, Lübeck, Germany).

The continuous positive pressure flow generator advantages are simple use, high portability, electricity independence, and lower costs. The disadvantages are high noise to patients and staff, lack of monitoring or alarms, and, mainly, low performance (decrease of pressure during inspiration or inability to attain the preset pressure). Two bench studies [2, 3] demonstrated that the multiple possible adjustments in a continuous flow generator (fraction of O_2, pipeline supply, valve load, and flow adjustment) make the performance of a continuous flow positive pressure generator excessively variable and unpredictable. Besides that, the ubiquitous mask/circuit leak, a condition not tested in those studies, would make the performance of the flow generators even more unpredictable and certainly more unsuitable.

6.2.2
Intensive Care Unit Ventilators (High-Pressure-Driven Ventilators)

The ICU ventilators offer CPAP mode, but they are designed to be used in intubated patients, so air leak, a ubiquitous condition in NPPV, is not contemplated. However, ICU ventilators can provide satisfactory CPAP since major air leaks are not present, and some adjustments are observed: adequate inspiratory flows, triggering sensitivity adjusted to prevent autocycling, and a mechanism available to limit inspiratory time and avoid inspiratory-to-expiratory ratio inversion [4]. Depending on the critical care ventilator selected, CPAP may be administered using "demand," "flow-by," or "continuous flow" techniques, with imposed work differing slightly between them in intubated patients [5].

The ICU ventilator manufacturers have been offering ICU ventilators that they claim are able to deliver NPPV in the presence of leaks. However, these ventilators were not tested in the CPAP mode. A study that evaluated the performance of those ventilators in NPPV during pressure support ventilation concluded that leaks interfered with several key functions, and the NPPV mode could correct part or all of this interference but with wide variations between machines in terms of efficiency [6].

6.2.3
Ventilators Designed to Administer Noninvasive Positive Pressure Ventilation

The NPPV ventilators are designed to be used in the presence of air leaks. They are microprocessed systems, turbine driven and with a single-limb circuit with nonrebreathing valve,

plateau exhalation valve, or whisper swivel. They offer alarms and a monitoring system. In theory, NPPV ventilators should be better than the other devices to offer CPAP in NPPV.

Two studies using lung simulators compared NPPV to continuous positive pressure flow generators or ICU ventilators. The first study compared an NPPV ventilator (BiPAP, Respironics Inc., Murrysville, PA) with two continuous positive flow generators (Adjustable Downs Flow Generator – Vital Sign, New Jersey; and WhisperFlow, Respironics-Philips, Murrysville, PA) to deliver CPAP. In that study, adjusted to their better oxygen supply pressure, flow generators had a similar or better capacity to maintain the CPAP level, but the NPPV ventilator was more reliable for attaining the preset CPAP [2]. The second study compared the same NPPV ventilator (BiPAP) to nine ICU ventilators in the NPPV mode. The NPPV ventilator and one ventilator (Servo I, Maquet, Solna, Sweden) were the only ventilators that required no adjustments as they adapted to increasing leaks [7]. The clinical significance of the differences between NPPV ventilators and ICU ventilators with the NPPV mode is unclear.

6.2.4
Boussignac CPAP

The Boussignac CPAP is a simple system for use on a face mask and is based on the generation of positive airway pressure by a jet [8]. Pressure is generated by the injection of gases, which pass through four microcapillaries (located all around the CPAP device), increasing in speed and generating turbulence, therefore creating a "virtual valve." The resulting CPAP level ranges from 2.5 to 10 cmH_2O according to gas flow. The CPAP device has two ports: one for injecting gases and another for controlling pressure through a manometer or monitoring CO_2 or adding oxygen.

Because of its simplicity, low weight, and small size, the Boussignac CPAP is a portable device. Its efficacy during bronchoscopy in hypoxemic patients [8] and in the treatment of acute cardiogenic pulmonary edema has been reported.

An improvement in the Boussignac CPAP was proposed (the Super-Boussignac) [9]. Inserting a T-piece between the Boussignac valve and the face mask and connecting the T-piece to a reservoir balloon receiving oxygen by an independent source allowed a smaller drop in airway pressure during inspiration and higher tidal volumes.

6.2.5
Bubble CPAP

The bubble CPAP can be set up with existing equipment (an ICU ventilator or oxygen blender) using the circuit of a ventilator. The interface is a mask or nasal prong. Pressure is generated by placing the expiratory limb under water. The number of centimeters under water the tubing is placed equals the CPAP level. In the circuit, a connection to a pressure-monitoring device or oxygen analyzer can be incorporated. Its use is advocated in neonates because the column of water causes a slight oscillation in the pressure waveform that is thought to decrease the incidence of bronchopulmonary dysplasia [10].

6.3
Discussion

There are different types of equipment to deliver CPAP in NPPV. They range from very simple equipment to sophisticated microprocessed ventilators. Unfortunately, there are no studies that simultaneously compared the performance of all these types of equipment. The few studies of this issue compared one type of equipment to deliver CPAP to another, and most were bench studies using lung simulators. Clinical trials comparing the different equipment that deliver CPAP in NPPV are required.

In theory, the NPPV ventilators and the ICU ventilators with NPPV mode are a better choice to deliver CPAP in NPPV because they are prepared to deal with air leaks, but few studies were done to verify this. An obvious advantage of these ventilators is the presence of alarms and monitoring.

Key Recommendations

> There are at least five types of equipment to deliver CPAP in noninvasive ventilation. The choice is based on availability of equipment and the staff's expertise.
> ICU ventilators with NPPV modes and ventilators designed to administer NPPV are preferred because they are prepared to deal with air leaks and have better monitoring and alarms.
> If continuous positive pressure flow generators, Boussignac or bubble CPAPs are used, it is recommended to provide close monitoring of the patient by the staff and monitoring of CPAP pressure and oxygen fraction by aggregated devices.

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Home Mechanical Ventilators

7

Frédéric Lofaso, Brigitte Fauroux, and Hélène Prigent

7.1
Introduction

A wide variety of patients requires mechanical ventilation; therefore, it is not surprising that numerous ventilators, ventilation modes, and equipment are necessary to select the most appropriate noninvasive ventilation technology for each patient. We voluntarily limited this chapter to positive pressure ventilation modes considering that negative pressure ventilation and abdominal pressure ventilation are used much less often now, and that no technological breakthrough has emerged in past years to improve or increase the use of these methods. We also do not present continuous positive airway pressure (CPAP) considering that this mode does not actively produce or assist inspiration. However, CPAP ventilation shares similar equipment with other methods of positive pressure ventilation.

7.2
Technology and Equipment

7.2.1
Ventilators

Home care ventilators have improved over the past 20 years, and now their characteristics and performance are close to critical care ventilators. They offer a variety of modes and features desirable for noninvasive ventilation. They have real exhalation valves that limit CO_2 rebreathing. Moreover, the exhalation valve can be located inside the ventilator, which

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allows improvement of monitoring, alarms, and loop regulation. Some ventilators are small and lightweight, thus portable, and can operate from a battery. Therefore, they can be easily transported (e.g., on wheelchairs). These ventilators are generally proposed when patients require full ventilatory support.

Besides these sophisticated devices, some very simple ventilators, bilevel positive airway pressure devices, are available specifically for noninvasive ventilation during sleep. They are blower devices that may deliver variable inspiratory and expiratory pressures in response to the patient's inspiratory effort. Therefore, they provide a pressure-targeted mode without a volume-targeted mode. These ventilators use a single hose that does not have a true exhalation valve. Expired gases pass through a hole preferably positioned at the mask level to reduce as much as possible CO_2 rebreathing [1]. Leaks through this hole depend on the level of airway pressure; to avoid the risk of rebreathing, manufacturers impose a minimal end-expiratory pressure of about 4 cmH_2O.

7.2.2
Mechanical Ventilation Modes

Positive pressure ventilation depends on three important variables: the signal allowing the initiation of positive pressure, the algorithm that controls how the gas is delivered by the ventilator during inspiration, and the signal terminating the gas delivery by the ventilator.

7.2.2.1
Initiation of Positive Pressure

When the patient is able to produce an inspiratory effort, assisted modes are preferred to controlled modes, with the limit that assisted modes have been shown to induce sleep fragmentation [2]. A controlled mode can be proposed for safety reasons; however, maintaining an assisted mode and using a backup rate can be an alternative. Controlled modes are also proposed when the ventilator is not able to detect the inspiratory effort or when inspiratory effort detection is systematically associated with autotriggering. In fact, the trigger variable used to detect the patient's inspiratory effort can be pressure, flow, volume, and flow waveform. With a pressure trigger, the patient triggers the ventilator when the patient decreases the pressure in the ventilator circuit to a certain preset value, whereas with flow and volume triggers patients have to produce a certain inspiratory flow or volume. With the flow waveform method, the ventilator detects the expiratory flow waveform distortion caused by the patient's inspiratory effort. Finally, some triggers combine both flow and pressure. However, since the variations of these parameters are much smaller in pediatric patients, trigger sensitivity is frequently insufficient for the pediatric population [3]. It can also be challenged in some situations, such as air leaking, which alters flow and pressure into the ventilator circuitry and facilitates autotriggering; or inability to detect the patient's effort [3]; or dynamic hyperinflation, which produces intrinsic positive expiratory pressure and ineffective efforts. One alternative solution could be to detect the activity of the diaphragm using either electromyography [4] or transdiaphragmatic pressure [5], but these tools are not yet available for home devices.

7.2.2.2
Gas Delivery by the Ventilator During Inspiration

It is usual to separate the volume-targeted ventilators from pressure-targeted ventilators. Historically, the first ventilators used a volume-targeted mode with a constant flow. These devices used a piston or a bellow. During the 1990s, pressure-targeted modes delivering a constant pressure (with a decelerating flow once the set pressure is reached) by using turbines, and now microturbines, were developed. With this mode of mechanical ventilation, it is possible to adjust the pressurization rate (the amount of time required to reach the targeted pressure), and the clinician has to find a compromise between a faster pressurization rate that better unloads inspiratory effort and a lower pressurization rate, which may decrease air leaks and improve tolerance.

The advantages of the pressure-targeted modes compared to the volume-targeted modes are that, for the same inspiratory time, the pressure-targeted mode usually delivers more volume than the volume-targeted mode and, for the same tidal volume, the pressure-targeted mode usually requires a lower peak inspiratory pressure than the volume-targeted mode. Therefore, tolerance is often better with pressure-targeted modes. Moreover, the pressure-targeted modes are able to compensate leaks, whereas the volume-targeted are not. Last, but not least, with a pressure-targeted mode the tidal volume depends on both the ventilator settings and the patient's inspiratory effort (tidal volume can increase with the patient's inspiratory demand), while with the volume-targeted mode obviously the patient cannot increase his or her tidal volume. The advantages of the volume-targeted modes are that pistons, or bellows, can provide higher ventilating pressure, which may be required in patients with high respiratory system impedance; that air stacking is possible with the volume-targeted modes [6]; and that volume-targeted ventilators can operate considerably longer on battery power than pressure-targeted ventilators, which generally use a turbine.

Now, several ventilators have the ability to combine the advantages of both modes of noninvasive ventilation. Some volumetric ventilators are able to deliver a volume-controlled breath with a descending-ramp flow waveform that approximates the shape of the flow waveform during pressure-targeted mode, and some ventilators that use a pressure-targeted mode are also able to ensure a minimal tidal volume delivered to the patients (which may decrease when inspiratory activity decreases, respiratory system impedance decreases, or a leak occurs) by increasing either the targeted pressure [7] or the inspiratory time [8]. In addition, the battery autonomy has improved over the years, and it is now possible to add a second battery on some devices.

Proportional assist ventilation (PAV) is an alternative mode of noninvasive mechanical ventilation [9]. It delivers a pressure proportional to instantaneous flow and volume with factors that take into account both the respiratory system compliance and resistance. This may approximate the patient's demand except when leaks occur. In this situation, the patient's demand is overestimated, and a runaway may occur. Finally, leaks frequently observed during noninvasive ventilation are an important limit of PAV use. An alternative could be pressurization proportional to the activity of the diaphragm using either electromyography [4] or transdiaphragmatic pressure [5], but these tools are not yet available for home devices.

7.2.2.3
Cycling Off Variable

The criterion for cycling off the ventilator and therefore allowing exhalation depends on the mode of support and may be time, volume, airway pressure, or flow. Ideally, the end of insufflation should coincide with the end of inspiratory effort. However, this rarely happens, demonstrating that the algorithm used to cycle off the ventilator has to be improved.

7.2.3
Interfaces for the Delivery of Noninvasive Ventilation

The choice of interface has a major impact on the success of noninvasive ventilation and therefore should be optimal. Different types of interfaces are available.

7.2.3.1
Nasal Interfaces

Nasal interfaces include nasal masks, which can be commercially produced or custom made, and nasal pillows. Nasal masks can induce facial side effects (skin injury, facial deformity on growing facial structures) [10]. When skin injury occurs with a commercial nasal mask, the use of a custom-made mask may reduce skin injury risks [10]. An alternative could be the use of nasal pillows considering that a Cochrane review [11] suggested that nasal pillows induced fewer side effects than nasal masks. Moreover, it is also possible to wear glasses with some nasal pillows. Leak through the mouth is common with these interfaces. A chin strap can reduce air leaks [12]; however, when it is insufficient, oronasal interfaces might be needed.

7.2.3.2
Oronasal Interfaces

Oronasal masks and full-face masks can be proposed when leaks occur. Full-face masks are also an alternative to the nasal mask when nasal skin breakdown occurs. Those with an antiasphyxia valve and quick-release features should be preferred. Helmets are not appropriate for home mechanical ventilation because of the risk of asphyxia in case of power failure.

7.2.3.3
Mouth Interfaces

Few individuals use mouthpieces. This is the predominant method of daytime ventilation when noninvasive ventilation must be permanent [13]. The mouthpiece has to be positioned close to the mouth so that the patient can connect and disconnect as he or she wants.

In this situation, volume-targeted ventilation is preferred, and the ventilator circuit can remain open without alarm because the resistance of the mouthpiece allows a residual inspiratory peak pressure inside the ventilator. The patient can receive insufflations when the patient decides by making a sip effort.

7.2.4
Humidification

Upper airway dryness commonly occurs during noninvasive mechanical ventilation, especially when leak occurs. In the presence of leaks, a heat-and-moisture exchanger is inefficient. A heated humidifier can be proposed (except during transportation).

7.2.5
Safety

The role of alarms and monitoring for noninvasive ventilation is controversial. It depends on patient respiratory autonomy. Nonetheless, disconnection and power failure alarms are recommended. Battery backup is desirable for patients who require full ventilatory support. Moreover, family should be trained in the use of a manual balloon resuscitator.

7.3
Conclusion

The use of noninvasive mechanical ventilation is increasing with the increasing evidence of improvement of life expectancy in some populations. The selection of equipment and the settings are based on the patient's needs, which may vary widely from one patient to another. The keys to the success of this therapy are the bedside caregiver's understanding of the equipment, the ventilation mode's functioning, and the time the caregiver can to devote to the patient and the patient's family.

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Maintenance Protocol for Home Ventilation Circuits

8

Michel Toussaint and Gregory Reychler

8.1
Introduction

Home mechanical ventilation has become a standard of care to effectively treat chronic respiratory failure either in patients with restrictive diseases such as neuromuscular and thorax cage disorders or in patients with obstructive diseases such as selected cases of lung and airway disorders. Depending on the group of patients, home ventilation may improve survival and quality of life in the long term and may decrease the rate of lower respiratory tract infections [1].

8.2
Equipment for Home Mechanical Ventilation

Home mechanical ventilation requires equipment consisting of a pressure generator (volume- or pressure-cycled ventilator), a circuit with tubing (with or without expiratory valve), and an interface to deliver air to the patient. In the majority of patients, a nasal mask is the most appropriate interface for nocturnal use. Full-face masks may be used in the rare cases for which nasal masks are useless. Finally, mouthpieces are preferentially used in waking patients for daytime noninvasive ventilation. Invasive ventilation via tracheostomy may be required when it is not possible to conduct further noninvasive ventilation.

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8.2.1
Dirtiness, Contamination, Colonization

Contamination of circuits infers the transient presence of bacteria in the circuits or in the airways, while *colonization* infers the multiplication of the germs in the airways of patients, which may lead to chronic respiratory infection. By contrast with the hospital setting, transmission of infection by cross contamination is rare in the home setting since patients receiving home mechanical ventilation use their own equipment and have no direct or indirect contact with other patients. In home use, the question is to what extent home ventilation circuits (HVCs) must be disinfected. Is dirtiness of an HVC a risk factor for HVC contamination and a patient's self-colonization? What is the best protocol for cleaning? Is disinfection needed, and how often is it recommended? The aim of this chapter is to answer these questions and to suggest an adequate protocol for maintenance of HVCs.

8.2.2
Maintenance Is Empirically Driven

Although home ventilation is widely used around the world, maintenance of HVC is empirically driven. Instructions given before discharging patients home are mostly taken from the recommended guidelines from other areas, such as lung function tests, nebulization techniques, or respiratory monitoring. These instructions are generally based on tradition rather than scientific evidence and vary depending on the countries and centers. Instructions are often too elaborate and not specifically adapted for patients receiving home ventilation. Current instructions often include the use of disinfectant solution, vinegar mixed with water, or a quaternary ammonium compound but generally fail to explain how basic maintenance may be achieved by simple cleaning with soap and hot water or with the dishwasher.

8.2.3
A European Survey on Maintenance

In a European survey [2] including more than 20,000 patients receiving home ventilation (two-thirds restrictive, one-third obstructive patients), only 60% of the participating centers provided written instructions on the cleaning and maintenance of the equipment. There was a significant positive correlation between the size of centers and the proportion of written instructions ($p < 0.001$). On average, only 56% of the centers had protocols for correct cleaning and maintenance of circuits and interfaces. These findings clearly demonstrate that a huge effort is needed to improve the communication to patients regarding adequate rules of maintenance before home discharge.

8.2.4
Patients Do Not Clean Their Equipment

In a recent study, two-thirds of patients who were taught cleaning instructions prior to discharge did not adequately clean their equipment at home [3]. Tubing and masks were most commonly found as ''unacceptably'' dirty. It was hypothesized that dirtiness of equipment exposes circuits and masks to a higher risk of contamination. Indeed, the dirtiest circuits were found significantly more contaminated than the cleanest ones [3, 4]. Dirtiness and contamination should potentially expose patients to a higher risk of airway colonization, which in turn should cause respiratory infections. However, this relationship has not yet been demonstrated with evidence.

8.2.5
Sensitivity to Infections

Clearly, regular cleaning appears to be the most important instruction that needs to be followed by all patients for the maintenance of HVCs. As previously seen, however, there needs to be considerable effort to target and institute this basic effective cleaning. By contrast with cleaning rules, the instructions for postcleaning disinfection will depend on the relative sensitivity of patients to respiratory tract infections and the related risks for bacterial colonization of the airways. Two groups of patients need to be considered here: those with restrictive and those with obstructive disease. Clearly, both groups are not equally sensitive to infections and, as a consequence, should not require a similarly elaborate disinfection level.

8.3
Analysis and Discussion

8.3.1
Restrictive Disorders

By contrast with patients affected by obstructive respiratory diseases, patients affected by restrictive respiratory diseases or hypoventilation syndrome are a priori at low risk for bacterial colonization of airways.

In an uncontrolled study with stable patients receiving written and verbal information on maintenance of HVCs (recommendation was for daily cleaning with soap and water), a Spanish group questioned patients regarding their cleaning habits [3]. They conducted both visual inspection of HVCs and sampling of masks (contamination) plus nostrils (colonization) in each patient. As a result, the frequency of cleaning was found as follows:

47% cleaned their HVCs once a week, 23% cleaned once a month, 15% cleaned sporadically, and 15% never cleaned their equipment. In total, 67% of HVCs were deemed as very dirty, and a positive relationship between circuit contamination and nostril colonization was highlighted. Bacterial colonization was more important in those patients with dirtier HVCs. The authors could not conclude whether colonization preceded or followed contamination. However, they suggested that adequate cleaning decisively decreased the rate of contamination. These authors did not provide a protocol for adequate maintenance of HVCs.

In another study [4], visual and bacterial inspections of HVCs were assessed before and after cleaning in a first experiment. In a second experiment, the authors randomly compared either cleaning with the household dishwasher or low-level disinfection with an ammonium–chlorhexidine complex. Their findings were in agreement with the findings of Rodriguez et al. [3]. Prior to cleaning, circuits were found dirty in 69% of the cases. HVCs were dirtier in invasive ventilation. There was a significant positive correlation between the level of visual dirtiness and bacteriologic contamination of HVCs ($r = 0.56$; $p < 0.001$). Bacteriologic contamination reached 22% of noninvasive HVCs with little presence of fungi. Nevertheless, by contrast with invasive HVCs, contamination of noninvasive HVCs did not include potentially pathogenic organisms (PPOs) such as *Serratia marcescens*, methicillin-resistant *Staphylococcus aureus* (MRSA), or *Pseudomonas aeruginosa*. In invasive HVCs, contamination affected 81% of HVCs, including the important presence of fungi; 19% of HVCs had PPOs, including *S. marcescens* in two cases and MRSA in one case, but no *P. aeruginosa* contaminated HVCs in this group. In the second experiment of this study, cleaning in the dishwasher was shown to be superior to the chemical compounds for both cleaning and disinfecting HVCs. In addition, gram-negative bacteria and fungi survived in the chemical complex but not in the dishwasher.

In accordance with the findings of Ebner et al. [5], we suggest using either a dishwasher at 65°C or basic soap and hot water as the best means of cleaning HVCs used by restrictive patients (Fig. 8.1). Nevertheless, a disinfective agent may be recommended (1) for the very dirty HVCs, (2) in circuits from invasive ventilation, and (3) in HVCs from patients known for their high sensitivity to respiratory infections, such as obstructive patients. Effective cleaning must always precede any disinfection. It is important to be sure that a thermostable HVC is used before cleaning or disinfecting at temperatures above 60°C. Effective disinfection is described in the next section.

8.3.2
Obstructive Disorders

The situation regarding hygiene of HVCs is slightly different in obstructive respiratory diseases such as cystic fibrosis (CF) and chronic obstructive pulmonary disease (COPD) compared to restrictive respiratory diseases. The major reason for this difference consists of a higher sensitivity to bacterial colonization of the airways in these patient populations. The rate of airway colonization often correlates with the severity or the speed of obstructive

Fig. 8.1 Protocol of maintenance for home mechanical ventilation circuits

Dirty circuits of Home Mechanical Ventilation

```
                        CLEANING:
                   - 65° dishwasher or
                   - brush, detergent and
                        hot water

                        RINSING
                        DRYING

   Restrictive        ← Diagnosis ? →        Obstructive
    patient                                    patient

            Very dirty circuits
                    or
            invasive ventilation?

         no              yes

                                          DISINFECTION:
    NO DISINFECTION                     -  hypochlorite solution (20
                                          minutes of soaking in a
                                          concentration of 0.5%)
                                       -  high temperature
                                          disinfection (>75°c)

     SPORADIC                           REGULAR CONTROL :
     CONTROL :                               -cleaning
     - cleaning                        - bacteriologic sampling
                                         in case of doubt
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disease progression. In addition, there is evidence that the need for noninvasive ventilation becomes more frequent after airway colonization in these patients.

Ventilator-associated pneumonia is well documented. In intensive care units, the use of mechanical ventilation is an important risk factor for the development of nosocomial pneumonia. Moreover, current risk is greater with the use of invasive mechanical ventilation compared with noninvasive ventilation. Unfortunately, the relationship between the use of noninvasive ventilation and an increased risk for nosocomial pneumonia is not demonstrated.

The greater number of manipulations and the presence of an endotracheal tube associated with invasive ventilation contribute to HVC contamination. It can be hypothesized that manipulations related to noninvasive ventilation also represent a potential risk for

contamination. This implies rigorous implementation of classical nonspecific rules of hygiene, including hand washing. Nevertheless, the ventilator, the circuit, and the interface do not represent major risk factors for contamination and colonization, but monitoring potential bacterial contamination of devices and paying attention to the basic rules of hygiene probably remain important challenges.

There is little published research to support the relationship between hygiene and noninvasive ventilation devices in obstructive diseases. Nevertheless, we can extrapolate findings from therapies such as respiratory physiotherapy devices to obstructive patients receiving long-term noninvasive ventilation. Indeed, the material involved in noninvasive ventilation is part of the semicritical devices that are in contact with mucous membranes as defined by the Centers for Disease Control and Prevention. Fortunately, recommendations on hygiene of these devices are available.

In patients affected by CF and COPD, nebulizers are considered potential vectors of bacterial colonization of airways. Notably, studies showed that nebulizers of CF patients are frequently contaminated [6]. Similarly, it was suggested that nebulizers can lead to nosocomial disease in COPD patients [7]. The bacterial contamination of an HVC is related to the duration of its use and the airway colonization of the patient.

Based on this evidence, several recommendations were proposed and could be applied to the pieces of the circuit involved in noninvasive ventilation in obstructive diseases. As shown in Fig. 8.1, regular cleaning of HVCs and masks is mandatory, at least as a basic hygiene procedure and, more specifically, to eliminate the biofilm deposited on the surfaces, which further decreases the efficacy of disinfectants [8]. The necessary frequency of cleaning is still being debated. Based on the results of studies on nebulizers, a daily cleaning could theoretically be the recommended timing. However, less-regular cleaning (i.e., once a week) could be acceptable in practice. The possibility of using tap water for cleaning must be taken into account if HVCs are contaminated by *S. marcescens* and *Stenotrophomonas maltophila*.

When considering disinfection, different methods may be proposed. The choice of the optimal method largely depends on the material chosen to disinfect. Thermal disinfection (i.e., sterilizer, boiling water) may be not suitable for some nonthermostable pieces of HVCs even though its efficacy is evident with all germs. There are a number of chemical methods, and each has its own characteristics. The duration of soaking and the concentration of the chemical will depend on the particular substance used, and the guidelines for each must be followed carefully. Acetic acid is not recommended due to its inefficacy on gram-positive and gram-negative bacteria [9, 10]. By contrast with acid acetic, hypochlorite solution (20 min of soaking in a 0.5% concentration) may be the best alternative of those readily available chemical solutions.

After disinfection, rinsing and drying is the last part of the cleaning and disinfection sequence. Drying seems important as a higher contamination rate was related to nondried nebulizers in CF patients. Because there is a paucity of specific data related to noninvasive ventilation, precise recommendations cannot be made. However, it could justify more studies on this topic. Finally, it appears critically important to investigate the relative effectiveness of the different established protocols for cleaning and disinfecting of HVCs to maintain their integrity.

Key Recommendations

> Cleaning the ventilator, circuits, and interfaces is required two to four times per month in all patients receiving mechanical ventilation at home.

> Written instructions on how to clean the equipment for home ventilation is useful. Regular assessment of whether circuits and interfaces are correctly cleaned and maintained is mandatory.

> In restrictive patients, cleaning in the dishwasher is effective and sufficient for thermostable circuits and interfaces. Cleaning with soap and hot water may be sufficient for all pieces. Disinfection is not mandatory.

> In obstructive patients, cleaning must be more frequent than for restrictive patients. Cleaning always precedes disinfection. After cleaning, rinsing and drying are important. An effective weekly disinfection may be achieved by using an hypochlorite solution (20 min of soaking in a 0.5% concentration).

> The expiratory valve must be washed specifically, with care so that the balloon is not placed underwater.

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Nocturnal Noninvasive Mechanical Ventilation

9

David Orlikowski, Hassan Skafi, and Djillali Annane

9.1
Introduction

Long-term mechanical ventilation in patients with neuromuscular problems was first introduced between 1950 and 1960 in France and Sweden as a consequence of the poliomyelitis epidemics. During the following decades, the concept of home mechanical ventilation expanded rapidly. Long-term mechanical ventilation was implemented in many other countries and for many other conditions, including neuromuscular or chest wall disorders, spinal cord injury, and chronic obstructive pulmonary disease. At the beginning of the 1990s, there were 26,000 people in France and 11,419 in the United States receiving long-term respiratory assistance. About 10% presented with neuromuscular or chest wall disorders. A European survey conducted between July 2001 and June 2002 reported the use of home mechanical ventilation in 483 centers in 16 countries. That study identified 27,118 participants with long-term mechanical ventilation for lung or neuromuscular diseases related to chronic respiratory failure. Then, the estimated prevalence was 6.6 per 100,000 people.

Chronic alveolar hypoventilation is a state characterized by reduced arterial oxygen tension (Pa_{O_2}) and increased carbon dioxide tension (Pa_{CO_2}), which the patient may correct at least partially by voluntary hyperventilation. In most cases, chronic alveolar hypoventilation leads to daytime fatigue, hypersomnia, and changes in psychological function. The mechanisms underlying hypercapnia in people with neuromuscular or chest wall disorders are multiple and not yet fully understood. They may involve impairment of lung mechanics or airway function and cough, ventilation–perfusion mismatch, blunted central ventilatory drive, or respiratory muscle fatigue. Abnormalities may occur while awake or during sleep. Numerous observational and uncontrolled studies suggested that nocturnal mechanical ventilation at least partially improves lung mechanics, respiratory muscle strength, or

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respiratory drive or reduces ventilation–perfusion mismatch, by day as well as night. A multicenter randomized trial of preventive nocturnal noninvasive positive pressure ventilatory assistance in 70 participants with moderate pulmonary insufficiency due to Duchenne muscular dystrophy showed that survival was significantly worse in participants receiving preventive nocturnal ventilatory assistance, although daytime blood gases were improved. Several other randomized trials, performed on parallel groups or based on a crossover design and small samples, suggested that nocturnal ventilation had beneficial effects on arterial blood gases or sleep parameters. The Consensus Conference of the American College of Chest Physicians recommended the implementation of long-term ventilation in patients with chronic hypercapnia during the day and in those with symptomatic nocturnal hypercapnia, particularly when secondary to neuromuscular or skeletal disorders.

9.2
Effect of Nocturnal Mechanical Ventilation

A systematic review from the Cochrane collaboration examined the effects of nocturnal mechanical ventilation in patients with chronic alveolar hypoventilation [1]. The primary objective of this review was to examine the effects of nocturnal mechanical ventilation in people with neuromuscular or chest wall disorders on the improvement of chronic hypoventilation. Subsidiary endpoints were to examine the effects of respiratory assistance on sleep quality, hospital admissions, quality of life, and mortality related to chronic hypoventilation. Participants with stable chronic hypoventilation, defined by an arterial CO_2 tension above 6 kPa during the day, or symptoms of nocturnal hypercapnia (i.e., any of the following: diurnal hypersomnia, headaches, nightmares, enuresis), including children and adults with all degrees of severity, whether living in institutions or in the community. Chronic hypoventilation due to one of the following medical conditions was considered according to the classification of the Consensus Conference of the American College of Chest Physicians: Central nervous system disorders, including Arnold–Chiari malformation, central nervous system trauma, cerebrovascular disorders, disorders of congenital and acquired central control of breathing, myelomeningocele, spinal cord traumatic injuries; neuromuscular disorders, including amyotrophic lateral sclerosis, spinal muscular atrophy, polio and postpolio syndrome, congenital childhood hypotonia, Guillain–Barré syndrome, infantile botulism, muscular dystrophy, myotonic dystrophy, phrenic nerve paralysis, myasthenia gravis; and skeletal disorders, including kyphoscoliosis, thoracic wall deformities, and thoracoplasty.

Types of interventions were analyzed as follows [1]:

1. Treatment with nocturnal mechanical ventilation (for at least 3 h per night) versus no ventilation.
2. Type of ventilation. Invasive techniques (i.e., tracheostomy [intermittent positive pressure]) versus noninvasive techniques using negative pressure or positive pressure. For negative pressure, the four available types of body enclosures were considered: (a) body tanks (iron lungs), (b) chest shells (rigid domes that fit over the chest and abdomen), (c) body wraps (nylon or plastic jackets that surround the chest and abdomen), and (d) abdominal pneumobelts (inflatable rubber bladders held firmly against the

abdomen by nylon corsets). For noninvasive positive pressure ventilation, nasal, mouthpiece, and oronasal interfaces were all considered.

3. Mode of ventilation. Volume-cycled, pressure-cycled mechanical ventilation or bilevel positive airway pressure.

Types of outcome measures were as follows: Primary outcome was reversal of daytime hypoventilation-related clinical symptoms (i.e., diurnal hypersomnia, headaches, nightmares, enuresis). Secondary outcomes included admission to hospital (other than routine visits); mortality; reversal of daytime hypercapnia (i.e., arterial CO_2 tension [on room air] below 6 kPa); and lung function measurements (i.e., forced vital capacity, respiratory muscle strength, ventilation–perfusion mismatch, sleep studies [i.e., apnea–hypopnea index or mean oxygen saturation], or the time spent with an arterial oxygen saturation below 90%). The primary and the secondary outcomes were recorded separately for the first 24 h (short-term effects) and for 12 months (long-term effects) following implementation of mechanical ventilation [1].

The authors concluded that the current evidence about the therapeutic benefit of mechanical ventilation was weak but directionally consistent, suggesting alleviation of the symptoms of chronic hypoventilation in the short term. In three small studies, survival was prolonged, particularly in participants with motor neuron disease. They also concluded that large randomized trials are needed to confirm possible long-term beneficial effects of nocturnal mechanical ventilation on hypoventilation-related symptoms, quality of life, unplanned hospital admission rate, and mortality and to evaluate its cost-effectiveness in people with neuromuscular diseases other than motor neuron disease as well as in people with chest wall disorders. Future trials should be stratified according to the type of disease and to whether the course is rapidly progressive or not. The comparisons between invasive and noninvasive ventilation and between volume-cycled and pressure-cycled ventilation also require well-designed multicenter randomized trials [1].

9.3
Equipment Requirements for Nocturnal Ventilation

Prolonged mechanical ventilation is a life-supporting technology that can be delivered at home. This therapy can be applied with a variety of interfaces, ventilator settings, and several reviews have focused on both the type of ventilators and interfaces [2, 3].

Body ventilators are used rarely, and the gold standard is actually noninvasive positive pressure ventilation (NPPV) [4].

9.3.1
Type of Ventilator

Ventilators used for home ventilation can provide NPPV in a volumetric (volume-cycled) or barometric way (pressure cycled). In the first case, a fixed tidal or minute volume is

delivered that will generate a pressure sufficient to achieve ventilation. In the case of high inflation impedance, a high pressure will occur to reach the targeted volume with a risk of barotrauma. Another major problem is that an appropriate tidal volume may not be delivered in case of leaks. The volume-cycled mode is useful because it permits breath stacking and cough assistance. These ventilators have alarms, operate from battery power, and are equipped with exhalation valves to offer secure home use even in very dependent patients.

The pressure-cycled ventilators deliver a predetermined pressure, and the resulting tidal volume depends on the impedance of the respiratory system. In the case of leaks, flow is increased to compensate, but in the case of obstruction, the tidal volume may be reduced. Air stacking is usually not possible with this type of ventilators. These ventilators can be equipped with alarms, battery, and exhalation valves or can be simpler, such as bilevel positive airway pressure. These portable pressure ventilators are well designed for NPPV and require a leak and positive expiratory pressure to avoid CO_2 rebreathing. They are usually not equipped with a battery and have no exhalation valve.

9.3.2
Modes of Ventilation

Mechanical ventilation can be controlled (respiratory frequency is determined by the ventilator) or assisted (ventilator cycles are triggered by the patient's spontaneous breaths) or a mix of both modes (assist control [A/C] or spontaneous-timed [S/T]). Modes of ventilation used for NPPV are volume-controlled ventilation (VCV), pressure support ventilation (PSV), or pressure-controlled ventilation (PCV). Pressure modes are actually the most commonly used [5]. Mixed modes using a pressing support technology but enslaved to a volumetric target have been developed. In theory, they seem interesting by mixing both advantages of pressure and volume ventilation [6]. In practice, studies are still lacking to recommend their broad use.

9.3.3
Type of Interface

Choice of the interface is a crucial issue when starting home ventilation.

Commercial or customized interfaces may be used and a broad variety of masks (nasal, oronasal, or even total face or helmet), mouthpieces, or pillows are available. The selection of the interface should take into account the type of disease; the severity of the respiratory weakness; the duration of ventilation per 24 h (night only or also use of daytime ventilation); the level of handicapping ability of the patient for placing or removing the interface; the presence of swallowing impairment; and patient morphology. Intentional leaks may be present on the mask if no exhalation valve is used. The type of interface may be modified secondarily by the occurrence of nonintentional leaks (need for a chin strap or change to an oronasal or facial interface) or presence of skin sores.

9.4
Conclusion

Nocturnal home noninvasive ventilation is a common treatment in neuromuscular disease or chest wall disorders. Actually, positive pressure ventilation that can be delivered via a broad range of interfaces is the gold standard for long-term ventilation. Different modes may be used and likely have similar efficacy. Home ventilators offer more choices in terms of settings and mode of ventilation. They also offer an increased possibility for monitoring and alarms, providing more secure use even in the most disabled and dependent patients. Quality control of the equipment used in home mechanical ventilation is therefore necessary to ensure safe and accurate ventilatory support.

Key Recommendations

> Noninvasive nocturnal ventilation is the treatment of choice for neuromuscular disease and chest wall deformities.
> There is no superiority of one mode of ventilation comparing to others.
> A regular follow up is needed by specialized team in order to indicate and to verify efficacy of home ventilation.
> A dedicated network of care including home healthcare practitioners is particularly important for this population.

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Section III

Patient–Ventilator Interactions

Patient–Ventilator Interaction During Noninvasive Pressure-Supported Spontaneous Respiration in Patients with Hypercapnic Chronic Obstructive Pulmonary Disease

10

Wulf Pankow, Achim Lies, and Heinrich Becker

10.1
Introduction

Noninvasive pressure support ventilation (NPSV) has become a standard of care in patients with acute exacerbations of chronic obstructive pulmonary disease (COPD). In stable COPD, hypercapnia is correlated with less respiratory muscle strength and greater muscle load. In selected patients, mechanical ventilation with NPSV may be indicated in addition to oxygen therapy to prevent worsening of hypercapnia and to improve sleep quality and quality of life. Epidemiologic studies on NPSV have shown that patient tolerance is a key factor predicting success or failure.

The objective of NPSV is to improve blood gases and to unload the respiratory muscles. Success of NPSV is related to many factors. One of the most important is the interaction of the patient and the ventilator. Important determinants are intrinsic positive end-expiratory pressure (PEEPi), pressure generated by the inspiratory muscles, triggering of the ventilator, and patient–ventilator synchrony.

10.2
Patient Response to the Ventilator

With NPSV, patient-initiated breaths are followed by a preset level of pressure assist. In theory, the respiratory system can respond to assisted ventilation in two ways. First, ventilator

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work is used to increase ventilation, while respiratory muscle activity is unchanged. Second, ventilator work is used to unload the respiratory muscles at a constant level of ventilation.

Several studies in patients with exacerbated COPD and with severe stable COPD have shown that, in clinical practice, both effects are combined. Blood gases are improved as ventilation increases, while respiratory muscle activity is reduced. Downregulation of respiratory muscle activity is attributed to feedback mechanisms, which are activated by unloading the muscles (nonchemical feedback) and by reducing P_{CO_2} (chemical feedback).

We investigated the physiologic effects of NPSV in seven patients with stable hypercapnic COPD [1]. Inspiratory positive airway pressure (IPAP) was applied with 12–14 cmH$_2$O and expiratory positive airway pressure (EPAP) with 3 cmH$_2$O. Compared to spontaneous breathing, ventilation with NPSV was increased, as indicated by a drop of Pa_{CO_2} from 58 to 50 mmHg. Respiratory muscle activity, measured with the transdiaphragmatic pressure–time product (PTPdi), was reduced by 33%. Others have demonstrated even stronger effects when NPSV was applied to patients with stable or exacerbated COPD [2]. Differences may depend on alternative ventilator settings and patient characteristics.

Behavioral feedback may also affect patient–ventilator interaction. In COPD exacerbation, dyspnea and anxiety cause rapid, shallow breathing. These mechanisms promote dynamic hyperinflation and PEEPi, affecting trigger sensitivity and patient comfort. As a result, the patient may fight with the ventilator rather then accept its support. Judicious sedation can help to initiate NPSV.

During sleep, breathing drive is reduced, and the dependence of the respiratory controller on P_{CO_2} is increased. The potential effect of NPSV to increase tidal volume and to decrease P_{CO_2} may induce apnea and periodic breathing with consequences on the patient–ventilator interaction. Indeed, a study showed that ineffective efforts are common during nocturnal NPSV, while no patient–ventilator asynchrony occurred during daytime [3]. Ventilator settings adjusted during wakefulness may therefore not be appropriate for nocturnal mechanical ventilation.

10.3
Ventilator Response to the Patient

The way in which the ventilator responds to inspiratory and expiratory efforts is influenced by the patient's respiratory system mechanics and by machine properties (triggering, cycling, and pressurization).

Respiratory mechanics in severe COPD is impaired by static and dynamic hyperinflation and PEEPi. PEEPi is the most common cause of ineffective triggering in COPD. To trigger the ventilator, the patient must first perform a certain amount of inspiratory muscle activity to counterbalance PEEPi and thus induce subatmospheric alveolar pressure. This delays inspiratory pressure assist, and patient–ventilator synchrony may be severely disturbed. Also, extra (ineffective) respiratory muscle activity is necessary to trigger the ventilator. At times, a patient's effort might not even be strong enough to lower the pressure at the airway opening below PEEPi and to trigger the ventilator (Fig. 10.1).
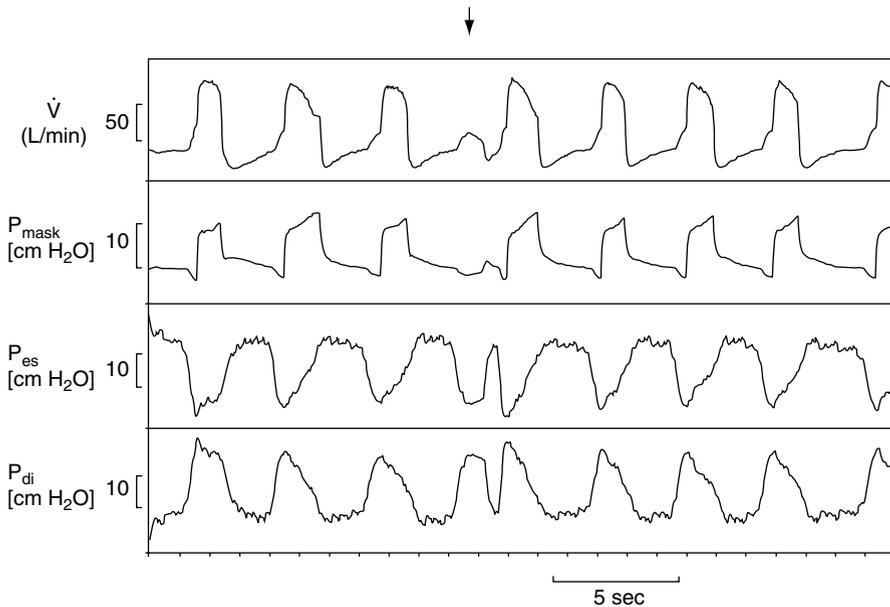
Fig. 10.1 Recordings of flow (V'), mask pressure (P_{mask}), esophageal pressure (P_{es}), and transdiaphragmatic pressure (P_{di}) in a patient with stable COPD receiving NPSV. *Arrow* indicates ineffective triggering: Positive deflection of transdiaphragmatic pressure is not followed by positive mask pressure, and flow remains at low level (Reproduced from Pankow et al. [1]. With permission. © Georg Thieme Verlag KG)

PEEPi in stable COPD normally ranges from 1 to 6 cmH$_2$O during spontaneous breathing. In overweight patients with hypercapnic COPD [1] and in acute respiratory failure, higher values up to 13 cmH$_2$O have been measured. The application of external pressure at the airway opening (PEEPe or EPAP) can effectively reduce the work of breathing and improve triggering. EPAP can be applied as mask CPAP (continuous positive airway pressure), but tolerance and respiratory muscle unloading are more effective in combination with IPAP. The combination of IPAP and EPAP also increases alveolar ventilation. In clinical practice, PEEPi cannot be measured, and the optimal level of EPAP is applied in a pragmatic way. An appropriate way is to start with 0–2 cmH$_2$O and increase EPAP slowly until ineffective efforts disappear. In addition, effective bronchodilator therapy may optimize patient–ventilator interaction by reducing expiratory flow limitation, dynamic hyperinflation, and PEEPi.

The respiratory muscle activity required to trigger the ventilator also depends on the trigger system. With pressure triggering, the patient's effort decreases the pressure in the ventilator system to open the demand valve. With flow triggering, a preset inspiratory flow is generated to activate inspiratory pressure assist. In patients with COPD, flow triggering reduces inspiratory effort compared to pressure triggering [4]. However, the clinical significance of this difference is unclear and might be of minor relevance.

Air leaking through the mouth or around the mask seal may interfere with ventilator triggering. In a study on patient–ventilator interaction, severe asynchrony with NPSV was observed in 43% of 60 patients [5]. The study population was heterogeneous: 40% suffered from COPD, and 55% were hypercapnic. Air leaks were identified as a major contributing factor to ineffective breaths and late cycling [5]. An intensive care unit (ICU) ventilator was used; therefore, these results may not be applicable to modern bilevel ventilators. They have the potential to compensate for leaks and thus improve triggering. However, with NPSV generated by a modern bilevel device, ineffective triggering has been identified as the dominant cause of patient–ventilator dyssynchrony in four of ten patients. In the same study, ineffective triggering was observed in three of ten patients using conventional ventilation [6]. To reduce air leaking, chin straps, tightening of the mask, or replacement of the nasal mask by an oronasal mask may be tried.

Delayed or premature cycling is another source of patient–ventilator asynchrony. Ideally, pressure support should be tightly coupled to the inspiratory drive of the patient. The ventilator detects the transition from inspiration to expiration by a predetermined decrease of inspiratory flow. In COPD, delayed cycling is a common problem. Airway obstruction is accompanied by a flattening of the flow curve. The flow determined to cycle off is reached late in the breathing cycle. This in turn shortens expiratory time, decreases lung emptying, and contributes to dynamic hyperinflation and PEEPi. Also, air leaking may prolong the reduction of inspiratory flow to the cycling threshold. Cycling can be improved when the default flow threshold is changed to a preset time. In acute respiratory failure, inspiratory time should be limited to below 1.0 s.

An important advantage of NPSV, compared to invasive ventilation, is that the patient can be asked how comfortable he or she interacts with the machine. Does the patient get enough air: pressurization? Is it easy or exhausting to obtain ventilator support (trigger threshold)? Does the machine interfere with breathing (cycling, leaks, PEEPi)? Visual evaluation of the patient's breathing effort and breathing rhythm is another important means to optimize patient–ventilator synchrony.

Key Recommendations

> In severe hypercapnic COPD, NPSV with expiratory PEEP (PEEPe or EPAP) can effectively reduce a patient's respiratory muscle effort and increase alveolar ventilation. Patient–ventilator synchrony is a prerequisite for achieving this effect.
> PEEPi is the most common cause of ineffective triggering. To counterbalance PEEPi, EPAP may be started with 0–2 cmH$_2$O and increased slowly until ineffective efforts disappear.
> Air leaks also interfere with ventilator triggering and cycling. To reduce leaking, tightening of the mask, replacement of the nasal mask by an oronasal mask, or chin straps may be appropriate.

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Asynchrony and Cyclic Variability in Pressure Support Ventilation

11

Antoine Cuvelier and Jean-François Muir

Adaptation between the patient and the ventilator has always been the first goal of the physician facing with a patient treated by mechanical ventilation. Sedation is commonly used under invasive ventilation to facilitate it, especially in difficult-to-ventilate patients with acute respiratory distress syndrome (ARDS). Adaptation to noninvasive ventilation (NIV) is often difficult to obtain in the acute phase as this mode of ventilation is a "leaky" ventilation, and spontaneous ventilation has to be respected, with contraindication of significant sedation. Thus, specific attention has been brought to this phenomenon called *synchrony*, which may be defined as the agreement between the patient respiratory efforts and the inspiratory and expiratory time of the ventilator. So, asynchrony may be explained by the inspiratory drive and the airways pressurization, which is secondary to the mechanical and technical characteristics of the machine and the interface, the ventilatory settings, and the pathophysiological abnormalities linked to the etiology of the respiratory failure [1]. This dyssynchrony is the mismatch between patient and ventilator inspiratory time and secondary wasted or ineffective efforts.

With asynchrony as the source of discomfort for the patient with increased sensation of dyspnea and impairment of the quality of ventilatory support, it is important to provide its precise semiology to evaluate its clinical relevance and its pathophysiology to correct it, mainly by an improvement of the settings of the respirator and special attention to the inspiratory and expiratory triggers. On the other hand, dyssynchrony, still today detected and analyzed during daytime, may significantly occur during night, generating sleep fragmentation and thus daytime fatigue and somnolence. It was necessary to have the opportunity to record more easily and for a long time such events to correct them through appropriate respirator setting modifications. Significant improvements in recording and detection of patient–ventilator asynchrony have been developed in our laboratory that may be derived from the pressure and flow traces on the screen of the respirator and thus used in the clinical setting. The three major determinants of the patient-ventilator synchrony are the ventilator triggering, the airway pressurization and the ventilator cycling (passage to expiration) [2].

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Poor patient–ventilator interactions, especially ineffective inspiratory triggering efforts (ITEs) may occur during noninvasive pressure support ventilation (PSV) in patients with cystic fibrosis (CF) [3, 4], in patients with chronic obstructive lung disease (COPD) with lung inflation and intrinsic positive end-expiratory pressure (PEEPi) [5, 6], and in patients with various other pulmonary diseases [7]. ITEs under PSV are more frequent during sleep [8, 9] and when increasing the level of ventilatory assistance [10, 11]. ITEs during NIV are associated with poorer gas exchange during sleep [12] and sleep fragmentation [13]. Moreover, ITEs may be a cause of PSV intolerance and failure in critically ill patients "fighting" against their ventilator. Otherwise, the incidence of ITE and its impact on PSV efficacy and comfort remain unknown. A simple noninvasive method to detect ITE during PSV is therefore highly desirable. Esophageal pressure (Pes) monitoring is commonly used as the standard for detecting the onset of inspiratory efforts, although diaphragmatic electromyography has been used by some authors [14]. This last technique requires esophageal or surface electrodes and cannot be performed on a routine basis during sleep or for domiciliary assessments. Consequently, most studies on ITE have assessed Pes or transdiaphragmatic pressure (Pdi) variations to identify the relationship between individual inspiratory efforts and ventilator triggering. However, esophageal recordings are not practical as a routine measure in most centers and are inadequate for prolonged or long-term assessments in patients treated by home ventilation, which require a real investigation of the frequency and duration of such events and which cannot be correctly identified, scored, and quantified from short recordings. On the other hand, manual scoring of ITE is time consuming. For this reason, a new research axis is currently being explored through algorithms that integrate airway pressure and flow variations to automatically detect ITE in real time. This automatic noninvasive method has been validated by comparing it with the manual detection of ITE using conventional Pes recordings [15–17]. This detection methodology, based on simple physiological data, is very sensitive and specific compared to the standard method (i.e., measurements of Pes variations). Also, the structure of the phase portraits reconstructed from the flow time series appears to be very sensitive to the dynamics of underlying patient–ventilator interactions [16]. Phase portraits provide global signatures of the quality of the ventilation from a mechanical point of view. Depending on loop dispersion and shape, patients with regular ventilatory patterns could be easily distinguished from patients not adapted to their ventilators. It should be noted that air leaks were easily detected by this approach since they induced loops with abnormal shapes and usually with large amplitudes. A parallel approach was developed by Mulqueneey et al. [18]. They built an algorithm that was able to detect ineffective triggering efforts based on significant alterations of the expiratory flow signal. However, their technology was connected to a specific ventilator and required an electronic signal delivered by this machine to detect the expiratory phase. Conversely, the algorithm of Achour et al. [15] runs with any noninvasive ventilator and has the ability to combine the analysis of flow/pressure time series and their mathematical transformation according to the nonlinear dynamic system theory. It quantifies the breathing pattern and also identifies significant inspiratory effort variations. Chen et al. [19] have also finalized an algorithm that works by analyzing minimal and maximal flow values during the expiratory phase of the ITE. By comparison, the algorithm of Achour et al. uses flow derivatives over each whole ventilatory cycle and not only during its sole inspiratory or expiratory phase and represents an efficient tool to identify repeated ITE.

The standard criteria commonly used to define ITE are based on a Pes decrease of more than 1 cmH$_2$O with a simultaneous drop in airway pressure or change in flow [8]. Giannouli et al. were the first to suggest that ITE could be detected exclusively from Paw and flow time series [9]. This approach is accurate in intubated patients, and an acceptable ITE underestimation may be encountered in case of severe patient–ventilator asynchronies. The previously cited articles showed that a similar approach can be automated and can also be applied to patients receiving noninvasive PSV. Such algorithms could be of potential clinical interest to identify ITE during prolonged recordings during sleep or when assessing domiciliary ventilation. This new approach for assessing patient–ventilator interactions avoids the inherent difficulties and discomfort associated with esophageal pressure assessments.

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Carbon Dioxide Rebreathing During Noninvasive Mechanical Ventilation

12

Francesco Mojoli and Antonio Braschi

12.1
Introduction

Partial reinhalation of previously exhaled carbon dioxide (CO_2) may impair the efficacy of noninvasive mechanical ventilation (NIMV) in improving CO_2 removal and unloading ventilatory muscles [1]. At constant alveolar ventilation, any CO_2 concentration above zero in inhaled gases causes an increase of arterial CO_2 tension by an equal amount. Accordingly, significant CO_2 rebreathing increases alveolar ventilation requirements to maintain desired arterial CO_2 tension. This can limit the beneficial effects of inspiratory assistance provided by NIMV. In this chapter, we review general mechanisms of CO_2 rebreathing and the effect of different interfaces, respiratory circuits, and ventilator settings.

12.2
General Mechanisms of Carbon Dioxide Rebreathing

During NIMV, inspiratory and expiratory flows share the distal part of the respiratory circuit and the inner volume of the patient–ventilator connecting interface, be it a mask or a helmet. Expired CO_2 fills this "common" space and is pushed by the ventilator again into the patient's airways during the following inspiratory phase. Anyway, this space is not

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really equivalent to the dead space we deal with during invasive mechanical ventilation. Such classic, or static, dead space is filled by the final part of expiratory tidal volume, having a CO_2 concentration equal to mean alveolar value (i.e., the end-tidal CO_2). Apart from a minor clearing effect of bias flow when flow-based triggering is selected, CO_2 does not leave this static dead space. Thus, reinhalation of this volume does not significantly decrease alveolar CO_2, finally resulting ineffective in removing carbon dioxide.

This is not the case for noninvasive ventilation. During mask ventilation, high expiratory flows through the exhalation port and significant air leaks at the interface with the patient's face can substantially decrease the CO_2 concentration below the alveolar value [2]; reinhalation of this partially cleared (i.e., dynamic) dead space is therefore not completely ineffective in removing CO_2. During helmet ventilation, CO_2 rebreathing is not due to dead space ventilation at all. Expired gases from the patient are indeed diluted in a space that is much larger than tidal volume, with CO_2 concentration inside the helmet mostly reduced by the flow of fresh gases from the ventilator. Therefore, helmet NIMV can be assimilated to breathing in a semiclosed environment [3, 4]. From what has been just mentioned, factors underlying rebreathing during mask and helmet NIMV are substantially different; therefore, they will be discussed separately.

12.3
CO_2 Rebreathing During Mask Ventilation

The amount of CO_2 rebreathed from the mask and respiratory circuit depends on dead space volume and its CO_2 content.

The volume of dead space may be modified by mask and respiratory circuit design, ventilator settings, and the patient's respiratory pattern. Masks with major inner volume (once fixed to the patient's face), like total-face masks, may improve comfort during NIMV but enhance CO_2 rebreathing [2]. Regarding circuit design, when a two-limb respiratory circuit is used, dead space volume is limited to the mask inner volume plus the volume of the respiratory circuit distal to the Y-piece (Fig. 12.1a).

Anyway, NIMV is often put in place using a single-limb respiratory circuit. In this case, gases exhaled by the patient are discharged in the environment by one or more exhalation ports, the position and design of which can significantly affect rebreathing [2]. As flow through exhalation ports is limited, in the first part of patient's expiration (when flow reaches its peak), some exhaled gases can go up the respiratory circuit, much beyond the exhalation port (Fig. 12.1b) [5]. Actual dead space can thus become larger than what theoretically attended (i.e., the volume between the patient's mouth and the exhalation port). Therefore, large tidal volumes of the patient and exhalation ports with high resistance may enlarge dead space [1]. In the second part of expiration, dead space may instead be reduced by the flow of fresh gases produced by the ventilator to maintain positive end-expiratory pressure (PEEP); this is due to intentional leaks through the expiration port and unintentional leaks between the mask and the patient's face. A higher PEEP level and a longer expiratory time increase, respectively, the quantity and duration of leak flows,

a Two-limb circuit

b Exhaust port on circuit

c Unidirectional expiratory valve

d Exhaust port within the mask
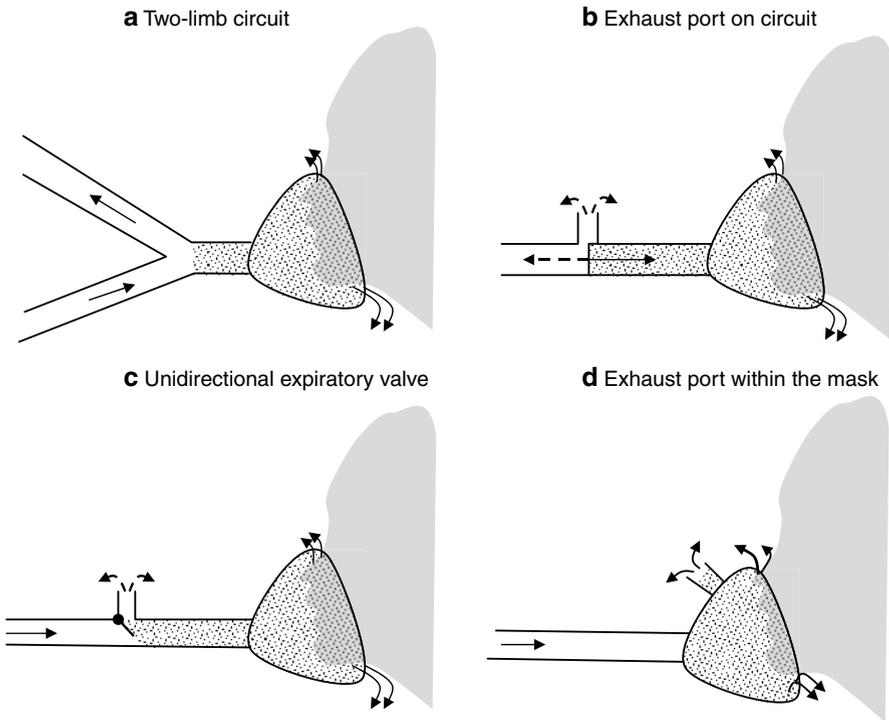
Fig. 12.1 (**a**) In a two-limb circuit, theoretical dead space is limited to the volume distal to the Y-piece. Due to unintentional leaks from the mask–patient interface, the CO_2 concentration in this volume can be substantially lo wer than the alveolar mean value (i.e., end-tidal CO_2), making it a dynamic "dead" space. (**b**) In this particular variety of single-limb circuit, theoretical dead space is the volume distal to the exhaust port. Actual volume of dead space is increased by large tidal volumes of the patient and high resistance of the exhalation port (*dashed arrows*), and decreased by *PEEP* and prolonged expiratory time. The balance between these factors determines actual volume of dead space. (**c**) The existence of a unidirectional valve on a single-limb circuit can decrease CO_2 dead space volume. A major drawback is increased circuit resistance. (**d**) Exhaustion ports within the mask decrease dead space volume and its CO_2 content

thus limiting dead space (Fig. 12.1b) [1]. Exhalation ports can be provided with a unidirectional (nonrebreathing) valve; this can significantly decrease dead volume (Fig. 12.1c) [5] but may increase inspiratory and expiratory circuit resistance, leading to both lower inspiratory pressurization and higher external PEEP [1]. Exhalation ports within the mask instead decrease dead space volume compared with those located in the circuit (Fig. 12.1d), without adverse effects [2].

During mask NIMV, the CO_2 content of dead space is directly related to the patient's end-tidal CO_2. Anyway, CO_2 concentration in the mask's dead space can be substantially lowered below this value by means of a "washing" effect of fresh gases delivered by the ventilator.

Higher PEEP levels, leaks between the mask and the patient's face, and for single-limb circuits, exhalation ports located within the mask (especially over the nasal bridge) increase the flow of fresh gases through the dead space and thus decrease its CO_2 content [1, 2].

Therefore, to limit CO_2 rebreathing during mask noninvasive ventilation the best option is probably the use of PEEP and, for single-limb circuits, face masks provided with exhalation ports over the nasal bridge. In these settings, rebreathing is negligible, and monitoring of inhaled CO_2 is not to be considered imperative.

12.4
CO_2 Rebreathing During Helmet Ventilation

Use of head helmets for noninvasive ventilation could be advantageous, compared to face masks, in terms of a patient's comfort and tolerance, with improved feasibility, continuity, and duration of noninvasive ventilatory assistance [6]. On the other hand, these advantages can be hindered by CO_2 rebreathing significantly higher than what is observed during mask noninvasive ventilation [6, 7]. At every breath, expired carbon dioxide does not completely leave the helmet but partly dilutes itself within the internal volume of the device and is subsequently inhaled again. In this setting, it can be demonstrated that the amount of CO_2 reinhaled by the patient depends on just two factors: the patient's carbon dioxide production (V'_{CO_2}) and the total gas flow passing through the helmet (F_{tot}) [3, 4]. In fact, when a steady state is reached and CO_2 is stable inside the helmet, the amount of CO_2 entering the helmet per minute (i.e., the patient's V'_{CO_2}), must be equal to the amount of CO_2 leaving the device in the same time. Because the last is a function of the mean CO_2 concentration inside the helmet (hCO_2) and the sum of all flows directed from inside the helmet to outside (F_{tot}), the equation of CO_2 steady state inside the helmet is

$$V'_{CO_2} = hCO_2 \times F_{tot}$$

or, once rearranged,

$$hCO_2 = V'_{CO_2} / F_{tot}$$

Total gas flow passing through the helmet is equivalent to the volume delivered by the ventilator every minute. This flow can be divided into three components: one reaches the patient's respiratory system; another intermittently distends the helmet; the last corresponds to leaks at the interface between the soft collar of the helmet and the patient's skin surface. The presence of a "helmet ventilation," due to the relatively high compliance of this device, is a unique feature of this technique. The theoretically derived equation of helmet CO_2 content was fully confirmed by experimental data obtained during both continuous positive airway pressure [3] and pressure support ventilation [4] delivered by helmet. In a bench study, all tested manipulations of the system affected CO_2 rebreathing insofar as they were able to change F_{tot} or V'_{CO_2} [4]. Therefore, significant rebreathing can be expected when the patient's metabolic requirements are high or the ventilator volume delivery is low. Remarkably, the volume of the helmet and the patient's end-tidal CO_2, in contrast with mask ventilation, do not affect CO_2 reinhalation. To increase F_{tot} and lower CO_2 inside the helmet, we can increase pressure support, add an intentional leak device, or implement a helmet

flow-by. Use of leak devices decreases CO_2 rebreathing but hinders helmet pressurization and the patient's inspiratory assistance, which are counterproductive for CO_2 removal [4, 8]. When pressure assistance to the patient's spontaneous activity is already optimal but CO_2 rebreathing is not, the addition of a flow-by can instead be considered [4]. An interesting option is the use of bias flow from the ventilator as a flow-by; once a flow-based inspiratory trigger is selected, the ventilator must be connected to the helmet by two independent ports, for inspiration and expiration, to force the bias flow to pass through the helmet. This trick effectively decreases rebreathing by increasing the flow inside the helmet, thus clearing away CO_2 without adverse effects.

During helmet NIMV, CO_2 rebreathing must be monitored. In mechanically ventilated patients, rebreathing is usually evaluated by end-inspiratory CO_2 value. Unfortunately, inhaled CO_2 inside the helmet can be grossly underestimated by this value due to the slow decrease of CO_2 concentration during the inspiratory phase of helmet ventilation (Fig. 12.2) [4]. The CO_2 value measured in a "quiet point" (not affected by flows to and
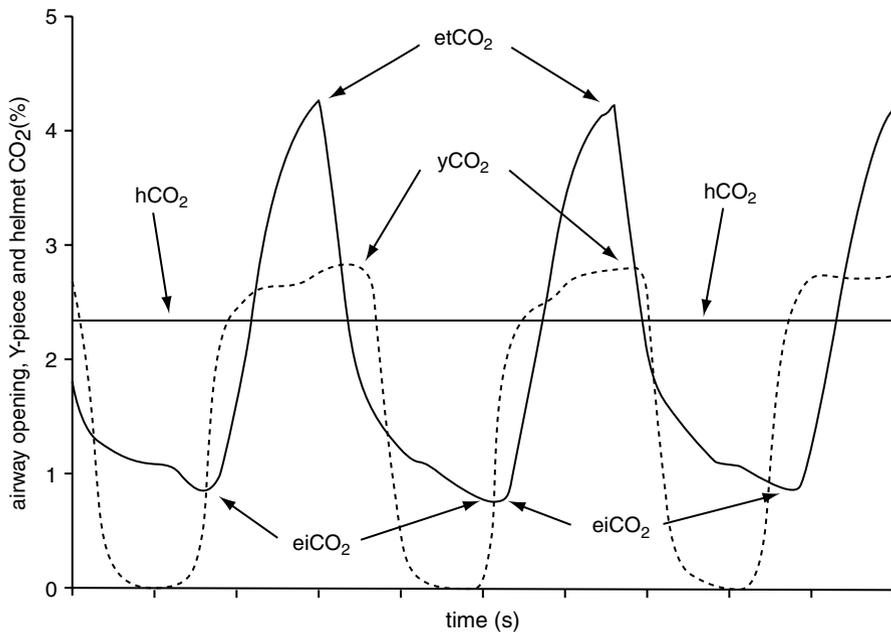
Fig. 12.2 Continuous CO_2 concentration recordings at the airway opening (*black line*), at the Y-piece of the ventilator circuit (*dotted line*), and inside the helmet (*gray line*) during helmet ventilation with 16.5 L/min of total minute ventilation and 350 mL/min of CO_2 production. At airway opening, the minimum value is end-inspiratory CO_2 (*eiCO₂*), and the maximum value is end-expiratory CO_2 (*etCO₂*). The CO_2 concentration measured at the Y-piece ranges from zero during inspiration (due to fresh gas flow from the ventilator) and the end-expiratory value (*yCO₂*), which is lower than etCO₂ because gases expired by the patient are diluted in the helmet internal volume. CO_2 concentration measured at a "quiet" point inside the helmet (*hCO₂*) is constant during the entire respiratory cycle and corresponds to the mean CO_2 concentration in inhaled gases

from the patient) inside the helmet is instead stable and corresponds exactly to mean inhaled CO_2 [4]. When a stable value inside the helmet cannot be obtained, the end-tidal CO_2 value measured at the Y-piece or at the expiratory port represents a fair estimate of CO_2 rebreathing [4].

Key Recommendations

❯ During mask ventilation, implement PEEP and use exhalation ports within the mask to reduce CO_2 rebreathing.

❯ While ventilating with a helmet, a total gas flow below 40 L/min is at high risk of significant CO_2 rebreathing. Increase total gas flow through the helmet by raising pressure support and/or by adding a flow-by.

❯ CO_2 rebreathing in the helmet must be monitored, at least periodically.

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Carbon Dioxide Rebreathing During Pressure Support Ventilation with Airway Management System (BiPAP) Devices

13

Frédéric Lofaso and Hélène Prigent

13.1
Introduction

In the 1980s, the development of noninvasive ventilation using pressure support ventilation with or without positive end-expiratory pressure (PEEP) constituted a major improvement in the management of both acute and chronic respiratory failure. Meanwhile, the first bilevel ventilator was designed (BiPAP; Respironics; Murrysville, PA). Initially intended to improve home treatment of sleep apnea syndrome, this device lacked alarms and monitoring systems but was easy to handle and low priced. It was a nasal continuous positive airway pressure device equipped with a solenoid magnetic valve system allowing separation of PEEP (with a minimal level below 2 cmH$_2$O [1, 2]) and inspiratory positive airway pressure adjustments. Like other nasal continuous positive airway pressure devices designed for home, it used a single-limb circuit with a leak port (i.e., Respironics Whisper Swivel). Therefore, there was a risk of CO$_2$ rebreathing, which was initially considered an important limitation for extending its use in the treatment of respiratory failure, especially hypercapnic respiratory failure, which was considered to have the best outcome with noninvasive ventilation.

13.2
Rebreathing Mechanisms

To ensure that no exhaled gas remains in the tubing at the end of expiration ("ready to be inhaled again"), the mean expiratory flow, that is, the ratio between tidal volume and expiratory time V_T/T_E, has to be lower than the intentional leak obtained through the leak port

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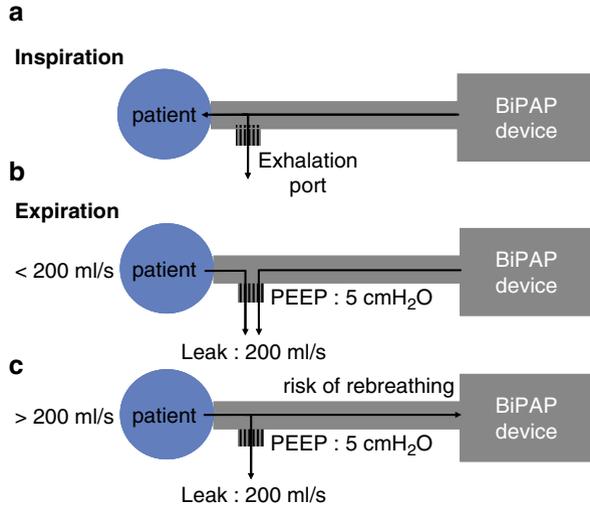
Fig. 13.1 BiPAP ventilation with an intentional leak flow of the Whisper Swivel connector of about 200 ml/s when PEEP is set at 5 cmH$_2$O. (**a**) Inspiration period. (**b**) Expiration period with a flow rate lower than the intentional leak through the leak port; no exhaled gas returns into the tubing at the end of expiration. (**c**) Expiration period with a flow rate higher than the intentional leak through the leak port; some of the exhaled gas remains in the tubing at the end of expiration and can be rebreathed during the next inspiration

during expiration. Therefore, rebreathing depends first on the pattern of breathing: high V_T and short T_E exposes a higher risk of rebreathing by increasing expiratory flow. Second, it depends on the size of the port and the PEEP level: A small port and low PEEP level constitute risk factors for rebreathing. For example, Lofaso et al. [2] observed that the intentional leak flow of the Whisper Swivel connector was about 200 ml/s when PEEP was set at 5 cmH$_2$O. Therefore, if a patient has to expire 500 ml in 2 s, the expired volume remaining in the circuit at the end of expiration would be approximately 100 ml (Fig. 13.1).

13.3
Bench and Clinical Studies

The inverse correlation between rebreathing and PEEP with the Whisper Swivel was demonstrated in a bench study [1] and a clinical study [3]. Moreover, it has been clinically demonstrated that CO$_2$ rebreathing observed with the Whisper Swivel worsened the patients' work of breathing (WOB) [2]. The use of a plateau exhalation valve and a nonrebreathing valve has been proposed to reduce or avoid CO$_2$ rebreathing. Ferguson and Gilmartin [3] observed that, with their use, CO$_2$ rebreathing became minimal in patients. The plateau exhalation valve consists of a diaphragm that limits air leaks at high pressure (during inspiration) and works as a larger leak port at low pressure (during expiration),

while the nonrebreathing valve is an antireturn valve with a lateral intentional leak. Lofaso et al. [1] confirmed that the substantial rebreathing observed with the Whisper Swivel disappeared when using a nonrebreathing valve. However, the drawback is that the nonrebreathing valve induces additional expiratory resistance [2], which may have some impact on intrinsic PEEP and therefore on WOB [4]. In contrast, in a crossover study with seven patients receiving long-term nocturnal noninvasive ventilation, the plateau exhalation valve did not improve daytime or nocturnal gas exchange or symptoms compared to the Whisper Swivel, most likely because of air leakage and CO_2 escape occurring via other routes [5].

13.4
Exhalation Port Characteristics

To explore the influence of the exhalation port position on CO_2 rebreathing, Shettino et al. [6] performed a bench study that observed that the CO_2 rebreathing was significantly lower when the exhalation port was placed within the mask rather than on the circuit. In addition, the smallest mask volume was associated with lower CO_2 rebreathing than the larger one. However, these differences may also be explained by differences in exhalation port sizes.

13.5
Devices Evolution

Now, these devices have been improved; all bilevel ventilators have a minimal PEEP setting of 4 cmH_2O by default, and the intentional leak through the leak port of most available masks exceeds 300 ml/s when PEEP is set at 5 cmH_2O (higher than what was observed with the Whisper Swivel leak [2, 7]). This greatly reduces and even abolishes the risk of rebreathing during noninvasive ventilation, except with the use of helmets [8]. This novel interface, aiming to improve comfort and to reduce local side effects, exposes the patient to a higher risk of CO_2 rebreathing [8] and is not currently adapted for home ventilation.

13.6
Conclusion

The risk of rebreathing during noninvasive ventilation is now low thanks to not only the improvements achieved since the first bilevel ventilators and their initial circuitry but also secondary to nonintentional air leakage and CO_2 escape almost constantly observed during noninvasive ventilation and sleep. The systematic use of a minimal PEEP level of 4 cmH_2O is usually efficient in reducing rebreathing but can be a limitation for the use of this device for some patients. However, CO_2 rebreathing systematically occurs during the use of helmet interfaces.

Key Recommendations

> Finally the clinician should be aware of risk of rebreathing, which can be a factor of mechanical ventilation, poor efficiency and this rebreathing is facilited by high respiratory frequency and low peep level.

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Carbon Dioxide Rebreathing in Noninvasive Ventilation

14

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14.1
Introduction

Several factors in noninvasive positive pressure ventilation (NIPPV) have proved to be potential causes of failure when this kind of mechanical respiratory assistance is used in patients who suffer from acute (ARF) or chronic (CRF) respiratory failure [1–3]. One such factor is carbon dioxide (CO_2) rebreathing [1–4]. This phenomenon consists of rebreathing part of the CO_2 expired by the patient during the ventilatory cycle as a result of an accumulation of this gas in the mask or the circuit. Such rebreathing takes place mainly in single-limb circuits (inspiration and expiration into the same tube). Besides the use of such a circuit, there are technical circumstances that play an active role in the presence or elimination of expired CO_2: the ventilatory mode [4, 5], type of mask and expiratory port [6–12], as well as the level of positive end-expiratory pressure (PEEP) used [4, 10, 11]. Since 1995, when Ferguson and his collaborators first described such a phenomenon, little research has been done on this issue. The development of technological innovations, mainly in interfaces, has restricted the potential clinical implications of this deleterious phenomenon. Likewise, research works conducted so far have not confirmed whether CO_2 rebreathing does have a significant influence on patients' clinical evolution or is just a potentially, but rarely, harmful phenomenon.

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14.2
Main Topics

As outlined in the introduction, there are several elements or circumstances that influence the CO_2 rebreathing scope.

- Type of circuit
- Type of mask: internal volume, exhaust vent (EV), or controlled leak holes
- Devices attached to the circuit (in case of masks without an EV): conventional or anti-rebreathing expiratory ports, cylindrical spacers
- Level of expiratory pressure (expiratory positive airway pressure, EPAP)
- Patient's features: ARF or CRF in normo- or hypercapnic patients and their ventilatory pattern

14.2.1
Type of Circuit

CO_2 rebreathing is an inherent characteristic of the single-limb circuit system [1–3] and is less frequent in two-limb circuits (separate inspiratory and expiratory limbs) or circuits with pneumatic expiratory valves (domiciliary volumetric ventilators). Logically, we can infer that expiration into the same tube into which the patient inspires leads to rebreathing previously expired gas if such gas is not appropriately eliminated from the tubing or mask.

14.2.2
Type of Mask

Masks with high levels of dead space [12, 13] can give rise to significant levels of rebreathing in case of inappropriate kinetics of expired gas elimination. Technological development has created EVs (controlled leak holes) in masks, which allow adequate elimination of gases before the next inspiration. Such holes are located in the mask itself as well as in the elbow-shaped tube joining the mask with the circuit. The key issue is to control the efficiency of new masks in eliminating CO_2 through their holes as research studies conducted so far have tested only a reduced number of trade models [10, 11] The existence of an inherent phenomenon in NIPPV, such as leaks, highly frequent in nasal masks, will certainly play a key role in preventing CO_2 rebreathing by reducing the air volume expired into the circuit.

14.2.3
Devices Attached to the Circuit

When hermetic masks (without EVs) and single-limb circuits are used, it is fundamental to add expiratory ports [4, 11, 12] that will allow air release before the following ventilatory

cycle. Somehow, these masks fell into disuse after the development of EV masks. However, they are still available in the market due to their low cost and use in domiciliary ventilators and in respiratory care units. Consequently, we should be aware of how to use them appropriately. There are traditional expiratory devices, such as the Whisper Swivel®, or devices with an anti-rebreathing system, such as Plateau valve®. Furthermore, some tubes have a built-in leak port.

Regarding the use of spacers (corrugated cylindrical tubes whose function is to keep any kind of potentially annoying element away from the patient because of its size or form) between the ventilator and the patient, at least in theory these could increase the dead space and therefore give rise to rebreathing. Our group [11] has proved that a single-limb circuit with its own pneumatic valve, even with large attached spacers, avoided rebreathing while using volumetric ventilation.

14.2.4
Level of EPAP Used

A certain level of expiratory pressure improves the elimination of expired gases within the mask and circuit. Although Ferguson's work suggested a minimum level of EPAP between 6 and 8 cmH_2O when using traditional expiratory valves, the use of antirebreathing devices as well as EVs (leak holes) in the mask has helped reduce such pressure to 4 cmH_2O or even less [11]. In clinical practice, the EPAP average level reaches 6–8 cmH_2O.

14.2.5
Patient Characteristics: Hypercapnia or Normocapnia

Hypercapnia has proved to be related to rebreathing levels [4]. Only one research study conducted in hypercapnic patients has shown a zero rebreathing level when using nasal masks with EVs and antirebreathing devices during NIPPV [14]. In addition, the patient's own ventilatory pattern (inspiratory time/total time T_i/T_{tot}; respiratory frequency/tidal volume f/V_t) may influence both the dead space and the degree of rebreathing, although this fact has not been demonstrated.

14.3
Discussion

CO_2 rebreathing is a potentially harmful phenomenon with a direct influence on the failure or success of NIPPV [1–3]. There are several factors involved in the existence and scope of this phenomenon. Many authors have described the importance of such factors, giving rise to opposing findings in some cases. The actual influence of CO_2 rebreathing in usual clinical practice has not been duly evidenced by any research. Hill et al. [15] compared gaseous
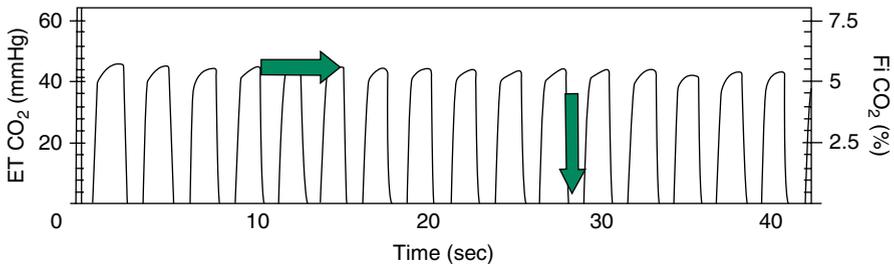
Fig. 14.1 Continuous analysis of CO_2 inside the mask. *Horizontal arrow*: $ETCO_2$ (end-tidal CO_2, mmHg). *Vertical arrow*: $FiCO_2$ (inspired CO_2 fraction, %)

interchange and symptoms in patients under NIPPV who used both a conventional expiratory port and an antirebreathing one. No difference was found between the two groups; even more, the antirebreathing valve was considered noisier and bad looking by patients. In addition, Farré et al. [16] suggested that rebreathing could be too deleterious in case of continuous positive airway pressure (CPAP) failure, an event that could be prevented by using an antirebreathing valve. Another controversial issue is the moment at which the CO_2 should be measured in the ventilatory cycle to show the amount of gas rebreathing as well as the place on the patient–ventilator unit where such value should be measured (Fig. 14.1). Several authors alleged that CO_2 at the end of expiration ($ETCO_2$) [7, 8, 10, 15] measurement has proved useful, whereas others argued that the value of CO_2 inhaled (CO_2 inspired fraction, $FiCO_2$) [8, 11] offers more accurate and beneficial information. Other research indicated a preference for measurement of CO_2 partial pressure in an arterial blood gas sample ($PaCO_2$) [4, 5], transcutaneous [4] CO_2, or simple continuous CO_2 quantification in the mask [4, 6, 16]. In fact, all these values could be regarded as interdependent values. According to our point of view, $FiCO_2$ is the most representative value in rebreathing as it shows the CO_2 amount in the patients' nostrils at the protoinspiratory phase. However, this measurement may undervalue rebreathing at the initial stage of breathing initial.

At present, and according to the studies carried out, we should take into consideration several key issues when setting up the respiratory–patient system in an attempt to limit the influence of CO_2 rebreathing:

- Use of masks with EVs, duly tested through technical studies that prove their ability to eliminate the expired CO_2 (only a small number of masks sold presently have been subject to such tests)
- Use of antirebreathing expiratory ports in case of using masks without EVs and single-limb circuits
- Use of circuits with pneumatic valves in case of volumetric ventilators
- Use of spacers with the corresponding volume stated in research works
- Optimization of the expiratory pressure level that allows adequate elimination of CO_2 from the mask
- Optimization of each and every parameter, taking into consideration patients' individual characteristics: CO_2 level, ventilatory level, other factors for NIPPV success or failure (leaks, asynchrony)

> **Key Recommendations**
>
> ❯ CO_2 rebreathing is a potential factor for failure in NIPPV.
> ❯ When single-limb circuits are used, the following elements should be used to avoid high levels of $FiCO_2$:
>
> – Mask with minimum volume or dead space
> – Duly tested masks with EVs
> – Antirebreathing expiratory ports in hermetic masks
> – Appropriate EPAP levels
>
> ❯ Knowledge of the current clinical importance of CO_2 rebreathing is still pending.

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New Adaptive Servo-Ventilation Device for Cheyne–Stokes Respiration

15

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15.1
Introduction

Several studies have shown that patients with congestive heart failure (CHF) often suffer from the complication of sleep-disordered breathing (SDB), including Cheyne–Stokes respiration with central sleep apnea (CSR-CSA) as well as obstructive sleep apnea (OSA). These two types of SDB often coexist in such cases. CSR-CSA is characterized by cyclical recurrence of central apneas and hyperpneas with waxing and waning of the flow amplitude, which results from instability of the respiratory control system characterized by a tendency to hyperventilate due to the heart failure condition. Central apnea occurs when the Pa_{CO_2} falls below the apnea threshold during sleep due to ventilatory overshoot. CSR-CSA is modifiable by several types of positive airway pressure (PAP) therapy; however, in the clinical setting, CSR-CSA patients with CHF tend to have poor adherence to the conventional PAP therapies, especially continuous PAP (CPAP), which are well established as treatments for OSA. Furthermore, they are well known to be "nonresponders" to conventional PAP as a therapy for CSR-CSA. In the CANPAP (Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial) study [1], CPAP only decreased the average apnea–hypopnea index (AHI) by about 50% (from 40 to 19/h). The post hoc analysis of the CANPAP. study [2] showed subjects with a residual CSR-CSA of AHI ≥ 15 using CPAP remained with a poor prognosis. These data suggest that other treatment options that can suppress the CSR-CSA more effectively (i.e., AHI < 15) and can produce better compliance are needed.

Adaptive servo-ventilation (ASV), a novel PAP device, has been developed as an effective therapeutic alternative to other conventional PAP technologies. The ASV can suppress not only OSA but also CSR-CSA. We review the ASV therapy for CSR-CSA mainly in patients with CHF.

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15.2
Methods

We searched for English articles using MEDLINE (PubMed and Ovid) from January 1996 through August 2009 using the related terminology of ASV and CSR (or SDB). The search was limited to clinical trial, humans, and all adults older than 19 years.

The ASV is a nocturnal PAP therapy through a mask and basically is similar to bilevel PAP therapy with a spontaneous/timed mode, which delivers two treatment pressures, inspiratory positive airway pressure (IPAP) to provide fixed pressure support and expiratory positive airway pressure (EPAP) to keep the upper airway patent and prevent obstructive apnea, hypopnea, snoring, and flow limitation; there is a transition to a timed mode with backup respiratory rate during sustained apnea. However, the current ASV has two novel therapeutic algorithms for CSR-CSA (Fig. 15.1a). The primary algorithm is an adaptive pressure control system that normalizes patient ventilation levels by adjusting each amount of pressure support (equal to the pressure difference between IPAP and EPAP) with almost breath-by-breath response toward the changes in tidal volume of CSR. Briefly, the algorithm rapidly increases pressure support in responsse to hypoventilation and decreases it during hyperventilation by varying the level of IPAP (or pressure support) between the two preset IPAPs (or pressure supports): minimum IPAP (pressure support) and maximum IPAP (pressure support). The secondary algorithm is an automatic backup system that allows the patient to take natural pauses in inspiration while still providing pressure support assistance during true apneas. The automatic backup system tracks the patient's spontaneous breath pattern. Based on these data, a backup breath with adjusted rate and pressure is automatically delivered to the patient during a central apnea event.

15.3
Results

There were ten articles about ASV therapy for CSR-CSA in patients with heart failure; all included a very small sample. The first was a crossover study by Teschler et al. in 2001, which was to compare the effects of a single night each of oxygen (2 L/min), CPAP, bilevel PAP, and ASV on CSR-CSA and sleep on five consecutive nights in random order in 14 patients with heart failure [3]. Patients preferred the ASV night to either the CPAP or bilevel PAP titration nights. ASV suppressed CSR-CSA and improved sleep quality better than CPAP or nasal oxygen. There were two other similar articles, in which heart failure patients with CSR-CSA underwent three nights of polysomnography: baseline, conventional PAP (CPAP or bilevel PAP) titration, and ASV titration [4, 5]. In both, compared with conventional PAP therapy, ASV significantly reduced CSR-CSA and was well tolerated. Oldenburg et al. reported that use of ASV for 5.8 ± 3.5 months significantly improved left ventricular ejection fraction (LVEF), amino-terminal pro-brain natriuretic peptide (BNP) level, and exercise tolerance to the cardiopulmonary exercise test as well as CSR-CSA in 29 male patients with heart failure [6].
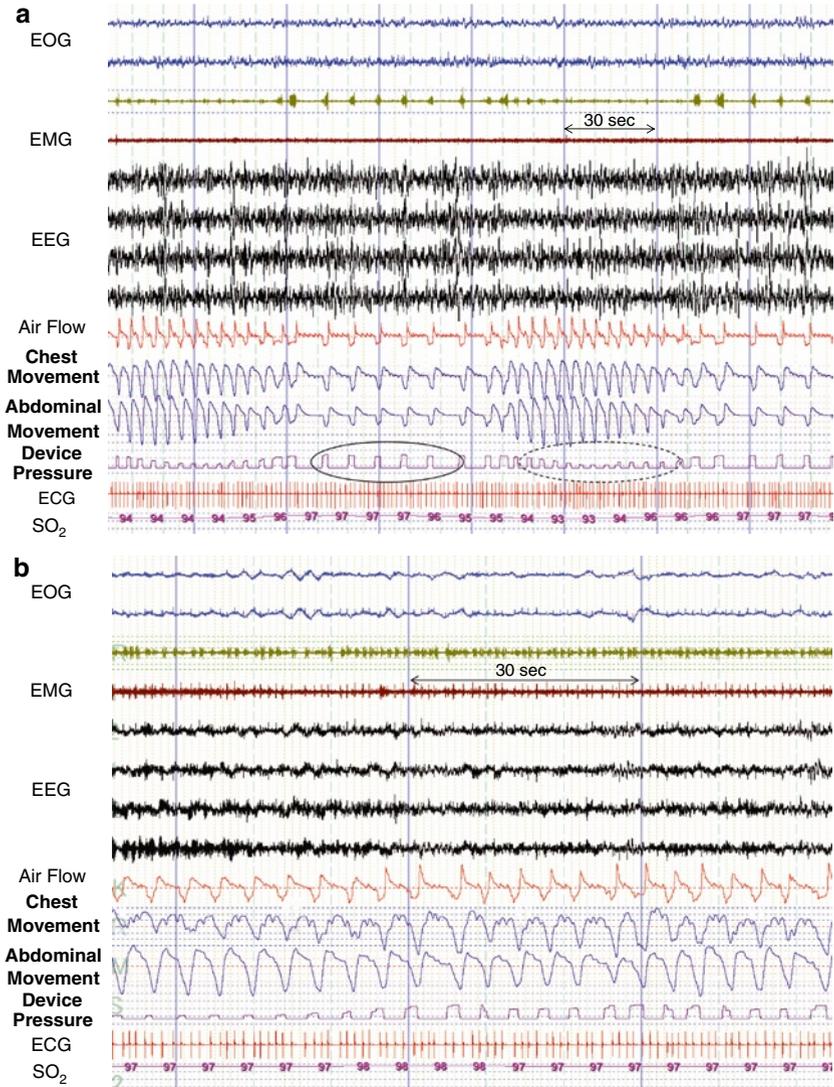
Fig. 15.1 Polysomnography during adaptive servo-ventilation (ASV) in a patient with Cheyne–Stokes respiration with central sleep apnea (CSR-CSA) and heart failure. (**a**) Initiation of ASV for CSR-CSA; note the backup ventilation during a central apnea with maximum inspiratory positive airway pressure (*inside solid line oval*) and the reduction in pressure support during the hyperventilation phase (*inside dotted line oval*). (**b**) Gradual stabilization of ventilatory state under ASV therapy; note the absence of backup ventilation and the adaptation of the ASV with the minimum necessary pressure supports on spontaneous breathing. Continuing ASV in turn corrects the fluctuation of Pa_{CO_2} and brings in the stabilization of breathing. *EOG* electro-oculogram, *EMG* submental electromyogram, *EEG* electroencephalogram, *ECG* electrocardiogram, *SO_2* oxyhemoglobin saturation

There were two prospective randomized controlled trials of ASV for CSR-CSA with heart failure. In one study, 30 subjects with heart failure and CSR-CSA were treated with 4 weeks of therapeutic ASV ($n = 15$) or subtherapeutic ASV ($n = 15$) [7]. Compared with a subtherapeutic control, there were significant falls in plasma BNP level and urinary metadrenaline excretion in the therapeutic ASV group. In the other study, 25 patients with heart failure and CSR-CSA were randomly assigned to either CPAP or ASV [8]. Both CPAP and ASV decreased AHI, but only ASV completely suppressed CSA-CSR, with AHI below 10. At 6 months, compliance with CPAP was significantly less than with ASV, the improvement in quality of life was higher with ASV, and only ASV induced a significant increase in LVEF.

There were a few reports of ASV for CSR-CSA in patients without CHF. Some reports showed the efficacy of ASV for complex sleep apnea syndrome (i.e., CPAP-emerged CSA) or idiopathic CSR that was unresponsive to CPAP or oxygen. On the other hand, the results of studies of the ASV for opioid-induced SDB were controversial.

15.4
Discussion

ASV has been designed to more effectively reduce the number of CSR-CSA episodes. In fact, some studies showed that ASV decreased the AHI more effectively than conventional PAP therapy in patients with CSR-CSA and heart failure [3–5, 8]. Moreover, it was reported that heart failure patients with CSR-CSA were more compliant with ASV than conventional PAP [3, 5, 8]. These results seem to be due to the unique algorithms of ASV, which can lead to reduced alteration in the Pa_{CO_2} level and maintaining the Pa_{CO_2} above the hypocapnic apnea threshold, which can in turn unspread the CSR, stabilize the breathing pattern, and improve sleep architecture and quality (Fig. 15.1b). On the other hand, bilevel PAP was also effective for CSR-CSA, but it could be that this fixed pressure support in CSR-CSA patients set up overventilation during phases of normal breathing or hyperpnea, which causes arousals and discomfort or leads to a fall in the Pa_{CO_2} level, which may induce central apnea. In practice, such patients tend to require the IPAP level to be set to lower values because of the perceived difficulty with higher-pressure support, and such reduction in IPAP often leads to insufficient management of the CSR-CSA. The ASV might be able to resolve this problem of bilevel PAP because the IPAP level is automatically and appropriately adapted.

Some studies showed that ASV improved not only the SDB but also cardiac function in patients with heart failure [6–8]. Increased intrathoracic pressure through PAP can reduce preload due to the decrease of the venous return and afterload due to the decrease of the left ventricular transmural pressure. It was reported that PAP causes dose-related increases in cardiac and stroke volume indices among patients with heart failure with elevated left ventricular filling pressure [9]. We studied the effect of 3-month ASV therapy on residual CSR-CSA with AHI ≥ 15 on CPAP and used ten patients with heart failure who already had undergone CPAP therapy [10]. In the study, the change of CPAP to ASV significantly improved AHI and sleep quality, increased LVEF, and decreased the levels of plasma BNP and urine noradrenaline. Remarkably, the compliance with ASV was significantly better than with CPAP. In theory, all kinds of PAP therapies can bring in these beneficial effects

on hemodynamics in patients with heart failure. However, ASV is likely to more effective than conventional PAP on cardiac function in patients with heart failure with CSR-CSA, which may result from better-suited pressure delivery of ASV, better compliance with ASV, or a more suppressant effect on the increased sympathetic nerve activity.

Currently, two ASV devices are clinically available on a global scale. One is AutoSet™ CS2/VPAP Adapt SV™ manufactured by ResMed (Sydney, Australia), and the other is BiPAP® autoSV™ by Respironics (Murrysville, PA, USA). In both products, pressure support is dynamically adjusted breath to breath as necessary to ensure that the patients' actual ventilation matches the target value. However, there are some differences between the devices; these are briefly shown in Table 15.1. The main points of difference are the mechanics to assess the ventilatory status and decide the target and the configurable parameters and setting ranges. AutoSet CS2/VPAP Adapt SV provides volume-targeted ASV, which sets a minute ventilation target that is 90% of the recent average minute volume in a 3-min collection period and tries to keep ventilation at the target. To make the synchrony with the patient's ventilation better, this device also learns the patient's recent flow pattern in an 8-s period. On the other hand, the BiPAP autoSV™ provides flow-targeted ASV, which monitors the peak inspiratory flow of the patient over a recent moving 4-min window by calculating an average peak flow at every point within this window to set a target peak flow, compares it to the internal target, and maintains a target peak inspiratory flow. The clinician has to set three types of pressure levels. The EPAP level is set to maintain upper airway patency as a management of any obstructive SDB. To determine the range of pressure support levels, minimum IPAP and maximum IPAP need to be set. The AutoSet CS2/VPAP Adapt SV always provides a pressure support of at least 3 cmH_2O. The BiPAP autoSV can conform EPAP to minimum IPAP and apply the same pressure during inspiration and expiration (which is the same as CPAP) in stable breathing. While both devices provide an automatic backup rate for sustained apnea, the BiPAP autoSV can also manually set the fixed backup rate. There are no studies comparing these two different ASV.

Table 15.1 Comparison between two adaptive servo-ventilation (ASV) products

	Volume-targeted ASV	Flow-targeted ASV
Product name	AutoSet CS2 or VPAP Adapt SV	BiPAP autoSV
Manufacturer	ResMed	Respironics
Target parameter	90% of minute ventilation	Peak flow
Calculation window	Recent average of 3-min window	Recent average of 4-min window
Backup ventilation	Auto (15 ± α/min)	Automode or fixed mode (off or 4–30/min)
EPAP	4–10 cmH_2O	4–25 cmH_2O
IPAP min	3–6 cmH_2O plus EPAP	EPAP level – 30 cmH_2O
IPAP max	8–16 cmH_2O plus EPAP	IPAP min level – 30 cmH_2O

EPAP expiratory positive airway pressure, *IPAP min*, minimum inspiratory positive airway pressure, *IPAP max*, maximum inspiratory positive airway pressure

Each manufacturer introduces the recommended methodologies to titrate each ASV device. We would emphasize that the titration for ASV application under attended polysomnography should be performed because these automatic algorithms do not always work appropriately for all patients without any titration studies.

There have been no data to evaluate the effect of ASV on long-term prognosis in patients with CSR-CSA and heart failure until now. However, a large randomized controlled trial is ongoing mainly in Europe; its purpose is to investigate the long-term effects of ASV on the morbidity and mortality of patients with stable heart failure who have SDB predominantly with CSR-CSA. The results of this study are important and may yield the primary evidence and determine the first-line therapy for CSR-CSA in patients with chronic heart failure.

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Section IV

Monitoring and Complications

Nocturnal Monitoring in the Evaluation of Continuous Positive Airway Pressure[1]

16

Oreste Marrone, Adriana Salvaggio, Anna Lo Bue, and Giuseppe Insalaco

16.1
Introduction

Continuous positive airway pressure (CPAP) counterbalances forces leading to upper airway narrowing or collapse during sleep and is the most widely used treatment for obstructive sleep apnea (OSA). In patients with OSA, progressively higher CPAP levels applied during sleep turn obstructive apneas into hypopneas, hypopneas into continuous inspiratory flow limitation, with or without snoring, and flow limitation into unobstructed breathing. When breathing becomes unobstructed, "respiratory arousals" (i.e., arousals that may follow increased inspiratory efforts associated with obstructed breathing) are eliminated, while sleep becomes more stable and sleep cycles more regular, contributing to improvements in subjective sleep quality, daytime sleepiness, and quality of life usually observed after just a few nights of CPAP application [1]. Also, relief of upper airway obstruction is associated with resolution of intermittent hypoxemia and hemodynamic swings that accompany obstructive events, with a consequent reduction in long-term cardiovascular morbidity and mortality [2].

The objectives of CPAP treatment are elimination of symptoms and of cardiovascular and, possibly, metabolic risk related to OSA. Today, the best way to accomplish these aims is usually considered to fully eliminate all degrees of upper airway obstruction during sleep. The lowest CPAP that eliminates upper airway obstruction in all sleep stages and body postures in a patient is indicated as "optimal" CPAP.

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There is much controversy about the most convenient procedures to adopt before CPAP prescription. At one extreme, official guidelines still consider the complex manual CPAP titration during assisted polysomnography the gold standard procedure before CPAP prescription [3]. At the opposite extreme, it has been claimed that neither pressure titration nor any instrumental monitoring with CPAP application is essential for prescription [4]. In this chapter, we review procedures for initiation of CPAP treatment and discuss their effectiveness.

16.2
Analysis and Discussion

The CPAP titration procedure consists of the application of various CPAP levels to assess their effects and to identify which level may be most appropriate for the correction of upper airway obstruction (optimal pressure). Manual CPAP titration in the sleep laboratory is the oldest method for the determination of optimal pressure. It is performed during a polysomnographic recording while a technician manually modifies pressure administered by a CPAP device. The titration polysomnographic study should fulfil some conditions: It should have an adequate duration (according to some indications, at least 3 h in subjects whose apnea–hypopnea (AHI) index is more than 40 or longer in subjects with milder disease) [5], and it should include the recording of some rapid-eye-movement (REM) sleep and of some sleep time in the supine posture since REM sleep and, even more, supine posture may require the application of higher CPAP levels. Then, the quality of the titration is evaluated with analysis of the characteristics of sleep and respiration, in each body posture, in relationship to the pressures that have been applied [3]. Therefore, all signals generally recorded during polysomnography have an important role: electroencephalogram, electro-oculogram, and chin electromyogram for recognition of sleep stages and arousals; body position; pressure at the mask to monitor the CPAP level that is administered; signals for detection of snoring, airflow, respiratory movements, and oxyhemoglobin saturation to observe modifications in breathing characteristics as CPAP level is changed and to make sure that regular unobstructed breathing is achieved. In particular, regarding airflow, monitoring by a pneumotachograph is recommended as a flattened shape in the inspiratory portion of the flow signal recorded by this method is indicative of flow limitation.

More recently, identification of optimal pressure by auto-CPAP devices has been introduced ("autotitration"). Auto-CPAP machines are designed to automatically deliver a variable CPAP level that should correspond to the lowest required pressure in each moment. They are able to record several types of information during their application, including pressures delivered, air leaks, and respiratory events detected, and can usually calculate an AHI.

Autotitration can be performed with the application of an auto-CPAP device during a standard polysomnographic study. A technician may assist autotitration to control the polysomnographic recording and the patient. Analysis of the polysomnographic study allows us to verify the relationship between pressures that have been delivered and breathing characteristics, sleep stages, arousals, and body postures. In this way, it is

possible to select the CPAP level that proves most appropriate for correction of upper airway obstruction. This method is now officially recognized as a valid alternative to traditional manual titration [6], but differences in costs and time required for the two procedures are limited.

As an alternative to the search for optimal CPAP with polysomnography, unassisted autotitration without any monitoring, except that provided by the auto-CPAP machine itself, has been introduced. With this method, an auto-CPAP is given to the patient for nocturnal self-application. Data collected and elaborated by the machine are downloaded, and periods with excessive air leaks are discarded from analysis. The 90th or 95th percentile pressure (i.e., the pressure that is not exceeded for 90% or 95% of the time of the auto-CPAP application, respectively) is usually considered equivalent to the optimal pressure. Lack of external monitoring during auto-CPAP application could lead to errors in the recognition of optimal CPAP level. Auto-CPAP devices have different principles of operation; although most of them are effective in the correction of upper airway obstruction and reliable in the vast majority of patients, their efficacy is variable. Both administration of excessively high pressures and undercorrection of obstruction are possible. Erroneous pressure administration may be easily recognized during polysomnography, while it is often undetected if no monitoring in addition to the one performed with the auto-CPAP is done. AHI values calculated by the auto-CPAP machines may help to identify some unsatisfactory autotitrations, but although some studies found these values reliable enough with some devices, they may substantially differ from AHI values obtained with external monitoring and evaluated manually. Other possible errors do not depend on auto-CPAP devices but on conditions possibly occurring during autotitration, like insufficient sleep or lack of supine posture during the auto-CPAP application. Again, these cases may be easily recognized with appropriate monitoring [7].

The strongest argument against nocturnal monitorings for very precise determinations of optimal CPAP is that pressures needed by each patient for the correction of respiratory disorders can change from night to night. Reproducibility of optimal pressure determined with accurate manual titration during polysomnography is limited, with night-to-night changes up to 3 cmH$_2$O [8]. Therefore, the results of single-night titrations, either manual or automatic, could be questionable, and costs for single-night assisted polysomnographic titration could be disproportionate, while an evaluation of optimal CPAP on several nights could be more reliable.

As polysomnographic monitoring may not be performed for multiple nights for practical reasons, it has been proposed to perform unassisted autotitration without external monitoring for several nights. The average of the 90th or 95th percentile pressures on all nights of auto-CPAP application could represent an appropriate pressure for treatment. Besides, progressive adaptation of the patient during consecutive nights to sleep with CPAP could prevent errors associated with poor sleep quality and minimize errors due to the lack of external monitoring. The number of nights for this autotitration method is not standardized. A small number of nights could make it an economical procedure due to the lack of complex monitorings and analyses, and of technical assistance. Multiple-night unassisted autotitration has been recognized as a possible valid alternative to polysomnographic titration, but it is recommended to rely on auto-CPAP devices that have been better validated and to strictly keep in touch with patients after initiation of CPAP treatment [6]. In our

experience, a disadvantage of unassisted autotitration is that, despite previous training, not all patients are able to start sleeping with CPAP if they have no assistance during the night. Besides, some cases of poor performance of the auto-CPAP machine may remain undetected if no nocturnal instrumental monitoring is performed during or after autotitration; in our opinion, even simple cardiorespiratory monitorings may be helpful for identifying uncommon but possible cases of unsatisfactory autotitrations.

It has been proposed not to titrate CPAP but to prescribe a pressure calculated by means of predictive equations, possibly modifying it thereafter, following patients' complaints or indications [9]. Different predictive equations for therapeutic CPAP have been elaborated. Calculated pressure values differ to some extent according to the equation. Generally, in an OSA population, most calculated pressures are close to the pressure values that are obtained most often when titrations are performed; so, for statistical reasons, calculated and titrated pressures are similar in most patients. However, agreement between calculated and titrated values drops when values highly differing from the average and most common levels are calculated or are required for treatment [10]. Therefore, predictive equations cannot be considered reliable substitutes for titration. A posteriori evaluation of clinical effects of the prescribed CPAP and of adherence to treatment has been used to assess efficacy of CPAP treatment based on the application of predictive equations. In fact, clinical evaluation is essential to evaluate the adequacy of CPAP treatment. Improvement in sleepiness is one of the aims of the treatment; it is essential that patients are able to tolerate CPAP and have good compliance to treatment; a better control and a reduction of blood pressure are possible effects of an effective OSA treatment. However, these criteria are not sufficient to validate a prescribed pressure; improvement in sleepiness may partly depend on a placebo effect, compliance to treatment may be good even with subtherapeutic pressure, and OSA treatment does not always result in effects on blood pressure. Incomplete treatment of OSA may expose patients to persistence of increased cardiovascular risk. Changes in body weight or sleep-related complaints may suggest the need to reevaluate CPAP titration.

Key Recommendations

- ❯ An instrumental nocturnal monitoring, either manual or automatic, should always be performed when titrating optimal CPAP.
- ❯ The higher the number of signals recorded during the nocturnal monitoring, the more reliable the determined therapeutic CPAP level will be.
- ❯ Subjective and clinical findings after initiation of CPAP treatment should be evaluated regardless of the procedure adopted for CPAP prescription.
- ❯ Lack of instrumental monitoring and reliance only on subjective reports can lead to consider acceptable CPAP levels that inadequately correct respiratory disorders.
- ❯ Subjective indications given by patients using previously titrated CPAP may help to suspect a poor previous CPAP titration or a change in pressure requirements and can be taken into consideration of making small changes in the administered CPAP.

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Complications During Noninvasive Pressure Support Ventilation

17

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17.1
Introduction

The term noninvasive pressure support ventilation (NPSV) refers to any form of ventilatory support applied without the use of an invasive conduit [1]. Goals of NPSV include the improvement of dyspnoea and of blood gas abnormalities from acute respiratory failure (ARF), the reduction of work of breathing and the avoidance of tracheal intubation. Long-term advantages of NPSV are the decrease of need for tracheal intubation, of nosocomial pneumonia, of stay in the intensive care unit (ICU) and in the hospital, and, most importantly, of the overall mortality rate [1, 2]. The patient interfaces most commonly employed for NPSV are a nasal or a face mask (mask NPSV) and a helmet (helmet NPSV). NPSV may have complications, some of which are frequent and predictable and some rare and unpredictable. The staff responsible for NPSV should be aware and be prepared to prevent, detect early, and cure these complications. NPSV is safe and well tolerated when applied optimally in appropriately selected patients [1].

17.2
Interface Related Complications

The most frequently encountered adverse effects and complications are minor and related to the NPSV interface (see summarizing Table 17.1).

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Table 17.1 Adverse events and complications of noninvasive ventilation (NIV) with different interfaces (IF) and patient conditions

	Frequency (%)	IF/Patient condition	Remedy	References
Interface related				
Carbon dioxide rebreathing	50–100	H > FM > NM	Reduce respiratory rate and IF size	2–4, 7, 8
Claustrophobia	5–10	FM > NM > H	Reduce inspiratory pressure, sedation	1, 2
Discomfort	30–50	FM > NM > H	Change IF, sedation	2–4, 7, 8
Facial skin erythema	20–34	FM > NM > H	Check IF fit	2
Nasal bridge ulceration	7–100	FM > NM > H	Change IF	2, 10
Arm edema and arm vein thrombosis	<5	H/ malnutrition	Check H armpits	3
Mechanical malfunction	<1	FM = NM = H	Check equipment	9
Noise	50–100	H > FM = NM	Change IF, use heat and moisture, earplugs, sound traps	11
Patient ventilator dyssynchrony	50–100	H > FM = NM	Add/increase PEEP	4, 7
Air Pressure and Flow Related				
Air leaks	18–68	NM > FM > H	Check IF fit, reduce pressure	2, 4–7, 13
Nasal or oral dryness and congestion	20–50	FM = NM > H	Add humidifiers and emollients, reduce inspiratory pressure	2, 10, 15
Gastric Distension	5–50	FM > NM >H	Reduce inspiratory pressure	2, 16
Patient Related				
Aspiration pneumonia	<5	All IF/ileum	Follow NPSV contraindications	2
Barotrauma	<5	All IF/COPD, neuromuscolar disease, cystic fibrosis	Follow NPSV contraindications	2, 17
Hemodynamic effects	<5	All IF/high blood pressure	Follow NPSV contraindications	2, 18

COPD chronic obstructive pulmonary disease; *FM* face mask; *IF* interface; *NM* nose mask; *NPSV* noninvasive pressure support ventilation; *PEEP* positive end-expiratory pressure.

17.2.1
Arm Edema and Arm Vein Thrombosis

The complication of arm edema is observed during helmet NPSV. The helmet is secured by two armpit braces to a pair of hooks on the plastic ring that joins the helmet to a soft collar. During helmet NPSV, the prolonged compression from the armpit brace may produce venous and lymphatic stasis with consequent edema. This is more frequent in patients with severe malnutrition and cachexia and may promote deep venous thrombosis in the axillary vein and anticoagulant therapy. Fixation of the braces in severely malnourished patients needs close attention [3].

17.2.2
Carbon Dioxide Rebreathing

The respiratory circuit and the interface for NPSV represent an additional dead space and increase chances of carbon dioxide (CO_2) rebreathing in proportion to their volumes. Compared with the tidal volume, the dead space of the masks is smaller than that of the helmet. The amount of CO_2 rebreathed is consequently smaller during mask NPSV than helmet NPSV. The helmet is less effective than masks in removing CO_2 during NPSV [3, 4]. Further, single respiratory circuits with no exhalation valve, high respiratory rates, no or low external positive end-expiratory pressure (PEEP), and a reduced expiratory time may all increase CO_2 rebreathing [5]. The issue of whether CO_2 rebreathing is clinically relevant remains an open question. According to some authors, CO_2 rebreathing is below 1.5% with both mask NPSV and helmet NPSV, and it is clinically not relevant [3]. According to others, however, CO_2 rebreathing may impair CO_2 elimination and ventilatory muscle unloading [6]. Decreasing the size of the helmet and increasing pressure support will not necessarily prevent CO_2 rebreathing during helmet NPSV [4]. However, if a rapid increase of alveolar ventilation is required in patients with severe ARF, helmet NPSV reduces hypercapnia less efficiently than mask NPSV [3]. Using a two-line circuit and a nonrebreather valve, lowering the respiratory rate, adding PEEP, and increasing the expiratory time have been advocated as measures to reduce CO_2 rebreathing [5].

17.2.3
Claustrophobia

Claustrophobia is the fear of enclosed spaces. Five percent to 10% of the general population may present fear of restriction and fear of suffocation. The development of claustrophobia involves the impossibility to begin or to continue the NPSV. The choice of device is crucial regarding claustrophobia and discomfort as well. The masks are often poorly tolerated by distressed patients compared to the helmet. In the case of mask NPSV, the

use of manual mask application at first can minimize the sense of claustrophobia [1]. The ventilatory support should be introduced gradually, starting with continuous positive airway pressure and adding inspiratory pressure support as required [1]. Ventilator settings should be adjusted to provide the lowest inspiratory pressure needed to improve patient comfort [1]. Sedation may prevent or be helpful for claustrophobic patients.

17.2.4
Discomfort

Discomfort represents an unpleasant sensation that it is related to the device or pressure values adopted during NPSV. In a direct comparison among different models of mask for NPSV, the tolerance was poorest for the mouthpiece followed by the nasal and oronasal masks [7]. Although all masks were reasonably comfortable for the eyes, all attachment systems were considered uncomfortable for the skin [7]. The helmet was tolerated better than masks because of the absence of the feeling of uncomfortable pressure on the face [3]. It allowed the patients to communicate, drink, and read better than the facial mask; improved the collaboration between the patient and the medical staff during the treatment period; and allowed maintaining continuous NPSV for a period of time longer than in the mask group [3, 8]. The possible advantages of the helmet on patient tolerability and comfort must be balanced with its interference with ventilation, greater dead space, and compliance compared to the face mask [4]. When pressure support ventilation is adopted, the comfort levels follow a U-shaped trend when level of assistance is modified, and the extreme levels of pressure support (both lowest and highest) are not associated with the best comfort. The nasal saline or emollients or heated humidification during nasal NPSV attenuates the adverse effects of mouth leak on effective tidal volume and nasal resistance and improves overall comfort. Sedation may represent a crucial issue for poorly tolerant patients.

17.2.5
Mechanical Malfunction

A variety of mechanical complications can occur during mechanical ventilation, such as accidental disconnection, leaks within the ventilator circuit, loss of electrical power, and loss of gas pressure. For these reason, the mechanical ventilator system should be checked frequently to prevent mechanical malfunctions. During helmet NPSV, an accidental interruption of gas flow causes five main effects: the CO_2 increases inside the helmet; the FiO2 diminishes due to the inspiration of ambient air and the inspired partial pressure of CO_2 increases; the PEEP is lost in a few seconds; dyspnea of increasing intensity and a sense of impending suffocation ensue; and a progressive increase in minute ventilation occurs. Some features of the helmet design, such as a high volume, a low-resistance inlet port, and the adjunct of a safety system can effectively limit and delay the clinical consequences of fresh gas supply interruption. There is a clear need to include a monitoring and alarm system, and clinical control is important [9]. In NPSV at home, the caregivers must be

prepared to provide bag-and-mask ventilation to patients in the event of an emergency. If the equipment is available, this simple technique may be lifesaving in the presence of mechanical malfunctions.

17.2.6
Nasal Bridge Ulceration

Nasal pain, either mucosal or on the bridge of the nose, and nasal bridge erythema or ulceration from mask pressure account for a large portion of reported complications of mask NPSV [2]. The incidence of skin necrosis or abrasion depends on the duration of mask usage and varies between 7% and 100% after 48 h of NPSV [10]. The mean pressure recorded on the bridge of the nose was much higher than that on the cheek (65 vs. 15 mmHg, nose vs. cheek), and this pressure can be close to the lower values of normal diastolic blood pressure [10]. Progressive tightening of the harness and increasing of the volume of air in the oronasal mask cushions increased the pressure on the bridge of the nose, and the effect of these two factors was additive [10]. The development of pressure necrosis is one factor that can limit the tolerance and duration of mask NPSV. Strategies used to decrease the incidence of pressure necrosis during NPSV include minimizing strap tension, using forehead spacers, routinely applying artificial skin to the bridge of the nose in the acute setting, applying a Granuflex dressing to the areas of the face that are exposed to pressure, using water instead of air to fill the cushion of a facemask, or switching to alternative interfaces such as nasal pillows, new prototype face masks, cephalic masks, and helmets [2, 10].

17.2.7
Noise

Noise exposure during NPSV may be underestimated among the factors that influence patient well-being during the ICU stay. The noise exceeds the usual ICU background noise, potentially increasing patient discomfort, causing sleep disruption, and affecting ear function. The intensity of noise inside the helmet during NPSV is about 105 dB and is mostly caused by the turbulent gas flow through the respiratory circuit. By contrast, the noise perceived during mask NPSV is probably mostly caused by the ventilator and is about 65 dB, not different from the background noise that is measured at patients' bedsides in the ICU [11]. The excess noise inside the helmet may have some detrimental effects on patient wellness. Noise may impair a patient's contact with the environment by masking sounds and hindering conversation, and this inconvenience may add to the physical barrier that the helmet constitutes. Such noise intensity has been regarded in the past as a major cause of sleep arousals in critically ill patients. More recent studies have reported that sleep disruption in the ICU is multifactorial, and that noise is responsible for only a limited proportion of arousals and awakenings [11]. Loud noise may damage the ear. Damage may result in permanent hearing loss but more frequently causes a temporary auditory threshold shift, which may require days to recover if caused by prolonged noise exposure (days) at 100 dB.

Tinnitus, usually transitory, may also occur after noise exposure, particularly in patients with preexisting hearing loss. Noise exposure during helmet NPSV may be attenuated by some devices. Heat and moisture exchanger filters did not affect noise intensity measured by the sound level meter but decrease the noise perceived by the subjects [11]. Other devices include earplugs and sound traps. Earplugs may be effective against sleep disruption but may also make contact with the environment more difficult. Conversely, adding sound traps to the inspiratory branch of the respiratory circuit may potentially limit noise inside the helmet without major inconvenience [11].

17.2.8
Patient–Ventilator Dyssynchrony

Considering that the algorithms regulating the beginning and the end of pressure support ventilation are pressure and flow based, the characteristics (i.e., dead space, compliance) of devices for NPSV have influence on the patient–ventilator interaction. Significant asynchrony between the beginning and the end of inspiratory support and the beginning and the end of patient inspiratory effort is commonly observed during NPSV [4]. Wasted efforts (i.e., when a patient's inspiratory effort is not followed by a ventilator cycle), autotriggering (i.e., when a ventilator cycle occurs without being preceded by a patient's inspiratory effort), and prolonged inspirations (i.e., when each insufflation lasts longer than 1.5 s) may also be expected during NPSV [4, 7]. The patient–ventilator dyssynchrony is significantly higher during helmet NPSV than during mask NPSV [4], and among the different masks, the dyssynchrony is more evident with a mouthpiece than with nasal or oronasal masks [7]. With regard to a helmet, the low elastance and high inner volume of the device causes significant overdamping of pressure assistance and a deviation of ventilator-delivered flow from the patient to expand the compliant helmet (in particular the soft collar) during NPSV [4]. These impaired patient–ventilator interactions represent underlying mechanisms responsible for the reduced efficiency of helmet NPSV in unloading the respiratory muscles in conditions of increased respiratory muscle workload [4]. A minimum PEEP of 6 cm H_2O might be helpful in the clinical setting, while the use of higher flows and higher pressures may reduce the compliance of the helmet and may optimize the efficiency of helmet NPSV [4]. On the other hand, it may not be well tolerated by normal subjects and may be associated to worsening of patient–ventilator synchrony and dyspnea sensation in patient with ARF [4]. A proportional assist ventilation may improve patient–ventilator interaction and patient comfort [12].

17.3
Air Pressure and Flow Related Complications

Air pressure and flow are required for NPSV but are also potential causes of efficiency loss and serious complications during NPSV. They should be monitored closely in any patient undergoing NPSV (see summarizing Table 17.1).

17.3.1
Air Leaks

Interfaces for NPSV do not provide a perfect seal of the airway. Some air leaking through the mouth (with nasal masks) or around the oronasal mask or the collar of the helmet is virtually universal with NPSV. Leaks are significantly larger with the mouthpiece, but no difference is observed between the other masks. They range from 18% (integral face mask) to 68% (mouthpiece). The leaks of large oronasal mask and small oronasal mask are similar (31% versus 34%) [3]. Leaks cannot be quantitated exactly during helmet NPSV but they are estimated to be at least comparable if not smaller than those obtained with the mask [4]. Besides the fitting of interface, high values of peak and plateau pressures can contribute air leaks during NPSV [2]. Air leaks are important because they can render NPSV ineffective and because they may affect triggering [13] and, in patients with neuromuscular disease, can cause persistent hypercapnia [6]. For these reasons, leaks should be monitored closely and taken into account for the choice of the interface by the NPSV staff. For patients with nasal mask measures to reduce air leaking include instructions to keep the mouth closed, application of chin straps, bite blocks or switching to oronasal mask or helmet. A tighter fitting of the mask or helmet and a reduction of pressures may be necessary to provide adequate ventilation in some patients [2, 4, 7]. In volume-targeted ventilators, small and moderate air leaks can be compensated for by increasing tidal volume whereas large leaks are difficult to compensate. Air leaks can be compensated much better by pressure-targeted ventilators thanks to specific compensating features that are present in some models [5, 14]

17.3.2
Nasal or Oral Dryness and Nasal Congestion

Nasal or oral dryness is caused by high airflow, and it is usually indicative of air leaking through the mouth. Measures to minimize leaks may be useful, but nasal saline or emollients and heated humidifiers are often necessary to relieve these complaints [2]. Generally, gases delivered from mechanical ventilators are typically dry. The physiologic effects of inadequate humidity can be due to heat loss or moisture loss. In particular, moisture loss from the respiratory tract and subsequent dehydration of the respiratory tract result in epithelial damage, particularly of the trachea and upper bronchi, drying of secretions and atelectasis. It would be desirable to have an adequate humidifying system to avoid excessive dehydration of airway mucus and, at the same time, to avoid the contamination of lung parenchyma by infectious agents as much as possible. Two humidifying devices are commonly used with intensive care ventilators: heated humidifiers and heat–moisture exchangers. The latter are frequently used because of their simplicity and lower cost. However, during NPSV the increased dead space of a heat–moisture exchanger can negatively affect ventilatory function and gas exchange in patients with ARF [15]. Nasal congestion and discharge are also frequent complaints and may be treated with topical decongestants or steroids and oral antihistamine/decongestant combinations.

17.3.3
Gastric Distension

Gastric insufflation is reported in up to 50% of patients receiving NPSV but is rarely intolerable. The lower esophageal sphincter pressure is the pressure at the esophageal-gastric junction (approximately 20–25 cmH_2O) that prevents regurgitation of stomach contents into the pharynx and insufflation of air into the gastrointestinal tract during ventilation. The frequency of gastric insufflation increases when high inflation pressures are used and may be worsened when the compliance of the abdomen is greater than that of the chest. This condition could occur if the NPSV ventilation system injects air while the patient's own respiratory cycle is in the expiratory phase so that the compliance of the chest increases while that of the abdomen is relatively free from the respiratory cycle [16]. Gastric insufflation, which worsens the patient's quality of life, can be fatal in severe cases. Gastric distension compresses the lungs, thereby decreasing their compliance and demanding higher airway ventilation pressure. The last is also associated with increased risk of gastric distension, thus generating a vicious cycle. Serious complications of gastric distension are regurgitation of gastric contents, pulmonary aspiration, intra-abdominal hypertension, and abdominal compartment syndrome. A condition clinically identical to a tension pneumothorax has been reported but was related to massive intrathoracic dilation of the stomach in a patient with a hiatus hernia who was treated with NPSV. Airway pressures higher than 20 cmH_2O should be avoided, and NPSV ventilation should be used in the sitting position about half an hour after a meal [2, 16].

17.4
Patient Related Complications

A careful patient selection is crucial for NSPV success. Indications and contraindications, either relative or absolute, have been proposed for NPSV [1, 2] but are being reviewed on the base of new studies (see summarizing Table 17.1). Even patients highly selected for NPSV, however, can present unpredictable and serious or even life-threatening complications because of their clinical conditions .

17.4.1
Aspiration Pneumonia

Aspiration pneumonia has been reported in as many as 5% of patients [2]. Rates of aspiration are minimized by excluding those with compromised upper airway function or with problems in clearing secretions and by permitting at-risk patients nothing by mouth until they are stabilized. A nasogastric tube can be inserted if the patient has excessive gastric distension, an ileum, nausea, or vomiting or is deemed to be at high risk for gastric aspiration. However, such patients are not ideal candidates for NPSV, and nasogastric or orogastric tubes should not be routinely used because they interfere with mask fitting, promote air leaking, and add to discomfort [2].

17.4.2
Barotrauma

Barotrauma is a well-recognized complication of positive pressure ventilation. It is a pulmonary injury resulting from alveolar overdistension and can lead to pulmonary interstitial emphysema, pneumomediastinum, subcutaneous emphysema, and pneumothorax. A pneumoperitoneum associated with pneumomediastinum and tension pneumothorax associated with extensive vascular air embolism has also been reported. Barotrauma is thought to arise from a high-pressure gradient between the alveolus and adjacent vascular sheet, causing rupture of the overdistended alveolus, forcing gas into the interstitial tissue and subsequent dissection along the pulmonary vessels. It is likely that the risk of barotrauma in patients using NPSV is less than in those receiving invasive ventilation. Until now, it has been described in the presence of chronic obstructive pulmonary disease, acute lung injury from pneumonia, cystic fibrosis, and neuromuscular disorders. During NPSV, there is usually a drop in inflation pressure across the upper airway, and the presence of the air leaks acts as a sort of "security valve" that may, to some extent, prevent airway damage from excessive positive pressure. However, the transitory rise of peak pressure into localized alveolar overdistension may be related to patient–ventilator desynchronization and lead to disruption of the alveolar capillary membrane. So, it is important not only that the peak alveolar pressure is kept as low as possible (i.e., <30 cmH$_2$O) but also that the patient–ventilator desynchronization is minimized as much as possible to reduce risk of barotraumas [2, 17].

17.4.3
Hemodynamic effects

In general, NPSV is well tolerated hemodynamically, presumably because of the low inflation pressures used compared with invasive ventilation [2]. A short-term use of NPSV reduces heart rate, systolic blood pressure, and systemic vascular resistance. In patients who are receiving optimal therapy, the reduction of systolic blood pressure is not significant and may be associated with increase of ejection fraction and cardiac output [18]. On the other hand, significant hypotension and reduced cardiac output may occur in patients with a tenuous hemodynamic status (i.e., patients who are hypertensive or have low fluid volume) or with an underlying cardiac disease without adequate pharmacologic therapy. A bilevel ventilation in patients with acute pulmonary edema increases the rate of myocardial infarction associated with a greater early drop in blood pressure compared continuous positive airway pressure alone that could have resulted from higher initial mean intrathoracic pressure, causing a greater reduction in venous return Thus, in these patients, clinicians are encouraged to begin with continuous positive airway pressure alone or NPSV using relatively low inflation pressures (i.e., 11–12 cmH$_2$O inspiratory, 4–5 cmH$_2$O expiratory pressures) while monitoring the clinical response. Also, NPSV should be avoided in patients with uncontrolled ischemia or arrhythmias until these problems are stabilized [2].

Key Recommendations

> During NPSV, air leaks, patient–ventilator dyssynchrony, and patient discomfort are all common problems that depend on patient–ventilator interaction. They should be looked for and improved with the appropriate choice and fitting of the interface and, when possible, slight reduction of pressure.

> Skin necrosis or abrasion depend on and limit the duration of mask NPSV. Alternative interfaces such cephalic mask or helmet may be considered.

> The noise during NPSV exceeds the usual ICU background noise and can be another cause of discomfort, sleep disruption, and ear damage. It should be diminished with ear plugs and sound traps.

> Gastric insufflation from NPSV increases with ventilation pressures, the upper safe limit being 20 cmH$_2$O.

> Barotrauma is a rare but a possible event during NPSV resulting from patient–ventilator asynchrony which should be closely monitored.

> Hypotension during NPSV is possible in hemodynamically instable patients. In patients with ischemia or arrhythmias NPSV should be avoided or delayed until these problems are stabilized.

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Section V

Chronic Applications of Noninvasive Mechanical Ventilation and Related Issues

Efficacy of Continuous Positive Airway Pressure in Cardiovascular Complications of Obstructive Sleep Apnea

18

Ahmed S. BaHammam and Mohammed K.A. Chaudhry

18.1
Introduction

Obstructive sleep apnea (OSA) is a form of sleep-disordered breathing (SDB) that is characterized by intermittent complete or partial collapse of the upper airway. This pattern of breathing has been considered a cause for several cardiovascular diseases, such as systemic hypertension, heart failure, arrhythmias, myocardial infarction, and pulmonary hypertension. The prevalence of OSA in the middle-aged population was first estimated in 1993 by the ongoing population-based Wisconsin Sleep Cohort Study [1] in a sample of 625 employed adults. The investigators found that 9% of women and 24% of men had at least five or more apneas or hypopneas per hour of sleep [1]. When the presence of extreme daytime sleepiness was included as a criterion, the prevalence was estimated to be 2% in women and 4% in men [1]. The incidence of SDB is independently influenced by age, sex, waist–hip ratio, and body mass index (BMI). The correlation between OSA and cardiovascular diseases has been well studied, and a linear relationship between severity of OSA and the comorbidities has been reported [2, 3]. The famous Sleep Heart Health Study revealed that the relative odds of heart failure, stroke, and coronary artery disease (CAD) (upper vs. lower apnea–hypopnea index [AHI] quartile) were 2.38, 1.58, and 1.27, respectively [3]. In this chapter, we review the best-available evidence supporting the use of continuous positive airway pressure (CPAP) in OSA patients with hypertension, CAD, heart failure, pulmonary hypertension, and stroke.

18.2
Pathophysiology

There are a number of pathophysiologic mechanisms underlying cardiovascular complications in OSA patients (Fig. 18.1). The most notable immediate mechanisms are (1)

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intermittent swings in blood gas chemistry that range from hypoxia–reoxygenation to hypercapnia–hypocapnia, (2) arousals, and (3) intrathoracic pressure changes [4]. Pathophysiological features that have been associated with OSA range from fragmented sleep, to daytime sleepiness, to recurrent episodes of apnea-related desaturation along with retention of CO_2. All of these factors disrupt the normal structured hemodynamic and autonomic responses to sleep. There is a substantial amount of evidence supporting the conception that intermittent hypoxia–reoxygenation is the key feature of the cardiovascular pathophysiology of the disorder [5]. Apneas and hypopneas cause intermittent hypoxia and consecutive intrathoracic pressure swings. This triggers the autonomic nervous system, leading to sympathetic overactivation [6]. This hyperactivity persists during the state of wakefulness. These patients therefore have faster heart rates during resting wakefulness. The cycle of hypoxia–reoxygenation releases increased quantities of reactive oxygen radicals, triggers oxidative stress mechanisms, and releases inflammatory markers [7]. The endothelium maintains harmony between vasodilation and vasoconstriction and regulates vasoactive mediators. Endothelial dysfunction leads to arterial wall damage. Many studies have implicated a relationship between OSA and endothelial dysfunction [8]. Figure 18.1 shows an algorithm for the proposed pathophysiologic mechanisms.
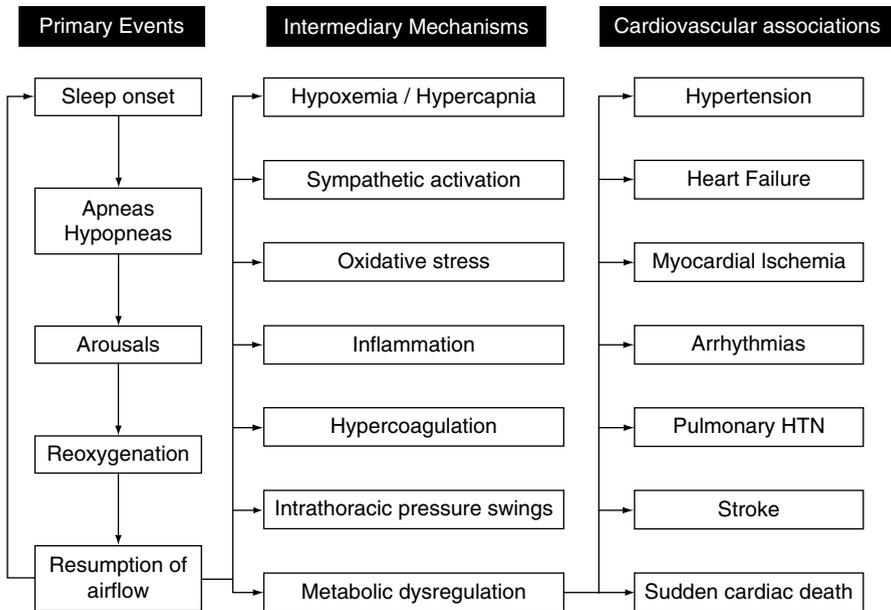
Fig. 18.1 An algorithm of the proposed pathophysiologic mechanisms. *HTN* hypertension

18.3
Cardiovascular Complications in Patients with OSA

Table 18.1 summarizes the main studies that examined the effects of treatment for OSA on outcomes contributing to cardiovascular diseases.

18.3.1
Systemic Hypertension

There is compelling evidence showing that OSA is an independent and important risk factor for hypertension [9]. Reported data from the Wisconsin Sleep Cohort Study documented a cause–effect relationship between OSA and hypertension after controlling for different confounders [10]. They reported a direct relationship between the prevalence of hypertension and the severity of OSA expressed as the AHI [11]. After adjusting for confounders, the risk of hypertension was twofold for those with an AHI of 5–15/h and threefold for subjects with an AHI above 15/h [11].

18.3.1.1
CPAP Therapy Effects

Controlled trials that studied the effect of CPAP on blood pressure level in patients with OSA showed conflicting results. All studies that did not show an effect of CPAP on blood pressure had significant limitations. Limitations included underpower, as most of studied subjects were normotensive; the short duration of therapy; or inadequate compliance. A critical review of the available literature showed that CPAP therapy drops blood pressure by around 10 mmHg on average in patients with moderate-to-severe sleep apnea [12, 13]. Nevertheless, this effect was less obvious in patients with mild OSA and patients with OSA who were normotensive.

18.3.2
Coronary Artery Disease

In general, the risk of developing acute coronary syndrome (ACS) or sudden cardiac death increases during the early morning hours after wakening. The fact that patients with OSA have increased risk of ACS and sudden cardiac death during sleep hours (midnight to 6 a.m.), which is the nadir of ACS in subjects without OSA, raises a concern about the role of OSA in inducing CAD [14]. In addition, an observational prospective study that evaluated the time course of SDB in patients with ACS revealed persistence of OSA in these patients 6 months after the acute event, suggesting that OSA might have preceded the ACS event and hence was a possible causal effect [15]. Studies have shown a high prevalence of CAD (20–68%) in patients with OSA referred to the sleep clinic [16, 17].

Table 18.1 Summary of the main studies that examined the effects of treatment for obstructive sleep apnea on outcomes contributing to cardiovascular diseases

Cardiovascular association	Study	Treatment	Patient population (n)	Treatment period	Treatment outcomes
Hypertension	Becker et al. [13]	Therapeutic vs. sham CPAP	60	Mean 65 days	10 mmHg decrease in systolic and diastolic blood pressure
	Pepperell et al. [12]	Therapeutic vs. sham CPAP	118	1 month	Therapeutic CPAP reduced mean arterial ambulatory blood pressure by 2.5 mmHg
Heart failure	Kaneko et al. [25]	Therapeutic CPAP vs. no CPAP	24	1 month	9% increase in LVEF; 10 mmHg decrease in systolic blood pressure; decrease in heart rate of 4 beats/min
	Mansfield et al. [26]	Therapeutic CPAP vs. no CPAP	55	3 months	CPAP treatment associated with significant improvements in LVEF
Stroke	Martinez-Garcia et al. [41]	CPAP in severe OSA vs. no CPAP	28	5 years	Long-term CPAP treatment in moderate-to-severe OSA and ischemic stroke associated with a reduction in excess risk of mortality
Coronary artery disease	Doherty et al. [21]	Therapeutic CPAP vs. no CPAP	168	7.5 years	Deaths from cardiovascular disease more common in the untreated group than in the CPAP-treated group during follow-up
	Marin et al. [20]	Therapeutic CPAP vs. no CPAP	1651	10.1 years	CPAP treatment reduced the risk of fatal and nonfatal cardiovascular events
Pulmonary HTN	Arias et al. [31]	Therapeutic vs. sham CPAP	33	18 weeks	Reduction of pulmonary systolic pressure (from 28.9 to 24.0 mmHg)

CPAP continuous positive airway pressure, *HTN* hypertension, *LVEF* left ventricular ejection fraction, *OSA* obstructive sleep apnea

18.3.2.1
CPAP Therapy Effects

Early recognition and treatment of OSA may be beneficial in terms of CAD prevention. Treatment with CPAP reduces angina and nocturnal myocardial ischemia [18]. Drager et al., in a small randomized controlled study, reported improvements in pulse wave velocity, carotid intima wall thickness, and carotid artery diameter after 4 months of CPAP therapy [19]. Marin et al. compared the fatal and nonfatal cardiovascular events in patients with treated and nontreated OSA [20]. Patients with severe OSA (AHI > 30) had significantly higher fatal and nonfatal cardiovascular events. Among the patients who had treated OSA, the incidence of both fatal and nonfatal cardiovascular events approached levels seen in simple snorers [20]. A long-term follow-up study of 168 patients with OSAs who had begun receiving CPAP therapy at least 5 years previously compared the cardiovascular outcomes of those patients who were intolerant of CPAP (untreated group, 61 patients) with those continuing CPAP therapy (107 patients) [21]. Deaths from cardiovascular disease were more common in the untreated group than in the CPAP-treated group during follow-up [21].

18.3.3
Heart Failure

A number of studies reported a high prevalence of OSA among patients with heart failure (11–38%), a prevalence higher than that reported in patients without OSA [22]. Patients with heart failure and OSA are usually overweight and snore habitually, which is different from the phenotype of patients with heart failure who have central sleep apnea and Cheyne–Stokes respiration. Even patients with mild heart failure have increased prevalence of OSA. Vazir et al. described a 15% incidence of OSA in patients with mild systolic left ventricular dysfunction [23]. Heart failure in OSA patients can be both systolic and diastolic.

18.3.3.1
CPAP Therapy Effects

CPAP therapy improves both systolic and diastolic functions. In a controlled crossover design study, Arias et al. reported significant improvement in diastolic dysfunction with CPAP therapy [24]. Two randomized controlled trials assessed the impact of CPAP therapy on systolic dysfunction in patients with OSA. One study reported an improvement from 27% to 36% in left ventricular ejection fraction (LVEF) in 24 patients after 4 weeks of CPAP therapy [25]. The second study reported an improvement in LVEF from 35% to 40%, a reduction in urinary catecholamines, and improved quality of life in 55 patients with CPAP therapy for 3 months [26]. A multicenter randomized study explored the efficacy of CPAP in 60 OSA patients with heart failure (LVEF < 45%) [27]. There was a significant improvement in the LVEF in the group of patients treated with CPAP but no such

improvement in the sham CPAP group. The improvement was more marked in patients with a LVEF above 30% [27]. On the contrary, a randomized, double-blind, crossover study did not elicit a significant change in LVEF after 6 weeks of CPAP use [28]. Nevertheless, CPAP usage was low (3.5 h per night) [28]. OSA has been associated with higher mortality in patients with heart failure [29]. The impact of CPAP therapy on mortality in patients with heart failure has not been shown. Currently, there are no guidelines for treatment of sleep apnea in heart failure. Well-designed, long-term studies are needed to see if treatment with CPAP prolongs survival.

18.3.4
Pulmonary Arterial Hypertension

The World Health Organization recognized SDB as a secondary cause of pulmonary arterial hypertension (PAH) in its second conference on PAH in 1998 [30]. Studies have shown that mild PAH (mean pulmonary artery pressure of 20–30 mmHg) is relatively common in patients with OSA. A prevalence of 17–43% has been reported in different studies. High AHI, low Pa_{O_2}, high Pa_{CO_2}, low FEV_1, and increased BMI have been associated with PAH in patients with OSA [31]. The clinical significance of this mild OSA-related PAH is not known.

The pulmonary vasculature, in contrast to the systemic vasculature, responds to hypoxia with vasoconstriction to maintain matched ventilation and perfusion. Sustained long-term hypoxia results in chronically present vasoconstriction that varies among individuals. Over time, this leads to remodeling of pulmonary vasculature. Experimental intermittent hypoxia for part of the day for a few weeks caused PAH, pulmonary arterial remodeling, and right ventricular hypertrophy in rodents [32].

18.3.5
CPAP Therapy Effects

Treatment of patients with OSA with CPAP has been shown to reduce pulmonary artery pressure. Arias and colleagues [31] have studied pulmonary hemodynamics and OSA in their randomized crossover study and found that CPAP treatment compared with sham CPAP significantly reduced pulmonary systolic pressure (from 29 to 24 mmHg). Patients who responded well were the ones who had PAH at baseline or with left ventricular dysfunction. A number of studies reported a significant decrease in pulmonary artery pressure in patients with OSA with PAH after 3–6 months of CPAP therapy [31, 33]. One study demonstrated reduction in the reactivity of the pulmonary circulation to hypoxia after CPAP therapy [33]. Nevertheless, it is important to mention here that some studies showed negative results [34].

Based on available data, it seems that a drop in pulmonary artery pressure is likely to occur in patients with severe OSA; those in whom PAH is caused by OSA not by comorbid

conditions; those with left ventricular dysfunction; and those who are adherent to thera-peutic CPAP.

18.3.6
Stroke

Cross-sectional studies showed strong association between OSA and stroke. The strength of association was similar to traditional risk factors for stroke like hypertension and smok-ing. In addition, even after adjustment for known confounding factors like obesity and hypertension, SDB remains an independent association [3]. Large observational cohort prospective studies have shown that OSA increases the risk of stroke and all-cause mortal-ity independent of known confounders [35, 36]. Moreover, severity of OSA was associated with a higher risk of stroke and death [35–37]. Those with an AHI above 36 had a more than threefold increased risk of stroke and death. A study that followed patients with OSA for 10 years showed that OSA was significantly associated with a higher risk of stroke in patients with CAD who were being evaluated for coronary intervention [38].

18.3.6.1
CPAP Therapy Effects

There is always a concern that individuals with OSA and stroke may not tolerate CPAP due to their acute illness. Studies addressing CPAP tolerance in this group of patients have reported conflicting results. While some investigators reported a similar improvement and acceptance of CPAP therapy as in patients with OSA without stroke [39], others reported poor tolerance and lack of benefit [40].

A prospective observational study explored SDB in 166 patients with acute stroke [41]. CPAP therapy was offered when AHI was 20/h or higher, and then patients were followed for 5 years. Patients with an AHI of 20 or higher who did not tolerate CPAP ($n = 68$) showed an increased adjusted risk of mortality (hazards ratio [HR] 2.69) com-pared with patients with an AHI below 20 ($n = 70$) and an increased adjusted risk of mortality (HR 1.58) compared with patients with moderate-to-severe OSA who toler-ated CPAP ($n = 28$). There were no differences in mortality among patients without OSA, patients with mild disease, and patients who tolerated CPAP therapy [41]. Furthermore, CPAP therapy may reduce the risk for stroke indirectly through different mechanisms. CPAP therapy has been shown to reduce blood pressure; eliminate inter-mittent hypoxia; decrease platelet aggregation and fibrinogen levels; reduce risk of atrial fibrillation; reduce sympathetic nerve activity, ambulatory blood pressure, and arterial wall stiffness; and increase sensitivity of the arterial baroreflex in patients with OSA [12, 42]. These effects may reduce the risk of CAD and stroke in this group of patients.

Key Recommendations

❯ OSA is a serious medical disorder that may cause and increase the risk for many cardiovascular disorders.

❯ Several mechanisms may account for this risk, including intermittent hypoxia, sympathetic overactivity, oxidative stress, endothelial dysfunction, inflammation cascade overactivity, intrathoracic pressure swings, metabolic dysregulation, and thrombosis.

❯ Early treatment of OSA patients with CPAP therapy may prevent cardiovascular complications.

❯ CPAP therapy has been effective in reducing a number of cardiovascular complications and cardiac-related mortality in patients with OSA.

❯ Clinicians should be aware of the seriousness of OSA and hence should recognize this disorder in its early stages, initiate CPAP therapy, and stress the importance of adherence to their patients.

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Obstructive Sleep Apnea and Atherosclerosis

19

Richard Schulz, Frank Reichenberger, and Konstantin Mayer

19.1
Introduction

Atherosclerosis is a progressive, chronic disease of large arteries in which various stages of vascular remodeling finally lead to significant narrowing of the vessel lumen. In the early phase of atherosclerosis, cholesterol particles are incorporated into the vascular wall (i.e., foam cell formation, development of fatty streaks). Later, plaques occur that are prone to rupture with consecutive thrombosis and complete vessel occlusion. In this case, acute clinical syndromes such as myocardial infarction may result. Atherosclerosis is viewed as an inflammatory process in which circulating leukocytes are attached to the endothelium, penetrate into the subendothelial space, and release a wide spectrum of cytokines. Known risk factors for atherosclerosis are, for instance, smoking, diabetes mellitus, and hyperlipidemia.

19.2
Relation of Obstructive Sleep Apnea to Atherosclerosis

Large-scale epidemiological studies such as the Sleep Heart Health Study and the Wisconsin Sleep Cohort Study have shown that patients with obstructive sleep apnea (OSA) have an increased risk for atherosclerotic sequelae such as ischemic heart and cerebrovascular disease [1, 2]. Of note, this effect was found to be independent of confounding factors such as obesity, metabolic disorders (i.e., diabetes mellitus and hyperlipidemia), and smoking.

Multiple pathways may be involved in the pathogenesis of atherosclerosis in OSA. First, oxidative stress probably plays an important role. In this context, neutrophils from patients with OSA have been found to display an enhanced release of free oxygen radicals after in vitro stimulation by various compounds. The radical flux associated with OSA may trigger

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lipid peroxidation and reduce nitric oxide bioavailability. Second, vascular inflammation may contribute to OSA-associated atherosclerosis. This is reflected by an upregulation of inflammatory biomarkers such as C-reactive protein (CRP), interleukin 6 (IL-6), tumor necrosis factor α (TNF-α), and soluble adhesion molecules in the blood of patients with OSA. Furthermore, different leukocyte subpopulations are activated in these subjects and may provoke injury to the vascular endothelium. Likewise, rats undergoing repetitive airflow limitations are characterized by increased leukocyte–endothelial cell interactions. The same has been found in mice subjected to chronic intermittent hypoxia (CIH). Third, untreated OSA is linked with increased insulin resistance or impaired glucose tolerance, which may be equally important for the emergence of atherosclerosis. Taken together, these changes provoke a shift of vascular homeostasis to vasoconstriction, inflammation, and thrombosis (i.e., endothelial dysfunction). This impairment of endothelial-dependent vasorelaxation is an established precursor lesion for atherosclerosis. Vasoreactivity studies employing venous occlusion plethysmography and flow-mediated vasodilation have clearly shown that endothelial dysfunction can be observed in otherwise healthy, nonsmoking patients with OSA [3].

Direct evidence that OSA may induce atherosclerosis comes from studies investigating subclinical markers of atherosclerosis in patients with versus without OSA. The best established of these markers is intima media thickness (IMT). It is determined by high-resolution ultrasonography, usually at the level of the common carotid artery, and reflects the early phases of atherosclerosis. Various studies have shown that patients with OSA have significantly increased IMT when compared to subjects without sleep-disordered breathing, and that this is also true for those patients without any comorbidities [4]. Furthermore, it was observed that IMT in OSA is related to the degree of nocturnal hypoxia and the apnea–hypopnea index (AHI). In addition, one study found that IMT correlated with serum concentrations of inflammatory markers (i.e., CRP, IL-6, and IL-18). It should be noted that the findings from these sleep lab-based studies were not replicated in the population-based Sleep Heart Health Study. However, in this study, patients with moderate-to-severe OSA in whom an increase of IMT can be expected to occur were underrepresented.

Coronary artery atherosclerosis can be visualized by electron beam computed tomography. Using this technique, Sorajja and colleagues reported that, in patients without clinically overt coronary artery disease, the presence and severity of OSA was independently associated with the presence and extent of coronary vessel calcifications. A further study in which coronary vessel architecture was evaluated by three-dimensional intravascular ultrasound found that, in patients with stable coronary artery disease, there was a significant relationship between the frequency of apneas or hypopneas and coronary atherosclerotic plaque volume.

The ratio of ankle-to-brachial systolic blood pressure (i.e., the ankle–brachial index) can be used to screen for the presence of peripheral vaso-occlusive disease. In patients with OSA, this index has been found to be higher than in patients without OSA. Atherosclerosis is characterized by enhanced arterial stiffness, which can be determined by carotid-to-femoral pulse wave velocity measurement. Patients with OSA have increased pulse wave velocities in comparison with matched controls without sleep-disordered breathing.

In addition to these human data, an animal experiment found that rats exposed to CIH and fed with a high-cholesterol diet developed accelerated atherosclerosis [5]. Interestingly, in this model, CIH alone was not sufficient to induce atherosclerosis, thus pointing to a rather permissive role of OSA in the pathogenesis of atherosclerosis.
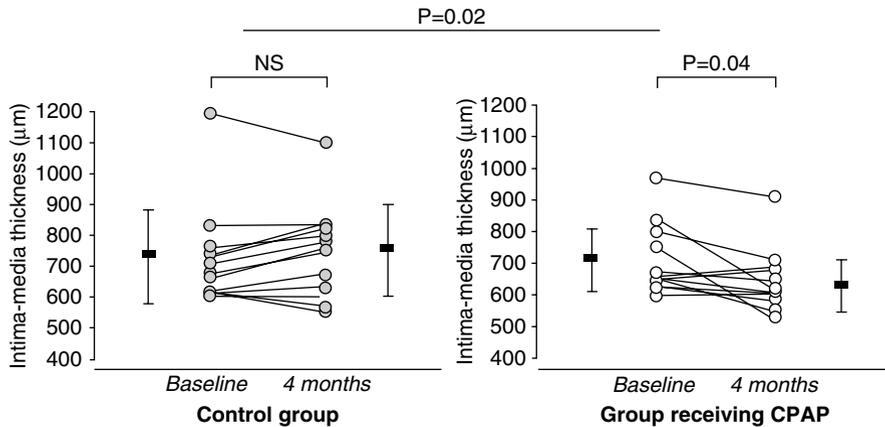
Fig. 19.1 Effects of 4 months of continuous positive airway pressure (CPAP) therapy on intima media thickness (IMT) in obstructive sleep apnea (OSA) in treated versus untreated patients (*n* = 12 in each group (From [6])

Continuous positive airway pressure (CPAP) therapy can restore the vascular micromilieu, improve endothelial function, and prevent deaths from myocardial infarction and stroke in patients with OSA with an AHI above 30/h. Therefore, one should expect that this form of treatment is able to inhibit or even reverse atherosclerosis. Indeed, one group from Brazil found that short-term CPAP therapy led to a modest decrease of IMT in a small sample of patients with OSA ([6]; Fig. 19.1). However, substantially more patients should be investigated over longer time periods to determine if CPAP really can reverse atherosclerotic remodeling of the vascular wall.

Key Recommendations

> The five major key messages of this review are as follows:

> Patients with untreated OSA have an increased risk for atherosclerosis and its related diseases independent of confounding factors.

> Presumably, the underlying mechanism is a disturbance of the vascular micromilieu (i.e., endothelial dysfunction) in response to the intermittent nocturnal hypoxia.

> Studies looking at different subclinical markers of atherosclerosis have clearly shown that patients with OSA have accelerated atherosclerosis when compared with controls without sleep-disordered breathing.

> Rats exposed to CIH and fed with a high-cholesterol diet develop accelerated atherosclerosis.

> CPAP therapy is likely to decrease atherosclerosis in OSA; however, long-term studies enrolling larger numbers of patients are necessary to definitively prove this assumption.

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Transnasal Insufflation — A New Approach in the Treatment of OSAs

20

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20.1
Introduction

Obstructive sleep apnea (OSA) syndrome leads to intermittent hypoxemia, sleep fragmentation, metabolic dysfunction, and increased cardiovascular morbidity and mortality. Current treatment options, including continuous positive airway pressure (CPAP), oral appliances, and surgical procedures, are often intrusive or invasive and not well tolerated, leaving a vast number of subjects untreated. Therefore, improved therapeutic strategies are required to treat sleep apneas and hypopneas and their associated morbidity and mortality. Currently, CPAP is most effective in eliminating apneas and hypopneas, although long-term effectiveness is compromised by low adherence, which is estimated at only 50–60% and even lower in children or patients with comorbid conditions like chronic obstructive pulmonary disease (COPD), stroke, or heart failure. An open nasal cannula system

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Fig. 20.1 Study participant wearing the treatment with nasal insufflation (TNI) cannula (cannula length is 1,800 mm, 5-mm outer diameter cannula and nasal prongs, 3.4-mm inner diameter)
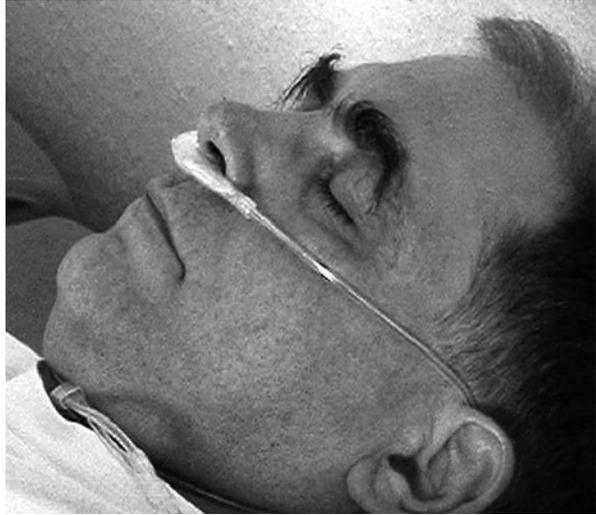
delivering warm and humidified air (Fig. 20.1) has been introduced as a method for increasing pharyngeal pressure [1]. This chapter summarizes the studies that were conducted with treatment with nasal insufflation (TNI) in adults and children with OSA and hypopnea across a spectrum of disease severity.

20.2
Mechanism of Actions of Nasal Insufflations

20.2.1
Effect on Upper Airway

Upper airway obstruction is due to increased pharyngeal collapsibility, which decreases inspiratory airflow, as manifested by snoring, obstructive hypopneas, and apnea. This defect in upper airway collapsibility can be overcome by elevating nasal pressure. In fact, somewhat greater levels of nasal pressure are required to abolish apneas than hypopneas and to restore normal levels of inspiratory airflow. Vice versa, in patients with mild forms of upper airway obstruction, low levels of nasal pressure through a nasal cannula may be sufficient to relieve sleep-disordered breathing. Several studies have been published to confirm this hypothesis.

The mechanism of action of TNI on upper airway function was first determined in adult patients with varying degrees of upper airway obstruction [1]. Airflow dynamics and supraglottic pressure responses to TNI were examined. At a rate of 20 L/min, TNI increases nasal pressure by approximately 2 cmH$_2$O and increases inspiratory airflow by approximately 100 mL/s. This increase in pharyngeal pressure and airflow can explain the improvement of snoring and hypopneas as follows: The peak inspiratory airflow for hypopneas and
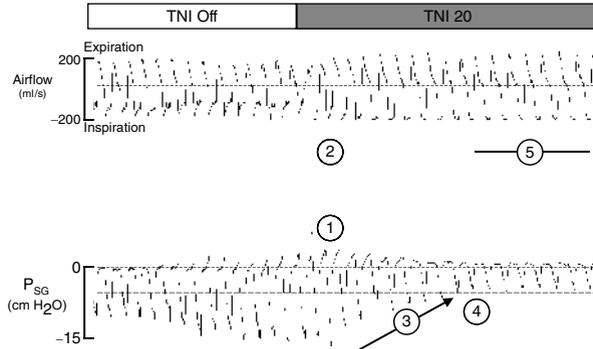
Fig. 20.2 Mechanism of action. Airflow and supraglottic pressure are shown during the transition from flow-limited breathing with TNI off to non-flow-limited breathing with TNI 20 L/min. P_{SG} supraglottic catheter pressure (cmH$_2$O). (*1*) Increase in end-expiratory P_{SG}, (*2*) increase in mean inspiratory airflow, (*3*) decrease in supraglottic pressure swings on a breath-by-breath basis, (*4*) P_{SG} threshold for inspiratory flow limitation, (*5*) a round, non-flow-limited inspiratory pattern

for flow-limited breaths averages approximately 150–200 mL/s. The additional flow from TNI will increase the inspiratory airflow to 250–300 mL/s, a level previously associated with stabilization of breathing patterns (see Fig. 20.2). However, unexpectedly, some individuals also showed improvements in the event rate of obstructive apneas. The mechanisms for these responses are not fully understood. Additional nonquantifiable factors may have contributed to this response. First, small increases in pharyngeal pressure may have increased lung volume, which may improve both oxygen stores and upper airway patency. Second, as ventilation improves during sleep, enhanced sleep continuity (decreased arousal frequency) may further stabilize breathing and reduce the event rate of apneas and hypopneas. Finally, additional benefits may have accrued from insufflating air directly into the nose, producing concomitant reductions in dead space ventilation.

20.2.2
Effect on Ventilation

New evidence exists that TNI may improve ventilation even in the absence of upper airway obstruction. In one study in patients with a mild degree of COPD (GOLD I–II : FEV$_1$/FVC = 70% predicted and FEV$_1$ < 80% and > 50% predicted), the use of TNI during sleep was associated with a reduction in arterial CO$_2$ compared to room air [3]. In another study [4], TNI was used during wakefulness in addition to supplemental oxygen since patients had severe COPD (GOLD IV - FEV$_1$/FVC < 70% predicted and FEV$_1$ < 30% predicted) requiring oxygen treatment. In these patients, TNI and supplemental oxygen also reduced the respiratory rate, which was associated with a reduction in arterial CO$_2$ from 58 to 49 mmHg, indicating that alveolar ventilation had improved, and ventilation had become more effective with TNI. Additional data for ventilator support independent of inspiratory flow
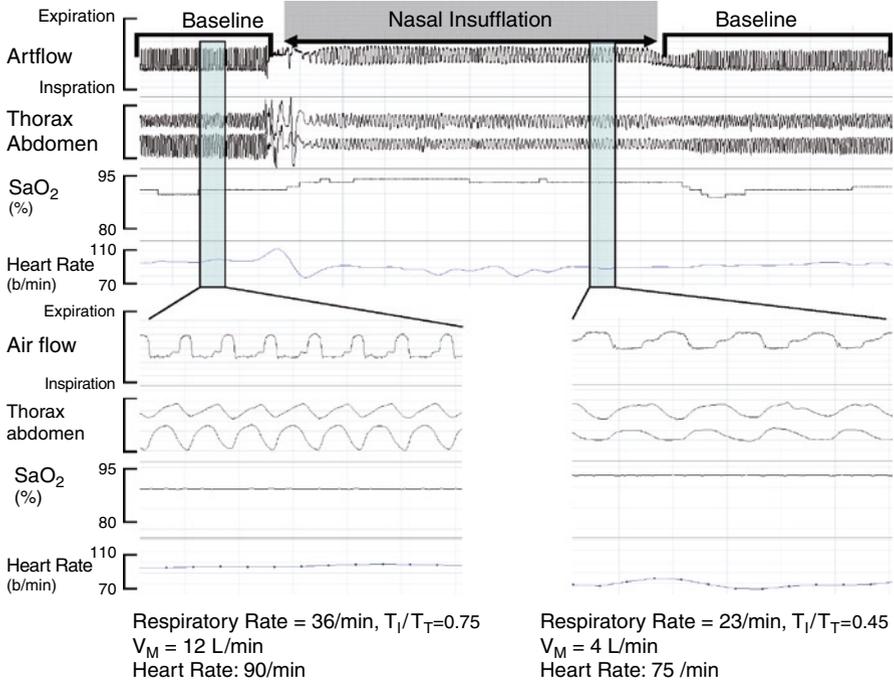
Fig. 20.3 Polysomnographic recording showing acute effects of nasal insufflations (TNI 20 L/min) on ventilation and breathing pattern in a child with obesity hypoventilation syndrome and inspiratory flow limitation during non-rapid-eye-movement (NREM) sleep. At baseline, a rapid shallow breathing pattern was present that was abolished with nasal insufflations. Note that inspiratory flow limitation was not abolished, indicating that improvements in ventilation are independent of inspiratory flow limitation

limitation were given by the data in children [5]. McGinley et al. demonstrated that, in patients with rapid, shallow breathing, TNI markedly reduced the respiratory rate and inspiratory duty cycle, even if inspiratory flow limitation was not fully restored (see Fig. 20.3). The precise mechanism for improving gas exchange and efficacy of ventilation is not fully understood. It is possible that TNI may have reduced CO_2 production by lowering the work of breathing, or it has reduced the dead space ventilation by washing out the anatomic dead space of the nasal cavity. Alternatively, TNI may have reduced intrapulmonary dead space by opening up atelectasis through the slight increase in positive end-expiratory pressure (PEEP). Regardless of the mechanism, the data in children and in individuals with COPD indicated that nasal insufflations reduced the load of breathing, particularly in patients with a rapid, shallow breathing pattern. Nevertheless, clinical data are warranted to determine the effectiveness of TNI in these patients.

20.3
Predictors for Therapeutic Responses to TNI in Adults with OSA

Polysomnographic responses to TNI were examined in a larger clinical sample of patients [5]. The primary purpose was to identify polysomnographic characteristics in a baseline sleep study that may be used to predict TNI treatment responses. In this study, we confirmed that TNI reduced the overall sleep-disordered breathing event rate below a clinically acceptable threshold in 30–50% of patients referred to a sleep laboratory for CPAP therapy. Patients with a wide range of sleep-disordered breathing event rate (ranging from 10 to 80 events/h) had similar response rates, indicating that treatment responses to TNI were independent of the sleep apnea disease severity. Moreover, the response rate was markedly increased in patients with predominantly hypopneas and patients with mild upper airway obstruction. In addition, the presence of more than 10% central apneas predicted poor response. Thus, TNI treatment responses depended on the severity but not the frequency of upper airway obstruction (see Fig. 20.4). The main conclusion from this study was that TNI may offer an alternative to the standard CPAP therapy in patients with predominantly obstructive hypopneas. In patients with apneas, TNI may also increase airflow, but that increase may be insufficient. As a result, in apneic patients TNI may shift apneas to hypopneas, leaving the overall event rate unchanged. Since the efficacy of TNI can be easily assessed within a single night, initiation of this treatment should be monitored to ensure treatment efficacy before recommending home treatment. Nevertheless, it can be predicted that treatment efficacy is higher in patients whose sleep-disordered breathing events consist of at least 90% hypopnea and RERAs. It is of note that these events are predominantly seen in children, women, and patients with comorbid conditions. Therefore, these populations may be ideal for this form of therapy. To date, the effect of TNI was determined in children.

20.4
Therapeutic Responses in Children with OSA

Children with upper airway obstruction during sleep differ markedly in regard to the distribution of obstructive events. They have obstructive apneas predominantly during rapid-eye-movement (REM) compared to non-rapid-eye-movement (NREM) sleep. In contrast to adults, children commonly exhibit periods of prolonged stable upper airway obstruction or hypopneas during NREM sleep. Thus, the application of low levels of pharyngeal pressure may have greater therapeutic effects in children. TNI responses were compared to CPAP and baseline in 12 morbidly obese, otherwise healthy, children with sleep apnea, for whom adherence rates to CPAP were so low that most children in this study were ineffectively treated [2]. TNI treated sleep apnea across a wide spectrum of disease severity in all but two children (see Fig. 20.5). Second, in the majority of children, the reduction in the sleep-disordered breathing event rate with TNI was comparable to CPAP. The authors concluded that TNI may offer an alternative to CPAP in some children for whom standard treatment approaches are not successful. The greater therapeutic response rate in children may be due to the milder degree of upper airway obstruction in children. Alternatively,
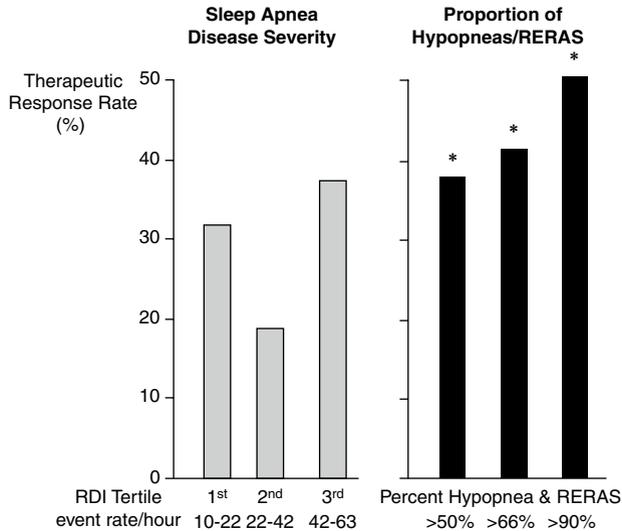
Fig. 20.4 Polysomnographic characteristics of the baseline sleep study that predict therapeutic response rates to TNI. A therapeutic response was defined by a fall in RDI below 10 events/h associated with a 50% reduction in the RDI from baseline sleep study. *Denotes a statistically significant difference ($P < 0.05$) to the expected night-to-night variability in sleep apnea severity of 13%: *Left panel*: sleep apnea disease severity was categorized into mild, moderate, and severe by calculating tertiles of the RDI at the baseline sleep study. *Right panel*: for degree of hypopneas, the proportions of obstructive hypopneas to all obstructive events (apneas, hypopneas, and RERAs) for each patient during NREM sleep were calculated, and therapeutic response rates to TNI are given for subgroups of patients who had more than 50% ($n = 34$), more than 2/3 ($n = 23$), and more than 90% ($n = 11$) hypopneas. Note that subgroups of patients overlap (e.g., those with >90% are also represented in those with >50% and >66%)

TNI might have increased pharyngeal pressure more in children than adults due to the relatively larger size of the nasal cannula compared to the size of the nares.

The greater therapeutic response rate in children may be due to the milder degree of upper airway obstruction in children. Alternatively, TNI might have increased pharyngeal pressure more in children than adults due to the relatively larger size of the nasal cannula compared to the size of the nares. Perhaps a slight increase in pharyngeal pressure might have increased lung volumes to a greater degree in children as a result of higher chest wall and lung compliance, particularly during REM sleep when the chest wall musculature is hypotonic. Increases in lung volume might have improved both oxygen stores and upper airway patency. Finally, it is also possible that children's reflex responses to insufflation of air are greater than in adults, leading to improvements in upper airway patency. The authors [2] concluded that, for the majority of children, the response to TNI was comparable to CPAP, that TNI might ultimately be a more effective treatment option than CPAP, and that TNI may have a particular role in younger children, for whom the use of CPAP carries concern for the potential of compression of bony facial structures. TNI is an open system that is not dependent on a tightly sealed nasal mask, obviating concerns of facial compression.
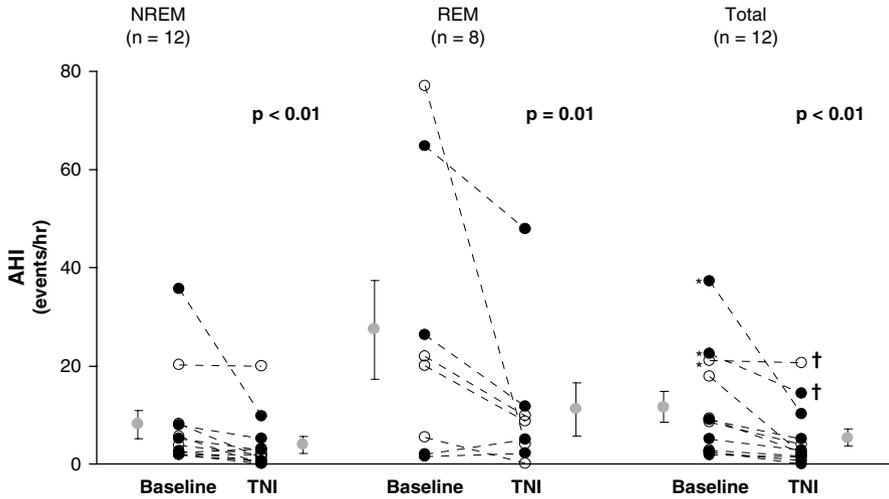
Fig. 20.5 The apnea–hypopnea indices (AHIs) are displayed for the baseline compared to TNI treatment night during non-rapid eye movement (NREM; *left panel*), rapid eye movement (REM; *middle panel*), and for the entire night (*right panel*). Data presented are mean ± standard error of the mean (SEM). * Participants with residual sleep apnea on TNI, † participants with suboptimal AHI responses on TNI compared to continuous positive airway pressure (CPAP), ○ children without adenotonsillectomy

20.5
Summary

An open nasal cannula system delivering warm and humidified air at a flow rate of 20 L/min (TNI) can effectively treat sleep-disordered breathing in a subset of adult patients and in a majority of children. TNI treatment responses depended on the severity (hypopneas rather than apneas) but not the frequency (event rate/h) of upper airway obstruction. TNI may also play a role in protecting patients with respiratory failure as it can reduce arterial CO_2 and alleviate rapid, shallow breathing, thereby increasing efficacy of breathing. Thus, TNI might be an alternative for non-invasive ventilation for patients at risk for developing respiratory failure.

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Cardiopulmonary Interventions to Prolong Survival in Patients with Duchenne Muscular Dystrophy

21

Yuka Ishikawa

21.1 Introduction

Duchenne muscular dystrophy (DMD) is caused by mutations in the dystrophin gene on the X chromosome at Xp21. DMD affects 1 of every 3,500 live male births. Progression of muscular weakness leads to loss of ambulation by 12 years of age, and the development of scoliosis is marked by the early teenage years.

Prior to the availability of effective ventilatory support and cardiac management, in DMD patients in their late teens or early 20s the leading cause of death was respiratory insufficiency, and those in their early to middle teens died from cardiac complications such as dilated cardiomyopathy and conduction abnormality.

Current therapies, including noninvasive ventilation (NIV) and cardioprotection have improved survival and quality of life for patients with DMD.

21.2 Respiratory Management

21.2.1 NIV for Chronic Respiratory Failure

Pulmonary function is evaluated annually or when signs first appear (Table 21.1).

When the vital capacity (VC) decreases, any symptom of chronic alveolar hypoventilation is manifested, or hypoxemia or hypercapnia is noted, use of high-span bilevel positive airway pressure (PAP) or a volume-cycled ventilator (with control mode) at night is considered.

For patients who develop symptomatic hypercapnia and hypoxemia when awake, daytime NIV is gradually increased. When the patient uses a motorized wheelchair, the ventilator is mounted on the wheelchair with a flexible tube, and a nasal plug or mouthpiece is fixed. Some patients can have a meal while using NIV (desirably using control mode with a volume-cycled ventilator or the positive end-expiratory pressure [PEEP] set at zero).

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Table 21.1 Cardiopulmonary evaluation in patients with DMD

1. General examination
Height (arm span)
Weight
Scoliosis
Chest deformity
Abdominal distention Symptoms of chronic alveolar hypoventilation or cardiac dysfunction Respiratory sound and heart sound
2. Pulmonary function
Respiratory rate
Abnormal breathing pattern: Row-a-boat phenomenon, glossopharyngeal breathing, etc.
Vital capacity (VC)
Saturation of pulse-oximetry oxygen (SpO_2): daytime and nighttime
Transcutaneous CO_2 gas tension ($PtcCO_2$)
or end-tidal CO_2 gas tension ($PetCO_2$): daytime and nighttime
or $PaCO_2$
Cough peak flow (CPF): unassisted CPF
CPF assisted by air stacking to deep lung volumes (CPFair)
CPF assisted by abdominal thrusts (CPFthrust)
CPF assisted by both air stacking and abdominal thrust (aCPF)
Maximum insufflation capacity (MIC) when %VC is <50%
3. Cardiac function
Heart rate
Blood pressure
Chest X-ray: CTR
ECG, Holter ECG
Brain natriuretic peptide (BNP)
Echocardiography

21.2.2
Airway Clearance

Children aged 12 years or older are taught how to perform manually assisted coughing when the cough peak flow (CPF) decreases to less than 270 L/min. Children under 12 years are taught how to perform manually assisted coughing if an episode of difficult airway clearance occurs. Coughing is performed after air stacking with assisted procedures

such as the use of a resuscitator bag, by inhaling several tidal volumes delivered by a volume-cycled ventilator under NIV, by performing glossopharyngeal breathing, or by raising the inspiratory positive airway pressure (IPAP) by 2–4 cmH$_2$O [1].

Once maximum assisted CPF becomes less than 270 L/min or ineffective for airway clearance, patients with DMD require mechanically assisted coughing (MAC) to prevent pneumonia and acute respiratory failure. MAC has been defined as the use of mechanical insufflation–exsufflation (CoughAssist, Phillips, Netherlands). It is used in conjunction with exsufflation-timed abdominal thrusts to further augment cough flows as part of MAC.

21.2.3
Management of Chest Colds

Once decreased VC or CPF is recognized in children with DMD, those patients and families should learn how to maintain an SpO$_2$ (saturation of pulse-oximetry oxygen) greater than 94% using assisted coughing and prolonged hours of NIV if the child has a chest cold.

NIV in combination with assisted coughing has been reported to reduce consultations with a general practitioner for respiratory tract infections (RTIs), the number of antibiotic treatments for RTIs, and the number of hospital admissions for RTIs [2].

21.2.4
Long-Term Continuous NIV

Many patients with DMD using continuous NIV for decades without tracheostomy have been reported. NIV has always been effective for continuous ventilatory support as long as the ventilator settings or interfaces are appropriate, even when patients are too mentally impaired to cooperate with it or bulbar-innervated musculature is too impaired to protect the airway from continuous saliva aspiration that results in oxyhemoglobin desaturation.

21.3
Cardioprotection

21.3.1
Cardiac Evaluation

By adulthood, almost all patients with DMD have cardiac involvement, including cardio-myopathy and arrhythmia. For patients with DMD, cardiac evaluation by echocardiogram, serum brain natriuretic peptide (BNP), and electrocardiogram (ECG) should be obtained once or twice a year (Table 21.1).

Due to impaired motor function, patients with DMD are less likely to experience inspiratory loading and thus inspiratory difficulty. However, when a load slightly higher than usual is imposed, symptoms are suddenly manifested. Cardiac symptoms include dyspnea, cyanosis, paleness, cough, fatigue, palpitations, sweating, chest and abdominal discomfort or pain, nausea, loss of appetite, headache, frequent nocturnal arousal, frequent

changes in need for turning at night, arthralgias, chills, decreased urinary output, irritability, difficulty in concentration, and edema (weight gain).

21.3.2
Combined Drugs and NIV

Preventive management of cardiac involvement with ACEi and beta-blockade in DMD is effective when standard respiratory management with NIV and assisted coughing are also applied. Fifty-two DMD patients received treatment for heart failure due to cardiomyopathy or asymptomatic left ventricular (LV) dysfunction with ACEi and beta-blockade during the period from 1992 to 2005 [3]. The 5- and 7-year survival rates of all patients were 93% and 84%, respectively. In the treatment group ($n = 12$, symptomatic heart failure due to cardiomyopathy), 5- and 7-year survival rates were 81% and 71%, respectively. The prevention group ($n = 40$, asymptomatic LV dysfunction, left ventricular ejection fraction [LVEF] < 45%), 5- and 7-year survival rates were 97% and 84%, respectively, and the 10-year survival rate was 72%. The prevention group showed a better survival rate compared with the treatment group.

The consequences of DMD cardiomyopathy are worsened by sleep-disordered breathing with hypoxemia and hypercapnia. In a patient with cardiac failure, reduced pharyngeal muscle tone during periodic breathing and increased pharyngeal edema associated with congestion can contribute to the obstructive apneas and hypopnea. Therefore, NIV can have direct cardioprotective effects.

21.4
Anesthesia and Sedation

The risks related to anesthesia and sedation in patients with DMD include potentially fatal reactions to inhaled anesthetics and certain muscle relaxants, upper airway obstruction, hypoventilation, atelectasis, congestive heart failure, cardiac dysrhythmias, respiratory failure, and difficulty weaning from mechanical ventilation. Therefore, expert recommendations are necessary regarding respiratory, cardiac, gastrointestinal (GI), and anesthetic management of patients with DMD who undergo general anesthesia or procedural sedation.

According to a statement by the American College of Chest Physicians, preoperative pulmonary assessment should be performed (Table 21.1). If the forced vital capacity (FVC) is below 30%, training in the use of NIV is recommended [4]. If the CPF is less than 270 L/min, training in assisted coughing and emphasis on the use of MAC is applied.

Optimization of the preoperative nutritional status may involve the use of NIV because patients with untreated respiratory failure may become malnourished due to the increased work of breathing or they may be unable to eat due to dyspnea.

Postoperatively, the SpO_2 should be monitored continuously until the cardiopulmonary status becomes stable. Whenever possible, assess carbon dioxide levels (e.g., $PtcCO_2$ [transcutaneous CO_2 gas tension]). Assess carbon dioxide levels if hypoxemia is caused by hypoventilation, atelectasis, or airway secretions and treat immediately with NIV and assisted coughing. Supplemental oxygen therapy should be used with caution because oxygen therapy can correct hypoxemia without treating the underlying cause (e.g., hypoventilation, atelectasis, or airway secretions), and oxygen therapy may impair the central respiratory drive.

In addition, patients with DMD may have gastroparesis, intestinal dysmotility, and constipation, all of which can be exacerbated postoperatively by pain medications. GI dysfunction can impair breathing if abdominal distention and increased intra-abdominal pressure occur, hampering diaphragmatic excursion. Gut dysmotility also increases the likelihood of gastric distention when NIV is applied. Bowel regimens should be employed to avoid and treat constipation, and selected patients may benefit from pharmacologic therapy with GI smooth muscle prokinetic agents. Appropriate postural management, feeding aids, gastrostomy insertion, or parenteral nutrition should be indicated.

21.5
The Parent as the "Lifeline" for a Child's Life Using NIV

Individuals with muscular dystrophy had average medical expenditures 10–20 times greater than individuals without muscular dystrophy (in the United States in 2004). But, most families felt that they had made the right choice in using NIV.

According to one study [5], family life changes significantly with the decision to place a child with DMD on NIV. Despite becoming expert caregivers, the parents experienced a recurrent sense of loss and uncertainty. Those who perceived insufficient support felt the weight of responsibility as sole care providers for their child. Since the parents' experience was as the "lifeline" for their child's life and quality of life, more support by health care professionals and the community is needed.

Key Recommendations

> As standard respiratory care for individuals with DMD leads to greater longevity, both recognition and preventive treatment of cardiac involvement, including cardiomyopathy and arrhythmia, become more important. The trend toward improving survival times of patients with DMD could be related to the salutary effect of NIV on cardioprotection in addition to the increasing use of ACEi and beta-blockers [3].

> For children with DMD with decreased VC or CPF, NIV in combination with assisted coughing reduces the frequency and severity of RTIs [2].

> Air stacking was significantly more effective than abdominal thrust in increasing CPF, but the combination was the most effective [1].

> Although the statement by the American College of Chest Physicians [4] includes advice regarding respiratory and cardiac management of patients with DMD undergoing anesthesia or sedation, specific studies needed to develop better guidelines that include the following: studies of the specific settings that optimize the efficacy of noninvasive positive pressure ventilation (NPPV) and MAC and studies that clarify the role of alternative mucus mobilization techniques.

> A multidisciplinary team that works for optimal management of DMD using NIV-specific multisystem complications is essential, and collaboration in this specific clinical network is recommended to support families in making their choice to use life-sustaining technologies [5].

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Noninvasive Ventilation Pressure Adjustments in Patients with Amyotrophic Lateral Sclerosis

22

Kirsten L. Gruis

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder of motor neurons. Patients with ALS develop diffuse skeletal muscle weakness in addition to respiratory muscle weakness, and respiratory failure is the most common cause of death. Tolerance to intermittent use of noninvasive ventilation (NIV) for 4 h or more a day is associated with improved survival and quality of life in patients with ALS [1, 5].

NIV decreases the work of breathing by providing bilevel positive airway pressure: inspiratory positive airway pressure (IPAP) and, to a lesser extent, expiratory positive airway pressure (EPAP). Typically, the positive airway pressure is administered noninvasively via a nasal-type mask interface. The amount of support provided to weak inspiratory muscles is the difference between IPAP and EPAP, termed *pressure support*.

Although NIV provides support for weakened respiratory muscles, it does not completely replace respiratory muscle function as can be done with airway cannulation and mechanical ventilation. In the setting of fully assisted mechanical ventilation, the medical provider can titrate the ventilator settings to correct gas exchange impairment. However, in a disorder with progressive respiratory muscle weakness treated with intermittent supportive NIV, it is uncertain how much pressure support to provide and when to alter the pressure support settings.

Initial studies of NIV that demonstrated a survival benefit in ALS used NIV titrated to patient comfort but did not provide information regarding pressure settings [2]. A survey of ALS clinic medical directors in the United States showed that the most frequently used protocol was to initiate NIV with 8 cmH_2O IPAP and 4 cmH_2O EPAP and to increase the IPAP by 2–3 cmH_2O as needed to improve symptoms [3]. In contrast, other experts have proposed that all ALS patients use "high-span" NIV with a pressure support of 10 cmH_2O or greater with a goal IPAP of 16–18 cmH_2O.

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While providing high levels (>10 cmH$_2$O) of pressure support for all ALS patients may appear prudent in a progressive disorder, exposing patients to high airway pressures may result in significant side effects that decrease NIV tolerance and subsequent benefits of therapy. In addition, by the time NIV is started ALS patients have learned to compensate for respiratory muscle weakness and small tidal volumes with increased breathing frequency. Therefore, titrating all ALS patients to high NIV pressures to correct reduced tidal volumes and increased breathing frequency may result in patient ventilator asynchrony and intolerance to NIV therapy.

Importantly, the lack of guidance in the medical literature regarding NIV pressure settings and adjustments for ALS patients may contribute to medical providers' unwillingness to prescribe NIV therapy. Therefore, we performed a retrospective, single-center, chart review assessment of NIV pressure settings used for symptomatic treatment of ALS patients. We assessed NIV pressure settings over time and compared survival between those ALS patients tolerant, defined by more than 4 h of use per night, and intolerant to NIV [4].

The ALS patients in our study were started on NIV, and pressures were titrated in a similar fashion to that described [3]. Therefore, the NIV pressures used were the minimum required to improve breathing comfort. We compared 18 patients who were tolerant to NIV therapy and 19 patients who were intolerant. The majority of tolerant patients (67%) used pressure support (IPAP–EPAP) of less than 10 cmH$_2$O until their deaths, while the remaining third of patients required pressure support greater than 10 cmH$_2$O to improve symptoms. The maximum pressure needed was 19/5 cmH$_2$O, while 4 of 18 patients (22%) found the original NIV settings of 8/3 cmH$_2$O sufficient to improve respiratory symptoms [4]. These findings are similar to a prospective, randomized study of NIV therapy in ALS patients that demonstrated an average pressure support of only 11 cmH$_2$O [5]. A wide range of NIV pressures (8.2–22.4 cmH$_2$O) has been associated with improved ALS patient ventilation as measured by gas exchange [6]. Taken together, these findings demonstrate that not all ALS patients need a pressure support greater than 10 cmH$_2$O to improve ventilation with NIV therapy.

In our study, most NIV pressure changes occurred within the first year of NIV therapy, and only 2 of 18 patients (11%) required more than two changes in NIV pressure settings [4]. This is contrary to the belief that ALS patients will need more frequent NIV pressure increases as the disease progresses. Instead, what likely occurs with progressive respiratory muscle weakness is increased hours of usage of NIV therapy rather than marked increases in NIV pressure support. A significant increase in NIV usage duration has been described in a prospective study of ALS patients, with NIV usage hours increasing 98–277%, with some patients eventually using NIV continuously [5].

Patients who tolerated NIV had a nearly 1-year increase in survival compared with those who were not tolerant of NIV. The survival association remained when adjusting for age and symptom onset location (bulbar vs. limb) – clinical characteristics associated with poor ALS survival – with a hazard ratio of 0.23 (95% confidence interval 0.10, 0.54). These findings are similar to the benefit found in a prospective, randomized clinical trial that demonstrated a median survival benefit of nearly 7 months in those patients treated with NIV therapy compared to those who received standard medical care without NIV [5]. Thus, our data suggest that even relatively low NIV pressure support is associated with an improvement in survival.

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Noninvasive Positive Pressure Ventilation in Amyotrophic Lateral Sclerosis

23

Daniele Lo Coco, Santino Marchese, and Albino Lo Coco

23.1
Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease of unknown origin that affects approximately 1.5 individuals per 100,000 every year; usually, these individuals are between 55 and 75 years of age [1]. ALS causes progressive weakness of voluntary muscle groups, including respiratory ones, and respiratory failure or pneumonia related to respiratory muscle weakness is the most frequent cause of death.

However, only a few patients present with respiratory muscle dysfunction, whereas the majority of them maintain an almost normal respiratory function for long periods of time. Patients thus need to be regularly and progressively evaluated to identify early signs of respiratory muscle weakness so that adequate treatment can be implemented. Furthermore, it is good practice to discuss respiratory issues well in advance with the patients and their family to avoid emergency decisions or unwanted treatments in case of a crisis.

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23.2
Respiratory Function Evaluation

Usually, when patients with ALS seek medical attention, pulmonary evaluation is within the normal range, and patients do not refer respiratory complaints. However, during the progression of the disease all patients eventually complain of dyspnea with exertion, orthopnea, and poor sleep quality with frequent awakenings, nightmares, early morning headaches, or excessive daytime sleepiness [2,3]. A clinical examination at this point might show respiratory paradox, rapid shallow breathing, or accessory muscle contraction. Nevertheless, the observation that many patients may remain asymptomatic even when there is a marked reduction of vital capacity limits the reliability of these signs and symptoms.

In addition to respiratory symptoms and signs, many exams are used in the evaluation of pulmonary function in ALS patients (Table 23.1) [2,3]. The most widely available measure for detecting respiratory decline is forced vital capacity (FVC) when sitting or supine. FVC is correlated with survival and usually presents an almost linear decrease during the course of the disease, but with a marked variability from patient to patient (within 2–4% of predicted value per month).

Well-known limitations of FVC are the low sensitivity in patients with bulbar involvement, because of reduced buccal strength, or cognitive involvement, and the relative insensitivity to detect mild or moderate diaphragmatic dysfunction.

Maximal inspiratory and expiratory pressure (MIP and MEP, respectively) are other sensitive measurements, but in many centers these are not routinely executed because many patients are unable to perform the test with the progression of disease.

Arterial blood gas analysis may also be of help in the evaluation of patients with ALS, especially in those with severe bulbar involvement since it could reveal resting hypercapnia ($PaCO_2 > 6.5$ kPa) or hypoxemia ($PaO_2 < 90$ mmHg). However, these are usually very late signs of respiratory failure in ALS.

Increasing attention has been drawn to measurement of sniff nasal inspiratory pressure (SNIP), which is regarded as a good measure of diaphragmatic strength. SNIP is probably more accurate than FVC, although even SNIP may underestimate respiratory function in patients with bulbar involvement because of upper airway collapse. However, a sniff nasal pressure test below 40% of predicted value is a significant predictor of nocturnal hypoxemia and mortality.

Finally, nocturnal hypoventilation and sleep-disordered breathing are also common in ALS with the progression of the disease and can occur even when respiratory muscle function is only mildly affected and daytime gas exchange remains normal. Then, since

Table 23.1 Objective measurements of pulmonary function of patients with amyotrophic lateral sclerosis (ALS) in addition to respiratory symptoms and signs

Forced vital capacity (FVC; both upright and supine)
Maximal inspiratory and expiratory pressure (MIP and MEP, respectively)
Sniff nasal inspiratory pressure (SINP)
Nocturnal oximetry
Arterial blood gas analysis

nocturnal oximetry is easy to perform and can be executed in the home, it has become frequently used in clinical practice for the evaluation of respiratory involvement in ALS patients. Polysomnography is not routinely recommended.

23.3
Noninvasive Positive Pressure Ventilation

In the last 10 years, there has been a revolution in respiratory assistance and ventilatory support in ALS that has had a significant impact on the natural history of the disorder. The application of ventilatory assistance, most frequently noninvasively, has been shown to alleviate respiratory symptoms, to extend survival considerably, and to improve quality of life and cognitive functions in most patients [1–3]. At present, noninvasive positive pressure ventilation (NIPPV), usually via nasal mask with bilevel positive airway pressure (BiPAP) machines, is the most effective treatment available for patients with ALS [4]. A proposed respiratory management algorithm for patients with ALS is shown in Fig. 23.1.

All patients with ALS can benefit from NIPPV therapy, and a trial with this appliance should never be discouraged, but marked bulbar involvement could be associated with reduced tolerance and maybe survival. Indeed, the increased risk of aspiration in patients with bulbar onset and problems because of difficulties in clearing secretions or obstructions, such as those related to abnormal function of the vocal cords, should be considered.
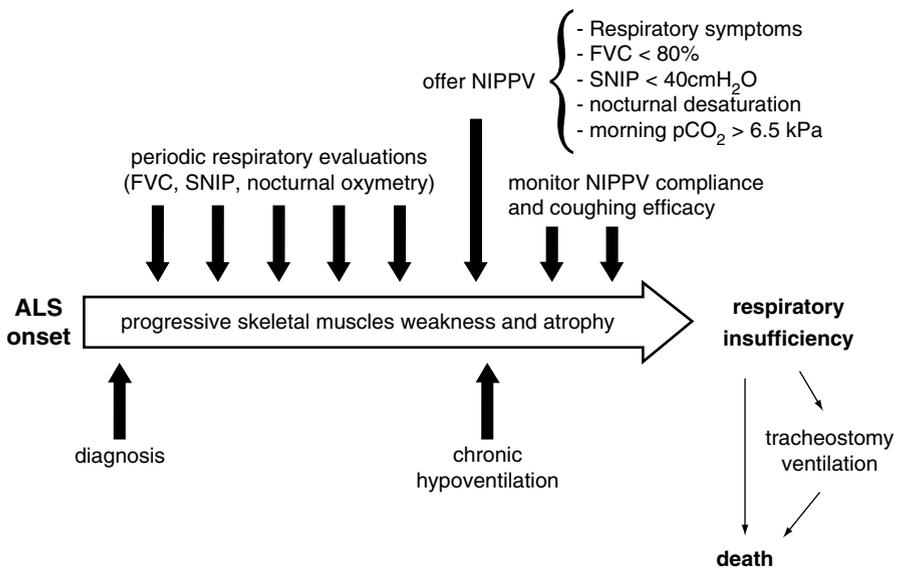
Fig. 23.1 Schematic representation of the progressive respiratory dysfunction in amyotrophic lateral sclerosis (ALS) over time and recommended respiratory management. *FVC* forced vital capacity, *NIPPV* noninvasive positive pressure ventilation, *SNIP* sniff nasal inspiratory pressure

In our experience, NIPPV can be well tolerated by both patients and caregivers, even in patients with bulbar involvement [5]. Special importance should be given to adaptation and compliance during the first few weeks of NIPPV use since this could be a crucial step in determining the efficacy of the treatment.

Factors predicting survival following NIPPV include advanced age, airway mucus accumulation, and lower body mass index.

The mechanisms by which NIPPV therapy could affect survival in ALS are not perfectly known, and it has been suggested that most of its effects could be related to a slowing of the rate of respiratory impairment, thus modifying the natural course of the disease. Among the hypotheses that have been generated to explain the sustained improvement in respiratory function and gradual resolution of symptoms associated with NIPPV, it has been postulated that NIPPV rests chronically fatigued respiratory muscles, thereby improving daytime respiratory muscle function. Another hypothesis suggests that NIPPV improves respiratory system compliance by reversing microatelectasis, thus diminishing daytime work of breathing. Finally, a third theory proposes that NIPPV improves central respiratory drive and the arousal mechanism (chronically depressed by habitual exposure to hypoventilation), leading to better ventilation during both waking and sleeping hours. All these theories are not mutually exclusive, with each possibly contributing to the ameliorations observed in patients undergoing NIPPV.

Notwithstanding the effects on respiratory symptoms, quality of life, and survival, many studies suggested that the employment of NIPPV in ALS is poor worldwide, with a need for more education of clinicians and patients regarding the benefits of NIPPV earlier in the course of the disease [6]. The reasons for such low uptake of NIPPV are multifactorial but are influenced by differences in the experience of physicians, its availability and cost, uncertainty of the benefits and timing for starting ventilation, and concerns that ventilatory support might prolong suffering, render home care less feasible, and lead to dependency or ventilator entrapment [1].

Moreover, there is still debate about the optimal timing to introduce ventilation in these patients and whether early NIPPV initiation could actually lead to increased survival rates.

At present, worldwide accepted guidelines propose NIPPV initiation in the presence of respiratory symptoms or evidence of respiratory muscle weakness (FVC $\leq$ 80% of predicted or SNIP $\leq$ 40 cmH$_2$O), evidence of significant nocturnal desaturation on overnight oximetry (<90% for >5% of the time asleep), or a morning arterial Paco_2 above 6.5 kPa [1].

NIPPV is usually initially used for intermittent nocturnal support to alleviate symptoms of nocturnal hypoventilation, although as respiratory function worsens, patients tend to require increasing daytime support and eventually continuous support. However, the disorder will eventually progress to the stage at which NIPPV will not be able to compensate for respiratory impairment, and in these circumstances only invasive ventilation by tracheostomy is able to prolong survival [1–3].

When placed on invasive ventilation, patients are supported from a respiratory point of view; however, the loss of motor neurons goes on progressively, leading to complete paralysis and muscular atrophy. Some patients may eventually reach a "locked-in"

state in which they cannot communicate at all because there is also total paralysis of the extraocular muscles. Despite this, when connected to tracheostomy tubes patients may survive for many years, with respiratory tract infections the most frequent cause of death.

Notwithstanding its effect on survival, only a minority of ALS patients receive invasive mechanical ventilation, at least in the Western countries. On the contrary, in Japan the frequency of invasive ventilation is considerably higher.

Furthermore, many patients undergo tracheostomy in emergency without advance planning because of a respiratory crisis, whereas the number of patients who electively choose this treatment is low. Socioeconomic reasons may be one of the possible explanations for the low prevalence of invasive ventilation in ALS since the treatment is costly. Moreover, there is a need for 24-h caregiving, which could be perceived as extremely burdensome for the whole family. The attitudes of the treating physician have also great influence, and there is concern that tracheostomy ventilation will prolong life beyond the point that the patient can communicate or interact with others or about the procedure to withdraw care.

Despite these many doubts and concerns, the majority of patients who underwent invasive ventilation were positive about their choice, reported a satisfying quality of life, and indicated that they would repeat the choice again in the same situation. Caregivers were more frequently burdened and distressed by this intervention, and they frequently witnessed a marked reduction of social life activities [1–3].

It is important to underline that unplanned and unwanted tracheotomy could be avoided by early discussion of the options for respiratory support and through advance directives. Indeed, once intubated, patients are rarely free from the ventilator. Advance directives should also be reviewed periodically during the course of the disease. On the contrary, emergency intubation and tracheostomy should be avoided [1–3].

23.4
Supportive Care

Apart from sustaining respiration with mechanical devices, special consideration has to be given to prevention of aspiration and development of pneumonia [1–3]. In this regard, it is of fundamental importance to reduce the amount of salivary secretions through the use of several medications (such as amitriptyline and botulinum toxin injections), to devote adequate time in teaching proper swallowing technique, and to maintain hydration. It is also useful to provide a portable mechanical home suction device. In addition, when dysphagia worsens, placement of a percutaneous endoscopic gastrostomy tube should be the preferred option, especially when the respiratory function is not too much compromised.

Another aspect of the patient's care that needs special attention is physiotherapy, which is a useful aid for the management of respiratory secretions [1–3]. Indeed, during the course of the disease, progressive inspiratory and expiratory muscle weakness and bulbar innervated muscle dysfunction result in the cough reflex becoming ineffective, causing

difficulties in the clearance of mucus. This is largely dependent on the magnitude of peak cough flows (PCFs), and a PCF below 2.7 L/s indicates an ineffective cough. However, since PCF decreases during respiratory tract infections, when the pressure generated by expiratory muscles is reduced, it has been suggested that once a patient's PCF is below 4.5 L/s, particularly in the presence of bulbar dysfunction, there is a risk for pulmonary complications, and that threshold could be an appropriate time to implement assisted cough techniques.

Methods to treat of respiratory secretions include breathing exercises, postural drainage, exercise regimens, and the use of assisted cough techniques. However, it has to be pointed out that patients with limited mobility and muscle weakness have difficulty with postural drainage and generally do not benefit from chest physical therapy. Moreover, intensive cycles of physiotherapy may be exhausting for many patients, particularly those with advanced disease, and may cause arterial desaturation.

Among noninvasive expiratory aids, manually assisted coughing techniques, such as anterior chest compression and abdominal thrust, have been effective in facilitating the elimination of airway secretions in patients with neuromuscular diseases, even if these maneuvers are labor intensive and often difficult for nonprofessional caregivers.

The mechanical in-exsufflator (MI-E) is a device that assists patients clear bronchial secretions. It consists of a two-stage axial compressor that provides positive pressure (which causes a deep insufflation), thereby generating a forced expiration in which high expiratory flow rates and a high expiratory pressure gradient are generated between the mouth and the alveoli. It is usually applied via a face mask. The use of MI-E is simple and safe enough for application by nonprofessional caregivers and is considered a complement to manually assisted coughing in the prevention of pulmonary morbidity in patients with neuromuscular diseases. Moreover, the use of MI-E prolongs noninvasive respiratory aids and delays the need for tracheostomy in patients with ALS. However, this device seems to be ineffective in patients with severe bulbar dysfunction, perhaps because the application of the exsufflation cycle of MI-E for those patients with weakness of the genioglossus muscle might produce a dynamic, total, or partial collapse of the upper airway.

It can be useful to remember that, for patients whose vital capacities are less than normal, manually assisted coughing is not optimally effective unless preceded by maximal lung insufflation, and MI-E is not optimal unless an abdominal thrust is applied during the exsufflation. Abdominal thrusts and MI-E are not mutually exclusive, and they should be combined for effective prevention of lower respiratory tract infection and respiratory insufficiency. Failure to correctly administer physical medicine aids continues to make respiratory failure inevitable for the great majority of people with neuromuscular diseases.

Finally, high-frequency chest wall oscillation (HFCWO) is another airway-clearance technique that has been tested on ALS patients. HFCWO is a technique that, through generation of high flow in the small airways, is thought to mobilize secretions from the distal airways to the larger airways, from where they can be more easily removed. Although we do not have specific knowledge about it, HFCWO seems to be well tolerated and helpful to a great proportion of patients, decreasing symptoms of breathlessness.

Conclusion and Key Recommendations

> Recent publications have made important contributions in particular to some aspects of respiratory care for patients with ALS, such as noninvasive ventilation and assisted cough.

> There is a need for regular assessment and follow-up of respiratory function, and investigations should include daytime assessment of respiratory function (including FVC and SNIP) as well as a sleep studies to ensure early recognition of patients with respiratory muscle impairment.

> NIPPV treatment alleviates respiratory symptoms, prolongs survival for longer than any available pharmaceutical agent, improves quality of life, and may probably modify the disease course. For this reason, NIPPV should be considered mandatory in any patient at risk of hypoventilation or in whom respiratory failure has become evident during sleep despite normal diurnal respiration.

> The degree of hypoventilation that should prompt introduction of NIPPV must be defined further, even if there is growing evidence from literature shifting the evidence-based indication for NIPPV toward earlier intervention. Nocturnal hypoventilation could be particularly useful for this purpose.

> Every effort should be made to improve NIPPV implementation in the management worldwide of patients with ALS since it is still underutilized.

> Prevention of aspiration and pneumonia and adequate management of bronchial secretions are two important issues. Adequate treatment of sialorrhea and dysphagia is important in the reduction of pneumonia risk. Insufficient cough is a condition that can be diagnosed by measuring peak cough flow and should, whenever present, be treated in patients with ALS. There is some evidence that mechanical cough-assisting devices could be of help in cough assistance, except for patients with severe bulbar dysfunction, but further research is needed.

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Noninvasive Mechanical Ventilation as an Alternative to Endotracheal Intubation During Tracheotomy in Advanced Neuromuscular Disease

24

David Orlikowski, Hélène Prigent, and Jésus Gonzalez-Bermejo

24.1
Introduction

24.1.1
Difficulties for intubation and invasive procedures in neuromuscular disease

Tracheotomy is a major step for patients with neuromuscular disease as it requires a higher level of care, which affects quality of life and increases dependence. Intolerance or nonfeasibility of noninvasive ventilation (NIV) is the most common reason for tracheotomy of patients with neuromuscular disease. Other reasons include worsening of respiratory failure with a low vital capacity (VC), persistent hypercarbia, and the need to increase ventilation time. One major condition to realize tracheotomy is to be able to maintain efficient ventilation throughout a procedure while providing efficient analgesia. Due to their severely impaired pulmonary function, respiratory management of patients with neuromuscular difficulties is very challenging. These individuals are at risk of severe complications when they require deep sedation or anesthesia with endotracheal intubation. They present many factors that can lead to difficult intubation: skeletal deformities, tracheal deviation related to kyphoscoliosis, reduced neck mobility due to cervical fusion or myopathy, tongue hypertrophy, and reduced mouth opening. The main risk in case of difficult intubation is a delay in efficient airway protection; adverse events in this setting include desaturation, hypoxemia, aspiration pneumonia, and prolonged stays in the intensive care

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unit (ICU) or hospital. Muscle relaxants and sedative anesthetic agents may induce severe respiratory depression and inefficient cough; moreover, muscle relaxants may cause rhabdomyolysis with fatal hyperkalemia [1]. A heightened maximal effect of vecuronium has been reported in patients with Duchenne muscular dystrophy (DMD), resulting in a large increase of time to recovery. Sedative agents can induce severe hypotension in patients with cardiac involvement, as seen in DMD; the potential depressive effect of sedatives on cardiac contractility must be considered when used in patients with cardiac dysfunction and at risk of life-threatening cardiac dysrhythmia.

The difficulties and risks associated with endotracheal intubation in patients with advanced neuromuscular disease prompted us to compare our experience of two tracheotomy procedures: conventional tracheotomy with sedation and intubation to tracheotomy with local anesthesia and NIV as proposed for the gastrostomy procedure in DMD or in amyotrophic lateral sclerosis (ALS) [2].

We published the results of a retrospective study [3] comparing an initial period when patients with advanced neuromuscular disease were deeply sedated and intubated for tracheotomy to a period when patients underwent tracheotomy with local anesthesia and NIV but without sedation. Conventional tracheotomy was performed in 7 patients and with NIV and local anesthesia in 13 patients. All but 3 patients had risk factors for difficult intubation. We showed that the number of respiratory complications such as pneumonia was higher in the conventional group (four vs. one) despite a similar hospital stay. We concluded that in patients with neuromuscular disease who require tracheotomy, use of NIV combined with local anesthesia may be helpful to avoid endotracheal intubation and reduce morbidity (Table 24.1).

Progress in medical management of neuromuscular disorders has resulted in increased survival. People with advanced neuromuscular disease, such as muscular dystrophy, more frequently require invasive and painful procedures and therefore deep sedation or anesthesia. Some neuromuscular diseases are associated with major skeletal deformities: limited neck extension, macroglossia, and reduced mouth opening (Fig. 24.1). No recommendation is available for intubation of patients with neuromuscular disease. The American Society of Anesthesiologists Task Force on Difficult Airway Management published an update of practice guidelines [1, 4]. Factors predictive of difficult intubation included an interincisor distance smaller than 3 cm, a Mallampati class higher than II, decreased mandibular space compliance, and a short, thick neck with impossible extension. Most of our patients had such risk factors. The relative risk for difficult intubation increases with the Mallampati class. NIV delivered through several interfaces (i.e., nasal mask, face mask, or mouth piece or to laryngeal mask) has been proposed in children with facial deformities, cervical spine rigidity, and neuromuscular disease who are undergoing several invasive medical or surgical procedures to provide safe respiratory support during deep sedation or anesthesia [2]. These techniques require well-trained physicians able to adapt the ventilator setting in response to the loss of spontaneous breathing due to sedation or to change the method of ventilation during the procedure. No change in ventilator settings was necessary in our patients. NIV may expose patients to the lack of efficient airway protection during the procedure, which must be counterbalanced with the risks linked to endotracheal intubation in these patients. Regional anesthesia is used to eliminate hazards associated with general anesthesia and to facilitate chest physiotherapy in patients with DMD [1]. Advantages in avoiding general anesthesia include maintenance of the ability to cough and

Table 24.1 Comparison of groups in terms of respiratory failure severity, risk factors for difficult intubation, and complications of tracheotomy

NIV	Neuromuscular disease	Risk factors for difficult intubation	Mallampati score	Hospital stay (days)	Complication
1	DMD	– Tongue hypertrophy – Reduced mouth opening – Neck immobility	IV	10	None
2	DMD	– Neck immobility	III	20	None
3	DMD	– Neck immobility	III	30	None
4	DMD	– Neck immobility	III	27	None
5	DMD	– Tongue hypertrophy – Reduced mouth opening – Neck immobility	IV	21	None
6	Acid maltase deficiency	– None	II	63	Early decannulation
7	DMD	– Reduced mouth opening – Neck immobility	IV	36	None
8	DMD	– Neck immobility	III	11	None
9	DMD	– Tongue hypertrophy – Reduced mouth opening – Neck immobility	IV	30	None
10	DMD	– Tongue hypertrophy – Reduced mouth opening – Reduced neck mobility	IV	20	SeizurePneumonia
11	DMD	– Tongue hypertrophy – Reduced mouth opening – Reduced neck mobility	IV	20	None

Table 24.1 (continued)

NIV	Neuromuscular disease	Risk factors for difficult intubation	Mallampati score	Hospital stay (days)	Complication
12	BMD	– Reduced neck mobility	II	21	None
13	DMD	– Tongue hypertrophy – Reduced mouth opening – Neck immobility	IV	20	None
Conventional	**Neuromuscular disease**	**Difficulties for intubation**	**Mallampati score**	**Hospital stay (days)**	**Complication**
1	DMD	– Kyphoscoliosis with tracheal deviation – Reduced mouth opening – Neck immobility	IV	41	Failed intubationPneumonia
2	DMD	– Tongue hypertrophy – Reduced mouth opening – Neck immobility	IV	11	Failed intubation
3	LGMD2C	– Tongue hypertrophy – Kyphoscoliosis with tracheal deviation	III	15	Pneumonia
4	DMD	– Tongue hypertrophy – Difficulties to open the mouth – Neck immobility	IV	21	Difficult intubationPneumonia
5	CMD1C (FKRP deficit)	– Tongue hypertrophy – Reduced mouth opening – Neck immobility	IV	35	None
6	DMD	– Tongue hypertrophy – Reduced mouth opening – Neck immobility	IV	15	Difficult intubation
7	LGMD2C	– Reduced neck mobility	II	25	Pneumonia

Duration of hospitalization and number of patients with a Mallampatti score greater than 2 were similar in both groups. The incidence of pneumonia was lower in the NIV compared to the conventional group. *DMD* Duchenne muscular dystrophy, *BMD* Becker muscular dystrophy, *LGMD* limb girdle muscular dystrophy, *CMD* congenital muscular dystrophy, *FKRP* Fukutin-related protein

Fig. 24.1 Chest X-ray: congenital muscular dystrophy presenting severe kyphoscoliosis and tracheal deviation

to swallow as well as to breathe spontaneously, even in the event of decannulation in patients with low VC and low respiratory reserve. Patients with neuromuscular disease often present piecemeal deglutition and impairment of the breathing–swallowing interaction [5]. Swallowing disorders and inability to clear the airway may be worsened by the use of sedative drugs, anesthetics, and muscle relaxants, increasing the risk of aspiration pneumonia [1]. Considering that intubation is often difficult and hazardous in patients with advanced neuromuscular disease, this additional factor may explain the high rate of aspiration pneumonia observed in the intubation group. On the other hand, the NIV procedure allowed patients to remain conscious, therefore preserving voluntary breathing, swallowing, coughing, and suctioning of oropharyngeal secretions, if needed, and reducing the risk of aspiration.

Tracheotomy is a surgical procedure that should be performed only by experienced physicians. Recently introduced techniques include percutaneous tracheotomy; to be performed, these methods do not require in-depth knowledge of neck anatomy compared to surgical tracheotomy. These techniques are not recommended in patients with cervical deformity and therefore do not seem suitable for patients with neuromuscular diseases; further evaluation of these techniques are necessary in this population. Cannula malposition has been reported in up to 25% of cases, and bleeding due to blood vessel injury can occur.

However, regardless of complications during or after a procedure, the posttracheotomy period is dedicated to the education of patients and their family regarding of the tracheostomy tube, suctioning techniques, and so on. Discharge from the hospital depends directly on the acquisition of these techniques and on the organization of the patient's environment. Therefore, the length of hospital stay is not solely influenced by the complications of the procedures, which might account for the lack of difference.

24.2
Conclusion

24.2.1
Use of NIV may decrease complications during invasive procedures in neuromuscular disease

NIV tracheotomy with local or locoregional anesthesia is an acceptable option for patients with neuromuscular disease who are at high risk of complications from endotracheal anesthesia. This new procedure could be favored over a procedure using intubation and general anesthesia in patients with advanced neuromuscular diseases.

Key Recommendations

> Use of local or loco-regional anesthesia should be preferred in case of invasive procedure in neuromuscular disease in order to limit the number of complications.
> Use of NIV should be added to local or loco-regional anesthesie or slight sedation in case of respiratory insufficiency and if possible intubation avoided.
> This techniques require well skilled care team with high knowledge of neuromuscular disease.

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Noninvasive Mechanical Ventilation in Patients with Myasthenic Crisis

25

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Myasthenia gravis is an autoimmune neuromuscular transmission disorder characterized by muscle weakness. This serious, but treatable, disease is the most frequent primary neuromuscular disorder.

In this clinical entity, the immune system produces antibodies that attack the receptors in the muscle endplates of the neuromuscular junction, and the acetylcholine receptors that receive the nerve signal are damaged (Fig. 25.1). It is unknown what triggers the immune reaction of the organism against its own acetylcholine receptors, but genetic predisposition plays an essential role in it.

Myasthenia gravis has an estimated prevalence of 0.5–12.5/100,000, an incidence of 0.4/100,000 among the general population, and a male-to-female ratio of 2:3.

The diagnosis of myasthenia gravis can often be confirmed using currently available methods, such as tests to detect anti-AChR (acetylcholine receptor) antibodies and electromyography.

The most common symptoms are eyelid ptosis, ocular muscle weakness that causes diplopia, and excessive fatigue of certain muscles after exercise. In 40% of the individuals with myasthenia gravis, the ocular muscles are the first to be affected, and with time, 85% of the patients have this symptom. Difficulties in speaking and swallowing and weakness of upper and lower extremities are also common.

About 17–20% of the patients with myasthenia gravis will eventually have a *myasthenic crisis* (MC), defined as a sudden worsening of respiration in which muscle weakness is so severe that it makes breathing impossible or impairs the adequate functioning of airways. The reasons for respiratory failure are dysfunction of upper airways, weakness of inspiratory and expiratory muscles, and associated complications.

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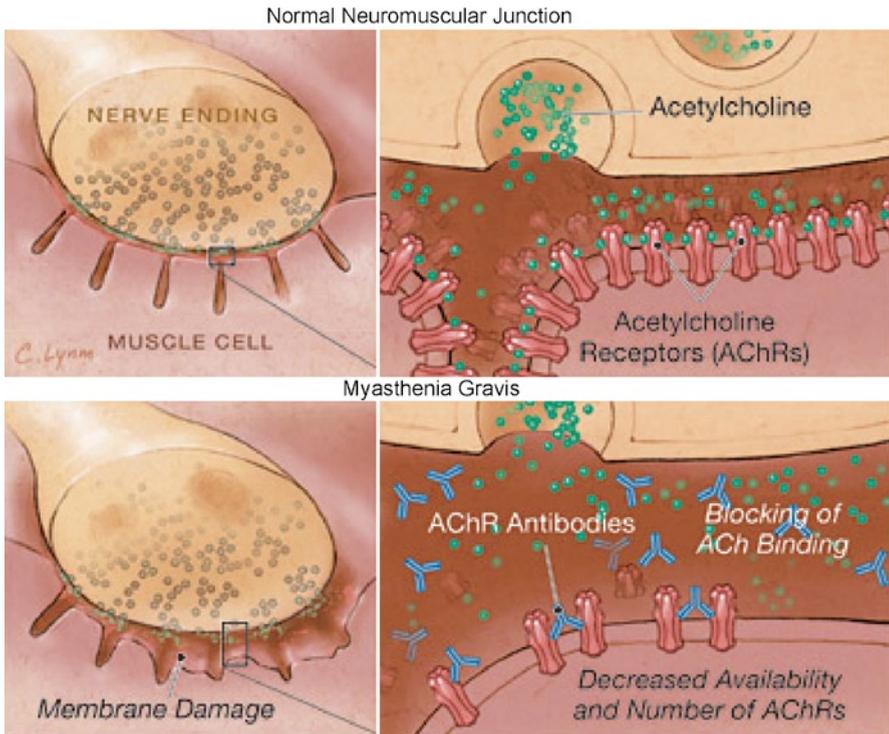
Fig. 25.1 [1]

Respiratory failure has several consequences, as described in Table 25.1. One of them is the reduction in the capacity to expand the thoracic cavity and of lung inflation.

When respiratory muscle weakness is mild or moderate, hyperventilation, normal blood pH, lower than normal P_{CO_2}, and normal or reduced Pa_{O_2} are usual findings. However, in more advanced stages of the disease, hypercapnia may develop because of hypoventilation secondary to respiratory muscle fatigue, which makes it difficult to move the rib cage and decreases normal lung compliance.

As a result of respiratory failure, many patients may require the use of ventilatory support.

Before mechanical ventilation was available, 70% of patients in MC died of respiratory failure. As intensive care units improved, this rate decreased to 30% in the 1950s and to

Table 25.1 Consequences of respiratory failure on lung mechanics

• Reduced capacity to expand rib cage
• Decreased lung inflation
• Decreased lung compliance
• Increased work of breathing
• Altered ventilation to perfusion ratio
• Diffuse lung microatelectasis

15% in the 1960s. The advent of mechanical ventilation in association with the generalized use of immunotherapy has substantially changed the prognosis of patients with an MC, which is reflected in a mortality rate that is now 4–8%.

Because of possible complications of mechanical ventilation, such as pneumonia, as well as other systemic complications, noninvasive mechanical ventilation has been used as an alternative to prevent reintubation and avoid the risks associated with intubation.

Seneviratne et al. [2] conducted a study with patients in MC who adapted well to noninvasive ventilatory support because they remained capable of initiating breaths. However, those patients became incapable of achieving a satisfactory flow volume, which increased the risk of microatelectasis and collapse of upper airways and did not ensure efficient gas exchange.

In this context, noninvasive ventilatory support is the first choice for patients in MC because the major concern is to avoid tracheal intubation and its complications.

The decision to use noninvasive mechanical ventilation depends on several factors. According to Agarwal et al. [3], the use of noninvasive mechanical ventilation depends on the severity of acute respiratory failure, the presence of bulbar involvement, and the association with other efficacious treatments. Severe anomalies in gas exchange and severe bulbar involvement that compromises the management of airways are absolute contraindications.

Patients treated with noninvasive mechanical ventilation during MC should be under careful cardiac monitoring because they may have cardiac arrhythmias.

During the use of noninvasive mechanical ventilation, clinical evaluation and arterial gas measurements should be made in the first 6–8 h to evaluate the efficacy of the method and the possible need to use conventional mechanical ventilation.

Two studies were optimistic about results despite the different intubation rates in patients who received noninvasive mechanical ventilation. According to Wu et al. [4], 57.1% of the patients did not require intubation, and Rabinstein et al. [5] found a 70% rate of success. However, their studies did not find any improvement in hyperventilation of patients with elevated Pa_{CO_2} and dyspnea. This confirms that patients with hypercapnia have a more severe degree of neuromuscular respiratory failure that cannot be treated only with positive pressure and requires the use of controlled volume ventilation.

In patients who require invasive mechanical ventilation, tracheal extubation failure is associated with high hospital morbidity, longer duration of ventilatory support, and high incidence of ventilation-associated pneumonia (VAP). Therefore, studies have investigated predictors of success of noninvasive ventilation when used as a weaning strategy. Adequate maximal expiratory pressure (PEmax) and strength to cough are significantly correlated with tracheal extubation success. Other predictors of noninvasive ventilation success are young age, low disease score, and good neurological score. Wu et al. [4] reported that patients with a low APACHE II score and a lesser degree of metabolic compensation for respiratory acidosis benefit the most from noninvasive mechanical ventilation.

25.1
Conclusion

The use of noninvasive mechanical ventilation in patients with MC may prevent intubation, help weaning from invasive mechanical ventilation, and avoid tracheal extubation failure.

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Predictors of Survival in COPD Patients with Chronic Hypercapnic Respiratory Failure Receiving Noninvasive Home Ventilation

Stephan Budweiser, Rudolf A. Jörres, and Michael Pfeifer

26.1
Introduction

Among the severe respiratory disorders that lead to chronic hypercapnic respiratory failure (CHRF), chronic obstructive pulmonary disease (COPD) is of major importance. Epidemiological surveys have demonstrated that COPD is one of the leading indications for long-term noninvasive ventilation (NIV). Nonetheless, the available data are still not fully conclusive with regard to the long-term benefits of NIV in severe COPD. The majority of randomized controlled trials have yielded more or less disappointing results, while some of the more recent, although predominantly observational, clinical investigations provided evidence for positive effects on health-related quality of life (HRQL), the frequency of hospital admissions, or long-term survival.

Some of these discrepancies can be traced to methodological factors, especially differences in the effectiveness of ventilation, including inadequate ventilator settings or insufficient adherence to NIV therapy in the randomized trials. This is supported by the observation that, in most instances, high inspiratory pressure levels were associated with high NIV success rates. Of similar relevance appear to be the selection criteria for choosing patients for the initiation of NIV, particularly when the long-term course of the disease and survival are taken as an outcome measure. Owing to the pathophysiological mechanisms involved in the development of chronic ventilatory failure, persistently elevated arterial carbon dioxide tension ($PaCo_2$) is currently considered the major objective measure to

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decide on the initiation of NIV. However, the association between chronic persistent hypercapnia and long-term outcome in COPD is far from uncontroversial. Moreover, when adopting the modern perspective of COPD as a multicomponent, systemic disease, it appears adequate not to rely on a single measure but to take a panel of factors known to affect severity and course of the disease as a basis for therapeutic decisions or as candidate measures for monitoring purposes.

26.2
Predictors of Long-Term Survival in Patients with COPD and CHRF

Based on the scientific background outlined, we performed a number of studies to evaluate predictors of long-term survival in large populations of patients with severe COPD receiving long-term NIV due to CHRF. In one of these studies, which covered an observation period of up to 10 years [1], a whole set of measures, including anthropometric data, nutritional status in terms of body mass index (BMI), spirometric, body plethysmographic, laboratory, and blood gas data, were considered. In view of the fact that the prognostic value of the Pa_{CO_2} is not clear, we also analyzed the potential role of base excess (BE) (i.e., the deviation of normal buffer base) as an obvious marker of long-term metabolic responses to chronic hypercapnia that is not as prone to a potential bias from short-term changes in ventilatory pattern as Pa_{CO_2}.

When analyzed separately in univariate analyses, quite a number of dimensions of the disease, including age, BMI, hemoglobin concentration, forced expiratory volume in 1 s (FEV_1), specific airway resistance, lung hyperinflation in terms of the ratio of residual volume to total lung capacity (RV/TLC), pH, and BE (but not Pa_{CO_2}), were significantly associated with long-term survival. It is noteworthy, however, that subsequent multivariate analyses revealed that among these measures only BMI, RV/TLC, and BE were statistically independent predictors.

26.3
Implications for the Assessment and Monitoring of Patients with COPD and CHRF

Despite the limitations posed by the retrospective design, the study [1] suggested some potential consequences for clinical practice. First, it supported the view that the prognosis of patients with severe COPD and CHRF is reflected in a broad panel of anthropometric, physiological, and functional measures. Although this panel became smaller in the multivariate analysis, at least three different predictors remained. Thus, the establishment of individual risk profiles in such patients is likely to be improved by a comprehensive assessment. According to these data, as a minimum this might include blood gas values (in particular BE), lung function (preferably body plethysmography), and nutritional data. The basic nutritional status is simple to assess by BMI, but there are studies indicating that fat-free mass index (FFMI) might be even better for this purpose (Table 26.1).

Table 26.1 Proposed measures for the multidimensional assessment of patients with chronic obstructive pulmonary disease (COPD) and chronic hypercapnic respiratory failure based on their prognostic value

Candidate measures for long-term assessment and prognosis
• Nutritional status (body mass index, BMI; fat-free mass index, FFMI) as integrative measure of functional and metabolic reserves
• Chronic arterial hypoxemia (Pao_2) as marker of gas exchange efficiency and organ stress
• Base excess (BE) as marker of the long-term metabolic response to chronic hypercapnia
• Lung function (hyperinflation as ratio of residual volume to total lung capacity, RV/TLC; forced expiratory volume in one second, FEV_1) as measure of organ-specific functional reserves
• Six-minute walking distance (6-MWD) as integrative measure of functional reserves
• Inflammatory (C-reactive protein, CRP) or cardiac (brain natriuretic peptide, BNP) as systemic markers from peripheral blood
• Anemia as reflected in low hemoglobin and hematocrit levels
• Modified Medical Research Council (MMRC) Dyspnea Scale as integrative measure of the subjective status
• Mouth occlusion pressure at 100 ms relative to maximal inspiratory pressure ($P_{0.1}/PI_{max}$) as a measure of the load-to-capacity ratio regarding respiratory muscles
• Cardiovascular, metabolic, and mental comorbidities as important confounders

In line with the literature, the data also indicated that the presence of anemia in terms of low hematocrit or hemoglobin levels should be considered for long-term survival in patients with COPD and CHRF. This was also found in the BODE cohort, which predominantly comprised patients with less-severe disease [2]. Moreover, the 6-min walking distance (6-MWD) and the Modified Medical Research Council (MMRC) Dyspnea Scale are known as valuable tools to improve the individual picture of functional capacity (Table 26.1). These data were not included in the study [1] but at least for 6-MWD an independent predictive value for long-term survival has been demonstrated. It also appears reasonable to take into account indices that more closely reflect the pathophysiology of CHRF. For example, mouth occlusion pressure 100 ms after start of inspiration relative to maximal inspiratory pressure ($P_{0.1}/PI_{max}$) is known as a noninvasive estimate of the load-to-capacity ratio of respiratory muscles. Indeed, this ratio was identified as a further independent predictor of long-term prognosis in patients with NIV and CHRF [3].

Therefore, an adequate assessment of advanced stages of the disease should probably move beyond existing scoring systems and cover various dimensions of the disease, including comorbidities or systemic markers, such as C-reactive protein (CRP), brain natriuretic peptide (BNP), or hypoxemia, as major predictors in severe respiratory diseases (Table 26.1). Future studies should address the appropriate definition and validation of such comprehensive, multidimensional scores as well as the question of a reasonable balance between information content and affordability.

Second, it was reassuring that the changes of BMI, RV/TLC, or BE observed 6 months after initiation of NIV were also linked to survival, at least in patients who showed an elevated risk for death according to their baseline values [1]. Besides indicating that the measures were statistically consistent, this observation also suggests that they might be useful in long-term monitoring, irrespective of the fact that in the study the effect of NIV

was inextricably mingled with that of the overall optimization of medical treatment. As an interesting aspect, the data especially confirmed that patients showing weight loss within 6 months experienced an increased risk for death. These patients might be primary candidates for nutritional support.

A number of studies have provided evidence that NIV could have additional positive effects through modification of known risk factors. There are both short-term randomized and long-term observational physiological investigations that found a reduction in lung hyperinflation after initiation of NIV, presumably due to a change in breathing pattern. Moreover, the beneficial effect of NIV on hypercapnia, provided that effective ventilation is guaranteed, is an established fact. Furthermore, there are observational data indicating a weight gain in patients with COPD and cachexia after initiation of NIV.

Taken together, the observations from this study, which comprised both baseline data and the longitudinal modification of risk factors, were in support of the hypothesis that on average NIV is capable of improving the long-term prognosis in patients with COPD and CHRF. At least formally, however, this hypothesis still has to be verified by randomized controlled trials in appropriate populations. Great care has to be taken that these populations match those actually treated in clinical practice with NIV, so it might turn out to be extremely difficult to circumvent major ethical problems.

26.4
Impact of the Decision to Initiate NIV in Severe COPD

Third, in addition to the implications regarding assessment and monitoring, there might also be implications for therapeutic decisions that are worth considering, particularly the initiation of NIV. According to international guidelines, the indication for long-term NIV in severe COPD is mainly based on symptoms of CHRF and the level of chronic hypercapnia. A critical $PaCO_2$ limit of 55 mmHg (7.3 kPa) or more has been specified to justify NIV in severe COPD [4]. It has to be stated, however, that the criteria of chronic hypercapnia have not been validated in large prospective trials, and it is common knowledge that $PaCO_2$ often exhibits large intraindividual and intraday variability, depending on the patient's condition and ventilatory state. Compared to this, the long-term metabolic compensation of hypercapnia and respiratory acidosis as reflected in BE is a slow process. Accordingly, BE seems to be a fairly stable measure of CHRF and disease severity, as indicated by the finding that BE but not $PaCO_2$ had relevant and independent prognostic information on long-term survival (Fig. 26.1). However, to establish the prognostic use of this specific measure in clinical routine, further studies on BE in comparison to daytime and nocturnal $PaCO_2$ under various conditions seem to be desirable.

According to the consensus statement [4], NIV is also recommended when $PaCO_2$ ranges below 55 (50–54) mmHg but two or more hospitalizations due to recurrent episodes of hypercapnic respiratory failure occurred within 12 months. As known, patients who survive acute hypercapnic respiratory failure and subsequently require NIV have a high risk for readmission, further life-threatening events, or death. Although studied primarily with regard to their long-term prognostic value [1], the markers identified could also be helpful in estimating the risk for respiratory decompensation or instability during or after severe
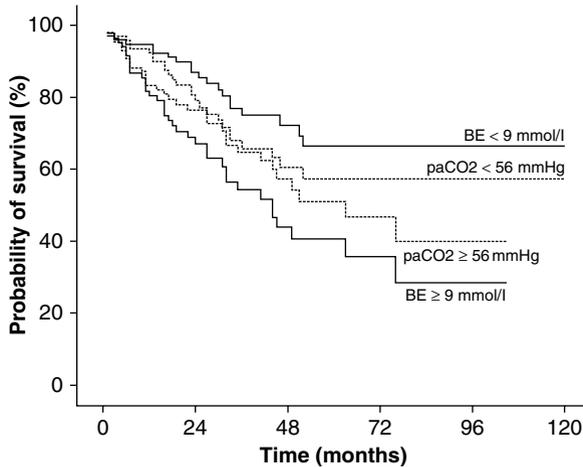
Fig. 26.1 Prognostic value of base excess (*BE*) versus that of carbon dioxide tension (*Pa*co$_2$). The figure illustrates the superiority of BE (HR 0.399; 95% CI 0.230–0.658; $p = 0.0004$) over Paco$_2$ (hazards ratio 0.787; 95% confidence interval 0.467–1.317; $p = 0.359$) in predicting long-term survival from baseline mean values in patients with severe chronic obstructive pulmonary disease (COPD), chronic hypercapnic respiratory failure, and noninvasive ventilation (Data from [1] but plotted in a different way)

exacerbations of COPD. Some of these measures could be implemented in the decision for NIV even under these conditions. This view is supported by an observational study that showed that patients presenting with a whole set of risk factors in this condition benefited most from NIV. Such an approach is not unusual since consideration of a panel of information on disease severity is everyday practice in therapeutic decisions, beyond the formal evidence provided by clinical trials. This individual approach is, for example, already customary in decisions on lung volume reduction surgery or lung transplantation.

Irrespective of the clinical usefulness of long-term NIV, the question arises regarding which mechanisms could underlie its lifesaving role, in particular if the benefit is only partially reflected in PaCo$_2$ levels. Sophisticated physiological and clinical studies have demonstrated that NIV induces a complex interplay among unloading of respiratory muscles, restoration of chemosensitivity, and improvement of alveolar ventilation. The beneficial effects are reflected in changes in breathing pattern, including an increase of tidal volume and a decrease of respiratory frequency [5]. Most important, they are not limited to the period of application of NIV but are maintained during subsequent periods of spontaneous breathing. If NIV preserves or even improves functional reserves via these mechanisms, it is reasonable to expect a positive impact, especially in conditions requiring augmented ventilation, and to assume lower vulnerability in episodes of acute deterioration or during exacerbations. This view is supported by clinical studies that demonstrated lower rates of hospitalization due to exacerbations of COPD after the initiation of long-term NIV. Despite the additional expenses for the ventilator, this reduction was associated with lower overall health care costs.

Table 26.2 Possible indications for long-term noninvasive ventilation in patients with severe chronic obstructive pulmonary disease (COPD) (Modified from [5])

Indications for noninvasive ventilation
• Symptomatic chronic hypercapnia (after optimization of standard therapy, including oxygen) and carbon dioxide tension levels ($PaCO_2$) of 55 mmHg or more
• Recurrent acute hypercapnic respiratory decompensations (≥2 within 12 months) requiring ventilatory support if $PaCO_2$ ranges between 50 and 54 mmHg
• High-risk profile for long-term mortality based on established prognostic factors
• State after prolonged invasive mechanical ventilation or a difficult weaning procedure

A similar argument probably applies to patients with severe COPD who undergo a difficult weaning procedure or an episode of prolonged invasive mechanical ventilation. Based on the high risk for respiratory decompensation and reintubation after invasive mechanical ventilation, NIV has become an important instrument in the management of respiratory failure during weaning in the intensive care unit setting. However, the value of NIV as a long-term treatment after weaning has not been demonstrated at a high level of evidence. Retrospectively collected data indicated a survival benefit in patients who were discharged with NIV after a prolonged period of weaning compared to patients who did not receive NIV for maintenance at home. In analogy to the arguments given, patients presenting with specific risk profiles are likely to benefit most from this treatment. Of course, the application of NIV under this condition does not abolish the need for a careful reevaluation after some time to assess whether NIV became dispensable owing to sufficient restoration of physiological strength. According to these considerations, possible indications for NIV are summarized in (Table 26.2)

Key Recommendations

> Patients with severe COPD and CHRF show a number of independent risk factors for mortality and thus need a multidimensional assessment and long-term monitoring of their clinical state.

> BE is a measure of the long-term metabolic response to chronic hypercapnia and is promising as an easily accessible, integrative marker of CHRF.

> Nutritional status, lung hyperinflation, and BE have been identified as statistically independent predictors of long-term survival. Other markers bear further, although related, information.

> The decision on initiation of NIV should probably not rely solely on symptoms and persistently elevated $PaCO_2$ levels. It should be based on an integrated analysis of a whole spectrum of risk factors that are relevant for long-term survival. This approach will naturally take into account the well-known heterogeneity of the disease.

> Owing to the physiological effects of NIV, patients with COPD and recurrent hypercapnic respiratory decompensation and patients experiencing prolonged mechanical ventilation or difficult weaning could be suitable candidates for successful long-term NIV.

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Withdrawal of Noninvasive Mechanical Ventilation in COPD Patients with Hypercapnic Respiratory Failure

27

Jacobo Sellares, Miquel Ferrer, and Antoni Torres

27.1
Introduction

Recent investigations in noninvasive mechanical ventilation (NIMV) have facilitated the increasing use of this type of ventilation worldwide. Indications of NIMV are better established, and the benefit of its use has been demonstrated in several studies, especially in acute hypercapnic respiratory failure (AHRF). However, some aspects of the use of NIMV still remain unclear and are under controversy. This is the case for which method is the best to withdraw NIMV. The paucity of information in defining a strategy to withdraw NIMV contrasts with all the information and studies related to weaning from invasive mechanical ventilation (IMV). There is a marked variability in the methods used to withdraw NIMV in the numerous studies of NIMV published, which reflects the absence of a prospectively validated protocol. In this chapter, we review the current recommendations to withdraw NIMV, and we suggest novel potential strategies. We especially focus on the withdrawal of NIMV in AHRF as this indication is the best established in NIMV, although some points of our review may also be extrapolated to other indications of NIMV.

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27.2
Use of NIMV in Acute Hypercapnic Respiratory Failure

Different studies have established the use of NIMV in patients who develop AHRF. Although chronic obstructive pulmonary disease (COPD) is the most frequent cause of AHRF, NIMV could also be useful in other types of chronic respiratory disorders, such as those caused by obesity and chest wall deformities. When a patient with a respiratory disorder is assessed in the acute setting, NIMV is initiated when there is a worsening of the respiratory status, the measurements of arterial blood gas tensions show respiratory acidosis, and no criteria for intubation or exclusion are present [1].

Once the NIMV is started, careful monitoring of the patients is necessary to ensure an optimal prognosis for the patient. Monitoring of patients on NIMV should include clinical assessment combined with pulse oximetry and arterial blood gas. Clinical features that should be routinely assessed during NIMV are as follows:

1. Chest wall movement
2. Coordination of respiratory effort with the ventilator
3. Accessory muscle recruitment
4. Heart rate
5. Respiratory rate
6. Patient comfort
7. Mental state

Continuous control of oxygen saturation in combination with periodic analysis of pH, Pa_{CO_2}, and Pa_{O_2} are necessary to assess the correct application of NIMV. The clinical and physiologic analysis will be useful to assess the adaptation of the NIMV to the patient and to detect early failure of NIMV. Different factors have been described [1] to establish the failure of NIMV:

1. Deterioration in patient's condition
2. Failure to improve or deterioration in arterial blood gas tensions
3. Development of new symptoms or complications such as pneumothorax, sputum retention, nasal bridge erosion
4. Intolerance or failure of coordination with the ventilator
5. Failure to alleviate symptoms
6. Deteriorating consciousness level
7. Patient and caregiver wish to withdraw treatment

Different options could be considered to optimize the NIMV, which include better conditioning of the interfaces and ventilation settings. Once the patient is clinically stable, the recommendation is that NIMV should be prolonged for at least 24 h [1], with small periods off the ventilator for medication as nebulizers and for meals. If patients with NIMV clinically improved and no signs of failure develop, physicians decide to withdraw the NIMV after 24 h. However, although to this point the clinical application of NIMV is relatively well described, no clear validated protocols are defined regarding the discontinuation of NIMV.

27.3
Rationale for Designing a Protocol to Withdraw NIMV

Although numerous protocols are established for weaning from IMV, the absence of prospective studies comparing different protocols to withdraw NIMV is astonishing. In weaning from IMV, weaning protocols are well defined and have demonstrated an improvement in survival of mechanically ventilated patients [2]. In analogy to weaning from IMV, we have to differentiate two stages in the withdrawal of NIV: In a first stage, we determine the readiness to withdraw NIMV, and in a second stage, we use a method to discontinue NIMV.

27.3.1
Determining the Readiness to Withdraw NIMV in Hypercapnic Respiratory Failure

During weaning from IMV, the readiness to wean a patient is decided by assessing different clinical and respiratory functional parameters [2]. Similarly, during IMV, we could decide the initial withdrawal of NIMV using the clinical and functional variables available in the care setting. However, defined parameters to withdraw NIMV are variable in the different studies published. In addition to resolution of the acute respiratory episode that was the cause for initiating NIMV, different functional parameters have been suggested to decide on the discontinuation of ventilatory support [1] (Fig. 27.1):
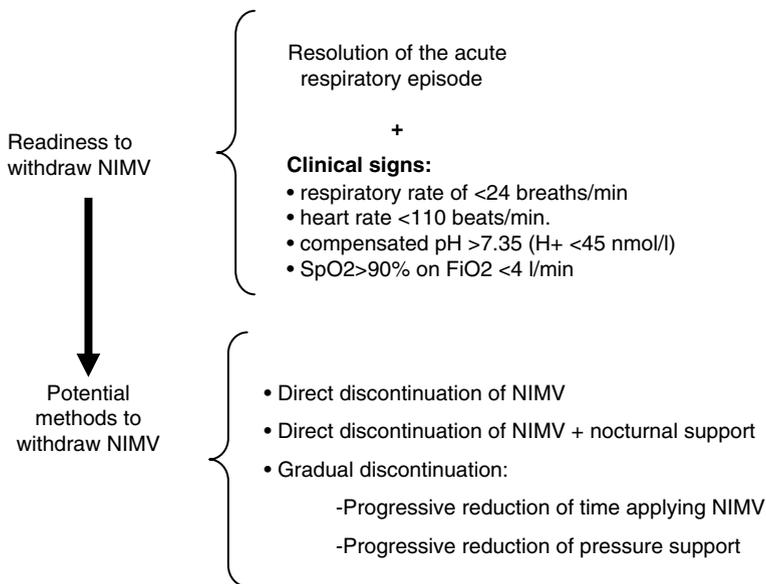
Fig. 27.1 Methods to withdraw noninvasive mechanical ventilation (NIMV) in hypercapnic respiratory failure

1. Respiratory rate below 24 breaths/min
2. Heart rate less than 110 beats/min
3. Compensated arterial pH above 7.35 (H+ <45 nmol/l)
4. SpO_2 above 90% on Fio_2 less than 4 l/min

27.3.2
Methods to Withdraw NIMV in Hypercapnic Respiratory Failure

The current recommendation for NIMV withdrawal is to gradually reduce the periods of ventilatory support when patient stability is achieved. However, no studies have validated this option, the specific points of these protocols differ between centers, and no comparisons with other approaches have been undertaken. From our point of view, three different approaches are possible as methods to withdraw NIMV:

1. Direct discontinuation of NIMV: The NIMV is stopped when patients fulfill the criteria for withdrawal. Oxygen is supplied as necessary. Afterward, the patient is clinically assessed during the next hours in spontaneous breathing. Periodic arterial blood gas analyses are performed. If the patient is clinically stable and arterial pH is over 7.35 and $Paco_2$ is stable with respect to the previous determination, NIMV is not restarted. No studies are available that assessed this strategy.
2. Direct discontinuation of NIMV with nocturnal support: NIMV is withdrawn in the same way as option 1, but nocturnal NIMV is kept for a few days. The rationale for using nocturnal NIMV is that, in patients with chronic respiratory disorders, especially COPD, typically there is the development of periods of transient hypoxemia associated with episodes of hypoventilation, which are more frequent during rapid-eye-movement (REM) sleep stages. These episodes could have clinical implications in patients who are recovering from an episode of hypercapnic respiratory failure. The application of nocturnal NIMV for a few days could avoid these episodes of hypoventilation, which could be deleterious for the ventilated patient. No studies are available that assessed this strategy.
3. Gradual discontinuation of NIMV: In this case, we could follow two strategies:

   (a) Progressive reduction of time applying NIMV: The period of the duration of NIMV is gradually reduced until the patient can breathe spontaneously. Damas et al. [3] reported their experience using this method of gradual withdrawal from NIMV in patients with acute exacerbation of chronic respiratory failure. In their protocol, they progressively reduced NIMV periods over 3 days, maintaining continuous NIMV during the night. While the patients were not receiving NIMV, supplementary oxygen was delivered. From the 65 patients who achieved clinical stability to begin the withdrawal of NIMV, no patients had to be reconnected to NIMV or required invasive ventilations during the hospital stay. The main limitation of this study is that it was merely descriptive and only represents the personal experience of a single center. However, there are no other reported studies that have focused on comparing this strategy with other methods to withdraw NIMV.

    (b) Progressive reduction of inspiratory and expiratory pressure support: Similar to the use of pressure support as a weaning method in IMV, some authors suggested the progressive decrease of inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP), assessing the patient's capability for sustaining ventilation in each step of corresponding pressure. Although this approach is interesting, no studies are available that used this particular mode of withdrawing NIMV.

These different strategies show different views for approaching NIMV withdrawal. The first strategy has the benefit of expending less time in the process of withdrawal, but patients may have an increased risk of a new episode of hypercapnic respiratory failure, especially during the night. The last strategy potentially could be the safest way to withdraw NIMV, but it could represent an unnecessary prolongation of NIMV and an increased risk of lateral effects (nasal ulcers, intolerance of NIMV, etc.). In fact, Damas et al. reported in their study a longer duration of NIMV compared to other studies [3]. Future studies must clarify which is the best method to withdraw NIMV that does not represent increased morbidity for the patient and has a minimum duration of NIMV and hospital stay.

27.4
Long-Term Dependency on NIMV

Although NIMV could usually be discontinued, some patients are considered for domiciliary NIMV after an episode of hypercapnic respiratory failure. Cuvelier et al. [4] defined this situation as long-term dependency (LTD)-NIMV, requiring the presence of all the criteria from Table 27.1. Moreover, physicians must consider long-term NIMV in the following clinical situations [1]:

1. AHRF secondary to

    (a) Spinal cord lesion
    (b) Neuromuscular diseases
    (c) Chest wall deformity (e.g., scoliosis, thoracoplasty)
    (d) Morbid obesity

2. COPD with

    (a) Recurrent episodes of hypercapnic respiratory failure (>3 episodes) requiring treatment with NIMV
    (b) Intolerance of supplementary oxygen (because of CO_2 retention) with symptomatic sleep disturbance

Table 27.1 Criteria for long-term dependency (LTD) on noninvasive ventilation (all required)

1. Stable resolution of the triggering factor
2. Inability to stop NIMV for at least 8 consecutive days (after two attempts) because of worsening clinical status, a rise in $Paco_2$ with respiratory acidosis (pH ≤ 7.35) or recurrent hypercapnic respiratory failure without any identifiable cause
3. Discharge home with domiciliary NIMV

However, LTD-NIMV is more common in pulmonary restrictive disorders than in COPD. The incidence of LTD-NIVM is estimated at 31% in patients noninvasively ventilated due to AHRF [4]. In an Italian survey of 26 respiratory intensive care units [5], LTD-NIMV was evident in 22% of the population of noninvasively ventilated patients. In hypercapnic respiratory failure, LTD-NIMV was independently associated with a decrease of baseline pH 6 months prior to the indication of NIMV (odds ratio 1.32, confidence interval [CI] 1.27–1.54) and with a noninfectious cause of AHRF (odds ratio 5.1, CI 1.8–14.0). The definition and standardization of prospectively validated protocols of withdrawal of NIMV are necessary also for early identification of those patients with LTD-NIVM.

Key Recommendations

❯ No standardized prospectively validated protocols are defined for withdrawing NIMV in AHRF.

❯ Clinical signs and gas exchange values must be monitored during the application of ventilation to decide the moment for withdrawing NIMV.

❯ Different strategies are possible as methods of withdrawing NIMV: direct discontinuation, partial ventilation during the night, or gradual discontinuation of NIMV.

❯ Future studies must define which method to discontinue NIMV is optimal in reducing length of stay and avoiding complications.

❯ The identification of LTD-NIVM patients during the process of withdrawal of NIMV is crucial for early detection of the patients who must continue with home noninvasive ventilation.

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Noninvasive Ventilation in Patients with Acute Exacerbations of Asthma

28

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28.1
Introduction

Asthma remains a common respiratory disorder, and despite advances in its outpatient management, patients continue to present to the emergency room department as a result of an acute exacerbation. While the vast majority of cases are managed with inhaled broncho-dilators and systemic steroids, some patients present with severe respiratory distress and require ventilatory support. Traditionally, the only option beyond medical therapy has been endotracheal intubation and conventional mechanical ventilation. However, care becomes more complicated after intubating a patient with severe asthma due to the potential for severe dynamic hyperinflation and cardiovascular collapse. While it is not the purpose of this chapter to discuss the approach to invasive mechanical ventilation of the asthmatic patient, it is sufficient to say that great care and attention are required by those skilled in these areas, and even this does not preclude significant morbidity. The use of noninvasive ventilation (NIV) for patients with severe acute exacerbations of chronic obstructive pulmonary disease (COPD) associated with respiratory failure has become increasingly recognized as first-line therapy after usual medical therapy and oxygen [1, 2]. The evidence supporting the use of NIV in acute exacerbations of asthma is more limited. The objective of this chapter is to provide a review of the current literature and summary recommendations for the use of NIV in this setting.

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Before reviewing the literature on the use of NIV in acute exacerbations of asthma presenting to the emergency room, it is important to recognize that asthmatic exacerbations represent a continuum of disease severity. At the extreme is the entity referred to as near-fatal asthma or status asthmaticus. These patients present with severe dyspnea and signs of dynamic hyperinflation with tachycardia, pulsus paradoxus, marked accessory muscle use, and at its most severe, signs of hypercarbia, including altered level of consciousness. Patients with refractory hypoxemia, persistent or worsening hypercarbia, signs of exhaustion, worsening mental status, or hemodynamic instability require urgent endotracheal intubation and should not be considered as candidates for NIV. Studies on the use of NIV in the setting of acute asthma vary in the severity of patients enrolled, and this will be highlighted as the literature is reviewed. Selected case series will be discussed first followed by randomized controlled trials (RCTs).

28.2
Case Series

The first study specifically reporting on the use of NIV in patients with acute asthmatic exacerbations was published in 1996 by Meduri and colleagues [3]. They retrospectively reviewed all patients admitted to their intensive care unit (ICU) with severe asthma over a 3-year period (1992–1995). Of the 26 patients presenting with severe asthma, 4 were intubated (2 respiratory arrest, 1 exhaustion, 1 hypotension), 7 responded well to medical therapy alone, and 17 underwent a trial of NIV. The patients receiving NIV were severely ill, with a mean pH of 7.25 ± 0.7 and Pa_{CO_2} of 65 ± 11 mmHg and respiratory rate of 29 breaths/min. Of the 17 patients, 2 (12%) required intubation and conventional mechanical ventilation; the rest demonstrated an improvement in respiratory rate and blood gases in the first couple of hours and continued to improve over 24 h.

Five years later, Fernandez and coworkers published a similar study of their experience over a 7-year period (1992–1998) [4]. During that period, 58 patients presented with severe asthma with marked respiratory acidosis, similar to those seen in the study of Meduri and associates. The authors defined criteria prior to reviewing the data for patients they felt were candidates for NIV: inclusion criteria included at least two of (1) severe dyspnea at rest, (2) respiratory rate above 30 breaths/min, (3) PaO_2 below 60 mmHg while breathing room air or less than 80 mmHg with additional oxygen, (4) Pa_{CO_2} of 50 mmHg or more, (5) pH 7.30 or less, and (6) active contraction of accessory muscles or paradoxical movement of abdominal muscles. Patients were excluded if there was a need for immediate intubation for respiratory or cardiac compromise. Of the 58 patients, 11 required immediate endotracheal intubation for respiratory arrest, and 14 responded well to medical therapy alone. Of the 33 patients who met criteria for NIV, 11 were intubated without a trial of NIV, and 22 received NIV as their initial ventilatory support. Of the 22 patients receiving NIV, 3 (14%) were intubated. Over the 7-year period, there was an increased use of NIV and less use of invasive ventilation, suggesting both an increased familiarity with NIV and confidence in its effectiveness. While there was significant variability in the number of patients

seen year to year and overall numbers were small, the study suggested the NIV was able to decrease the number of patients receiving invasive ventilation.

28.2.1
The Randomized Controlled Trials

The first RCT was reported in 2001 by Holley and colleagues, who randomized patients presenting with acute exacerbations of asthma to their emergency room to either nasal NIV and standard therapy or standard therapy alone [5]. They had estimated a sample size of 336 patients per group to have sufficient power to detect a 5% reduction in rates of endotracheal intubation. Unfortunately, they were only able to enroll 35 patients due to an increasing bias to use NIV for these patients outside the study. They also had not realized the number of repeat admissions by the same patients. As a result of this major selection bias, the validity of the study results is significantly compromised. They found no significant difference between the two groups in any outcome measures. From Table 28.1, it is clear that their patients were not as severely ill as those presenting in the two case series, although they clearly were sick, with a pH toward the acidic range and a high respiratory rate. This is also suggested by the need for intubation in 3 of 35 patients (1 in the NIV arm and 2 in the control).

The second RCT was published by Soroksky and colleagues in 2003 and was unique in its design [6]. These authors randomized 30 patients to either nasal NIV or "sham" NIV. The latter included a subtherapeutic pressure of 1 cmH$_2$O, holes cut in the tubing, and encouragement of mouth breathing. It is possible that the sham control patients had increased

Table 28.1 Summary of studies on use of noninvasive ventilation (NIV) in asthma

Study	Study design	Number of patients	pH of NIV	Pa$_{CO_2}$ of NIV	Respiratory rate	Intubation rate
Meduri et al. [3]	Case series	26 (17 NIV)	7.26 ± 0.05	65 ± 11	29 ± 5	2/17 (12%)
Fernandez et al. [4]	Case series	58 (22 NIV)	7.28 ± 0.008	63 ± 24	32 ± 6	3/22 (14%)
Holley et al. [5]	RCT	35 (19 NIV)	7.35 ± 0.04	40 ± 11	28 ± 5	1/19 (5%)
Soroksky et al. [6]	RCT	30 (15 NIV)	7.41 ± 0.04	33.6 ± 3	34.8 ± 1.8	0/15 (0%)
Soma et al. [7]	RCT (three arms)	40 (26 NIV)	na	na	20 ± 6	0/26 (0%)
Thill et al. [8]	RCT (crossover)	20 children	na	36.5±11.1	49.8 ± 14.6 (trans cutaneous)	1/20 (5%)

RCT randomized controlled trial, *na* not available

work of breathing related to the sham NIV. Regardless, the authors reported a more rapid reduction in FEV$_1$ (forced expiratory volume in 1 s) and in need for hospital admission (3/17 in NIV group vs. 10/16 in control group). From Table 28.1, it is clear that these patients had milder exacerbations of asthma as many did not require hospitalization, and none required intubation. Their baseline pH was normal, and they were hypocarbic, unlike the patients in the case series studies, who presented with acute respiratory acidosis.

The most recent RCT by Soma and associates differed in a few ways from the earlier studies [7]. The authors randomized patients to three arms: 14 to an inspiratory positive airway pressure (IPAP) of 8 cm H$_2$O and expiratory positive airway pressure (EPAP) of 6 cm H$_2$O, 12 to IPAP of 6 cm H$_2$O and EPAP of 4 cm H$_2$O, and 14 to oxygen therapy alone. All received other standard therapy, including oxygen. The authors reported a more rapid reduction in breathlessness, using the Borg scale, in both NIV arms and a more rapid improvement in FEV$_1$ in the higher pressure NIV arm compared to controls. This study used very low levels of pressure support ventilation (2 cm H$_2$O) and was almost more of a study of continuous positive airway pressure (CPAP) alone. The patients studied had very mild asthma with respiratory rates of about 20 breaths/min on presentation, and no patients required intubation.

The final study that should be mentioned was conducted in children with lower airway obstruction; the study used a randomized crossover design [8]. Children received both 2 h of nasal or full-face mask NIV and 2 h of conventional therapy applied in a random order and were assessed at the end of each 2-h period. They found significantly less wheezing, dyspnea, and accessory muscle use at the end of a 2-h trial of NIV compared to control.

28.3
Summary

From this review of the literature, the first conclusion to be drawn is that we do not have adequate data to make strong recommendations. To date, two small case series and four small RCTs have been published. Information from the RCTs suggests that NIV is associated with a reduction in breathlessness and a more rapid improvement in lung function (see Table 28.2) in mild-to-moderate exacerbations of asthma. To date, we have only case series data suggesting that NIV may be of benefit in patients with severe exacerbations. Suggesting that a large, multicenter trial in acute exacerbations of asthma should be conducted to provide a definitive answer generally follows when confronted with such a gap in the

Table 28.2 Summary of randomized controlled trial (RCT) results

Study	Halley et al. [5]	Sorosky et al. [6]	Soma et al. [7]	Thill et al. [8]
Breathlessness	–	√	√	√
FEV$_1$/PEFR	–	√	√	–
Hospitalization	–	√	–	–

FEV$_1$ forced expiratory volume in 1 s; PEFR peak expiratory flow rate

evidence. However, such a study will be challenging for a number of reasons. First, severe exacerbations of asthma occur with less frequency these days due to improving outpatient management. Second, those patients who do present with such an exacerbation tend to account for a large number of repeat admissions and can only be enrolled once. Third, there is a potential bias to use NIV based on current literature, success in other patient groups such as those who have COPD and cardiogenic pulmonary edema, and anecdotal experience. Finally, to recruit a larger number of patients there will be temptations to include those who present in larger numbers with mild-to-moderate exacerbations, which will make it harder to detect differences in intubation rates as these milder presentations rarely require intubation.

In the interim, it may be more useful to ask the question: Why not use NIV in acute exacerbations of asthma? To date, we have good evidence of effectiveness in patients with acute exacerbations of COPD, who are physiologically related. We have evidence to suggest that it helps reduce breathlessness and improves lung function more rapidly. However, we believe that waiting too long to intubate hypoxemic patients receiving a trial of NIV can lead to harm. The balance of evidence from the literature and the experience of experts would suggest that it is reasonable to offer a trial of NIV to patients with acute exacerbations of asthma, but that these patients are among those who need to be extremely closely monitored in an ICU setting to ensure rapid recognition of deterioration and intubation if necessary.

Key Recommendations

› There is little published evidence supporting the use of NIV in patients with acute exacerbations of asthma.
› NIV does appear to reduce breathlessness and improve lung function more rapidly in patients with mild-to-moderate exacerbations of asthma.
› Use of NIV in severe exacerbations requires intensive monitoring and personnel available for immediate intubation if deterioration occurs.

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Noninvasive Positive Pressure Ventilation During Acute Asthmatic Attack

29

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29.1 Introduction

Asthma is characterized by reversible airway obstruction caused by a triad of bronchial smooth muscle contraction, airway inflammation, and increased secretions.

In most patients, control of disease activity is easily achieved. However, in a small minority, asthma may be fatal. In between the two extremes, some patients with severe asthmatic attacks refractory to standard treatment are steroid dependent and typically have frequent admissions to emergency room departments and consequently are a substantial burden on health care systems. A few of these patients have a history of severe asthmatic attacks that necessitated mechanical ventilation.

These and other factors are known predictors of recurrent severe attacks. These mandate extra caution by the physician, with need for closer monitoring, intensive care unit (ICU) admission, and as a last resort invasive mechanical ventilation.

Invasive mechanical ventilation of asthmatic patients, in addition to the usual complications of mechanical ventilation, is associated with other risks. These patients are often difficult to ventilate, have low compliance with high inspiratory pressures, and have frequent patient–ventilator asynchrony.

As a result, mechanical ventilation of the asthmatic patient is a challenge to the intensivist and often necessitates permissive hypercapnea, deep sedation, and at times neuromuscular blockade.

In spite these protective approaches, mechanically ventilated asthmatic patients are at higher risk for barotrauma with resultant pneumothorax and prolonged ICU stay.

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Invasive mechanical ventilation is therefore a measure of last resort. Nevertheless, it should be applied promptly when needed. Hence, patients refractory to standard treatment who are at risk for respiratory failure should be identified sooner rather than later. These patients have the potential to benefit from early respiratory support in the form of noninvasive positive pressure ventilation (NPPV).

NPPV has gained wide acceptance and is now used more frequently. It has been shown to be beneficial for a variety of clinical conditions. Prospective, randomized, controlled trials have demonstrated the efficacy of NPPV in acute exacerbation of chronic obstructive pulmonary disease (COPD), acute cardiogenic pulmonary edema, hypoxemic respiratory failure, immunocompromised patients, and as an adjunct to weaning in postoperative patients and in patients with COPD.

However, reports of NPPV in asthmatic patients are scarce, and its use in asthmatic attacks is therefore still controversial.

29.2
Evidence for Use of NPPV in Asthmatic Attacks

Evidence for application of NPPV in asthma has been sparse. Only a few reports have appeared over the last decade. Other reports dating back to the 1980s and 1990s are more scarce and are case series.

Table 29.1 summarizes recent reports of noninvasive ventilation in asthmatic attack. These are mostly with small number of patients and with problematic methodology. [1–4].

Most exacerbations of asthma are easily controlled, and only a minority are refractory to standard treatment, with even fewer patients deteriorating to the point of respiratory failure with need for mechanical ventilation. This could explain the paucity of reports and the small number of patients in these trials.

Nevertheless, the reports that do exist clearly indicate that selected patients with severe asthmatic attacks can benefit from a carefully and closely monitored trial of NPPV.

The key to successful NPPV application is choosing the right patient. Patients with easily controlled disease probably do not need any respiratory support. At the other extreme are patients with severe status asthmaticus with pending respiratory failure and on the verge of endotracheal intubation. A trial of NPPV in these patients might delay inevitable endotracheal intubation and subject them to unnecessary risks. Therefore, these patients should be considered for endotracheal intubation sooner rather than later.

In between these two groups are patients with severe asthmatic attack who, if not treated aggressively, may progress to respiratory failure. These are the patients who could benefit from a closely monitored trial of NPPV.

Table 29.2 summarizes the contraindications to NPPV and the subgroup of patients at risk of respiratory failure who could benefit from an NPPV trial. These are usually the patients who by definition are considered to have a severe asthma attack.

Contraindications for NPPV in respiratory failure are subject for debate. Over the last decade, NPPV has gained wide acceptance for various indications. With the increased use of NPPV, we gained new knowledge and experience. We therefore believe that under

Table 29.1 Recent reports of NPPV in asthmatic patients

	Type of study	No. of patients	Study design	Mode of ventilatory support/ duration of application	Outcome
Meduri et al. [1]	Prospective observational	17	Report of 17 episodes of status asthmaticus treated with NPPV over 3 years	CPAP mask with pressure support using commercial ventilator for 16 h	NPPV improved gas exchange in status asthmaticus
Fernández et al. [2]	Retrospective observational	33	Retrospective comparison of 22 patients treated with NPPV vs. 11 patients treated with invasive mechanical ventilation	CPAP with or without pressure support using commercial ventilators for 12 h	Improved gas exchange in both groups, with the possibility of prevention of endotracheal intubation in NPPV group
Soroksky et al. [3]	Prospective, randomized, sham controlled	30	Fifteen patients on BiPAP compared to sham BiPAP with standard treatment	BiPAP circuit for 3 h	Improved FEV_1 and decreased hospitalization rate in NPPV group
Soma et al. [4]	Prospective randomized trial	44	Prospective comparison of low- and high-pressure groups to standard medical group	BiPAP circuit for 1 h	Improved FEV_1 with increasing pressure support

BiPAP bilevel positive airway pressure, *CPAP* continuous positive airway pressure, *FEV$_1$* forced expiratory volume in 1 s, *NPPV* noninvasive positive pressure ventilation

appropriate conditions and with experienced respiratory teams, NPPV use can now be extended to new diseases such as asthma and be used in conditions that previously were considered contraindications.

Significant hypoxia or hypercapnea, while previously considered a contraindication for NPPV, is now no longer considered by us as an absolute contraindication. It is our impression that, with experienced personnel and in the appropriate environment (e.g., admission to an ICU), these patients can safely be treated with a closely monitored NPPV trial.

Patients with unstable hemodynamics who cannot be stabilized with vasopressors or patients with worsening hemodynamic instability necessitating increasingly higher

Table 29.2 Indications and contraindications for noninvasive positive pressure ventilation (NPPV) trial

Contraindications for NPPV trial	Patients at risk for respiratory failure who could benefit from NPPV trial
Absolute contraindications • Need for immediate endotracheal intubation • Decreased level of consciousness • Excess respiratory secretions and risk of aspiration • Past facial surgery precluding mask fitting *Relative contraindications:* • Hemodynamic instability • Severe hypoxia and/or hypercapnea (PaO_2/FiO_2 ratio of <200, $PaCO_2$ > 60) • Poor patient cooperation • Severe agitation • Lack of trained or experienced staff	*Diagnostic criteria for severe asthma (at least one of the following criteria):* • Use of accessory muscles • Paradoxical pulse above 25 mmHg • Heart rate above 110 beats/min • Respiratory rate above 25–30 breaths/min • Limited ability to speak • PEF or FEV_1 less than 50% of predicted • Arterial oxygen saturation less than 91–92% *Risk factors for severe asthma exacerbation* • Recent hospitalization • Prior ICU admission with mechanical ventilation • Poor adherence to therapy • High allergen exposure

FEV_1 forced expiratory volume in 1 s, *ICU* intensive care unit

vasopressor doses should probably be intubated. However, unstable patients who can be rapidly stabilized with fluids and low doses of a vasopressor could probably benefit from an NPPV trial as well.

Agitation and poor cooperation can be controlled with low doses of benzodiazepines and, as published recently, with dexmedetomidine. These measures may relieve agitation and promote patient cooperation, thus preventing endotracheal intubation. However, sound clinical judgment should be applied, and these measures should be pursued only to a certain limit. Endotracheal intubation should not be delayed more than necessary.

The yield of routine chest radiography is questionable; however, in severe asthmatic attacks additional pathologies should be considered, including lung infiltrates, pneumothorax, or lung collapse. Therefore, in severe and refractory asthmatic attacks, chest radiography should probably be obtained.

29.3
Pathophysiology and Mechanism of Action

The mechanism by which NPPV improves the forced expiratory volume in 1 s (FEV_1) and clinical outcome in acute asthma is not exactly understood. A combination of factors could explain at least some of the benefit. As early as 1939, Barach and Swenson [5] showed that gas under positive pressure (continuous positive airway pressure [CPAP] of 7) can dilate small-to-moderate size bronchi. Similar findings were later reproduced by showing that CPAP application resulted in bronchodilation and decreased airway resistance. Furthermore,

aerosolized bronchodilators delivered through a bilevel positive airway pressure (BiPAP) circuit resulted in improved FEV_1 and PEFR, suggesting that perhaps positive airway pressure could disperse the bronchodilators to more peripheral airways. These findings strongly suggest that NPPV application may result in bronchial dilation by mechanical effect.

Promoting bronchial dilation decreases airway resistance, expands atelectatic regions, and facilitates clearance of secretions.

FEV1 and peak expiratory flow rate are used as measures of airflow obstruction. These measures can ascertain severity of disease and quantify the response to treatment. It has been shown that progressive reduction in FEV_1 is associated with a proportional increase in the work of breathing.

Concomitantly, expiratory airflow limitation increases and results in a dynamic increase in end-expiratory lung volume. This phenomenon is called *dynamic hyperinflation*. Increasing obstruction and tachypnea result in a relatively short expiratory time. As a result, the respiratory system does not reach static equilibrium volume at the end of expiration. This results in positive end-expiratory pressure (PEEP), termed *intrinsic or auto-PEEP*.

The resultant dynamic hyperinflation interferes with inspiratory muscle function and reduces the mechanical efficiency of the muscles, which further contributes to muscle fatigue. This results in increased physiologic dead space and eventually ventilatory failure. As airway obstruction worsens and the work of breathing increases, CO_2 production is in excess of what can be eliminated by the decreased alveolar ventilation. This has been shown to occur with a concomitant reduction of FEV_1 to less than 25% of predicted.

29.4
Setting Up Ventilatory Support and Patient–Ventilator Interaction

Noninvasive ventilatory support may be applied by dedicated CPAP or BiPAP circuits or by commercially available ventilators.

We do not recommend the use of CPAP alone in asthma as this mode is in effect external PEEP that is used mainly for improving oxygenation. In addition, CPAP has no pressure support and therefore does not possess the added benefit of increased ventilation. Adding pressure support to CPAP increases tidal volume and helps to unload fatigued respiratory muscles. Therefore, we recommend the use of commercially available BiPAP circuits or commercially available ventilators with pressure support.

When using BiPAP, we recommend starting with mild-to-moderate support; this will enhance patient comfort and cooperation. When setting up the expiratory positive airway pressure (EPAP) value, we aim at counterbalancing auto-PEEP. Previous reports have indicated that most obstructed patients have intrinsic PEEP, which results in increased work of breathing. We usually start with an EPAP of 3 cm H_2O and increase gradually to 5 cm. This is considered to be a mild-to-moderate externally applied PEEP. We do not apply more than 5 cm H_2O unless there is good clinical evidence of a higher auto-PEEP. Setting up the inspiratory positive airway pressure (IPAP) is based on arbitrary values; we often start with 7 cm H_2O and titrate it to respiratory rate and patient comfort. We increase IPAP gradually to 15 cm H_2O or less until the respiratory rate is less than 25–30 breaths/min. This approach

was used by our group in a pilot study of NPPV in severe asthmatic attack [3]. We found it to be safe and comfortable in most patients. Furthermore, once NPPV was applied, we observed that in most patients tachypnea decreased and anxiety resolved (data not reported). We presume this to be due to muscle fatigue that was alleviated with NPPV application.

We use nasal or facial masks. Due to the tight fit, facial masks are more effective; however, nasal masks are preferred by some patients as this allows them to speak and to clear secretions.

29.5
Cycling in Commercial Ventilators

Setting up a commercial ventilator is based on the same principle as a BiPAP circuit but with some differences. When we set up PEEP, we use the same consideration as with EPAP on a BiPAP circuit. However, the equivalent to IPAP (e.g., pressure support) is different and more advanced on the commercial ventilator.

Most modern commercially available ventilators can deliver pressure support breaths with two types of cycling or expiratory triggers (e.g., time cycling or flow cycling). By setting up appropriate expiratory criteria, we enhance patient comfort and synchrony with the ventilator. The usual criterion used in most pressure support ventilators is a decrease in inspiratory flow from a peak to a threshold value (usually 25% of peak flow). Previous reports have indicated that by increasing the flow threshold from the usual 25% of peak flow to 50% or even to 70% shortens inspiratory time.

A common problem with any NPPV is leaks from the mask that may impair the expiratory trigger or flow cycling when inspiratory pressure support ventilation is used. In the presence of air leaks, modern ventilators do not decrease inspiratory flow due to leak compensation. As there is no decrease in flow, the ventilator will not cycle to expiration. This leads to prolonged inspiratory time and patient–ventilator asynchrony. An alternative to flow cycling is time cycling. Limiting inspiratory time independent of air leaks allows a shorter inspiratory time. We usually set the inspiratory time to 1–1.3 s. However, this should be adjusted on an individual basis, and at times shorter inspiratory times are needed in severely obstructed patients.

Modern ventilators allow adjustable flow cycling, which, in the case of leaks, can also be time limited. This is probably the ideal way for an expiratory trigger in noninvasive ventilation.

Therefore, in the presence of air leaks we prefer an adjustable flow-cycled expiratory trigger that can be limited by time. This provides better patient–ventilator interaction than a simple flow- or time-cycled expiratory trigger.

29.6
Possible Risks and Side Effects of NPPV in Asthma

Pneumothorax has been reported previously when NPPV was applied in acute asthma. However, acute asthma in itself carries an increased risk for pneumothorax. Therefore, these reports are sporadic and do not necessarily indicate an increased risk with the use of NPPV.

With the use of NPPV, there is always a risk of delay in endotracheal intubation. Therefore, NPPV should be applied in an ICU environment, preferably by experienced personnel. Patients who are on the verge of endotracheal intubation or with pending respiratory failure should probably be intubated without NPPV trial.

Finally, inadvertent application of extrinsic PEEP that is higher than auto-PEEP could contribute further to dynamic hyperinflation. In addition, a combination of relative hypovolemia and auto-PEEP decreases venous return and subjects the patient to the risk of hemodynamic compromise.

29.7
Conclusion

The advantage of NPPV is supported by evidence that NPPV may have a direct bronchodilating effect, offset intrinsic PEEP, recruit collapsed alveoli, improve ventilation–perfusion mismatch, and reduce the work of breathing. NPPV should probably be applied in select patients who have or are at risk for severe asthma attack.

No doubt, a multicenter and perhaps an international effort has to be conducted to answer some of these questions before we can conclusively recommend the routine use of NPPV in asthma.

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Noninvasive Positive Pressure Ventilation for Long-Term Ventilatory Management

30

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30.1
Introduction

In this chapter, we discuss noninvasive positive pressure ventilation (NPPV) for patients with respiratory paralysis due to high-level spinal cord injuries (SCIs). Especially in the acute phase, 84% of those with SCIs with a level of C1–C4 and Frankel grade A, B, C suffered from respiratory complications such as pneumonia, ventilator failure, and atelectasis [1]. Another study [2] reported that the 1-year survival rate of ventilator-dependent persons with SCIs was 25.4%. However, among those who survived the first year, cumulative survival over the next 14 years was 61.4%. We recommend them this technology, which does not have complications and maintains their long-term quality of life.

30.2
Patients Who Need This Technology and Equipment

Patients with high-level SCIs cannot ventilate effectively because their respiratory muscles, which include the diaphragm and the intercostal muscles, are paralyzed due to SCIs. Hypoventilation induces not only respiratory insufficiency but also atelectasis and pneumonia. If they did not have respiratory diseases before onset, this technology plays a big part in their healthy life.

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Dysphagia and lack of cooperation are the main contraindications for NPPV for these patients [3]. It was reported that age, tracheostomy and mechanical ventilation, and spinal surgery via an anterior cervical approach are three significant predictors of risk for dysphagia [4]. In NPPV, we cannot prevent aspiration, and we cannot suction sputum via a tracheostomy tube.

The cooperation and comprehension of the patients are important for safe NPPV. In tracheostomy positive pressure ventilation (TPPV), patients are ventilated passively; in NPPV, they have to master how to inhale air from the ventilator. They also have to master how to cough effectively by this method.

30.3
Purpose of This Technology

NPPV technology conveys these patients more benefits than TPPV.

First, NPPV can provide efficient ventilation to maintain good gas exchange without a tracheostomy. Therefore, the complications due to use of a tracheostomy tube (e.g., atelectasis, pulmonary infections, cardiac arrhythmia, mucous plug, granulation formation, stomal infection, tracheomalacia, tracheal perforation, hemorrhage and tracheal stenosis, etc.) decrease [5].

Second, NPPV maintains lung and chest wall compliance. In this method, they can air stack by ventilator to reach their maximum insufflation capacity (MIC). Some patients can do air stacking by glossopharyngeal breathing (GPB). They can obtain MIC by these methods. If they are controlled by a tracheostomy, they cannot air stack and do GPB.

A strong cough is made by air stacking and chest thrusting. For most cases, airway secretions dramatically decrease after removing the tracheostomy tube. In addition, these individuals can cough strongly by assisted chest thrust after air stacking by NPPV or GPB. Usually, their peak cough flows exceed 270 L/min by these methods. They can expel tough sputum when they have a cold or pneumonia [6].

Patients can vocalize naturally when using NPPV. After inhaling air from a ventilator, they vocalize. If they want to speak louder or longer, they should vocalize after air stacking.

By NPPV, individuals' ventilator-free breathing time (VFBT) usually increases more than if they are ventilated with a tracheostomy tube. If they are ventilated with tracheostomy tube, they cannot train their inspiratory muscles by themselves without the assistance of removal from the ventilators. Otherwise, if they are ventilated by NPPV and the mouthpieces are set in a range that the mouth can reach, they can easily be trained to ventilate by their inspiratory muscles. GPB also secures VFBT.

30.4
How to Introduce This Technology

In the acute phase, most patients with SCI who need ventilator support are ventilated via cuffed tracheostomy tube. We change their ventilator setting to large tidal volume and a cuffless tube according to the clinical practice guideline of the Consortium for Spinal Cord Medicine [7] (Table 30.1).

Table 30.1 Ventilator setting

On admission	
MODE	A/C or CMV
VT	Set per previous hospital setting
RR	12
FiO$_2$	Titrate O$_2$ to maintain saturation greater than 92%
PEEP	Same as previous hospital setting
Day 2 and thereafter	
MODE	A/C or CMV
VT	If peak pressure is under 40 cmH$_2$O, then VT is increased by 100 cc/day until 20 cc/kg ideal body weight
RR	12
PEEP	PEEP is decreased by 2 cm/day until the PEEP is entirely removed
Fio$_2$	If O$_2$ saturation is greater than 92%, the Fio$_2$ may be decreased via titration to maintain Sao$_2$ of greater than 92%

Fio$_2$ fraction of inspired air, *PEEP* positive end-expiratory pressure, *A/C* assist/control, *CMV* continuous mandatory ventilation, *VT* tidal volume, *RR* respiratory rate, *SaO$_2$* saturation

After changing these settings, patients are trained to use NPPV. During training, tracheostomy tubes are plugged, and patients are ventilated by NPPV via mouthpieces, nose masks, or nose plugs. The time for training is gradually increased. If patients can use NPPV all day long, we remove their tracheostomy tubes and close their tracheostomies.

To assure the patients of the safety of NPPV, we must coach them how to remove their sputum and how to increase their VFBT using their reserved respiratory muscles or GPB.

30.5
Ventilators and Ventilator Setting

In the NPPV method, we use portable volume-controlled ventilators. The reasons why we use volume-controlled ventilators, not pressure-controlled ventilators, are as follows: First, air stacking is achieved effectively by volume-controlled ventilators. The peak inspiratory pressure after MIC is more than 40 cm H$_2$O, up to 70 cm H$_2$O. If they use pressure-controlled ventilators, they cannot perform efficient air stacking that reaches the MIC. Therefore, it will be difficult to maintain lung and chest wall compliance and to cough strongly. Second, many use mouthpiece NPPV during meals or except for sleep. They hold the mouthpiece in the mouth and release it according to their needs. Pressure-controlled ventilators do not allow such a method.

Assist/control or control modes are applied. The respiratory rate is set to 10–15 times/min, usually 12 times/min. Tidal volume is 20 mL/kg ideal body weight. Peak pressure is under 40 cm H$_2$O. We do not use positive end-expiratory pressure (PEEP). The Inspiratory/Expiratory (I/E) ratio is set between 1/1.5 and 1/2.0. Oxygenation is not necessary for most cases.

30.6
Interfaces

There are many shapes and sizes of interfaces. They are divided mostly into three categories: mouthpiece, nose mask, and nose plug. In a rare case (e.g., increased air leak from the mouth), the full-face type is selected. To obtain efficient air stacking, the expiratory ports of nose plugs and nose masks are closed.

Fit is most important. The shapes of the face and nose are diverse. High-volume leakage due to bad fit causes dyspnea and other difficulties. Leakage to the eyes must be avoided because it causes dry eyes. In the case of a nose mask, pressure ulcers on the bridge of the nose are common. Nose plugs sometimes make a pressure ulcer on the wall between the bilateral nares. These troubles occur when NPPV is introduced and result in rejection of NPPV.

Situations for use are the second important point in choosing an interface: Will they be used only during sleep or all the time, at home or in the community? While using NPPV, will the individual be able to use a computers or an environment control systems? We must choose better interfaces that are suitable for each patient's lifestyle and the abilities of their respiratory systems.

30.7
Surrounding Machines

We recommend patients and their family have monitors for avoiding accidental ventilator troubles and disconnection. Ventilators have some alarm systems, but they cannot become aware of all types of ventilator accidents. Therefore, we strongly recommend preparing a pulse oximeter for the second alarm system.

If the patients cannot cough strongly enough, they should use mechanically assisted coughing (MAC). This machine delivers deep insufflations and immediately delivers deep exsufflations. A combination with assisted chest thrust in the exsufflation period will be more effective for removing airway secretions.

Key Recommendations

❯ NPPV will reduce complications that long-term artificial respiratory management with a tracheostomy tube cause. Patients will have a healthier and higher-quality life.
❯ To introduce NPPV safely, we must strictly evaluate the indication for it. Dysphagia and lack of cooperation are the most important contraindications.
❯ How to remove airway secretions and how to obtain VFBT as long as possible are taught to patients and their caregivers.

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Home Ventilation for Chronic Obstructive Pulmonary Disease

31

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31.1
Introduction

Severe chronic obstructive pulmonary disease (COPD) is considered the most common cause of chronic respiratory failure, although exact estimations of incidence and prevalence are not available. The standard treatment of this condition is long-term oxygen therapy (LTOT), which improves survival [1,2]. Patients with hypoxemia who then develop hypercapnia tend to have the worst prognosis [2–7]. In addition, patients with COPD who remain hypercapnic after surviving an acute episode of ventilatory failure that requires mechanical ventilation have a worse prognosis than patients with only hypoxemia [8].

The benefit of noninvasive ventilation (NIV) for the treatment of acute respiratory failure in COPD has been well documented by multiple studies and meta-analyses [9]. However, the benefit of NIV for treatment of chronic respiratory failure in patients with COPD has not been established despite various randomized and nonrandomized studies. This review highlights some pathophysiologic peculiarities of NIV for this indication and summarizes the available evidence. Finally, some practical aspects of home NIV are discussed, such as to how to identify patients with COPD who are likely to benefit from home NIV.

31.2
Physiologic Effects of NIV in COPD

In chronic respiratory failure secondary to COPD, hypoxemia can be viewed as a consequence of ventilation/perfusion mismatch and diffusive impairment. Hypercapnia, on the other hand, is a marker of alveolar hypoventilation. In stable COPD, hypercapnia is increasingly regarded as the result of a compensatory mechanism aimed at unloading the ventilatory muscle pump. More specifically, the effective work of breathing is reduced due to rapid shallow breathing,

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thus preventing ventilatory muscle fatigue. The cost of this breathing pattern is hypercapnia, which results from lower tidal volumes and increased dead space ventilation [10,11].

The exact magnitude and mechanisms of the physiologic effects of long-term mechanical ventilation in COPD are unclear. In some studies, hypercapnia was reduced [12–14], while in others it was not [15–19]. This discrepancy is likely dependent on the effective ventilatory pressure applied during NIV. Nocturnal application of NIV decreases $Paco_2$ and may reset the $Paco_2$ sensitivity of the blunted respiratory centers in COPD with subsequent increases in diurnal respiratory drive [20]. Improvement of nocturnal Pao_2 may also improve diurnal oxygenation due to improved compliance of the chest wall and the lungs [21] and an increased respiratory drive [20].

It is unclear whether and to what extent home NIV improves respiratory muscle function, reduces oxygen consumption of the ventilatory pump, increases respiratory muscle efficiency, or reduces chronic respiratory muscle fatigue [22,23]. NIV reduced the activity of the ventilatory muscles in many studies [12,23–28]. However, only one study showed a sustained improvement in maximum inspiratory force [29]. Other studies showed only a trend toward improvement or no change [15–18,27,30–32].

NIV reduced pulmonary hyperinflation in two studies, but the exact mechanism was unclear [12,33]. Additional beneficial effects of NIV in COPD include a reduction in pulmonary arterial pressure [34] and improved nutritional status [35].

31.3
Summary of Available Clinical Evidence

31.3.1
Mortality and Hospital Admissions

To date, three prospective randomized studies have investigated the effect of home NIV on the survival of patients with COPD. Casanova et al. [17] and Clini et al. [18] investigated patients over 1 and 2 years, respectively. Both were unable to demonstrate improved survival in those patients. However, the study by Casanova et al. also included normocapnic patients, suggesting absence of chronic ventilatory failure. Currently, the largest ($n = 144$) and longest (mean follow-up 2.2 years) randomized study was undertaken by McEvoy et al. [19] in Australia; this study showed a small survival benefit of NIV only after adjustment of baseline gas exchange and symptoms. In all three studies, rather small levels of effective ventilatory pressure support were applied.

The studies by Clini et al. [18] and McEvoy et al. [19] showed no reductions in hospital admission in the NIV group compared to the LTOT group. In contrast, Casanova et al. [17] observed a reduction in the number of hospital admissions after 3 months; however, this finding was not sustained after 1 year. In an older study, Tuggey et al. showed that domiciliary NIV, applied in patients with COPD with recurrent admissions for acute-on-chronic respiratory failure requiring NIV, reduced hospital admissions [36].

A small, randomized, pilot study of home NIV in patients who remained hypercapnic after acute-on-chronic respiratory failure showed an increased probability of clinical

worsening (i.e., death, intubation, resumption of NIV, progressive hypercapnia, or intolerable dyspnea) when NIV was withdrawn [37].

31.3.2
Quality of Life, Exercise Capacity, and Sleep

Because the effect of home NIV on mortality and hospitalization rate is uncertain, changes in quality of life (QOL) are becoming ever more important treatment goals [38–40]. Measuring QOL is a challenge because it is determined not only by functional status but also by psychological, social, and sexual factors [41]. The disease-specific St. George's Respiratory Questionnaire (SGRQ) is usually used to quantify QOL in patients with respiratory diseases. In addition, the Maugeri Foundation Respiratory item set (MRF-28) was developed as a more sensitive instrument to measure disease-specific QOL treatment effects in patients with respiratory failure [18,42]. In most studies, including the randomized studies, QOL was improved by NIV [14,18,29]. In contrast, McEvoy et al. did not observe any change in the SGRQ as a consequence of home NIV [19]. In this study, patients treated with NIV had even poorer general and mental health (as measured by the Short form 36 (SF 36) health survey questionnaire) and reported less vigor and more confusion and bewilderment. The reasons for worsening of mood and QOL in this study were unclear. These conflicting findings implicated the need to closely measure QOL in future randomized, controlled trials in this patient group.

Whether exercise capacity is affected by home NIV is also unclear. While some studies showed an improvement in the 6-min walking test [13,29], others did not [14,18]. Similar considerations apply to the quality of sleep during NIV. Some studies found improvements [14,18,43], while others did not [15,16,29].

31.4
Practical Aspects of Home NIV in COPD

31.4.1
Ventilators and Interfaces

Ventilators for home NIV in patients with COPD should be reliable and simple to use. A battery-operated system is only required when ventilation is needed more than 12 h/day. Alarms must be set to detect airflow obstruction, disconnection, or ventilator failure. With regard to the mode of ventilation, volume-preset and pressure-preset ventilation modes appear to be equivalent [44–46].

Frequently, pressure support ventilation is the primary mode of choice because it is easier to adjust and synchronize with the patient. If pressure support is ineffective or not well tolerated, pressure-controlled or flow-preset ventilators may be used, depending on individual patient conditions [47]. Newer pressure support ventilators can deliver real volume ventilation with the average volume-assured pressure support (AVAPS) mode [48].

When establishing pressure support ventilation, the level of inspiratory aid is increasingly raised from 10 cm H_2O to approximately 20 cm H_2O with a level of expiratory positive airway pressure around 5 cm H_2O. These ventilator settings allow optimal CO_2 removal with simultaneous control of autopositive end-expiratory pressure, according to individual patient tolerance. Levels of inspiratory pressure aid that are too low may be associated with long-term failure of NIV [32]. The inspiratory duration is generally set to be as short as possible and limited at a maximum of 1.3 s to avoid leak-induced prolongation of inspiration. The fraction of inspired oxygen is adjusted to correct for nocturnal hypoxemia, as ascertained by nocturnal oximetry. Subjective patient comfort is key for long-term compliance with the therapy. Strategies using patient comfort at acceptable blood gases are equivalent to strategies using more rigorous physiologic control algorithms [49]. The choice of the interface is personal. In principle, the same nasal or facial masks that are used in sleep medicine are also apt for ventilating patients with COPD.

31.4.2
NIV Initiation and Follow-Up in COPD Patients

The initiation phase of home NIV is crucial for the patient to adapt to the new therapy. Well-informed patients are motivated and more likely to have greater future compliance with the therapy. Patients with COPD are best trained to use NIV during a 3- to 5-day stay in a specialized respiratory care center. This stay allows doctors to optimize patient–ventilator interactions and to obtain and react to nocturnal oximetry as well as serial arterial blood gases. Successful home NIV requires a basic amount of intellectual capacity; patients who are unable to understand the intention and procedures of NIV are unlikely to use and benefit from home NIV. During an initiation phase in the hospital, various obstacles to successful usage of home NIV can be identified and removed. In addition, this phase also allows for the identification of patients who will be unable to successfully use home NIV.

After a primary initiation of home NIV, patients should have regular follow-up visits at the hospital every 3–6 months. At these visits, the functional status of the patient as well as the hour meter and hygienic conditions of the ventilator are reassessed and readapted, if needed. Technical supervision at home is usually provided by home respiratory care organizations and ventilator manufacturers.

Although study results conflict with regard to the usefulness of home NIV and NIV also conveys potential discomfort, almost all studies found a high compliance with home NIV once it was successfully established [14,15,17–19,31,50].

31.5
Selection of Patients for Home NIV

The generally high patient acceptance of home NIV and some clinical evidence suggest that home NIV can be beneficial for patients with COPD with chronic respiratory failure. The difficulty lies in identifying individual patients who are most likely to benefit from it.

The most recent The American College of Chest Physicians (ACCP) guidelines on clinical indications for noninvasive positive pressure ventilation in chronic respiratory failure suggest using home NIV in the presence of well-documented and well-treated disease associated with certain symptoms and physiological findings (Table 31.1) [51]. However, these recommendations do not describe appropriately clinical problems of patients with COPD [52]. In addition, stable oligosymptomatic hypercapnia is probably not an indication for home NIV.

The progressive deterioration and destabilization of a formerly stable patient, based on clinical and biological criteria, has been suggested as an indication for home NIV in patients with COPD with chronic respiratory failure [52]. Typical candidates are patients with chronic hypercapnic respiratory failure who experience repeated life-threatening episodes of acute-on-chronic respiratory failure. These episodes are associated with worsening of hypercapnia and frequently require acute NIV [53]. Patients who remain hypercapnic after such an acute episode and require NIV have a particularly dismal prognosis and may benefit from NIV [8,37]. It also appears reasonable that home NIV should be initiated in patients who cannot be totally weaned off acute NIV but stabilize in the hospital with nocturnal NIV only [54,55]. These patients would alternatively be candidates for tracheotomy, which may be avoided by home NIV.

Apart from the scenario of repeated acute-on-chronic respiratory failure, alternative indicators of instability may be slow and progressive worsening of hypercapnia associated with increasing symptoms despite optimal medical therapy. If a trial of NIV in the hospital

Table 31.1 Clinical indicators for the introduction of home NIV in patients with COPD (Adapted from [51])

Disease documentation
1. Establish and document an appropriate diagnosis of COPD using history, physical examination, and results of diagnostic tests
2. Assure optimal management of COPD (inhalative treatment, rehabilitation, including smoking cessation and oxygen therapy when indicated)
3. Optimal management of other underlying disorders (e.g., multichannel sleep study to exclude associated sleep-disordered breathing, if clinically indicated)
Indications for usage
1. Symptoms: fatigue, dyspnea, morning headache, *etc*.
2. Physiological criteria (one of the following): $Paco_2$ 55 mmHg or above $Paco_2$ between 50 and 54 mmHg with nocturnal desaturation (Sao_2 by pulse oximetry $\leq$ 88% for 5 min continuously while receiving oxygen therapy $\geq$2 L/min) $Paco_2$ between 50 and 54 mmHg with hospitalization related to recurrent episodes of hypercapnic respiratory failure (more than two in a 12-month period)

COPD chronic obstructive pulmonary disease

appears promising in such a patient with improved symptoms and gas exchange, home NIV should be considered.

Associated comorbidities, such as obstructive sleep apnea syndrome, congestive heart failure with Cheyne–Stokes breathing, or obesity, are conditions that also influence the decision to establish home NIV in COPD patients with chronic respiratory failure.

Key Recommendations

> Long-term domiciliary noninvasive ventilation (home NIV) may be considered in COPD patients with chronic hypercapnic respiratory failure who experience progressive destabilization despite optimal non-ventilatory treatment.
> The indication for home NIV should based on both symptoms and blood gases.
> In order to avoid tracheotomy, home NIV may be initiated in patients who cannot be weaned off acute NIV but stabilize in hospital with nocturnal NIV.
> The long-term success of home NIV requires a motivated and well-informed patient.
> Initiation of home NIV, patient education and regular follow-up visits should be provided by a specialized respiratory care centre.

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Section VI

Critical Care Applications of Noninvasive Mechanical Ventilation and Related Issues

Current Strategies and Equipment for Noninvasive Ventilation in Emergency Medicine

32

Keisuke Tomii

32.1 Introduction

Growing evidence indicates that noninvasive ventilation (NIV) is the standard first-line therapy for cardiogenic pulmonary edema (CPE) and chronic obstructive pulmonary disease (COPD). NIV is also starting to be tried out in the emergency department (ED) for other diseases, such as asthma, acute exacerbation of other types of hypercapnic failure, pneumonia, and acute respiratory distress syndrome (ARDS). Furthermore, since respiratory distress due to CPE can be rapidly retrieved even with continuous positive airway pressure (CPAP), which has the great advantage of easy application, prehospital CPAP for presumed CPE is considered to be at the cutting edge of emergency medicine.

32.2 Analysis of Main Topics

32.2.1 NIV Trial in the ED

In emergency medicine, NIV has been applied for more than 10 years in cases of respiratory distress regardless of the etiology. One study by Wood et al. in 1998 [1], which randomly allocated 27 patients with various types of acute respiratory distress to either NIV or conventional medical therapy in the ED, was unable to produce any benefit and showed a trend toward a greater hospital mortality rate, probably due to a delay in performing intubation. In 1999, however, a prospective nonrandomized pilot study by Thys et al. [2] revealed rapid improvement in clinical and laboratory parameters in almost all

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of their 62 patients, who had various etiologies and who had no deleterious effects from NIV when implemented for short periods of time. Thus, this was the first study to support an NIV trial strategy in the ED.

In 2002, Thys et al. [3] performed a prospective, randomized, placebo-controlled study in which the early application of NIV in patients with severe acute respiratory failure (ARF) due to CPE or COPD revealed a rapid and significant improvement in clinical parameters, pH, and carbon dioxide tension in arterial blood; respiratory frequency; and sternocleido-mastoid electromyogram activity. Park et al. [4] reported on a randomized controlled trial of patients with severe CPE in a tertiary hospital emergency room and demonstrated a lower rate of endotracheal intubation and no cardiac ischemic complications with this first-line NIV strategy. In 2006, Collins et al. [5] reported on a meta-analysis of 494 patients and the use of NIV in the ED for acute CPE and found that NIV significantly reduced hospital mortality (relative risk [RR] 0.61, 95% confidence interval [CI] 0.41–0.91).

As mentioned, NIV was used for ARF of various etiologies other than CPE and COPD; however, no evident survival benefit was shown. A newly reported retrospective cohort study by Tomii and colleagues [6] was the first to demonstrate an overall reduction in mortality after introducing NIV trial strategy in the ED for the whole population of ARF, excluding recurrent aspiration pneumonia (RR 0.51, 95% CI 0.31–0.84).

32.2.2
Prehospital CPAP

As we have shown, NIV or CPAP is clearly effective as the first-line treatment for CPE and will increasingly be so if we can deliver it before the patient's arrival at the hospital. Kosowski et al. [7] first reported a case series of 19 patients in 2001; prehospital use of CPAP was feasible and may have averted the need for endotracheal intubation in patients with ARF presumably due to CPE. In 2008, Thompson et al. [8] performed a randomized control trial of out-of-hospital mask CPAP (Fig. 32.1) in 71 patients with severe respiratory failure mainly due to CPE, COPD, and asthma and revealed a 30% reduction in intubation and a 21% reduction in mortality. Helmet CPAPs (Fig. 32.2) have been widely used in Italy, and preliminary data for their use as first-line prehospital treatment were reported in 2009. Prehospital helmet CPAP with an oxygen flow of at least 30 L/min was applied, with or without standard medical treatment, to 121 patients with mostly presumed CPE and resulted in no prehospital intubation and significant improvement in oxygenation and hemodynamics [9].

32.3
Discussion

There are two directions in which NIV can make further progress in emergency medicine. One is in increasing its indications, and the other is its more rapid application. NIV trial strategy, meaning its first-line use for all possible indications, should be promoted more widely in the ED, where causes of ARF cannot be easily defined in a short space of time.
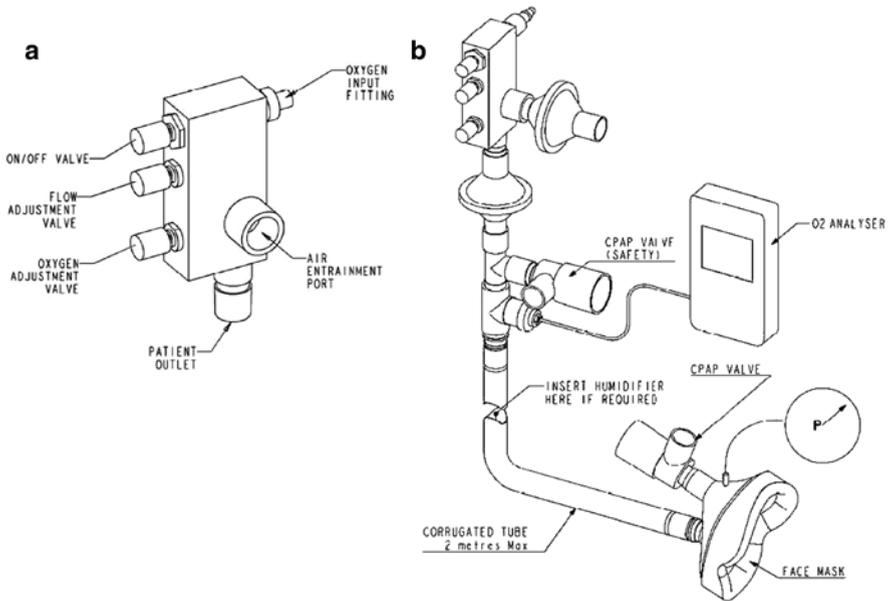
Fig. 32.1 Noninvasive high-flow *CPAP* (continuous positive airway pressure) system for prehospital and emergency care. (**a**) Flow generator (WhisperFlow Variable, Respironics Inc., Murrysville, PA). (**b**) Flow generator and other parts; mask, positive end-expiratory pressure (PEEP) valve, tubing, and filter (WhisperPak, Respironics)
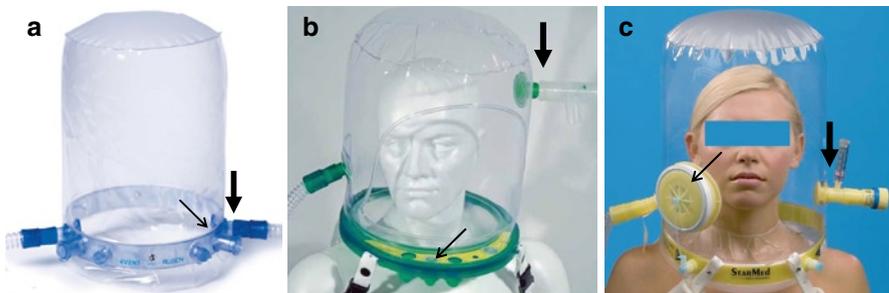
Fig. 32.2 Helmets for continuous positive airway pressure (CPAP). (**a**) 4Vent (Rusch GmbH, Kernen, Germany). (**b**) HelmHar (Harol, Via Marcora, Italy). (**c**) CaStar (StarMed, Mirandola, Italy). *Thick arrows* indicate locations to connect positive end-expiratory pressure (PEEP) valves. *Thin arrows* indicate locations of antisuffocation devices or port of connecting safety valves: (**a**) two connectors on each side for the connection of PEEP and safety valves, (**b**) integrated antisuffocation device and pop-off valve, (**c**) bidirectional antiasphyxia valve with automatic opening

The equipment for such broadly indicated NIV should not only have both CPAP and bilevel mode but also a high-level oxygen blender that can produce up to 100% FiO_2. Moreover, since a certain amount of mask leakage is inevitable in the initial phase of mask NIV in the ED, NIV-compatible intensive care unit (ICU) ventilators, which can barely

tolerate unexpected mask leakage and often produce patient–ventilator asynchrony in that situation, should be avoided. Therefore, Bipap-Vision (Respironics Inc., Murrysville, PA) has been frequently used for this purpose to date, and the newly introduced Carina (Dräger Medical AG & Co. KG, Lubeck, Germany) would be another choice.

Simple CPAP with oxygenation can rapidly ameliorate the respiratory distress of CPE; hence, equipment for administering constant positive pressure and variable FiO_2 up to 100% in the ambulance would contribute greatly to the care of emergent patients. A high-flow CPAP system composed of a mask with positive end-expiratory pressure (PEEP) (CPAP) valve and a specialized flow generator (Fig. 32.1), which enables stable CPAP (5.0, 7.5, 10 cm H_2O); variable FiO_2 (30–100%); and maximum 140 L/min flow is now available. Another device that is a possibility for out-of-hospital CPAP is helmet CPAP. Since the helmet acts as a compliance chamber, the airway pressure is kept above PEEP throughout the respiratory cycle, provided that gas flow through the expiratory valve is always present [10]. It does not require critical fitting and is easily applied, even by a crew with minimal training. It does, however, require a high flow of oxygen (>30 L/min) to prevent accumulation of CO_2 inside the helmet and rebreathing. For both systems of prehospital CPAP, an antisuffocation safety device and a dedicated monitoring and alarm system are crucial (Figs. 32.1 and 32.2). Data from prehospital CPAP for CPE are being accumulated [7–9], while that for other etiologies, although still lacking, might prove to be promising [8].

Key Recommendations

> Try NIV first for CPE in the ED.
> NIV trial strategy for other varieties of ARF should be promoted more widely in the ED.
> Prehospital CPAP could be applied as first aid treatment for CPE.
> Ambulances should be equipped with prehospital CPAP systems: high-flow mask CPAP or helmet CPAP.

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Noninvasive Ventilation Outside of Intensive Care Units

33

Davide Chiumello, Gaetano Iapichino, and Virna Berto

33.1
Introduction

When individuals with acute respiratory failure became unresponsive to standard medical therapy, they may require invasive mechanical ventilation. However, endotracheal intubation increases the risk of nosocomial infection, induces airway trauma, and requires the use of sedation.

Noninvasive ventilation (NIV), which avoids endotracheal intubation and its related complications, has been shown in several studies to be an effective treatment in selected patients with respiratory failure due to an acute exacerbation of chronic obstructive pulmonary disease (COPD), hypoxemic respiratory failure, community-acquired pneumonia, or cardiogenic pulmonary edema and in immunocompromised patients [1–3].

Although in randomized trials the reduction in intubation rates and death are the primary endpoint, in everyday clinical practice, the relief of dyspnea, palliation, and comfort are also acceptable goals of NIV, especially in patients with a poor prognosis or who refuse advanced life support.

Traditionally, all forms of ventilatory assistance have been managed in intensive care units (ICUs), where personnel, knowledge, skills, and monitoring capabilities amply exceed those of a general ward. Now, however, with the shortage of intensive care beds and the growing ease of application, NIV is frequently started outside the ICU not only in the emergency department under the indications and direct management of the duty anesthesiologist, but also in general wards with scant monitoring facilities and usually inadequate medical or nursing knowledge and skills [4].

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33.2
NIV Outside Intensive Care

The most common reported locations for the initiation of NIV are the ICUs, followed by the emergency departments and the general hospital wards [5]. In addition, NIV not only is initiated but also is maintained for hours and days outside the ICU.

The recent British Thoracic Society guidelines "Non-invasive Ventilation in Acute Respiratory Failure" suggested that NIV can be provided in a number of locations outside the ICU, including the high-dependency units and the respiratory wards [1]. "However, to optimize the efficacy and not to harm the patients, each hospital should have a specific designated area with an available staff cohort with appropriate experience, together with structures to ensure that patients requiring NIV can be transferred to this area with a minimum delay" [1].

A possible advantage of applying NIV outside the ICU is the possibility of starting NIV with more patients at an earlier stage of the acute respiratory failure, which is associated with minor utilization of medical resources.

A British survey conducted from 268 hospitals in 1998 showed that NIV was available in only 48% of these hospitals, in particular in 34% of the intensive care and in 16% of the general wards [6]. In addition, the criteria used to select the patients requiring NIV varied from different blood gas analysis values to a simple clinical judgment, such as exhaustion or failure to improve during standard treatment [6]. A study conducted at a university hospital in Canada found that NIV was most often begun in the emergency department, and the most common indications for the application were acute cardiogenic pulmonary edema and the exacerbation of COPD [7].

During a period of 1 year, Antro et al. found that 190 patients were admitted for acute respiratory failure, and for these 200 NIV trials were delivered [8]. The main indications were cardiogenic pulmonary edema (70%), acute exacerbation of COPD (39%), and pneumonia (48%); there was an overall success rate of about 60%.

A prospective study conducted in a typical British district general hospital (i.e., covering a population of 727,000 inhabitants) aimed to identify the rate of acute exacerbation of COPD; it found that 983 patients were admitted during a period of 1 year [9]. In more than 90% of the patients, an arterial blood gas analysis was recorded: 46% of these were hypercapnic; only 20% presented a respiratory acidosis. However, 20% normalized their pH on arrival in the ward, leaving 16% to meet criteria for NIV. Acidosis was the only variable associated with the subsequent ICU admission. Based on these data, the authors hypothesized that, for a general hospital covering a population of 250,000 inhabitants, every year 90 patients should be admitted for acute exacerbations of COPD, and 72 of these will require NIV.

A single retrospectively study reported that in general surgical patients NIV was administered in 40% directly on surgical wards. The majority of the patients received NIV following an emergency surgery, and the primary reasons were chest infection, acute respiratory distress syndrome, and heart failure [10].

33.3
Evidence of NIV Success Outside the Intensive Care Unit

The most commonly reported locations for starting NIV outside ICUs and high-dependency units were the emergency department and more recently a general hospital ward [5, 11], particularly a respiratory ward staffed by standard caregivers [1, 9]. However, to optimize the efficacy and avoid harm to patients, each hospital should have a specific designated area staffed by personnel with appropriate experience and with structures to ensure that patients requiring NIV can be transferred to this area with minimum delay.

33.3.1
Acute Exacerbation of COPD

The acute exacerbation of COPD is one of the most frequently cited reasons for requiring the use of NIV.

In a seminal study comparing NIV with conventional treatment in patients with COPD admitted to the hospital with respiratory failure and presenting arterial oxygenation less than 7.5 kPa and a carbon dioxide value higher than 6 kPa, Bott et al. showed that NIV improved gas exchange at 1 h and survival rate at 30 days [12]. The visual analog scores over the first 3 days showed significantly lower scores for breathlessness for the NIV group. Although the application of NIV outside the ICU can sometimes be a difficult and a time-consuming procedure, the authors did not find any difference in the nursing care required. Thus, the authors (several years ago) suggested offering NIV for every acidotic and hypercapnic compliant patients without a face abnormality for whom conventional therapy does not produce a prompt clinical response.

Similarly, in a multicenter study of patients with COPD with mild-to-moderate acidosis with a pH between 7.25 and 7.35 and with a carbon dioxide value higher than 6 kPa, Plant et al. showed decreased need for intubation and hospital mortality [13]. The NIV led to more rapid correction of acidosis and a greater decrease in respiratory rate compared with the standard group. In addition, 15% of the patients met the criteria for intubation, and the subgroup of patients that presented at enrollment with a pH below 7.30 had a significantly higher failure rate and hospital mortality than patients with a pH higher than 7.30. Hence, it is important to rapidly recognize the necessity for starting invasive ventilation. In contrast to the Bott et al. study [12], the group treated with NIV caused a modest but significant increase in nursing workload in the first 8 h of admission compared to those receiving a conventional treatment.

Two further studies, with similar admission criteria, did not show any statistical difference for gas exchange, rate of endotracheal intubation, length of stay, or mortality between the NIV and conventional treatments [14, 15] Compared to the two positive studies [12], in these the patients were enrolled relatively later after the hospital admission, and the NIV was only used for only a few hours every day.

Concerning the clinical predictors for NIV success at hospital admission in patients treated with NIV, Poponick et al. found only an improvement in pH and $PaCO_2$ during 30 min of clinical trials [16]. The failure to improve after 30 min of NIV should be an indication for the discontinuation and initiation, if indicated, of controlled mechanical ventilation.

However, it is important to note that these studies excluded patients with a pH lower than 7.25 because the prognosis without NIV is very poor. It would have been unethical not to administer the NIV and not to admit these patients directly to the ICU [17].

33.3.2
Acute Cardiogenic Pulmonary Edema

Acute cardiogenic pulmonary edema is a common medical emergency and has a hospital mortality varying from 10% to 20% [18]. Similar to patients with COPD, the rationale for using NIV in acute cardiogenic pulmonary edema is to not only improve gas exchange and respiratory mechanics but also decrease left ventricular afterload [19, 20]. However, the best therapy for treating an episode of acute respiratory failure due to acute cardiogenic pulmonary edema is still a controversial, and the potential for harm using NIV has not been completely excluded [21–28]. In a large randomized prospective study of patients with acute cardiogenic pulmonary edema presenting with severe arterial hypoxemia (a PaO_2/FiO_2 ratio less than 250 with an oxygen flow of at least 10 L/min) and a respiratory rate higher than 30 breaths/min and treated in the emergency department with NIV, no differences in the rate of endotracheal intubation or hospital mortality compared to conventional medical therapy were found [22]. However, the percentage of patients needing intubation was significantly lower in those with a $PaCO_2$ greater than 45 mmHg. After 30 min, patients receiving NIV had significantly higher oxygenation, lower respiratory rate, and better hemodynamics.

Subsequently, Gray et al. performed a multicenter study of 26 emergency departments, enrolling more than 1,000 patients with acute cardiogenic pulmonary edema randomized to three treatment groups: standard oxygen therapy, NIV delivered as continuous positive airway pressure (CPAP), and NIV as pressure support ventilation [29]. There were no differences in 7- and 30-day mortality and intubation rates between the three groups. However, NIV was associated with greater reductions in dyspnea, heart rate, acidosis, and hypercapnia than the standard oxygen therapy. Patients receiving CPAP or pressure support ventilation presented similar rates of tracheal intubation, admission to intensive care, and myocardial infarction.

The only studies that gave useful information are those that enrolled patients unresponsive to full medical treatment, testing NIV, or comparing NIV with invasive ventilation. A prospective trial in emergency departments with noninvasive pressure support ventilation by a mask on patients with acute pulmonary edema unresponsive to full medical treatment (morphine, oxygen mask, diuretics, nitrates) [30] showed that 90-min NIV was enough to restore respiratory competence in the oxygen mask, thus avoiding the need for ICU admittance. This is possible if the mean arterial pressure at emergency department admission is 95 mmHg or above (heart response to stress reaction) and the patient does not have COPD. All other patients have to be given invasive ventilatory support without delay.

33.3.3
Hematological Malignancy and Mixed Etiology

Especially in immunosuppressed patients, it is fundamental to limit the risk of nosocomial infection as much as possible. Consequently, NIV can play a significant role. Principi et al., in a small group of hypoxemic patients with hematological malignancies, found that NIV delivered directly in the hematology department with a helmet achieved better oxygenation with longer duration of application and higher survival rates compared to a historical group of patients [31]. However, in this study the hematologist and intensivists collaborated closely in treating the patients, illustrating the importance of interdisciplinary collaboration to ensure the efficacy of NIV and carefully evaluating the duration of treatment.

33.4
Monitoring

The minimum suggested monitoring for NIV patients should include regular assessment of the respiratory, hemodynamic, and neurologic functions by adequately trained personnel 24 h/day [1, 32, 33]. This implies

- Arterial blood gases after 1 h of NIV and at least every 2 h, with continuous monitoring of cutaneous oxygen saturation. Caregivers need to know the factors that can influence this [34]: anemia, ambient light, motion artifacts, skin pigmentation, or skin perfusion.
- Circulatory assessment: noninvasive blood pressure every 5–10 min, skin perfusion (cold, clammy, cyanotic), and urinary output.
- Electrocardiogram (EKG): continuous monitoring of rhythm at the second lead and if possible ST analysis.
- Overall continuous overall clinical evaluation: adequacy of respiratory mechanics, use of accessory muscles and, above all, neurological status.
- A standardized supervision system regarding length of treatment is needed (call if oxygen saturation in 1 h does not reach 90% or falls below this level). Complete material for emergency intubation should be immediately available.

33.5
Conclusion

- NIV can be delivered outside ICU in selected patients with respiratory failure.
- Minimum NIV monitoring showed include regular assessment of the respiratory, hemodynamic, and neurological functions.
- Carefully check patients in the first 30-90 minutes after starting NIV.
- Consider a precocious admission in Intensive Care in non-responsive NIV patients.

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Noninvasive Positive Airway Pressure and Risk of Myocardial Infarction in Acute Cardiogenic Pulmonary Edema

34

Giovanni Ferrari, Alberto Milan, and Franco Aprà

34.1
Introduction

Acute cardiogenic pulmonary edema (ACPE) is a common cause of respiratory failure. While many patients respond to conventional medical treatment with diuretics, vasodilators, morphine, and oxygen, a subset of patients develops severe respiratory failure and requires ventilatory support and endotracheal intubation (ETI). Noninvasive ventilation, administered either with continuous positive airway pressure (nCPAP) or with pressure support ventilation (nIPSV), has been employed in patients with severe respiratory distress, avoiding the need for ETI and reducing the complications related to intubation.

Both nIPSV and nCPAP have been successfully used in ACPE, improving gas exchange and vital signs; however, it remains controversial whether one mode is superior to the other. Moreover, for several years many concerns existed about the use of nIPSV in ACPE because a higher percentage of myocardial infarction was observed in patients treated with nIPSV.

The objective of this chapter is to analyze, according to recent data existing in literature, the relationship, if any, between noninvasive ventilation and development of new cases of acute myocardial infarction in patients with ACPE.

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34.2
Rationale for the Use of Noninvasive Ventilation in Acute Cardiogenic Pulmonary Edema

ACPE is a common cause of acute respiratory failure. In these patients, the main priority is to achieve adequate oxygenation levels to prevent organ dysfunction and the onset of multiple organ failure. The maintenance of an oxygen saturation (SpO_2) in the normal range is important to maximize oxygen delivery to the tissues. Notwithstanding optimal medical treatment with vasodilators, diuretics, morphine, and supplemental oxygen, a subset of patients with severe respiratory distress is not able to improve gas exchange and requires ETI. ETI is associated with significant morbidity, increased hospital length of stay, and upper airway complications.

In several randomized trials, the application of positive intrathoracic pressure (ITP), by either nCPAP or nIPSV, has been employed for the treatment of patients who do not respond to standard medical treatment (SMT) and require respiratory assistance for the severe respiratory failure due to the ACPE, avoiding the need for ETI.

With nCPAP, positive pressure is constantly applied to the airway throughout the entire respiratory cycle to a spontaneously breathing patient. nIPSV is a mode of partial ventilator assistance in which the positive pressure increases during the inspiratory phase; however, the airway pressure is maintained positive also during expiration, although to a lesser extent, the so-called positive end-expiratory pressure (PEEP). Compared to nCPAP, nIPSV has the potential to unload the respiratory muscles more effectively and to reverse or to prevent more effectively ventilatory failure, alveolar hypoventilation, and hypercapnia. However, nIPSV, to the best of our knowledge, has no advantage as opposed to nCPAP in patients with ACPE in improving gas exchange and clinical–physiological parameters.

The mechanisms responsible for improvement of clinical parameters in patients with pulmonary edema may be more related to the application of an intrathoracic positive pressure than to the ventilatory technique itself. By increasing ITP, the application of positive pressure to the airways has both respiratory and hemodynamic effects. The respiratory effects are reduced oxygen cost of breathing and improvement in functional residual capacity and pulmonary compliance through recruitment of atelectatic alveoli. The hemodynamic effects are reduced venous return and lower left ventricle transmural pressure (i.e., afterload), which is primarily due to the reduction in the negative swings of the ITP during inspiration. In fact, in patients with ACPE, the increased amplitude of inspiratory swings leads to a lower ITP. A decreased ITP contributes to the increase in left ventricle afterload by increasing left ventricle transmural pressure (i.e., the difference between the inside and the outside of the heart). The increase in transmural pressure leads to a greater preload and afterload of the heart during diastole and systole, respectively. So, filling of the left ventricle is increased while emptying is reduced; the result is an increased left ventricle afterload and pulmonary vascular congestion. Instead, reduction in intrathoracic inspiratory pressure swings (by either nCPAP or nIPSV) reduces left ventricle transmural pressure and thus left ventricle afterload and pulmonary congestion. These mechanisms may explain why the application of a positive ITP (even without pressure support) improves pulmonary compliance and respiratory mechanics and optimizes left ventricle function, providing efficacy in treating patients with ACPE.

34.3
Noninvasive Ventilation and Risk of Acute Cardiogenic Myocardial Infarction

Although nCPAP and nIPSV are both effective in improving gas exchange and clinical–physiological parameters in ACPE, for several years many concerns existed about the use of nIPSV in ACPE. In 1997, Mehta and coworkers [1] interrupted prematurely a randomized study comparing nCPAP to nIPSV because a higher percentage of myocardial infarction rate was detected in patients enrolled in the nIPSV group. The authors pointed out the possible hazard of the higher intrapulmonary pressure delivered by nIPSV as opposed to nCPAP; in fact, they delivered nIPSV with a ventilator not provided with a sophisticated expiratory trigger system, so that air leaks, when present, could interfere with cycling off the system (so-called inspiratory hangup). However, the most important issue in this study was that 71% of patients in the nIPSV group, as compared to 31% of patients in the nCPAP group, had chest pain on study entry, suggesting that the observed difference in myocardial infarction rate was probably consequent to a bias in the selection and allocation of patients rather than to the ventilatory treatment assigned.

nCPAP has been shown to be safe and effective in patients with ACPE without increasing the myocardial infarction rate. Several studies have compared nCPAP to SMT in patients with ACPE. As assessed in a recent review of the Cochrane Collaboration [2], no difference in myocardial infarction risk was evident between the two groups. Moreover, in 1998, Takeda and coworkers [3] showed that nCPAP was safe and effective in treating patients with acute myocardial infarction complicated by ACPE. In this study, 22 patients with myocardial infarction associated with ACPE were randomized to nCPAP or to SMT. The ETI rate and hospital mortality were significantly lower in the nCPAP group.

In the following years, other studies suggested caution in treating ACPE with nIPSV. In 2000, Sharon and coworkers [4] compared, in patients with ACPE, the efficacy and safety of nIPSV plus a low dose of isosorbide dinitrate versus no ventilatory treatment plus high doses of isosorbide dinitrate. Forty patients were randomized to receive nIPSV plus standard dose isosorbide dinitrate versus oxygen plus high-dose isosorbide dinitrate. Patients treated with nIPSV had significantly more adverse events; in fact, the authors reported a high percentage of myocardial infarction and deaths in the first group compared to patients treated with medical therapy only. However, it should be noted that the amount of inspiratory and expiratory pressures applied to the airway in the nIPSV group were extremely low (with a mean of 9.3 [2.3] cmH_2O of pressure support and 4.2 [3.1] cmH_2O of PEEP), and that medical treatment was significantly different in the two groups, which makes comparison unfair. Moreover, the treatment was delivered in a prehospital phase by mobile intensive care units, which could have affected the correct application of noninvasive pressure support ventilation.

In an uncontrolled study, Rusterholtz [5] observed a higher percentage of myocardial infarction in patients with ACPE who failed nIPSV treatment, suggesting the need to avoid nIPSV in patients with acute myocardial infarction.

In another study, Crane and coworkers [6] did not observe a significant difference in myocardial infarction rate between patients treated with nCPAP as opposed to nIPSV, although a nonsignificant trend toward higher median peak creatine kinase was observed in the nIPSV group as compared to the nCPAP group.

Other randomized controlled studies [7–9] compared nCPAP to nIPSV and found no increased incidence of new onset of myocardial infarction even though the new onset of myocardial infarction was not the primary endpoint in these studies.

In studies comparing nIPSV to SMT, no association between nIPSV and myocardial infarction was observed. In fact in the studies of Masip and coworkers [10] and Nava [11] and coworkers, the authors found a similar proportion of patients with myocardial infarction in both groups.

Finally, the studies did not distinguish clearly between myocardial infarction at randomization or evolving during or after ventilatory treatment (with either nCPAP or nIPSV). Moreover, in many studies, myocardial infarction criteria were not clearly established, and it was not specified if myocardial necrosis was primary or if the increase in cardiac markers, which sometimes is observed in patients with ACPE, is secondary to an imbalance between myocardial oxygen demand and supply, even in absence of coronary stenosis. Cardiac markers, in fact, reflect myocardial necrosis but do not indicate its mechanism.

To clarify the potential harm of nIPSV in treating patients with ACPE, two randomized controlled studies [12, 13] analyzed the relation between the two ventilatory modalities (nCPAP and nIPSV) and the incidence of new onset of myocardial infarction. To avoid any potential confounding factor, both studies excluded all patients with a history of chest pain, electrocardiogram (ECG) modifications such as ST segment elevation or depression, T-wave inversion, new onset of left bundle-branch block, and elevated markers of cardiac ischemia at presentation. In both studies, myocardial infarction was defined according to the international guidelines [14], when chest pain, modifications of 12-lead ECG, and increase in cardiac markers (troponin I) were all present. The main difference between these two studies is that while the study of Bellone [12] included patients who had an airway tract infection as the main precipitating cause of ACPE, in our study [13] we included only patients with a cardiogenic precipitating factor. Both studies demonstrated than nIPSV is as effective as nCPAP in improving clinical–physiological parameters, and that the rate of new-onset myocardial infarction is not different with the two techniques.

According to a meta-analysis published in 2006 [15], there was no difference in myocardial infarction risk between patients treated with nCPAP and SMT. However, results comparing nCPAP to nIPSV showed a not significant trend toward an increase in new onset of acute myocardial infarction in patients treated with nIPSV (relative risk [RR] 2.10, 95% confidence interval [CI] 0.91–4.84; $p = 0.08$; $I^2 = 25.3\%$). But, this meta-analysis did not include three studies [9, 13, 16], two of them published in 2007 and one in 2008. The relative risk graph of acute myocardial infarction after inclusion of all studies comparing nCPAP and nIPSV is shown in Fig. 34.1.

Figure 34.1 shows that the risk ratio for acute myocardial infarction was not significantly different between patients treated with nIPSV and patients treated with nCPAP (RR 1.31, 95% CI 0.70–2.45; $p = 0.40$; $I^2 = 34\%$).

We can conclude that there is no evidence of the increase of new-onset acute myocardial infarction during treatment with nIPSV plus SMT as compared to nCPAP plus SMT.

Study or Subgroup	nIPSV Events	Total	nCPAP Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Bellone 2004	2	24	3	22	10.7%	0.61 [0.11, 3.32]	
Crane 2004	9	20	3	20	18.6%	3.00 [0.95, 9.48]	
Ferrari 2007	4	25	8	27	20.3%	0.54 [0.19, 1.57]	
Mehta 1997	10	14	4	13	25.2%	2.32 [0.96, 5.60]	
Moritz 2007	3	50	2	59	10.2%	1.77 [0.31, 10.18]	
Park 2004	0	27	0	27		Not estimable	
Rusterholtz 2008	3	17	4	19	15.1%	0.84 [0.22, 3.22]	
Total (95% CI)		**117**		**187**	**100.0%**	**1.31 [0.70, 2.45]**	
Total events	31		24				

Heterogeneity: Tau^2 = 0.20; Chi^2 = 7.56, df = 5 (P = 0.18); I^2 = 34%
Test for overall effect: Z = 0.85 (P = 0.40)

0.01   0.1   1   10   100
Favours experimental   Favours control

Fig. 34.1 Risk ratio of acute myocardial infarction in the studies comparing *nIPSV* (noninvasive pressure support ventilation) versus *nCPAP* (noninvasive continuous positive airway pressure). (Note: In their study, Rusterholtz and coworkers used proportional assisted ventilation [PAV] and not pressure support ventilation)

Key Recommendations

> nCPAP and nIPSV are equally effective in treating patients with severe acute respiratory failure secondary to ACPE.

> nCPAP is recommended, in addition to SMT, in patients with severe respiratory distress due to cardiogenic pulmonary edema (class IIa recommendation, level of evidence A).

> No difference in myocardial infarction risk has been shown between patients treated with nCPAP versus oxygen plus SMT or patients treated with nIPSV versus patients treated with oxygen plus SMT [2].

> nCPAP can be considered the first-line intervention in patients with ACPE because of the ease of use and of the lower cost and because nIPSV did not show better efficacy.

> In conclusion, the analysis of the current literature showed that noninvasive ventilation was not harmful, and that the rate of acute myocardial infarction was not different with both nCPAP and nIPSV.

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The Role of Continuous Positive Airway Pressure in Acute Cardiogenic Pulmonary Edema with Preserved Left Ventricular Systolic Function: A Preliminary Study

35

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35.1 Introduction

Many patients presenting with acute cardiogenic pulmonary edema (ACPE) have preserved left ventricular (LV) systolic function and are affected by diastolic dysfunction. In these patients, survival is similar to that of patients with reduced ejection fraction [1,2].

The aim of our preliminary study was to evaluate, in the emergency setting, the effects of continuous positive airway pressure (CPAP) in patients with ACPE and preserved LV systolic function with regard to resolution time.

35.2 Methods

Patients diagnosed with ACPE in the emergency room were recruited and enrolled. All patients underwent a morphological echocardiographic investigation shortly before CPAP. Two-dimensional echocardiogram was performed to qualitatively estimate the LV systolic function. Patients were considered to have LV systolic dysfunction if the ejection fraction was estimated as less than 45%. In the absence of this condition and significant valvular abnormalities, patients were considered to have preserved systolic function. The competency of emergency physician ultrasonographers was demonstrated through multiple steps.

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35.3
Study Design

Patients with preserved systolic function ACPE (group A = 18 patients) and systolic dysfunction ACPE (group B = 18 patients) were immediately submitted to echocardiographic evaluation just before they began treatment with nitrates, furosemide, morphine, and CPAP. Patients were fitted with an oronasal mask and were connected to CPAP adjusted to 10 cm H_2O. The fraction of inspired oxygen (FiO_2) was delivered to achieve an SpO_2 of 96%. When the goal SpO_2 of 96% was reached, the FiO_2 was maintained constant. Standard medical treatment was started and consisted of the following: continuous infusion of glyceryl trinitrate (15 mg/250 mL of saline) at a rate of 50 mL/h and subsequently according to the arterial blood pressure response, 60 mg furosemide IV, and 2 mg morphine sulfate IV as needed. We used a systemic systolic pressure of 90 mm Hg as the lower-limit criterion for stopping glyceryl trinitrate.

Resolution of acute pulmonary edema was defined as evident clinical improvement with both a respiratory rate of less than 30 breaths/min and SpO_2 of ≥96% with oxygen (FiO_2 = 0.35). The time for these criteria to be met was called the *resolution time.*

35.4
Results

The results are reported in Tables 35.1–35.3.

35.5
Discussion

The results of the present preliminary study showed that, in patients with ACPE and preserved LV systolic function, resolution time was not significantly different in comparison with patients affected by systolic dysfunction. Thus, this might suggest that CPAP in patients with ACPE with preserved or depressed systolic ventricular function is equally well tolerated. Diastolic dysfunction is determined by abnormal passive elastic properties of the left ventricle and an impaired process of active relaxation [3]. Under these circumstances, an elevated arterial blood pressure, myocardial ischemia, tachyarrythmia, or respiratory infection may result in acute pulmonary edema by an increase in atrial and venous pulmonary pressures [3].

The diagnosis of diastolic heart failure can be made on the basis of clinical evidence of heart failure in a patient has a normal LV ejection fraction, no valvular abnormalities and abnormal LV relaxation, diastolic distensibility, or diastolic stiffness on echocardiography [3].

Table 35.1 Baseline characteristics of the patients, history, and causes of acute pulmonary edema (data expressed as absolute number or mean ± standard deviation or number [%])

	Group A (n = 18)	Group B (n = 18)
Age	80.1 ± 6.8	75.2 ± 11.2
Sex, male/female	5/13	11/7
APACHE II score [4]	17.3 ± 2.4	16.8 ± 3
History		
Arterial hypertension	15 (83%)	8 (44%)*
OSAS	1 (5%)	1 (5%)
Diabetes	11 (61%)	9 (50%)
Atrial fibrillation	3 (16%)	4 (22%)
Chronic renal failure	3 (17%)	5 (28%)
Chronic heart failure	0	2 (11%)
Ischemic heart disease	7 (39%)	13 (72%)*
COPD	1 (5%)	0
Causes of ACPE		
Hypertension	12 (67%)	6 (33%)*
Myocardial infarction	5 (28%)	4 (22%)
Lower airway infection	7 (39%)	6 (33%)
Atrial fibrillation	3 (17%)	5 (28%)

COPD chronic obstructive pulmonary disease, *OSAS* obstructive sleep apnea syndrome
*$p < 0.05$ (Fisher test)

Aurigemma and colleagues [3] suggested that the effects of positive pressure therapy compromise venous return and decrease LV end diastolic volume, further limiting stroke volume and hence cardiac output because of the steep curve for LV diastolic pressure in relation to volume with resultant deterioration in hemodynamics. In contrast, our results seem to demonstrate that CPAP is equally as safe and effective in patients with impaired systolic and diastolic ventricular function and ACPE.

In conclusion, the results of this preliminary study showed that ACPE resolves as fast in patients with preserved systolic function as in those with systolic heart dysfunction. CPAP results well tolerated in both clinical conditions.

Table 35.2 Physiological data at study entry and progression

	Group A ($n = 18$)		Group B ($n = 18$)	
	Study entry	After 1 h	Study entry	After 1 h
pH	7.26 ± 0.13	7.35 ± 0.06*	7.27 ± 0.09	7.36 ± 0.05*
$PaCO_2$	51 ± 12.5	41.6 ± 7.8*	51.7 ± 10.2	42 ± 4.2*
PaO_2/FiO_2	182.2 ± 34.9	231 ± 72*	177.9 ± 39.9	232 ± 68*
SpO_2	76 ± 11.4	93.4 ± 4.1*	80.9 ± 9.3	92.5 ± 7.6*
HCO_3	21.8 ± 4.1	22.7 ± 3.4*	21.8 ± 3.5	23.1 ± 2.5*
Heart rate	111 ± 15	91 ± 17*	106 ± 19	88 ± 16*
Respiratory frequency	44 ± 4	24 ± 6*	41 ± 6	27 ± 6*
Systolic pressure	195 ± 22	128 ± 24*	170 ± 38**	134 ± 22*
Diastolic pressure	102 ± 15	67 ± 11*	86 ± 18**	75 ± 10*
Ejection fraction	>45%		$31\% \pm 5\%$**	
Glycemia	226 ± 67		236 ± 75	
BNP	1142 ± 643		1566 ± 1317	

BNP brain natriuretic peptide

*$p < 0.05$ (Student *t* test) in group between study entry and after 1 h

**$p < 0.05$ (Student *t* test) between groups at study entry

Table 35.3 Patients' outcome

	Group A ($n = 18$)	Group B ($n = 18$)	*p* value
CPAP treatment failure	1	1	–
In-hospital deaths	0	0	–
Endotracheal intubation	1 (5%)	0	0.99*
Resolution time[a]	64 ± 25 min	80 ± 33.4 min	0.17

CPAP continuous positive airway pressure

*Fisher's exact *p*, two tailed

[a]$n = 15$, Mann–Whitney U test

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Noninvasive Ventilation in Acute Lung Injury/Acute Respiratory Distress Syndrome

36

Ritesh Agarwal

36.1
Introduction

The acute respiratory distress syndrome (ARDS) is a clinical syndrome of lung injury characterized by severe dyspnea, refractory hypoxemia, and bilateral radiographic opacities. It is clinically defined by the following criteria: acute onset (less than 7 days), bilateral alveolar opacities consistent with pulmonary edema, $Pao_2/Fio_2 < 200$, pulmonary artery occlusion pressure less than 18 mmHg, or no clinical evidence of left atrial hypertension [1]. It is now recognized that there is a gradation of the severity of clinical lung injury: patients with less-severe hypoxemia (defined by a Pao_2/Fio_2 ratio of 300 or less) are considered to have acute lung injury (ALI), and those with more severe hypoxemia (defined by a Pao_2/Fio_2 ratio of 200 or less) are considered to have ARDS [1]. The mainstay of treatment for patients with ALI/ARDS is intubation and mechanical ventilation. However, endotracheal intubation is associated with significant morbidity, including upper airway trauma, barotrauma, and pneumonia [2–4]. As a result, any intervention that obviates the need for endotracheal intubation in ALI/ARDS is welcome.

Noninvasive ventilation (NIV) is the application of ventilatory support without an invasive endotracheal airway. It has revolutionized the management of diverse causes of acute respiratory failure (ARF) [5]. It not only avoids the need for endotracheal intubation but also reduces other complications, such as occurrence of nosocomial infections, duration of intensive care unit (ICU) stay, and the overall cost of hospitalization [6]. The term NIV encompasses a range of modes to augment alveolar ventilation without an artificial airway; continuous positive airway pressure (CPAP) and noninvasive positive pressure ventilation (NIPPV) are the most commonly used modes. In NIPPV, two different pressures are used: inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP), whereas CPAP maintains a constant positive airway pressure throughout the respiratory cycle. Theoretically, NIPPV may confer an advantage over CPAP by reducing the work of breathing during inspiration by providing additional inspiratory pressure [7].

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Relatively little debate surrounds its use for ARF due to exacerbations of chronic obstructive pulmonary disease [8]. However, its appropriate use to treat hypoxemic respiratory failure, particularly regarding patients with ALI/ARDS, remains unclear.

36.2
Physiological Basis for NIV in ALI/ARDS

There is a strong physiological basis for the use of NIV in ALI/ARDS. In a study on the physiological effects of NIV in ARDS, L'Her et al. measured breathing pattern, neuromuscular drive, inspiratory muscle effort, arterial blood gases, and dyspnea with NIPPV and CPAP. Although the oxygenation increased with CPAP, tidal volume increased only with NIPPV but not with CPAP alone. The work of breathing was lower and dyspnea relief was significantly better with the NIPPV. In patients with ALI/ARDS, NIPPV can thus reduce inspiratory muscle effort and dyspnea, and the application of optimal levels of CPAP can improve oxygenation [9]. However, one has to balance CPAP to improve oxygenation on the one hand and increase the pressure support above the CPAP to augment the tidal volume, relieve dyspnea, and diminish respiratory muscle effort on the other.

Patients with ALI/ARDS have diffuse alveolar damage and represent those with the most severe form of hypoxemic respiratory failure. The main goals of NIV in patients with ALI/ARDS are to improve oxygenation, unload the respiratory muscles, and relieve dyspnea. All these effects would translate into clinical endpoints of diminution of intubation rates. In patients with hypoxemic ARF, NIPPV is as effective as conventional ventilation in correcting gas exchange [10]. However, only limited data are currently available in the literature on the role of NIV in ARDS (Table 36.1) [11–19], and many recent studies have suggested that ALI/ARDS is an independent factor of NIV failure in patients with hypoxemic ARF [13, 20, 21]. Currently, the role of NIV in ALI/ARDS is at best controversial. In ARDS, transient loss of positive end-expiratory pressure (PEEP) during ventilation leads to lung derecruitment and may seriously compromise gas exchange. A systematic review suggested that the addition of NIPPV to standard medical therapy in patients with hypoxemic ARF reduces the rate of endotracheal intubation, ICU length of stay, and ICU mortality. However, the trial results were significantly heterogeneous [22]. Further, this review did not specifically report outcomes in patients with ALI/ARDS.

36.3
Studies Investigating the Use of NIV in ALI/ARDS

NIV has been successfully used in cases of ALI/ARDS, which are rapidly reversible with treatment [23, 24]. Only three randomized controlled trials with a total of 111 patients have studied the effects of NIV in ALI/ARDS [11, 20, 25]. A meta-analysis of these three studies suggested that the addition of NIV to standard care in patients with ALI/ARDS did not reduce the rate of endotracheal intubation or ICU mortality [26].

Table 36.1 Baseline characteristics of the patients included in studies investigating the use of NIV in ALI/ARDS

Study	Type of study	No. of patients	No. of ALI/ARDS	Age, mean (SD)	Female gender, No. (%)	Severity score, mean (SD)	Respiratory rate, mean (SD)	pH, mean (SD)	Pao_2/Fio_2 ratio, mean (SD)	$PaCO_2$, mean (SD)
Delclaux [11][a,b]	P	40	40	60 (18–88)	23 (39)	32 (6–87) SAPS II	34 (20–60)	7.42 (7.21–7.62)	140 (59–288)	37 (23–61)
Hilbert [12]	P	64	64	45 (16)	29 (45)	56 (16) SAPS II	–	–	128 (32)	–
Antonelli [13]	P	354	86	–	–	–	–	–	–	–
Confalonieri [14]	P	24	24	37 (9)	–	37 (9) SAPS II	35 (7)	7.44 (0.06)	122 (44)	29 (7)
Cheung [15]	P	20	20	51.4 (14.2)	9 (45)	–	28.9 (6.2)	–	137.5 (51.6)	33.9 (4.6)
Rana [16][c]	P	54	54	60 (46.2–83.7)	21 (39)	55.5 (43–103.5) APACHE III	23 (21–39)	7.37 (7.26–7.45)	112 (70–209)	36 (32–48)
Antonelli [17]	P	147	147	53 (17)	54 (37)	35 (9) SAPS II	36 (5)	7.4 (0.08)	110.5 (33.5)	40 (13)
Yoshida [18]	R	47	47	69 (11)	13 (28)	17.5 (8) APACHE II	29 (6)	7.35 (0.07)	123.5 (47)	38 (10)
Agarwal [19]	P	40	21	41.5 (23.9)	12 (57.1)	14.9 (2.9) APACHE II	48.3 (9.1)	7.42 (0.06)	131.2 (45.7)	32.2 (7.3)

ALI/ARDS acute lung injury/acute respiratory distress syndrome, *APACHE* Acute Physiology and Chronic Health Evaluation, *NIV* noninvasive ventilation, *P* prospective, *R* retrospective, *SAPS* Simplified Acute Physiology Score, *SD* standard deviation

[a]Details of the whole group receiving NIV and not specifically ALI/ARDS patients

[b]All values in this study were expressed as median (5th–95th percentile)

[c]All values in this study were expressed as median (range)

Antonelli et al. investigated the use of NIV for ARF in patients undergoing solid organ transplantation and observed more patients in the NIV group improving their PaO_2/Fio_2 ratios. Also there was significant reduction in intubation rates and ICU mortality overall, but this was not significant if only the subgroup of patient with ALI/ARDS was included [25]. Delclaux et al. found that, despite early physiologic improvement, the application of CPAP neither reduced the need for intubation nor improved outcomes in patients in ALI/ARDS [11]. In a large multicenter study investigating predictors of NIV failure in those with hypoxemic ARF, the intubation rate was 30% overall but was 51% in patients with ARDS. The study identified the following predictors of NIPPV failure: age more than 40 years, PaO_2/Fio_2 ratio less than 146, Simplified Acute Physiology Score (SAPS) II score more than 34, and the ARDS/pneumonia as an etiology of hypoxemic ARF. Confalonieri et al., in a series of severe pneumocystis pneumonia-related ARF, found that NIPPV avoided intubation in two thirds of patients. Not only was the avoidance of intubation associated with improved survival (100% vs. 38%), but also NIPPV decreased the need for invasive devices and ICU-related workload [14]. In an interesting observational study, Rana et al. observed NIV failure in all patients with ARDS and concomitant shock. In the subgroup of patients with ARDS but without shock, metabolic acidosis and severe hypoxemia predicted NIPPV failure [16]. In a multicenter study of 147 patients with ARDS, NIPPV decreased intubation rates in 54% of patients. A SAPS II score more than 34 and a PaO_2/FiO_2 score less than 175 after 1 h of NIPPV were independently associated with NIPPV failure and need for endotracheal intubation [17]. Our experience has also been almost similar. In a prospective study of 40 patients with hypoxemic ARF, we observed NIV failure in 57.1% (12/21) in the ALI/ARDS group and 36.8% (7/19) patients in the group with AHRF due to other causes. In the univariate logistic regression model, the only factor associated with NIPPV failure was the baseline PaO_2/FiO_2 ratio [19].

If we combine all the studies in Table 36.1, the intubation and ICU mortality rates with the use of NIPPV in ALI/ARDS are 47% (95% confidence interval [CI] 37–58) and 33% (95% CI 22–44), respectively (Figs. 36.1 and 36.2).

36.4
Practical Application of NIPPV in ALI/ARDS

NIPPV is definitely beneficial in selected patients with ALI/ARDS and can potentially prevent intubation in almost 50% of patients. The issue is the choice of the right patient who will benefit from NIV. The identification of patients with ALI/ARDS who should be managed with NIV is challenging, partly because there are few reliable selection criteria. Overall, the findings of various studies (Table 36.1) suggest a prudent approach, and it seems sensible to exclude patients who have multiorgan dysfunction or are poor candidates for NIV by virtue of inability to cooperate or protect the airway or because of excessive secretions. Clearly, NIV should be avoided in patients with shock, severe hypoxemia, or acidosis. The more difficult issue is to decide the threshold of severity for hypoxemia and acidosis beyond which NIV should be considered contraindicated. There are no answers for this, and the application of NIPPV in those with ALI/ARDS should be limited
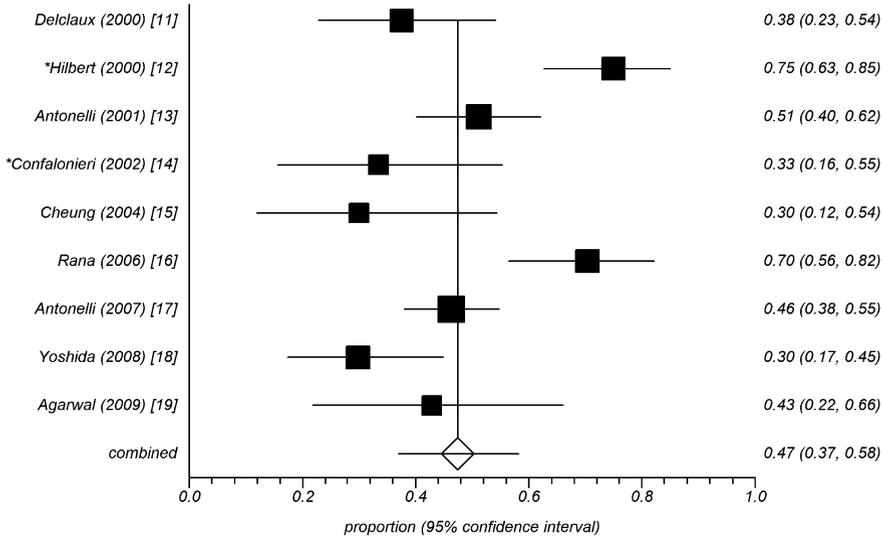
Fig. 36.1 Intubation rates in patients with ALI/ARDS (acute lung injury/acute respiratory distress syndrome) managed with noninvasive ventilation (random effects model). The intubation rates in the individual studies are represented by a *square* (percentage) through which runs a horizontal line (95% confidence interval). The *diamond* at the *bottom* represents the pooled intubation rates from the studies. *Immunocompromised patients
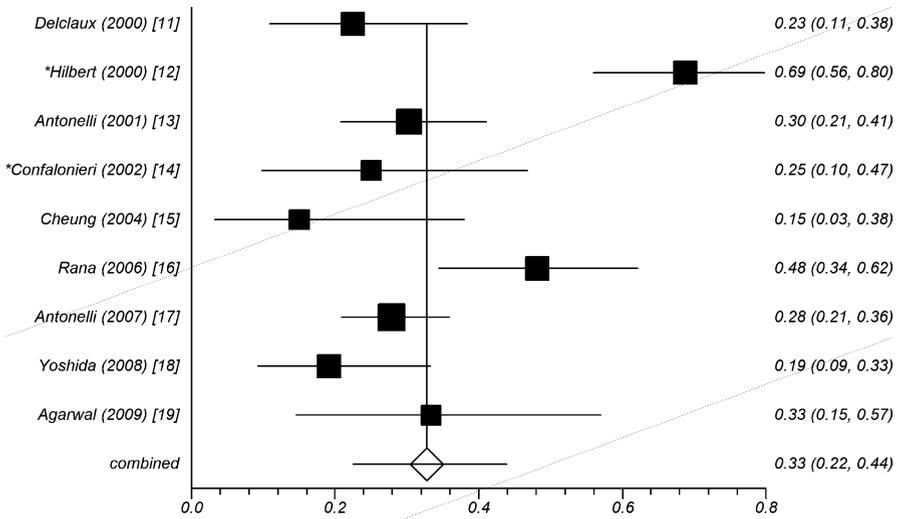
Fig. 36.2 Mortality rates in patients with ALI/ARDS (acute lung injury/acute respiratory distress syndrome) managed with noninvasive ventilation (random effects model). *Immunocompromised patients

Table 36.2 Practical approach to the use of noninvasive ventilation in patients with ALI/ARDS

1. Use judiciously.
2. Likely to benefit selected patients with ALI/ARDS, especially early during the course:
(a) Absence of severe hypoxemia at the outset
(b) No major organ dysfunction [12] (such as acute renal failure requiring dialysis)
(c) Absence of hypotension [16] or cardiac arrhythmias
(d) Simplified Acute Physiology Score (SAPS) II of 34 or more [17]
3. Use of NIPPV preferred over CPAP [9].
4. Use of critical care ventilator with oxygen blender preferred over domiciliary ventilator with external oxygen supply.
5. Position: head end elevated at 45° angle.
6. Interface: oronasal mask.
7. Protocol: start with IPAP/EPAP of 8/4 cmH_2O. IPAP is increased in increments of 2–3 cm H_2O (maximum 20 cm H_2O) to obtain an exhaled tidal volume of 6 mL/kg and a respiratory rate of 30 breaths/min. EPAP is increased in increments of 1–2 cmH_2O (maximum 10 cm H_2O) to ensure an oxygen saturation of 92% with the lowest FiO_2 possible [17].
8. Trial of NIPPV for 1–4 h:
(a) Monitor respiratory rate, pH, Pao_2/Fio_2 ratios
(b) High likelihood of failure if Pao_2/Fio_2 is 175 or less after 1 h [17]: close observation
9. Weaning: during the initial period, continuously administer NIPPV, then for majority of the time until oxygenation and clinical status improved. Progressively reduce the use of NIPPV in accordance with the degree of clinical improvement. Once EPAP requirements decrease to 5 cm H_2O, evaluate while the patient is breathing supplemental oxygen without ventilatory support for 15 min. NIPPV is discontinued if the patient maintains a respiratory rate of 30 breaths/min or less and a Pao_2 of 60 mmHg with an FiO_2 of 0.3 without ventilatory support and activation of the accessory muscles of respiration [28].
10. Watch for late failures even if patients show early improvement.
11. Close monitoring of respiratory, cardiovascular, and arterial blood gas parameters.
12. Facilities for intubation and invasive ventilation must be readily available.

ALI/ARDS acute lung injury/acute respiratory distress syndrome, *CPAP* continuous positive airway pressure, *EPAP* expiratory positive airway pressure, *IPAP* inspiratory positive airway pressure, *NIPPV* noninvasive positive pressure ventilation

to hemodynamically stable patients who can be closely monitored in the ICU, where endotracheal intubation is promptly available. A reasonable clinical approach would be to use NIV judiciously in patients with ALI/ARDS (Table 36.2). Although the optimal duration of the initial NPPV trial remains uncertain, a response within 1–4 h of initiation is a reasonable expectation. Finally, patients who are failing NIV trial should be promptly intubated and mechanically ventilated as delays in endotracheal intubation in patients managed with NIV have been associated with decreased survival [27].

36.5
Conclusions

ARDS represents one the ultimate frontiers in investigating the application of NIPPV in patients with ARF, and achieving a 50% reduction in intubation rate would positively affect ARDS outcome. The challenging issue is the proper identification of patients who are likely to benefit from NIPPV and avoiding potential complications of a delayed intubation.

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Noninvasive Positive Pressure Ventilation in Acute Hypoxemic Respiratory Failure and in Cancer Patients

37

S. Egbert Pravinkumar

37.1
Introduction

Acute respiratory failure (ARF) is a common occurrence in cancer patients and is associated with a high mortality rate. The role of NPPV in immunosuppressed, hematological malignancies, and solid tumor is an area that interests researchers and clinicians alike. Several randomized controlled trials and systematic reviews have confirmed the benefits of noninvasive positive pressure ventilation (NPPV) in patients with exacerbation of chronic obstructive pulmonary disease (COPD). Benefits achieved from NPPV in COPD patients are largely due to avoidance of invasive mechanical ventilation (IMV) and its complications including worsening of preexisting infections, morbidity and mortality, ventilator associated pneumonia (VAP), ventilator associated lung injury, increased need for sedation resulting in prolonged ventilation, ventilator dependence, and upper airway complications related to endotracheal tube [1]. The use of NPPV in COPD with hypercapneic ARF is no longer debated and is now considered as first-line intervention before considering endotracheal intubation (ETI) and IMV.

The role of NPPV has been most recently studied in hypoxemic ARF. In this group of patients, several studies have shown that NPPV not only reduced mechanical ventilation, length of intensive care unit (ICU) stay but was associated with fewer complications [2]. Since one of the major benefits of NPPV is the reduction of nosocomial infection, patients who are at high risk such as immunosuppressed, hematological malignancies, chemotherapy induced neutropenia, and organ transplantation patients may be particularly likely to benefit from NPPV. Recent guidelines published by the American Thoracic Society and the Infectious Diseases Society of America in the management of nosocomial infections has provided high grade evidence based recommendations in the prevention of nosocomial infections. The guideline recommends the use of NPPV whenever appropriate in the management of ARF and the avoidance of ETI and IMV whenever possible [3].

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37.2
Epidemiology of Hypoxemic ARF

Hypoxemic ARF is the most common reason for ICU admission and ventilatory support. An epidemiological prospective survey (Carlucci) of 42 ICUs in Europe (26 university and 16 nonuniversity hospitals) looked at 1,337 admissions over a period of 3 weeks; 689 patients required ventilatory support. ETI and IMV was the mode of treatment in 581 (84%) and NPPV was used as first-line treatment in 108 (16%). The conditions precipitating ARF were hypoxemic ARF, including acute cardiogenic pulmonary edema (55%), coma (30%), and hypercapneic ARF (15%).

In this epidemiological study of patients who needed ETI and IMV, mortality rates were much higher in the hypoxemic ARF group than hypercapneic ARF (47% vs 27%). The 28-day hospital mortality was 41% in those who needed ETI and IMV, compared to 22% in those who received NPPV ($p < 0.001$). The incidence of VAP was 2% in those who were successfully managed with NPPV compared to 19% in those who needed IMV ($p < 0.002$) [4].

37.3
NPPV in Hypoxemic ARF

Studies in acute hypoxemic respiratory failure (ARF) using noninvasive positive pressure ventilation (NPPV), has shown varied results and the outcome is dependent on selective population. More and more trials are emerging looking at the benefits of NPPV in selected groups with hypoxemic ARF. Systematic review randomized controlled trials (RCTs) of NPPV use in hypoxemic ARF [5] shows convincing evidence that NPPV decreased the need for ETI and IMV. NPPV also decreased the ICU length of stay and mortality. However, unlike hypercapneic ARF, hypoxemic ARF encompasses several diagnoses and comprises a heterogeneous population. This heterogeneity was observed in multiple studies. Hence, it would be misleading to conclude that NPPV is beneficial for all patients with hypoxemic ARF. Notably NPPV has had limited success in patients with acute respiratory distress syndrome (ARDS) and lobar consolidation. Further study of specific patient groups with hypoxemic ARF will provide insight in the management of ARF using NPPV [5].

A well conducted systematic review assessed the effects of NPPV for patients with Hypoxemic ARF not due to CPE. The study looked at eight RCTs from six countries that compared NPPV plus standard therapy versus standard therapy alone in 366 patients. The study results are as follows; NPPV was associated with a significantly lower rate of ETI and IMV (RR 0.23, 95%CI: 0.10, 0.35), reduction in length of ICU stay of 1.9 days (95%CI: 1, 2.9), reduced ICU mortality of 17% (95%CI 8, 26) and no statistically significant effect on hospital mortality. Based on currently available evidence, routine use of NPPV for hypoxemic ARF is not recommended. However based on selected population analysis, NPPV should be strongly considered for immunosuppressed and post-thoracotomy patients and their use in other groups should be carefully monitored to ensure beneficial effect [1].

37.4
ARF in Imunosuppressed and Cancer Patients

Hypoxemic ARF is a common occurrence in immunocompromised and in malignancies, both hematological malignancy and solid tumor. It is often the dreaded condition in cancer patients due to associated high mortality related to ETI and IMV. New types and modalities of chemotherapy and radiation therapy, circulating pluripotent hematopoietic cell grafts and bone marrow transplantation have contributed to the increase in successful treatment of solid and hematologic malignancies. However, these regimens may predispose patients to various life-threatening complications, such as infection, hemorrhage, capillary leak syndrome, radiation toxicity, or drug-related toxicity. The lung is the target organ most frequently involved in these complications.

Since most of the cancer patients have muscle fatigue, diffuse pulmonary infiltrates, and depressed organ function and reserve due to treatment, they are more vulnerable to rapid clinical deterioration and developing ARF. The commonest type of respiratory failure in this group of patients is "lung" failure, although it is not uncommon to see "ventilatory pump" failure as the cause of ARF. Several studies [6] have looked at the outcome of patients with acute myelogenous leukemia and recipients of bone marrow transplantation, who needed ETI and IMV. Only two variables have been shown to be independently associated with mortality of cancer patients in the ICU and neither the type of cancer (i.e., solid or hematologic malignancy) nor the presence or absence of neutropenia was independently associated with mortality. The first independent predictor of ICU mortality is the severity of the patient's clinical condition on admission as recorded by various scores, such as the Simplified Acute Physiologic Score (SAPS I and SAPS II) and the Acute Physiologic and Chronic Health Evaluation (APACHE II and APACHE III). The second and "stronger" independent predictive factor of mortality is the need for ETI and IMV, since VAP and worsening of a preexisting infection are significant complications in intubated patients.

37.5
NPPV in Cancer Patients

In a retrospective study of patients with solid or hematologic cancer admitted to ICU for ARF, the survival rate for cancer patients ($n = 105$) in the period 1996–1998 was significantly higher than those ($n = 132$) admitted between 1990 and1995 (39% vs 18%, respectively; $p = 0.0003$). Multivariate analysis showed that, the use of NPPV in the later period was associated with a marked improvement in survival [7]. Other studies using NPPV in cancer patients are summarized in Table 37.1.

37.6
Indications and Contraindications

The immediate goals of NPPV therapy should be aimed at relieving patient symptoms and reducing the work of breathing. The intermediate goals should be to improve and stabilize gas

Table 37.1 NPPV in cancer patients with hypoxemic ARF [6]

Study	Patient population and intervention	Outcome
Tognet 1994	Hematological malignancies (HM)	ICU mortality: IMV vs NPPV: 100% vs 55% significantly lower mortality in NPPV group
Meduri 1994	Cancer patients with do-not-intubate orders Solid tumor (ST)and HM	Improved survival and hospital discharge in NPPV group
Conti 1998	Immunosuppressed and HM	Improvement in blood gases and respiratory rate <1 h of NPPV – 68% survived to discharge
Hilbert 2000	Fever, neutropenia, AHReF, HM Intermittent CPAP	CPAP avoided ETI in 25% CPAP success: all survived
Hilbert 2001	RCT, NPPV vs standard care (SC) fever, pulmonary infiltrate, immunosuppresed, HM n = 52	Reduced ETI, complications, ICU death, and hospital death in NPPV group
Principi 2004	Pulmonary infiltrate, HM Mask vs helmet NPPV	NPPV intolerance: helmet NPPV(0%) vs mask NPPV (50%)
Rocco 2004	Helmet NPPV vs Mask NPPV Fever, immunosuppressed, organ transplant, pulmonary infiltrates, HM	Helmet NPPV vs Mask NPPV ETI: 36% vs 63% ICU Mortality: (31%) vs (47%) Hospital mortality: 37% vs 53%
Meert 2003	Solid tumors and HM NPPV for hypoxemic ARF	ICU survival: 57% ETI: 25%

exchange, optimize patient ventilator comfort and synchrony, and the ultimate goal is avoidance of ETI and IMV. The success of the therapy depends on a highly motivated, committed and knowledgeable team, and careful patient selection with the help of a well structured NPPV guideline (Table 37.2). Application of NPPV early in the process of ARF along with careful and rigorous monitoring is vital to the success of NPPV therapy. Other factors include; location, availability of wide variety of interfaces to suit the patients morphological and comfort needs.

NPPV failure should be identified early on in order to avoid unnecessary delay in ETI and IMV. For this reason several centers offer NPPV therapy in the ICU, high dependency care units and respiratory intermediary care units. Staffing ratios and 24 h physician cover is also important in considering NPPV outside the ICU. Some of the predictors of NPPV failure include; elevated ICU severity of illness scores, presence of ARDS or lobar consolidation, PaO_2/FiO_2 ratio <150 even after 1 h of NPPV, pH− <7.30 on initiation, and failure of pH improvement in 1–2 h

Table 37.2 NPPV for cancer patients (©The University of Texas M.D. Anderson Cancer Center NPPV guideline)

Eligibility criteria	Contraindications
Clinical (all)	Absolute (any)
– Acute respiratory failure	– Cardiopulmonary arrest
– Dyspnea	– pH < 7.25
– Accessory Resp. muscle use	– Upper airway obstruction
– Paradoxical abdominal movement	– Facial trauma
– RR ≥ 25	– Uncontrolled arrhythmia
– Adequate airway protection	– Untreated SBP ≤ 90 mmHg
– Adequate secretion clearance	– GCS ≤ 8
	– Undrained pneumothorax
Gas exchange criteria (any)	Relative
– $FiO_2 ≥ 0.60$	– Copious secretions
– $PaO_2 ≤ 60$ mmHg on room air	– Confusion/agitation
– $PaO_2 ≤ 75$ mmHg on any FiO_2	– GCS 9–13
– $PaO_2:FiO_2 < 200$	– Two or more organ failure
– $PaCO_2 ≥ 50$	– Focal consolidation on CXR
– pH ≥ 7.30	
Radiological criteria (any)	– Bowel obstruction
– Pulmonary Infiltrates	– Recent facial/ upper airway/GI surgery
– No pneumothorax	– Pregnancy
	– Thoracic surgery < 6 weeks

Table 37.2 (continued)

Blood gases 1 and 4 h post NPPV	Blood gases 1 and 4 h Post NPPV
NPPV success	NPPV failure
Clinical criteria (two or more)	Clinical criteria (any)
– Patient tolerates NPPV	– Patient intolerant to NPPV
– Tolerates periods "off" NPPV	– Persistent dyspnea
– Dyspnea reduced (score)	– RR $\geq$ 35
– RR $\leq$ 35	– Urgent need for ETI
– Awake and alert	– Development of contraindications
	– GCS $\leq$ 8 (worsening mental status)
Gas exchange criteria (2 or more)	Gas exchange criteria (any)
– Improvement in ABG	– Failure of ABG improvement
– $FiO_2 \leq 0.7$ and $SpO_2 > 92$	– $FiO_2 \geq 0.7$ and $SpO_2 \leq 92$
– $PaO_2 \geq 65$ on $FiO_2 < 0.6$	– $PaO_2 \leq 65$ on $FiO_2 > 0.6$
– pH $\geq$ 7.30	– pH $\leq$ 7.30
– $PaO_2:FiO_2 \geq 100$ from baseline	– $PaO_2:FiO_2 \leq 100$ from baseline

37.7
Complications of NPPV

Complications of NPPV are predominantly interface related, such as, facial discomfort (30–50%), skin erythema (20–35%). Less common (5–10%) problems include; claustrophobia, nasal ulceration, and acneiform rash. Complications related to pressure and flow include; nasal congestion (20–50%), sinus/ear pain (10–30%), nasal/oral dryness (10–20%), eye irritation (10–20%), gastric distension (5–10%). Major complications such as aspiration pneumonia, hypotension, and pneumothorax are less than 5%.

Key Recommendations

❯ NPPV can be effectively used in the management of ARF.
❯ It has several benefits including; decreased rate of ETI and IMV, decreased VAP, decreased mortality, decreased ICU, and hospital length of stay.
❯ Patient selection and early application are crucial.
❯ Highly committed and motivated team along with a structured guideline is important in NPPV success.

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Noninvasive Ventilation as a Preoxygenation Method

38

Christophe Baillard

38.1
Introduction

Usually, preoxygenation (3 min of spontaneous ventilation with bag and mask with 100% O_2) is recommended in delaying arterial desaturation during the apnea related to endotracheal intubation (ETI) procedures [1]. In a healthy apneic adult patient, the time course to reach an oxygen hemoglobin saturation (SpO_2) <90% after 3 min preoxygenation is about 6–8 min. Numerous factors are involved in the oxygen loading process during preoxygenation, such as those able to interfere with alveolar, arterial, tissue, and venous compartments and those interacting with the delivered inspired fraction of oxygen (FiO_2). The extent of oxyhemoglobin desaturation also depends on the duration of apnea, which corresponds to the time elapsed between the onset of apnea and successful intubation with the subsequent oxygen provision. The difficulties encountered during airway management prolong the duration of apnea. Finally, the capacity for oxygen loading and the condition of intubation will be determinants of the efficiency of preoxygenation.

To consider the factors affecting the rate of oxyhemoglobin desaturation during apnea, Farmery and Roe developed a model [2]. Of note, this model was adapted to a postoperative scenario to predict the consequences of such a nonphysiological condition on the time course of arterial oxyhemoglobin desaturation. The authors stated that it represented to some extent a worst-case scenario in which the combined effect of hypovolemia (4 L), reduced cardiac output (4 L/min), anemia (10 g/dL), increased V/Q (ventilation/perfusion ratio) mismatch and increased shunt (0.1), preapnea hypoventilation, and reduced alveolar volume (2 L) are involved. The combination of such abnormalities (which are usual in critically ill patients) dramatically accelerated the rate of oxyhemoglobin desaturation. Without preoxygenation, the oxyhemoglobin saturation reached 85% only 23 s after the onset of apnea.

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The expected duration of apnea in critically ill patients requiring intubation is also of interest. In a prospective study investigating emergency tracheal intubations outside the operating room ($n = 297$), Schwartz and coworkers showed that more than two attempts at intubation were required in 11% of cases [3], with most intubations performed in critical care units (78%). Jaber and colleagues reported data on 253 intubations carried out in seven intensive care units (ICUs) [4]. They observed that 13% of the intubations still required two attempts for success. When now considering both the rate of oxyhemoglobin desaturation and complexity of intubation, it is not surprising to observe that severe hypoxemia ($SpO_2 < 80\%$) occurred in more than 25% of patients during the intubation performed in ICUs [4]. There is also evidence for a strong relationship between the difficulty of intubation and hypoxemic events. In a large prospective cohort of 2,833 patients requiring emergency intubation outside the operating room, Mort et al. found that the relative risk of severe hypoxemia occurrence (defined as $SpO_2 < 70\%$) was multiplied by 14 when the procedure required more than two attempts [5]. Two major determinants can be individualized: the amount of oxygen that can be stored before the onset of apnea and the complexity of intubation. We now focus on the preoxygenation.

38.2
Preoxygenation in Critically Ill Patients

Whereas the complications associated with airway management in critically ill patients have been well identified for several decades, the effectiveness of preoxygenation in the ICU was evaluated for the first time only 4 years ago. We have Mort to thank for the comprehensive study that began the investigation into preoxygenation [6, 7]. In that prospective and observational study, the effectiveness of preoxygenation was assessed in 42 critically ill ICU patients requiring invasive ventilation (unstable patients). At the same time, 34 American Society of Anesthesiologists class IV patients scheduled for cardiac surgery were investigated as a control group (stable patients). Unstable patients were already receiving a range of 60–100% oxygen therapy in concert with continuous positive airway pressure (CPAP) as a ventilatory support ($n = 16$) or with a nonrebreathing device. The preoxygenation consisted of use of a manual resuscitator bag with reservoir (tube) connected to high-flow oxygen in the flush mode (20 L/min). (Such a method was consistent with the preoxygenation consideration discussed.) The effectiveness of preoxygenation was defined as the ability to improve Pao_2, the arterial pressure of oxygen (ETO_2, end-tidal O_2, was not monitored in this study). Among unstable patients, 4 min of preoxygenation resulted in little change in their baseline Pao_2 (+37 mmHg) compared to the stable preoperative patients (+325 mmHg). Moreover, in the unstable patients, two populations were individualized according to the diagnosis of ventilatory failure. In those requiring intubation for airway protection, the preoxygenation improved Pao_2 by 105 mmHg, whereas in those suffering from cardiopulmonary disease (the most severe hypoxemic patients) preoxygenation was marginally effective, with only +22 mmHg increase in PaO_2.

The results are quite alarming and are open to criticism. Considering that the amount of oxygen already delivered did not correctly oxygenate the patient, the little effect of the subsequent preoxygenation on Pao_2 was expected. However, the technique of preoxygenation

described was well designed, even probably optimized regarding the oxygen delivery (high-flow oxygen at 20 L/min in the flush mode) and that the Dr. Mort's patients are representative of "true" critically ill patients usually managed in the ICU. Moreover, conversion from CPAP to a bag-mask system was unlikely to improve PaO_2. Again, the conversion from noninvasive ventilation (CPAP) to a bag-mask system for the purpose of preoxygenation was unlikely to be effective, but such a conversion is still used throughout ICUs [4].

Atelectasis is a common problem in critically ill patients. When preoxygenation is initiated to manage patients who manifest acute respiratory failure, the limited alveolar volume and the enhanced shunt fraction are important determinants in the underlying lung disease. The use of high FiO_2 delivery is also a well-known contributing factor affecting early atelectasis formation during preoxygenation. This phenomenon, called *absorption atelectasis*, occurs when the rate of the alveolar gas absorption into the blood exceeds the flow gas delivered to the alveoli. Complete airway occlusion and very low ventilation/perfusion ratio are the two situations promoting absorption atelectasis [8].

38.3
Noninvasive Ventilation as a Preoxygenation Method

The ability of noninvasive ventilation (NIV) to prevent atelectasis formation in healthy and obese patients during preoxygenation and subsequent induction of anesthesia in the operating room has been well investigated by Magnusson and coworkers [8].

To address this problem, we conducted a prospective, randomized study in critically ill patients requiring tracheal intubation for invasive ventilation. Patients manifested hypoxemic acute respiratory failure before inclusion [9]. We compared preoxygenation prior to ETI with the use of NIV to a bag-valve mask device for 3 min. For the control group ($n = 26$), preoxygenation was performed using a nonrebreather bag-valve mask with a reservoir driven by 15 L/min oxygen. Patients were allowed to breathe spontaneously with occasional assistance (usual or conventional preoxygenation method). For the NIV group ($n = 27$), pressure support ventilation (PSV) was delivered by an ICU ventilator through a face mask adjusted to obtain an expired tidal volume of 7–10 mL/kg. The FiO_2 was 100%, and a positive end-expiratory pressure (PEEP) level of 5 cmH_2O was used. The baseline characteristics of the two groups were similar in term of age (62 years) and Simplified Acute Physiologic Score (52). Pneumonia was the main diagnosis on admission (68%). The mean PaO_2 value was below 70 mmHg under 15 L oxygen flow in both groups.

Preoxygenation improved SpO_2 in the control group from 90% ± 5% to 93% ± 6% and in NIV group from 89% ± 6% to 98% ± 2% (mean ± standard deviation [SD], $p < 0.05$). However, SpO_2 was statistically higher in the NIV group, and preoxygenation failed to improve SpO_2 in 6 patients receiving the conventional method ($p < 0.05$). During intubation, 12 patients in the control group and 2 in the NIV group had a fall in SpO_2 below 80% ($p < 0.01$). Conventional preoxygenation failed to improve the mean PaO_2 value whereas PaO_2 increased significantly in the NIV group. At the end of preoxygenation, the PaO_2 was statistically higher in the NIV group compared with the control group (203 [116–276] vs. 97 [66–163] mmHg; median [Interquartile Range], $p < 0.01$), and this difference persisted at 5 and 30 min after ETI.

The result of this study was opened to criticism because the Fio_2 delivered in the control group was not measured. If the Fio_2 delivered was suboptimal, this simple fact could have explained the difference reported. In acute respiratory failure, similar to invasive ventilation, NIV improves oxygenation by delivering a high oxygen concentration, unloading respiratory muscle efforts, recruiting alveoli, and increasing lung volumes [10]. By recruiting alveoli, positive pressure ventilation not only enhances lung volume (the store) but also reduces true shunt. The latter effect improves the Pao_2/Fio_2 ratio, resulting in more complete hemoglobin saturation in hypoxemic patients. Prevention of atelectasis formation during preoxygenation can be prevented with a CPAP of 6 cm H_2O, whereas reexpansion usually requires a higher level of pressure [8]. Further studies are required to ascertain whether short-duration NIV, as used for the preoxygenation, is effective at reducing true shunt.

NIV as a preoxygenation method increases both the contents (Fio_2/FAO_2 [alveolar fraction of oxygen]) and the container (FRC, functional residual capacity) and could be view as one of the best ways to enhance the oxygen stores before apnea. However, little is known about the time necessary to load the oxygen stores, and 3 or 5 min may be short. El-Khatib and colleagues described the beneficial effect of noninvasive bilevel positive airway pressure (BiPAP) for the purpose of preoxygenation in a critically ill morbidly obese patient [11]. From a baseline SpO_2 and Pao_2 of 79% and 51 mmHg, respectively, the conventional preoxygenation (3 min using a circle system, tidal volume breathing at an oxygen flow rate of 5 L/min) improved the SpO_2 and Pao_2 only to 90% and 60 mmHg, respectively. After 3 min of BiPAP application (inspiratory positive airway pressure [PAP] of 17 cm H_2O and expiratory PAP of 7 cm H_2O, oxygen flow rate of 5 L/min), the SpO_2 and Pao_2 values increased to 95% and 81 mmHg, respectively. Finally, a change from 5 to 10 L/min oxygen flow further improved the SpO_2 and Pao_2 up to 99% and 95 mmHg, respectively. In our study, 3 min of noninvasive positive pressure ventilation was adequate to improve oxygenation and to reduce hypoxemia during intubation [9]. Moreover, the beneficial effect on Pao_2 was still observed 30 min later. One explanation could be the residual effect of NIV in recruiting alveoli and increasing lung volume.

PSV unloads the respiratory muscles through chemical or load-related reflex feedback [12]. In awake patients, the reduction of $Paco_2$, an important determinant of respiratory motor output, causes a reduction in the sense of dyspnea and greater acceptability of NIV. However, 3 min of preoxygenation using NIV (PSV + PEEP) failed to improve the $Paco_2$ value in critically ill patients [9].

38.4
Noninvasive Ventilation Complications and Outcome

Critically ill patients are usually considered to have a full stomach, and pulmonary aspiration of gastric contents during ETI is frequently encountered in this clinical setting [3]. Facial mask positive pressure ventilation may increase the gastric air content and may hence promote pulmonary aspiration. This risk is enhanced when the insufflation pressure is above 20 cmH$_2$O, a value easily obtained when using manual ventilation. In our study, NIV was used in a pressure-limited mode, and none of the NIV group of patients received

an insufflation pressure higher than 20 cmH$_2$O [9]. In addition, the NIV preoxygenation was followed by a rapid sequence induction known to avoid the regurgitation of gastric contents. Overall, regurgitation was observed in 3 patients, and new infiltrates were observed on the chest radiograph obtained after intubation in 4 of 53 patients. NIV did not increase regurgitation or new infiltrates. Duration of mechanical ventilation, ICU length of stay, and ICU mortality were not different between groups. However, the conclusion on morbidity and outcome was limited, and it is still uncertain whether NIV will improve clinical outcomes. From the result of that study, a French consensus guideline suggested that the use of NIV as a preoxygenation method could be used in hypoxemic critically ill patients [13]. A multicenter study is currently under way to find out whether NIV as a preoxygenation method is more effective at reducing the degree of organ dysfunction or failure than standard preoxygenation following ETI [14]. The results of this study could have a positive impact on airway management in critically ill patients.

38.5
Discussion and Recommendations

Critically ill patients are predisposed to severe oxyhemoglobin desaturation during intubation [4, 5]. For the intubation of hypoxemic patients, the usual preoxygenation is marginally effective [6, 7]. Theoretically, because NIV increases both the contents (Fio$_2$/FAO$_2$) and the container (FRC), it could be viewed as one of the best way to enhance the oxygen stores before apnea. A short application (3 min) of NIV is more effective at reducing arterial oxyhemoglobin desaturation than using a nonrebreather bag-valve mask with reservoir [9]. However, it is also important to consider that NIV may promote pulmonary aspiration by increasing the gastric air content. The impact of NIV on morbidity or mortality is currently under investigation. Careful analysis of the risks and benefits on an individual basis should hence be made until further studies are available for the intensivist dealing with hypoxemic critically ill patients.

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Influence of Staff Training on the Outcome of Noninvasive Ventilation for Acute Hypercapnic Respiratory Failure

39

José Luis López-Campos and Emilia Barrot

39.1
Introduction

The education and training of medical personnel in noninvasive ventilation (NIV) is essential in improving outcomes, reducing failures, and avoiding complications associated with the use of ventilation [1]. Furthermore, adequate training of staff provides a cost reduction in patient care. In this regard, a proper training period should be part of the education of respiratory health care professions who are part of the multidisciplinary respiratory team dealing with the NIV.

Respiratory physicians are key components of this multidisciplinary respiratory team. They should be familiar with the different diseases underlying the respiratory failure, treatments, and knowledge of how and when to initiate and control NIV.

Nurses are key actors in the management of patients under NIV. They provide 24-h patient care within the hospital setting, and their contribution is essential for the multidisciplinary respiratory team. The quality of the nurse's relationship with patients and their relatives may also be a key factor for the success of the ventilation. As a key in the coordination of patient care, nurses may contribute to the collaborative cost-effective approach for patients under NIV.

Physiotherapists need to work closely with other members of the multidisciplinary respiratory team to promote the best care for the patient on NIV. Physiotherapist treatment is achieved through a combination of education and intervention. The main goals are not only to mobilize secretions and aid expectoration but also to reduce fear and anxiety, dyspnea, and work of breathing [2].

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39.2
Influence of Staff Training Regarding Where NIV Occurs

The best location for an NIV treatment will depend on several factors, including particularly the skill levels of doctors, nurses, and therapists in this technique. If there are relatively few patients per month, NIV is best performed in a single location within every center to facilitate staff training and to maximize the results. Interestingly, when deciding where to start NIV, staff training and experience are more important than the location itself. An adequate number of NIV-skilled staff must be available 24 h a day. Ideally, NIV usually is best carried out in a single location with one nurse responsible for no more than a total of three to four patients every shift [3].

39.3
Use of Staff to Initiate NIV

NIV has been reported to be a time-consuming procedure, especially at the beginning of the training period. A number of studies on the intensive care unit have shown that a significant amount of time is required in the initial stages to establish the patient on NIV. However, there is a learning curve, and with time, these requirements smooth out, with no difference in workload between skilled nurses and doctors applying NIV and those who do not. Obviously, as more sophisticated ventilators become available, much more training would be needed. However, even in this case, this will be compensated with time and the plateau of the learning curve. So, although a considerable amount of time is needed when a unit first starts to provide NIV, as long as a critical mass of nurses and therapists remains, new staff will gain the necessary skills from their colleagues, and this amount of time will be similar to other units thereafter.

39.4
Importance of Training in NIV

It is well known that a proportion of patients will fail with NIV, requiring intubation and invasive mechanical ventilation. In this regard, it is important that personnel and the facility for intubation are rapidly available if needed. This is essential for a respiratory unit to avoid an increased mortality trend with NIV.

Several variables recorded at the time NIV is initiated and after a short period of ventilation have been described as predictive of the likelihood of success or failure with a reasonable degree of precision. One of the most important ones is the level of pH after a few hours of ventilation [4]. This reflects the importance of well-adapted ventilation from the beginning. Accordingly, there are several prognostic factors that depend on staff training, like leak minimization, coordination with the ventilation, and compliance.

In one study, a group of consecutive patients requiring NIV due to acute hypercapnic respiratory failure (AHRF) were included in a prospective observational cohort study

performed in conventional wards aiming to analyze variables related to NIV outcome for AHRF [5]. Although the number of patients was small, the authors were able to identify an inadequate use of NIV due to lack of personnel training in all patients in which NIV failed ($p = 0.007$). Some of the errors detected were that there was a bad-fitting mask with excessive leaks, the personnel did not know how to deal with ventilator alarms, the personnel did not know how to control oxygen therapy using high flow rates, or simply the ventilator was not used during that shift because the staff did not know how to operate it. The authors concluded that staff training is a key factor influencing NIV outcome. Centers attending patients with acute respiratory problems should have an area of focus in which this requirement is fulfilled. The application of NIV by a trained and experienced team, with careful patient selection, should optimize patient outcomes.

39.5
Training Programs

Training programs should build knowledge in a progressive manner to ensure knowledge about various topics regarding NIV. This training should be compulsory for all health care professionals dealing with NIV at any time, including not only respiratory and intensive care physicians but also nurses and physiotherapists.

Discussion of the training time needed for adequate training of health personnel involved in the NIV is variable between studies, and there are currently no agreed standards. There are guidelines and training protocols for a recommendation for training tailored to the type of school that are based mainly on the place where ventilation is applied. Some authors [1] have suggested that an initial session of 2 h three times a month may give a basis to start using NIV safely. These sessions can distance themselves in time with increasing experience of staff. Although the contents may vary slightly depending on the target audience (doctors, nurses, physiotherapists), generally they should include at least those topics in Table 39.1.

Table 39.1 Minimum requirements for a training program for noninvasive ventilation (NIV) in the acute setting

- Respiratory system:
  - Physiology
  - Symptoms and signs of respiratory failure
  - Main respiratory diseases leading to NIV
- NIV technique:
  - Types of ventilators
  - Definition and selection of the ventilator mode
  - Initial operation of the equipment
  - Selection of masks
  - Ventilator circuit
- Monitoring technique:
  - Noninvasive cardiorespiratory monitoring
  - Complications of NIV
  - Problem solving

Key Recommendations

> The education and training of medical personnel is essential in improving outcomes, reducing failures, and avoiding complications associated with the use of ventilation.

> When deciding where to start NIV, staff training and experience are more important than the location itself.

> The application of NIV by a trained and experienced intensive care unit team, with careful patient selection, should optimize patient outcomes.

> Centers attending patients with acute respiratory problems should have an area of focus in which staff training is a key element.

> The training time needed for adequate training of health personnel involved in the NIV is variable but should include repetitive sessions depending on the degree of expertise.

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Section VII

The Role of Sedation

Sedation for Noninvasive Ventilation in Intensive Care

40

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40.1
Introduction

At the end of the first decade of the 21st century, noninvasive ventilation (NIV) is increasingly being used to manage patients with acute respiratory failure (ARF). Notwithstanding the advantages of NIV in critically ill patients, NIV is associated with a high risk of failures, including patient refusal to continue the often-uncomfortable sessions. Compared with those who avoid intubation, patients who fail NIV have worse outcomes, including death, so maintenance of patient comfort to optimize the chances of success during NIV is an important goal of therapy. Since the description of ARF and its treatment with NIV and sedation with morphine and midazolam by Rocker et al. [1], the conventional approach to ventilation has been to use tracheal intubation in cases of low tolerance. Some authors have proposed the use of sedation to increase patient comfort and NIV tolerance. In a world survey on sedation for NIV [2], the physicians who responded reported using sedation or analgesia in less than 25% of patients. Current sedation practices were heterogeneous and mainly determined by clinical experience. These observations emphasize the lack of evidence-based information or recommendations for the use of sedation during NIV. Notwithstanding, if sedation could decrease NIV failure, it should be used with caution by a trained team with some recommendations.

40.2
Which Drug for Sedation?

In the world survey by Devlin et al., sedation and analgesia were more commonly used by North Americans than Europeans (41% vs. 24% for sedation, 48% vs. 35% for analgesia). In North America, benzodiazepine alone was the preferred agent (33%), followed by an

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opioid alone (29%). Europeans were less likely to use a benzodiazepine alone (25%) but more likely to use an opioid alone (37%). Sedation was usually administered as an intermittent intravenous bolus, outside a protocol, and was assessed by nurses using clinical endpoints rather than a sedation scale [2].

On a rational point of view, the ideal drug for sedation during NIV should be short acting, have a constant half-life, and have no accumulation in case of renal or liver failure. It also should not decrease respiratory drive or hemodynamics status. At the end, it should have anxiolytic and analgesic properties. Obviously, this drug does not exist. But some drugs, alone or in association, have pharmacological properties that are not so far from the ideal drug.

Remifentanil is an opioid with pharmacodynamic properties similar to those of other opioids but with a unique pharmacokinetic profile. It is a potent, short-acting opioid with a μ-selectivity. Its metabolism is not influenced by hepatic or renal dysfunction; it is metabolized by nonspecific blood and tissue esterases into a pharmacology-inactive metabolite. The elimination half-life of remifentanil is less than 5 min, which is independent of infusion duration. Since it interacts almost exclusively with μ1-receptors, remifentanil has been used in patients under pressure support ventilation. At low dose, remifentanil increases comfort without decreasing respiratory drive. Our group has conducted a study of remifentanil-based sedation in case of NIV failure [3]. In this pilot study, continuous administration of remifentanil was associated with an increase in NIV tolerance. Remifentanil did not increase $PaCO_2$. No aspiration pneumonia occurred after 1,200 h of sedation during NIV.

Dexmedetomidine, an α2-agonist, is a new sedative agent used in the United States. It currently lacks approval in Europe. Dexmedetomidine stimulates α2-adrenergic receptors in the locus ceruleus to provide sedation and in the spinal cord to enhance analgesia. It also causes sympatholysis via central and peripheral mechanisms. Continuous infusion maintains unique sedation (patients appear to be asleep but are readily roused), analgesic-sparing effect, and minimal depression of respiratory drive. It has been used for sedation during NIV in ten patients in ARF who were subsequently uncooperative (rated as 1 on the Ramsay score and −1 or more on the Richmond Agitation–Sedation Scale [RASS]) [4]. All patients satisfied the target criteria of a Ramsay score of 2 or more and a RASS score of 0 or less within 1 h, experiencing adequate sedation even at low initial loading dose or without an initial loading dose. Although this study showed no substantial changes in hemodynamics in any patient, an initial loading dose of dexmedetomidine may cause cardiovascular adverse drug reactions such as hypertension, hypotension, or bradycardia. Results of this study suggest that, for agitation, dexmedetomidine initiated at a low initial loading dose followed by continuous infusion can provide adequate sedation and safer control for patients on NIV.

Propofol, a widely used drug for sedation in the intensive care unit (ICU), has some interesting properties for sedation during NIV. Target-controlled infusion (TCI) allows rapid and precise adjustment of the propofol concentration according to the clinical response of the patient. Physiological studies on the effects of subhypnotic concentrations of propofol on respiratory mechanics, pharyngeal function, and airway protection have suggested the possibility of carrying out NIV while patients are under sedation. Unfortunately, no data have yet been published regarding this drug. TCI is available for remifentanil and should be an interesting administration mode for this indication.

Benzodiazepines do not have the same pharmacokinetic properties as the previously described drugs, and continuous administration should be discouraged. However, anxiolytic properties may be attractive in this indication. A single-shot administration of benzodiazepines followed, or not, by another sedative drug (remifentanil or propofol) should be a valuable compromise.

40.3
Monitoring Sedation During NIV

Several articles have shown that "too much NIV will kill NIV." Monitoring sedation decreases mortality in mechanically ventilated patients. Monitoring sedation during NIV is a key point of a successful procedure.

As for all ICU patients, evaluation of sedation should be performed by nurses and others according to a scale. Moreover, sedation for NIV should be included in a sedation protocol used in the ICU.

In the protocol, we could recommend an evaluation of pain and consciousness. Evaluation of pain should be performed by numeric or analogic scale in self-reporting patients. In patients unable to self-report pain due to deep sedation or delirium, a new tool has been published. It seems that this scale, proposed by Chanques et al.[5], is the only way to evaluate sedation of noninvasively ventilated patients unable to self-report.

Many scales have been published to evaluate consciousness. There is a lack of data comparing these different scales. We could recommend use of the scale routinely used in the ICU. If no sedation protocol exists in the ICU, the first point is to implement a scoring system. Sedation used for NIV is often a moderate sedation, called "awake" sedation. So, we could recommend use of a modern scale with precise description of low sedation levels.

40.4
Conclusion

Sedation for NIV can reduce NIV failure and so decrease morbidity in selected patients. It should be highlighted that this procedure is a high-risk one. It must be performed in an ICU with trained individuals and with all the conventional monitoring. A sedation protocol must be implemented in the ICU. Evaluation of sedation and administration of drugs could be efficiently done by nurses and others according to the protocol. The ideal drug does not exist today. We could recommend the use of remifentanil or propofol. In a country where dexmedetomidine is available, it could represent an interesting alternative. The continuous administration of benzodiazepines should be discouraged, but the anxiolytic properties of these drugs may be used in a single-shot administration. Nonpharmacological sedation, like hypnosis, could increase NIV tolerance with fewer adverse events and could be encouraged [6].

Sedation for NIV could be helpful in the management of ARF with NIV, but during the procedure, the benefit/risk ratio must be carefully evaluated.

Key Recommandations

> Sedation for NIV must be included in a sedation protocol.
> Evaluation of pain and consciousness must be performed by specifics scale.
> Only short acting without accumulation drugs should be used in a continuous administration mode.
> Benefit/risk ratio must be carefully evaluated all along procedure.

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Use of Dexmedetomidine in Patients with Noninvasive Ventilation

41

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41.1
Introduction

Agitation and delirium are relative contraindications for noninvasive ventilation (NIV) in acute care [1]. These cause serious complications, and even if indicated, NIV sometimes fails with these complications. Although sedation therapy can play an important role in NIV success, it is also potentially dangerous because respiratory depression is a concern when using potent analgesics or sedatives. Routine use of sedatives such as opioids and benzodiazepines can lead to a fatal outcome when overdosed.

A high concentration of alpha-2 receptors is found in the locus ceruleus, which is involved in regulating sleep. Dexmedetomidine is considered a full agonist of the alpha-2 receptor, with an alpha-2/alpha-1 binding affinity ratio of 1,620:1, which appears to promote sedation, hypnosis, analgesia, sympatholysis, neuroproteciton, and inhibition of insulin secretion [2]. In contrast to infusions of opioids, benzodiazepines, or propofol, dexmedetomidine is able to achieve its sedative, hypnotic, and analgesic effects without causing any clinically relevant respiratory depression. It has been used successfully to facilitate tracheal extubation in patients who had previously failed extubation because of excessive agitation [3, 4].

Dexmedetomidine would be effective as a sedative during NIV and could be used without adversely affecting the respiratory state of patients on NIV.

41.2
Analysis Main Topics

Devlin et al. investigated practices and attitudes regarding sedation during NIV [5]. The most influential factors for choice of sedation were clinical experience with the agent and lack of effect on respiratory drive. Benzodiazepines alone (33%) or opioids alone (29%)

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were most frequently chosen as preferring the sedation regimen of choice. Lorazepam alone (18%) was next in frequency of use, followed by midazolam (15%), morphine (21%), and fentanyl (8%). Propofol-containing regimens (7%) and dexmedetomidine-containing regimens (5%) were rarely chosen as a first line. Fifteen percent and 6% of physicians never used sedation or analgesia, respectively, for patients with acute respiratory failure patients treated with NIV. Furthermore, physicians used sedation therapy or analgesic therapy more than 25% of the time in only 45% and 26% of patients, respectively.

Akada et al. have shown the efficacy of dexmedetomidine in patients treated with NIV in a preliminary study [6]. This study population consisted of ten patients with acute hypoxemic respiratory failure who were received NIV. Inclusion criteria were patients receiving NIV who subsequently experienced noncooperation rated as 1 on the Ramsay score and +1 or greater on the Richmond Agitation–Sedation Scale (RASS score). After confirmation of response level, administration of dexmedetomidine was started either at an initial loading dosage of 3 μg/kg/h over 5 min followed by continuous infusion at a dosage range of 0.2–0.7 μg/kg/h or by continuous infusion at a dosage of 0.7 μg/kg/h. The infusion rate was adjusted to maintain a target sedation level of Ramsay score 2–3 and RASS score of 0 to −2. At baseline, all patients showed response levels of Ramsay score 1 and RASS score 1.5 ± 0.8. Maintenance of the Ramsey score and the RASS score at 2.94 ± 0.94 and −1.23 ± 1.30, respectively, and obtainment of effective sedation were demonstrated in all cases during dexmedetomidine infusion. Oxygenation improved significantly, and all patients were successfully weaned from NIV, with none intubated, and all were discharged from the intensive care unit (ICU) alive. All patients could cough and expectorate without assistance. None was newly complicated with pneumonia during the stay in the ICU.

A case report demonstrated two cases in which dexmedetomidine facilitated the induction of NIV without inducing respiratory depression for the treatment of acute respiratory failure caused by severe asthma [7]. In the first case, because of frequent complaints of dyspnea with progressive agitation after application of NIV, dexmedetomidine was given intravenously for sedation. One hour after the institution of NIV, respiratory symptoms were markedly improved. The patient was cooperative with the mask ventilation with the continuous dexmedetomidine infusion, which was adjusted by maintaining the Ramsay sedation scale at 2 or 3. In the second case, as soon as paradoxical respiratory movement with agitation developed, the patient was treated with NIV and dexmedetomidine administered intravenously. One hour after the institution of NIV with dexmedetomidine, the paradoxical respiratory movement had almost disappeared, and the gas exchange had improved. With the continuous dexmedetomidine infusion, the Ramsay sedation scale was maintained at 2 or 3, and the patient was able to cough sufficiently to excrete infectious sputum.

41.3 Discussion

Most physicians infrequently use sedation and analgesic therapy for NIV to treat acute respiratory failure. The sedation and analgesic regimens that physicians prefer to use during NPPV are quite varied. The choice of sedation is also heavily influenced by perceived respiratory depressant effects of the agent. Most physicians want to use a sedation agent

that does not depress respiration or hypoxic drive. Dexmedetomidine is a centrally acting alpha-2-adrenergic receptor agonist that produces clinically useful sedation dose dependently without respiratory depression. There is no evidence of respiratory depression when dexmedetomidine is administered by intravenous infusion at doses within the recommended dose range of 0.2–0.7 μg/kg/h. Sedation induced by dexmedetomidine has the respiratory pattern and electroencephalogram changes commensurate with natural sleep [8].

A study used dexmedetomidine in patients who became agitated during NIV, and its efficacy for sedation was demonstrated [6]. In this study, all patients were successfully weaned from NIV and discharged from the ICU without experiencing aggravation of the respiratory state. All patients satisfied the target criteria of a Ramsay score of 2 or greater and RASS score of 0 or less within 1 h, experiencing adequate sedation even at low initial loading dose or without an initial loading dose. After intravenous injection, dexmedetomidine has an onset of action after approximately 15 min. Peak concentrations are usually achieved within 1 h after continuous intravenous infusion [2]. The most frequently observed treatment-emergent adverse events are cardiovascular. Although this study showed no substantial changes in hemodynamics in any patient, an initial loading dose of dexmedetomidine may cause cardiovascular adverse drug reactions such as hypertension, hypotension, or bradycardia. Results of this study suggest that dexmedetomidine initiated at a low initial loading dose and a continuous infusion can provide adequate sedation and safer control. Dexmedetomidine also blocks bronchoconstriction in dogs, but this effect has not been confirmed in humans [9]. Dexmedetomidine, a sedative unlikely to cause respiratory depression, provides the possibility of achieving effective sedation during NIV, ultimately leading to an increase in the rate of NIV success.

Key Recommendations

> Dexmedetomidine has favorable respiratory pharmacologic properties at therapeutic doses.
> Dexmedetomidine is a good candidate for the ideal sedation of patients with agitation who are supported by NIV.
> These beneficial effects are expected in patients with mild (not severe) agitation or delirium with a Ramsay score and +1 or +2 as a RASS score.

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Section VIII

Weaning from Conventional Mechanical Ventilation and Postextubation Failure

Extubation and Decannulation of Unweanable Patients with Neuromuscular Weakness

42

John Robert Bach

42.1 Introduction

42.1.1 Respiratory Muscle Aids

The three respiratory muscle groups are the inspiratory muscles, expiratory muscles, and bulbar-innervated muscles. The inspiratory and expiratory muscles can be assisted or supported indefinitely by applying pressure to the body or airways such that no extent of dysfunction should result in respiratory failure or need to resort to tracheotomy. Inspiratory and expiratory muscle aids are devices and techniques that involve the manual or mechanical application of forces to the body or pressure changes to the airway to assist or substitute for inspiratory or expiratory muscle function. Negative pressure applied to the airway during expiration assists the expiratory muscles for coughing, just as positive pressure applied to the airway during inhalation (noninvasive intermittent positive pressure ventilation [IPPV]) assists inspiratory function [4]. A manual thrust applied to the abdomen during expiration or exsufflation, especially when in combination with mild chest compression, assists expiratory muscle function and increases cough flows. Patients with little or no measurable vital capacity (VC) or any ability to autonomously sustain alveolar ventilation or cough can be managed without invasive tubes using these methods. However, even when inspiratory and expiratory muscles are functional, patients with bulbar-innervated muscle dysfunction to the extent that continuous aspiration of airway secretions results in decrease in an oxyhemoglobin saturation (SpO_2) baseline below 95% need to undergo tracheotomy to survive [15]. At the point that this occurs, the patient has usually already

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lost the ability to speak and swallow food. This essentially only occurs for patients with advanced bulbar amyotrophic lateral sclerosis (ALS) and the occasional patient with spinal muscular atrophy type 1 (SMA1).

42.1.2
Acute Respiratory Decompensation and Conventional Management

Inspiratory and expiratory muscle aids can be used at home or in the hospital to prevent episodes of pneumonia and respiratory failure that would otherwise occur during intercurrent upper respiratory tract infections (URIs) and episodes of bronchitis due to ineffective coughing. Both mechanically assisted coughing (MAC) and up to continuous noninvasive ventilatory (NIV) support are often needed during these episodes when quite possibly not required at other times [5, 14–16, 21]. Extremely important is the feedback obtained by using an oximeter during acute URIs to guide in the use of NIV and, especially, MAC to keep the SpO_2 over 94% or to return it to over 94% quickly if it should decrease below 95%. This is because the SpO_2 is only normal when 95% or greater. It is impossible to develop respiratory failure with SpO_2 greater than 94% in ambient air. Any SpO_2 below 95% must indicate some combination of hypoventilation, airway secretion congestion, and intrinsic lung disease such as atelectasis or pneumonia. When the SpO_2 cannot be kept above 94%, then patients usually require hospitalization for pneumonia and perhaps impending respiratory failure [21].

Typically, the dyspneic patient arrives at the emergency room of a local hospital and immediately receives supplemental oxygen. His or her already elevated CO_2 level further increases, and CO_2 narcosis results in ventilatory arrest, intubation, and then failure to wean from invasive ventilatory support via a translaryngeal tube; a tracheotomy is done before extubation, and patients are left with a lifetime of invasive ventilatory support. Once a tracheostomy tube is placed, the patient often loses all ventilator-free breathing ability (VFBA). This most often occurs because the tracheostomy tube causes airway secretions that block the respiratory exchange membrane, ventilation via the tube causes inspiratory muscle deconditioning [23], and chronically and invasively ventilated patients tend to be hypocapnic and thereby tolerate less ventilator-free breathing [22]. Their demand for increased ventilator volumes and pressures may be related to bypassing upper airway sensory input.

Supplemental oxygen should not be given until attempts are made to normalize SpO_2 (>94%) by using full-setting NIV to normalize ventilation ($Paco_2$) and MAC to clear the airways of secretions. Intubation becomes appropriate when optimal use of NIV and MAC fail to maintain normal SpO_2 and the patient develops respiratory distress, most usually due to pneumonia.

42.1.3
Conventional Outcomes of Acute Respiratory Failure

Intubated patients who fail spontaneous breathing trials (SBTs) are conventionally told that tracheostomy is their only option. Conventionally, unweanable intubated patients are only extubated following tracheotomy. Once a tracheostomy is placed, the majority of

patients will eventually die from complications directly attributable to the tube, including hemorrhage, tracheoesophageal fistulae, respiratory infection, trachectasis, pneumonia, accidental disconnection from the ventilator, and ventilator failure. In a review of four articles discussing outcomes of tracheostomy ventilation for Duchenne muscular dystrophy (DMD) in the literature [18–20, 24], 17 patients survived more than 2 years, including one for 18 years. Three died from complications of the tube in less than 2 years, and two died after 2 years of use. In a relatively large study, Bach et al. reported mean survival for 17 DMD tracheostomy IPPV users of 7.3 ± 8 years (range 7 days to 12 years). At least 4 of the patients died from complications associated with the tube [10]. Thus, only two studies reported mean prolongations of survival of over 6 years by tracheostomy IPPV.

42.2
Extubation of Unweanable Patients to NIV/MAC

There are no guidelines for extubating unweanable patients with neuromuscular disease (NMD) or with critical care ventilatory failure. Despite this, many such patients may have been continuously NIV dependent with no autonomous breathing ability for decades before being hospitalized and intubated, whether for general anesthesia or an intercurrent pneumonia. These patients typically do not desire to switch from continuous NIV to tracheostomy ventilation [3]. In 1996, a different approach to extubation and decannulation was described. Instead of ventilator weaning with oxygen supplementation, then extubation to supplemental oxygen and continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP), the invasive tube was removed and the patient set up with a mouthpiece or nasal NIV (Fig. 42.1) to wean himself or herself in ambient air by taking fewer and fewer IPPVs via a 15-mm angled mouthpiece or nasal interface [9]. All patients with assisted cough peak flows (CPFs) greater than or equal to 160 L/min were

Fig. 42.1 Ten-year-old girl with neurofibromatosis status post-spinal cord tumor resection, extubated with a vital capacity (VC) of 180 mL and no ventilator-free breathing ability, using 15-mm angled mouthpiece (Malincrodt-Puritan-Bennett, Pleasanton, CA) for ventilatory support

successfully extubated to NIV and MAC [9]. Subsequently, we successfully extubated over 140 unweanable NMD patients with ALS, myopathies and muscular dystrophies, critical care myopathy, postpolio, myasthenia gravis, spinal muscular atrophy, and spinal cord high tetraplegia. Once satisfying the extubation criteria noted in Table 42.1, 100% of the patients with CPFs greater than 160 L/min and 85% with CPF less than 160 L/min succeeded with extubation despite having failed extubation or SBTs in other institutions. These patients had been told that they could only survive by undergoing tracheotomy.

Successful extubation of continuously ventilator-dependent patients with no VFBA was achieved by using the following protocol: Normal alveolar ventilation was maintained and MAC used (pressures 40–60 cmH$_2$O to −40 to −60 cmH$_2$O with exsufflation-timed abdominal thrust) via the translaryngeal tube as needed until SpO$_2$ remained 95% or above in ambient air for 12 h or more. Once SBTs were failed but extubation criteria were met, the nasogastric tube was removed if present to facilitate immediate postextubation NIV. The VC was measured. The patient was then extubated directly to NIV on pressure control of 18–20 cmH$_2$O or assist/control mode of 800–1,500 mL delivered volumes and backup rate of 10–12/min. The NIV was provided via mouthpiece [12], nasal, or oronasal interface. The patients using mouthpiece NIV kept 15- or 22-mm angled mouthpieces accessible to their mouths (Fig. 42.1). Patients weaned themselves, when possible, by taking fewer and fewer mouthpiece IPPVs as tolerated. Diurnal nasal IPPV was used for children and for those who could not grab or retain a mouthpiece because of oral muscle weakness, inadequate jaw opening, or insufficient neck movement. Being open systems, the patients took as much of the delivered volumes as needed for comfortable alveolar ventilation. No supplemental oxygen was used. For episodes of SpO$_2$ below 95%, the following were evaluated: ventilator positive inspiratory pressure (PIP), interface air leak, CO$_2$, and ventilator settings.

The success in extubating patients with little or no measurable CPF was due to a variety of factors but most importantly to the experience of our respiratory therapists with NIV and MAC and reliance on family members to provide MAC every 20–30 min as needed postextubation until the SpO$_2$ no longer dipped below 95%. Such a regimen simulates the normal coughing frequency during episodes of bronchitis or pneumonia. The aggressive use of MAC via the endotracheal tube was the main intervention that resulted in normalization of SpO$_2$ in ambient air, the most important criterion for extubation.

Table 42.1 Extubation criteria for continuously ventilator-dependent patients

• Diagnosis of neuromuscular weakness (including critical care ventilatory failure) with inability to pass SBTs or autonomously breathe
• Afebrile
• Normal white blood cell count
• Some residual bulbar-innervated muscle function
• Oxyhemoglobin saturation (SpO$_2$) ≥ 95% for 12 h or more in ambient air
• All oxyhemoglobin desaturations below 95% reversed by MAC via translaryngeal tube
• Fully alert and cooperative, receiving no sedative medications
• Chest radiograph abnormalities cleared or clearing
• Sufficient air leakage via upper airway for verbalization after tube cuff deflation
• Normal Paco$_2$ at peak inspiratory pressures less than 35 cmH$_2$O with the cuff deflated

Fig. 42.2 Twenty-six-year-old man with Duchenne muscular dystrophy (DMD) transferred for extubation after failing three extubations over a 26-day period. He used a 15-mm angled mouthpiece, as in Fig. 42.1, for daytime ventilatory support and a lip-seal phalange with nasal prongs (Hybrid, Teleflex Medical, Research Triangle Park, NC) for nocturnal ventilatory support

Generally, pressures of 40–60 cmH$_2$O to −40 to −60 cmH$_2$O were also used with an exsufflation-timed abdominal thrust postextubation. Thus, the hospital staff and patients' care providers used oximetry as feedback to maintain SpO$_2$ of 95% or above by MAC and NIV. Extubation was only considered successful if the patient was discharged home without requiring reintubation.

Ventilator-dependent patients with NMD can achieve successful extubation using full NIV and MAC. Because of these extubation success rates for unweanable NMD patients, we no longer consider tracheotomy for ventilator-dependent NMD patients who have some residual bulbar-innervated muscle function and who can be made to satisfy Table 42.1 criteria. We now offer extubation and decannulation even to those with CPFs less than 160 L/min.

42.3
Decannulation of Unweanable Patients

Any patient with an indwelling tracheostomy tube who has understandable speech when the tube cuff is deflated is evaluated for decannulation. Patients without severe speech and swallowing impairment are usually good candidates. The ability to effect glottic closure and then to maintain airway patency during the cough is critical for successful decannulation. Any unweanable patient for whom CPF can approach 160 L/min by MAC with the tracheostomy tube capped and the patient using NIV is a strong candidate for decannulation even if inspiratory and expiratory muscles are completely paralyzed (VC = 0 mL). If PCFs are much lower than 160 L/min with the tube in place, it is removed, at least temporarily, and the site covered. This decreases obstruction to upper airway airflows, allowing

more accurate measurement of assisted CPF and facilitating the use of noninvasive IPPV as well as autonomous breathing. If despite air stacking and coordinated abdominal thrusts levels still fail to approach 160 L/min, vocal cord paralysis, hypopharyngeal collapse, tracheal stenosis, or other reasons for fixed airway obstruction are considered, and the patient is referred for fiber-optic evaluation of the upper airway.

Any nasogastric tube that may be present is removed before decannulation. The patient is decannulated directly to full NIV and a pressure dressing placed over the ostomy until the skin is closed (Tegaderm, 3M Company, St. Paul, MN) [2, 7, 8, 25, 26].

On decannulation, most continuously and invasively ventilator-dependent patients with VCs greater than 250 mL wean to nocturnal-only NIV [9, 17]. All patients transferred from continuous invasive ventilatory support via a tracheostomy tube to NIV without one prefer it for safety, convenience, swallowing, speech, appearance, comfort, and overall [3]. Noninvasive management also minimizes cost and facilitates return to the community rather than long-term institutionalization [11]. Whereas tracheostomized ventilator users will always be afraid of asphyxia from ventilator failure and accidental disconnection, two thirds of NIV users with no inspiratory or expiratory muscle function and little or no measurable VC can be taught to glossopharyngeal breathe for security in the event of ventilator malfunction or loss of access to the NIV interface [18, 19, 23]. The need to decannulate tracheostomized ventilator users to NIV can be avoided, however, if (unweanable) ventilator-dependent patients can be extubated without resort to tracheotomy. We have decannulated over 100 continuously ventilator-dependent patients without a single failure [3, 15, 18, 19]. In all, 31 patients temporarily regained partial independent respiration before returning to continuous (noninvasive) ventilatory support with advancing disease. In some cases, our decannulated and extubated continuously ventilator-supported cases have depended on NIV for over 30 years for prolonged survival. Unfortunately, very few centers decannulate continuously ventilator-dependent patients [2, 25, 26].

Finally, after years of debate and consensus conferences of "experts" whose knowledge of NIV is limited to CPAP and the use of low-span BiPAP for patients with "sleep-disordered breathing," a Centers for Disease Control panel of respiratory experts has recommended that NIV be used for up to and including 24-h/day ventilator dependence long term for DMD patients [1]. Despite the fact that our center has managed over 100 NIV-dependent DMD patients and has not needed to resort to tracheotomy to prevent respiratory mortality for DMD patients in over 25 years, it has taken this long for recognition of the fact that, even in the absence of inspiratory or expiratory function, patients, even those with minimal bulbar-innervated muscle function, can be managed using NIV and MAC (Fig. 42.2). Unfortunately, even this expert consensus refers to resorting to tracheotomy for (1) patient and clinician preference, (2) lack of success with NIV, (3) inability of the medical system to "support" NIV, (4) three extubation failures to NIV, and (5) failure of NIV and MAC to prevent SpO_2 decreases below 95%. Yet, we have shown that no informed DMD patient trained in NIV and MAC "prefers" to undergo tracheotomy [3], virtually none of our over 1,000 symptomatic patients refused NIV [6], the equipment needed for NIV is simpler than for invasive ventilation, and with the required family and caregiver involvement for providing NIV and MAC, hospitalizations and strain on medical facilities long term is diminished [13]. None of thus far 148 consecutive patients who failed extubation or ventilator weaning and were transferred to our units failed successful extubation to

NIV and MAC. The only appropriate one of the five "indications" for possible tracheotomy is the last [2], the fact that failure of NIV and MAC to maintain normal SpO_2 can be an indication for tracheotomy. However, in our experience, this only occurs for patients with advanced bulbar ALS. Paradigms shift slowly.

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Mechanically Assisted Coughing and Noninvasive Ventilation for Extubation of Unweanable Patients with Neuromuscular Disease or Weakness

43

John Robert Bach

43.1
Introduction

There is just one point I would like to mention, which has just come along which, I think, makes it [noninvasive positive pressure ventilation] even more feasible. It is so simple that why it wasn't thought of long ago I don't know. Actually, some of our physical therapists, in struggling with the patients, noticed that they could simply take the positive pressure attachment, apply a small plastic mouthpiece … , and allow that to hang in the patient's mouth. You can take him to the Hubbard tank by such means and you can do any nursing procedure, if the patient is on the rocking bed and has a zero vital capacity [VC], if you want to stop the bed for any reason, or if you want to change him from the tank respirator to the bed, or put the cuirass respirator on, or anything to stop the equipment, you can simply attach this, hang it by the patient, he grips it by his lips, and thus it allows for the excess to blow off which he doesn't want.

It works very well. We even had one patient who has no breathing ability who has fallen asleep and been adequately ventilated by this procedure, so that it appears to work very well, and I think does away with a lot of complications of difficulty of using positive pressure. You just hang it by the patients and they grip it with their lips, when they want it, and when they don't want it, they let go of it.

It is just too simple.

Dr. John Affeldt, Rwd Table Conference on Poliomyelitis Equipment, Roosevelt Hotel, New York City, sponsored by the National Foundation for Infantile Paralysis Incorporated, May 28-29, 1953

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Since the use of noninvasive ventilatory (NIV) support via a mouthpiece was described in 1953, many hundreds of patients with severe neuromuscular disease, weakness, or paralysis (NMD) and no ability to autonomously sustain their alveolar ventilation have used strictly noninvasive methods of ventilatory support with no need to resort to tracheotomy [1]. This has been realized by considering the respiratory muscles and how to evaluate and support them and by understanding how to extubate or decannulate these patients back to noninvasive respiratory muscle aids as needed.

43.2
The Respiratory Muscle Groups

The three respiratory muscle groups are inspiratory muscles, expiratory muscles, and bulbar-innervated muscles. The inspiratory and expiratory muscles can be assisted or supported indefinitely by applying pressures to the body or airways such that no extent of dysfunction should result in respiratory failure or need to resort to tracheotomy. Inspiratory and expiratory muscle aids are devices and techniques that involve the manual or mechanical application of forces to the body or pressure changes to the airway to assist or substitute for inspiratory or expiratory muscle function. Negative pressure applied to the airway during expiration assists the expiratory muscles for coughing, just as positive pressure applied to the airway during inhalation (noninvasive intermittent positive pressure ventilation [IPPV]) assists inspiratory function. A manual thrust applied to the abdomen during expiration or exsufflation, especially when in combination with mild chest compression, assists expiratory muscle function and increases cough flows. Patients with little or no measurable vital capacity (VC) or any ability to autonomously sustain alveolar ventilation or cough can be managed without invasive tubes using these methods. However, even when inspiratory and expiratory muscles are functional, patients with bulbar-innervated muscle dysfunction to the extent that continuous aspiration of airway secretions results in decrease in an oxyhemoglobin saturation (SpO_2) baseline below 95% need to undergo tracheotomy to survive [2]. At the point that this occurs, the patient has usually already lost the ability to speak and swallow food.

Inspiratory and expiratory muscle aids can be used at home or in the hospital to prevent episodes of pneumonia and respiratory failure that would otherwise occur during intercurrent respiratory tract infections and episodes of bronchitis due to ineffective coughing. Both mechanically assisted coughing (MAC) and up to continuous NIV support are often needed during these episodes when quite possibly not required at other times [2–6]. Sometimes, however, patients with or without access to NIV or MAC develop pneumonia and acute respiratory failure. Typically, the dyspneic patient arrives at the emergency room of a local hospital and immediately receives supplemental oxygen. His or her already elevated CO_2 further increases, and CO_2 narcosis results in ventilatory arrest, intubation, and then failure to wean from invasive ventilatory support via a translaryngeal tube; tracheotomy is done before extubation, and patients are left with a lifetime of invasive ventilatory support. Once a tracheostomy tube is placed, the patient often loses all ventilator-free breathing ability (VFBA). This most often occurs because the tracheostomy tube causes

airway secretions that the block respiratory exchange membrane, ventilation via the tube causes inspiratory muscle deconditioning [7], and chronically and invasively ventilated patients tend to be hypocapnic and thereby tolerate less ventilator-free breathing [8]. Their demand for increased ventilator volumes or pressures may be related to bypassing upper airway sensory input.

Whatever the reasons, most continuously and invasively ventilator-dependent patients with VCs greater than 250 mL wean to nocturnal-only NIV once their tracheostomy tubes are removed and they are converted to NIV [9]. Unfortunately, few centers decannulate continuously ventilator-dependent patients [10–13]. If done, though, all patients transferred from continuous invasive ventilatory support via a tracheostomy tube to NIV without one prefer it for safety, convenience, swallowing, speech, appearance, comfort, and overall [14]. Noninvasive management also minimizes cost and facilitates return to the community rather than long-term institutionalization [15]. The need to decannulate tracheostomized ventilator users to NIV can be avoided, however, if (unweanable) ventilator-dependent patients can be extubated without resort to tracheotomy.

Conventionally, unweanable intubated patients are only extubated following tracheotomy. All conventional "ventilator-weaning parameters" assess lung health and ability to autonomously sustain alveolar ventilation. "Spontaneous breathing trials" (SBTs) must also be passed before extubation attempts are undertaken. Since this is often impossible for the patient with NMD, critical care studies report very few, if any. NMD patients (i.e., 18 of 162 [14]; 17 of 900 [16]), and they completely exclude these patients unless they are weanable [17,18]. While most critical care NIV trials either excluded patients with NMD [19] or failed to mention any [20,21], a randomized trial conducted in 37 centers by Esteban et al. that did include 7 patients with NMD of 221 failed to show that NIV prevented need for reintubation or reduced mortality [22]. Further, another multicenter prospective randomized study by Confaloniere et al. comparing standard treatment plus NIV versus standard treatment alone for acute respiratory failure in severe community-acquired pneumonia excluded patients on home mechanical ventilation and did not have any patients with NMD [23]. The "NIV" in all studies was either not specified or it was continuous positive airway pressure (CPAP) or bilevel positive airway pressure (PAP) at spans that provide less than full ventilatory support, and none of them reported the use of assisted coughing or air stacking [17].

Patients with NMD typically have ineffective cough peak flows (CPFs), which can result in extubation failure due to airway secretion accumulation [18,19], but no studies reported CPF or the use of MAC [16]. Indeed, there are no ventilator-weaning parameters that address the ability to cough. Thus, there are no guidelines for extubating unweanable patients with NMD or critical care ventilatory failure. Yet, many such patients may have been continuously NIV dependent with no autonomous breathing ability for decades before being hospitalized and intubated whether for general anesthesia or an intercurrent pneumonia. These patients typically do not desire to switch from continuous NIV to tracheostomy ventilation [14].

In 1996, a different approach to extubation was described. Instead of ventilator weaning with oxygen supplementation, then extubation to supplemental oxygen and CPAP or BiPAP, the new paradigm consisted of invasive tube removal and then allowing the patient to wean himself or herself in ambient air by taking fewer and fewer IPPVs via a 15-mm

Table 43.1 Extubation criteria for continuously ventilator-dependent patients

- Age 4 years and older
- Diagnosis of neuromuscular disease (NMD; including critical care ventilatory failure)
- Afebrile
- Normal white blood cell count
- VC less than 20% of normal

- Pa_{CO_2} of 40 mmHg or less on full ventilatory support

- Oxyhemoglobin saturation (SpO_2) 95% or above for 12 h or more in ambient air
- All oxyhemoglobin desaturations below 95% reversed by mechanically assisted coughing (MAC) via translaryngeal tube

- Fully alert and cooperative, receiving no sedative medications

- Chest radiograph abnormalities cleared or clearing
- Sufficient air leakage via upper airway for verbalization on tube cuff deflation
- Normal Pa_{CO_2} at peak inspiratory pressures less than 35 cmH_2O with the cuff deflated

angled mouthpiece or nasal interface [24]. All patients with assisted CPF greater than or equal to 160 L/min were successfully extubated to NIV and MAC, whereas all patients with less than 160 L/min failed [24].

Subsequent to our earlier data on decannulation to NIV, we extubated 146 unweanable patients with NMD with amyotrophic lateral sclerosis (ALS), myopathies and muscular dystrophies, critical care myopathy, postpolio, myasthenia gravis, spinal muscular atrophy (SMA), and spinal cord high tetraplegia. Once satisfying the extubation criteria noted in Table 43.1, 100% of 94 consecutively referred patients who had failed extubation or SBTs and were told that they could only survive by undergoing tracheotomy were successfully extubated to full NIV and MAC and found to have assisted CPF greater than or equal to 160 L/min. Likewise, 47 of 53 extubations also succeeded on patients who turned out to have CPFs less than 160 L/min. Successful extubation of continuously ventilator-dependent patients with no VFBA was achieved by using the protocol that follows.

43.3
Extubation Protocol

Normal alveolar ventilation was maintained and MAC used (pressures 40–60 cmH_2O to −40 to −60 cmH_2O with exsufflation-timed abdominal thrust) via the translaryngeal tube as needed until SpO_2 remained at 95% or higher in ambient air for 12 h or more. Once SBTs were failed but extubation criteria were met, the nasogastric tube was removed if present to facilitate immediate postextubation NIV. The VC was measured. The patient was then extubated directly to NIV on pressure control at 18–20 cmH_2O or assist/control mode at 800–1,500 mL delivered volumes and backup rate of 10–12/min. The NIV was provided via mouthpiece [25], nasal, or oronasal interface. For a mouthpiece, NIV patients kept 15- or 22-mm angled mouthpieces accessible to their mouths (Fig. 43.1). Patients

Fig. 43.1 Ten-year-old girl with neurofibromatosis status postspinal cord tumor resection, extubated with a VC of 180 mL and no ventilator-free breathing ability, using 15-mm angled mouthpiece (Malincrodt-Puritan-Bennett, Pleasanton, CA) for ventilatory support

weaned themselves, when possible, by taking fewer and fewer mouthpiece IPPVs as tolerated. Diurnal nasal IPPV was used for children and for those who could not grab or retain a mouthpiece because of oral muscle weakness, inadequate jaw opening, or insufficient neck movement. Being open systems, the patients took as much of the delivered volumes as needed for comfortable alveolar ventilation. No supplemental oxygen was used. For episodes of SpO_2 less than 95%, the following were immediately evaluated: ventilator positive inspiratory pressure (PIP), interface air leak, CO_2, and ventilator settings. Patients with more than 2 min of VFBA postextubation were excluded.

The care providers were trained in and provided MAC via an oronasal interface every 30–60 min postextubation until airway secretion expulsion was no longer a problem and the SpO_2 no longer dipped below 95%. Generally, pressures of 40–60 cmH_2O to −40 to −60 cmH_2O were also used with an exsufflation-timed abdominal thrust postextubation as well. Thus, the hospital staff and patients' care providers used oximetry as feedback to maintain SpO_2 at 95% or above by MAC and NIV.

Extubation was only considered successful if the patient was discharged home without requiring reintubation. When, postextubation, the SpO_2 decreased and could not be returned to and maintained over 90% by full NIV via mouthpiece or nasal IPPV and MAC as needed, the patient was switched to using a closed system, often of nasal prongs with lipseal (Fig. 43.2). Continued desaturation could necessitate supplemental oxygen to approach SpO_2 to 95% and reintubation. If reintubated, the patient was again prepared to achieve the Table 43.1 criteria for reextubation. Only patients with bulbar ALS failed extubation. Postextubation weaning from continuous ventilator dependence took 3–21 days and in most cases was accomplished at home.

The success of our protocol, especially in patients with CPF less than 160 L/min, stemmed from the fact that MAC was used up to every 30 min and was applied by family members and personal care attendants, rather than only once or twice a nursing shift, to maintain ambient air SpO_2 over 94%. Such a regimen simulates the normal coughing

Fig. 43.2 Twenty-six-year-old man with Duchenne muscular dystrophy (DMD) transferred for extubation after failing three extubations over a 26-day period. He used a 15-mm angled mouthpiece, as in Fig. 43.1, for daytime ventilatory support and a lip-seal phalange with nasal prongs (Hybrid, Teleflex Medical, Research Triangle Park, NC) for nocturnal ventilatory support

frequency during episodes of bronchitis or pneumonia. The aggressive use of MAC via the endotracheal tube was the main intervention that resulted in normalization of SpO_2 in ambient air, the most important criterion for extubation.

The 87% (47 of 53) first attempt extubation success rate on patients with maximum CPF less than 160 L/min is comparable to the 82.4% (61 of 74) success rate reported for extubating ventilator-dependent infants and small children with SMA type 1 according to an almost identical protocol (46). The difference is most likely due to the ability of these patients, as opposed to babies, to fully cooperate with NIV and MAC. The higher pneumonia risk and extubation failure rate in the SMA1 population is in large part due to the severe bulbar-innervated muscle dysfunction associated with their unmeasurable CPF. This makes the extubation failure risk comparable to that of our adults with CPF below 160 L/min. Thus, it is not surprising that the extubation success rates for adult patients with CPF below 160 L/min were higher than those for a comparable pediatric population but not nearly so good as for patients with CPF greater than 160 L/m. The lower the maximum assisted CPF, the less likely that any patient can maintain airway patency for effective use of MAC because of glottic dysfunction.

The general notion that early tracheotomy after intubation somehow facilitates ventilator weaning [26] should be reassessed for patients with NMD. In most instances, on extubation, patients with VC of 250 mL or more eventually weaned from continuous to nocturnal-only aid by taking fewer and fewer mouthpiece IPPVs. Thus, the paradigm of weaning then extubation can be changed to extubation then weaning. Employing noninvasive rather than invasive mechanical ventilation has also been reported to decrease risk of ventilator-associated pneumonia by 75% or greater [27] and other complications associated with invasive airway tubes. Use of mouthpieces rather than other methods of ventilatory support also facilitated speech, oral intake, comfort, and air stacking to deep lung insufflations to maintain pulmonary compliance [25], diminish atelectasis, and augment CPF [28–30]. Nasal interface skin pressure was also avoided.

Thus, ventilator-dependent patients with NMD can achieve successful extubation using full NIV and MAC. Noninvasive management of both acute and chronic ventilatory failure

maintains quality of life, maximizes ventilator-free breathing, facilitates community management, and should be more widely offered. Because of these extubation success rates for unweanable patients with NMD, we no longer consider tracheotomy for ventilator-dependent patients with NMD who have some residual bulbar-innervated muscle function and who can be made to satisfy Table 43.1 criteria; we now offer extubation even to those with CPF less than 160 L/m.

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Noninvasive Positive Pressure Ventilation in the Postextubation Period

44

Hasan M. Al-Dorzi and Yaseen M. Arabi

44.1
Introduction

Noninvasive positive pressure ventilation (NPPV) has been demonstrated to be effective in various types of acute respiratory failure. Level I evidence has been established for its use for acute respiratory failure due to acute on chronic obstructive pulmonary disease (COPD) exacerbations [1, 2] or cardiogenic pulmonary edema [3], and in immunocompromised hosts [4]. By avoiding intubation, NPPV has many advantages and benefits. These include the ease of application; preservation of the airway defense mechanisms; maintenance of the patient's ability to speak, eat, and cough; and reduction of complications related to intubation, especially ventilator-associated pneumonia [5]. These reasons sway physicians to utilize NPPV in other settings, including the postextubation period [6, 7]. In a cross-sectional postal survey, approximately 40% of 385 attending physicians and residents in four specialties at 15 Canadian teaching hospitals used NPPV for postextubation respiratory failure, which was the third most frequent indication after COPD and congestive heart failure (CHF) [6]. At Massachusetts General Hospital, 458 patients were treated with NPPV for acute or acute-on-chronic respiratory failure in 2001, the indication in 21% of them being postextubation respiratory failure [7]. This chapter discusses the evidence related to the use of NPPV in the postextubation period, which happens in one of three settings:

1. Facilitation of weaning from invasive ventilation and extubation
2. Prevention of postextubation respiratory failure and reintubation
3. Treatment of postextubation respiratory failure

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Table 44.1 Evidence-based grading system used to rank recommendations

Grade of recommendation	Benefits versus risks	Supporting evidence
Grade 1A, strong recommendation, high-quality evidence	Benefits clearly outweigh risks or vice versa	RCTs without important limitations or on exceptionally strong observational studies
Grade 1B, strong recommendation, moderate-quality evidence	Benefits clearly outweigh risks or vice versa	RCTs with important limitations or on very strong observational studies
Grade 1C, strong recommendation, low-quality evidence	Benefits clearly outweigh risks or vice versa	Observational studies, case series, or RCTs with major limitations or indirect evidence
Grade 2A, weak recommendation, high-quality evidence	Benefits closely balanced with risks	RCTs without important limitations or on exceptionally strong observational studies
Grade 2B, weak recommendation, moderate-quality evidence	Benefits closely balanced with risks	RCTs with important limitations or on very strong observational studies
Grade 2C, weak recommendation, low-quality evidence	Benefits closely balanced with risks	Observational studies, case series, or RCTs with major limitations or indirect evidence

RCT randomized controlled trial

In our evaluation of the evidence, we used an evidence-based grading system adopted from the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines for antithrombotic agents [8] as summarized in Table 44.1.

44.2
NPPV to Facilitate Weaning and Extubation

This section applies to patients on invasive ventilation who are not ready for extubation as per extubation criteria and are extubated and supported with NPPV. In 1992, Udwadia and colleagues were the first to report that difficult-to-wean patients could be freed from mechanical ventilation after extubation with a brief period of NPPV [9]. This was followed by other uncontrolled studies [10, 11]. Nava et al. performed the first randomized controlled trial (RCT) in which NPPV was used to wean patients with COPD ($n = 50$) with hypercapnic respiratory failure who had been intubated for longer than 48 h and failed spontaneous breathing trials (SBTs) using a T-piece [12]. Twenty-five patients were extubated to NPPV, and the other 25 patients were kept on pressure support ventilation (PSV) with intermittent SBTs and were extubated when ready. Compared to conventional weaning, extubation to NPPV was associated with shorter duration of mechanical ventilation (10.2 ± 6.8 vs. 16.6 ± 11.8 days, $p = 0.021$) and intensive care unit (ICU) stay (15.1 ± 5.4 vs. 24.0 ± 13.7 days, $p = 0.005$),

lower incidence of nosocomial pneumonia (0% vs. 28%) and higher 60-day survival rate (92% vs. 72%, $p = 0.002$).

Girault et al. evaluated the role of NPPV in 33 patients who failed a 2-h T-piece weaning trial. These patients had acute-on-chronic respiratory failure; 17 patients had COPD, 8 had restrictive lung disease, and 8 had combined obstructive and restrictive lung disease. Patients were randomized to receive either invasive pressure support ventilation (IPSV group, $n = 16$) or intermittent NPPV with a nasal or face mask applied immediately after extubation (NPPV group, $n = 17$) [13]. Compared to the IPSV group, the NPPV group had shorter duration of endotracheal mechanical ventilation (4.6 ± 1.9 vs. 7.7 ± 3.8 days, $p = 0.004$) but similar need for reintubation (23% vs. 25%), ICU and hospital stay, and in-hospital death.

Ferrer et al. conducted a prospective RCT of 43 mechanically ventilated patients who had failed a weaning trial for 3 days consecutively [14]. Most of the patients (58%) had COPD. Twenty-one patients were extubated and immediately received bilevel NPPV continuously for at least 24 h. The other 22 patients remained intubated and had daily weaning attempts. There was no difference in the prevalence of chronic pulmonary disease in the two groups. Compared with the conventional weaning group, the NPPV group had shorter duration of invasive ventilation (9.5 ± 8.3 vs. 20.1 ± 13.1 days, $p = 0.003$) and ICU (14.1 ± 9.2 vs. 25.0 ± 12.5 days, $p = 0.002$) and hospital stays (28.8 ± 15.6 vs. 40.8 ± 21.4 days, $p = 0.026$), less need for tracheotomy to withdraw ventilation (1.5% vs. 13.6%, $p = 0.001$), and lower incidence of nosocomial pneumonia (5.2% vs. 13.6%, $p = 0.042$). It was also associated with increased ICU survival (90% vs. 59%, $p = 0.045$).

Trevisan and colleagues randomized 65 patients who were intubated for longer than 48 h and then failed a T-piece weaning trial to either bilevel NPPV by facemask ($n = 28$) or continued weaning with invasive ventilation ($n = 37$) [15]. COPD exacerbation, postoperative acute respiratory failure, and heart disease were the most common indications for invasive ventilation in both groups. Although both groups had similar duration of mechanical ventilation after randomization, ICU length of stay, and mortality, the NPPV group had lower incidence of pneumonia (3.6% vs. 45.9%, $p < 0.001$) and tracheotomy (0% vs. 18.9%, $p = 0.01$).

Burns et al. conducted a systematic review of 12 randomized and quasi-randomized controlled trials enrolling 530 participants and examining early extubation with immediate application of NPPV compared with continued invasive weaning on important outcomes in intubated adults with respiratory failure [16]. Compared with invasive weaning, NPPV weaning was significantly associated with reduced mortality (relative risk [RR] 0.55; 95% confidence interval [CI] 0.38–0.79), ventilator-associated pneumonia (0.29; 95% CI 0.19–0.45), length of stay in ICU (weighted mean difference −6.27 days; 95% CI −8.77 to −3.78) and hospital (−7.19 days; 95% CI −10.80 to −3.58), total duration of ventilation, and duration of invasive ventilation. The benefits for mortality and weaning failures were nonsignificantly greater in trials that exclusively enrolled patients with COPD compared to mixed populations.

Therefore, the best of current evidence supports the use of NPPV as a weaning modality for early extubation in patients with COPD (recommendation 1B). The evidence for using NPPV to facilitate weaning in patients without COPD who fail SBT is less convincing (recommendation 2C), and further research is required before it can be adopted for general application.

44.3
NPPV for Prevention and Treatment of Postextubation Respiratory Failure

Extubation failure is commonly defined as the inability to tolerate spontaneous breathing without translaryngeal ventilatory support within 48–72 h of extubation [17–19]. Approximately 12.5% of extubated patients develop extubation failure requiring reintubation [20]. This rate varies depending on the type of patient population, with the rate being higher (12–20%) in pediatric, medical, and neurological ICUs and lower (5–8%) in surgical and trauma ICUs [21]. Extubation failure can occur because of imbalance between respiratory muscle capacity and load that became apparent after extubation [22], persistence of the primary process that led to intubation, postextubation cardiac ischemia or failure, postextubation COPD exacerbation, upper airway obstruction, excessive or inability to clear secretions, aspiration, respiratory muscle weakness, and neurologic dysfunction [23].

Predictors for extubation failure have been sought. Large endotracheal secretions [24–26], weak cough [24, 25], depressed mental status [24, 25], and hypercapnia [27] are associated with the requirement for reintubation after a successful breathing trial. A retrospective evaluation of 900 patients on mechanical ventilation for longer than 48 h, 13% of whom required reintubation, showed that increasing rapid shallow breathing index (RSBI) (odds ratio [OR] 1.01 per unit; 95% CI 1.003–1.015), positive fluid balance (OR 1.70; 95% CI 1.15–2.53), and pneumonia as the reason for initiating mechanical ventilation (OR 1.77; 95% CI 1.10–2.84) were independent predictors of extubation failure [28].

Extubation failure is associated with higher ICU and hospital mortality compared to patients who do not require reintubation within 48–72 h [29, 30]. It also leads to increased duration of mechanical ventilation, length of ICU and hospital stay, need for postacute care hospitalization, and the need for tracheostomy [29]. This increased morbidity and mortality compels intensivists to find ways to avoid reintubation. NPPV has such potential because it has been shown to improve oxygenation and ventilation and to reduce respiratory distress and work of breathing in patients with persistent acute respiratory failure after early extubation [31].

44.3.1
NPPV to Prevent Postextubation Respiratory Failure

This discussion applies to patients extubated from mechanical ventilation after successful weaning in whom NPPV is used prophylactically to avoid postextubation respiratory failure and reintubation.

Jiang and colleagues studied the effect of prophylactic NPPV use in 93 patients, 40% of whom had unplanned extubation [32]. These patients randomly received either NPPV ($n = 47$) or unassisted oxygen therapy ($n = 46$). There was no significant difference in the reintubation rate in the two groups (27.7% vs. 15.2%, respectively, $p = 0.14$).

Nava et al. carried out a multicenter study of 97 patients who required invasive mechanical ventilation for more than 48 h and were thought to be at risk of extubation failure

(hypercapnia, CHF, ineffective cough, excessive secretions, more than one failure of a weaning trial, more than one comorbid condition, and upper airway obstruction) [33]. The patients were randomized after a successful weaning trial to NPPV by full-face mask for longer than 8 h/day in the first 48 h ($n = 48$) or standard medical therapy (SMT) ($n = 49$). NPPV significantly reduced the need for reintubation (8% vs. 24%, $p = 0.03$) and resulted in risk reduction of ICU mortality by 10% ($p < 0.01$).

Severely obese patients are at increased risk of respiratory complications that might occur in the postextubation period [34, 35]. El Solh et al. studied 62 consecutive severely obese patients (body mass index ≥ 35 kg.m^{-2}) treated with bilevel positive airway pressure (PAP) via nasal mask for at least 48 h immediately postextubation and compared with 62 historically matched controls who were treated with conventional therapy [36]. Compared with the conventionally treated group, NPPV resulted in a 16% absolute reduction in the risk of respiratory failure (10% vs. 26%, $p = 0.03$) and reduced stay in the ICU (12 ± 8 vs. 18 ± 11 days, $p < 0.001$) and in the hospital (21 ± 11 vs. 26 ± 11 days, $p = 0.007$). The use of NPPV was associated with significantly lower hospital mortality (16% vs. 50%, $p = 0.03$) in the subgroup of patients with hypercapnia during SBT.

Based on this information, there is limited evidence to support the routine use of NPPV to prevent postextubation failure (recommendation 2C). High-risk patients for extubation failure, like those with COPD, CHF, obesity, and patients who had weaning difficulty, may benefit from NPPV to prevent postextubation failure (recommendation 1B).

44.3.2
NPPV to Treat Postextubation Respiratory Failure

This section discusses the use of NPPV to treat patients successfully weaned from mechanical ventilation and developed respiratory failure within 48–72 h.

Two clinical trials in this setting were conducted in general ICU patients with postextubation failure. Keenan et al. randomized 81 patients who required ventilatory support for longer than 48 h or had a history of either CHF or chronic lung disease and developed respiratory distress within 48 h of extubation to receive either SMT alone ($n = 42$) or NPPV by face mask plus SMT ($n = 39$) [37]. In the two groups, there were no differences in the rate of reintubation (72% vs. 69%, $p = 0.79$), duration of ICU and hospital stay or ICU and hospital mortality.

Esteban and coworkers carried out a randomized trial at 37 centers in eight countries and evaluated 221 patients who were on mechanical ventilation for more than 48 h then developed postextubation respiratory failure within 48 h of elective extubation [38]. The patients were assigned to either face mask NPPV ($n = 114$) or SMT ($n = 107$). The rate of reintubation was similar in both groups (48%). ICU mortality was higher in the NPPV group than in the SMT group (25% vs. 14%; RR 1.78; 95% CI 1.03–3.20, $p = 0.048$). This difference in ICU mortality seemed to be due to a high mortality rate in the patients on NPPV who required reintubation (38%). As the median time from respiratory failure to reintubation was longer in the NPPV group (12 h) than in the SMT group (2 h 30 min, $p = 0.02$), the delay in intubation may have been deleterious. The trial included mainly patients without COPD; only 10% had COPD.

Hilbert et al. conducted an RCT on patients with COPD who had postextubation hypercapnic respiratory failure (defined as respiratory distress, RR > 25, increase in $P_{CO_2} > 20\%$, pH < 7.35) within 72 h of extubation [39]. The patients were randomized to NPPV by full-face mask for 30 min or longer every 4 h ($n = 30$) or SMT ($n = 30$). Compared to those on SMT, the NPPV group had a lower reintubation rate (20% vs. 67%, $p < 0.001$) and a shorter duration of ventilator support (6 ± 4 vs. 11 ± 8 days, $p < 0.01$) and ICU stay (8 ± 4 vs. 14 ± 8 days, $p < 0.01$). There was no difference in ICU mortality in the two groups.

NPPV has also been studied for the management of postextubation respiratory failure in special patient populations, including those involving burns, cardiac surgery, lung resection surgery, and patients with Do-Not-Resuscitate or Do-Not-Intubate orders. In a retrospective review, Smailes reported on the use of NPPV in 30 patients with severe burn injuries who experienced respiratory insufficiency postextubation [40]. Twenty two patients avoided endotracheal intubation, seven patients were reintubated, and one patient died. De Santo et al. reported the results of an observational study on the use of NPPV in 43 patients who developed extubation failure after cardiac surgery. The investigators reported that NPPV prevented reintubation in 74.4% of the patients, with the best results in those after cardiopulmonary bypass lung injury and those with cardiogenic dysfunction (reintubation rates 9.5% and 30.8 % respectively) and poor results (55% reintubation rate) in those treated for pneumonia. However, the study design and the lack of control group make the generalizability of the results difficult without further study [41]. Auriant et al. compared SMT ($n = 12$) with nasal mask NPPV plus SMT ($n = 12$) in patients with acute hypoxemic postextubation respiratory failure following lung resection surgery [42]. Compared to SMT, NPPV was associated with a significant decrease in the requirement for intubation (50% vs. 21%, $p = 0.035$) and mortality (37.5% vs. 12.5%, $p = 0.045$). A special group of patients includes those with orders not to intubate after discontinuation of mechanical ventilation. If they develop postextubation respiratory failure, NPPV might be an acceptable option to alleviate respiratory distress. One study showed that such patients have a high hospital mortality of 77% [43].

Hence, the available literature suggests that the indiscriminate use of NPPV in general ICU patients without COPD with postextubation respiratory failure should be avoided (recommendation 1A). In patients with COPD, NPPV might be useful (recommendation 1B). In other settings, including burns, cardiac surgery, lung resection surgery, and patients with orders not to intubate, the use should be individualized considering the limited evidence (recommendation 1C).

44.4
Conclusions

Current evidence suggests that NPPV has a role in the care of patients in the postextubation period based on the indication and patient population. Figure 44.1 is a flow chart of an evidence-based decision algorithm for the use of NPPV in the postextubation period. NPPV is beneficial in facilitating extubation in patients who fail SBT, especially those with COPD exacerbation. NPPV may also benefit patients with COPD exacerbation and severely obese patients who are extubated after successful SBT to prevent postextubation
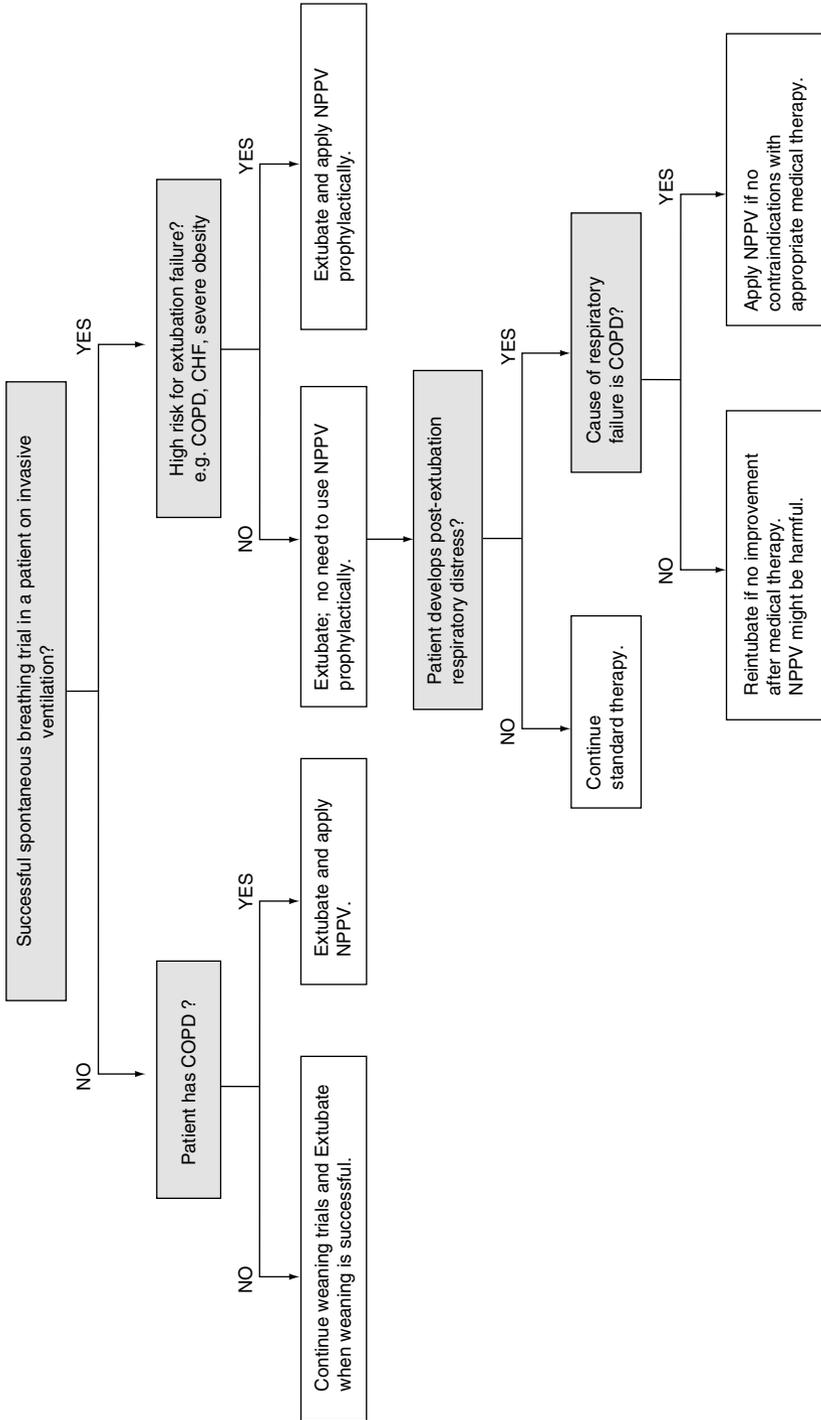
Fig. 44.1 Evidence-based decision algorithm for the use of noninvasive positive pressure ventilation (*NPPV*) in the postextubation period

respiratory failure. It might be useful in patients with COPD exacerbation who develop postextubation respiratory failure. However, its indiscriminate use is not beneficial, and might be harmful, in general ICU patients without COPD who develop postextubation respiratory failure, and it should be avoided in this setting. Further research is required to better define patients who are most likely to benefit from NPPV.

Key Recommendations

> NPPV should be considered to facilitate discontinuation of invasive mechanical ventilation in patients with COPD exacerbation who failed SBTs (Grade 1B).
> NPPV may be used to facilitate discontinuation of mechanical ventilation in other high-risk patients who fail SBTs (Grade 2C).
> NPPV should be considered to prevent postextubation respiratory failure in high-risk patients, like those with COPD, CHF or obesity and patients who had weaning difficulty (Grade 1B).
> NPPV should not be routinely used in general ICU patients with postextubation respiratory failure (Grade 1A).
> NPPV should be considered in COPD patients with postextubation respiratory failure (Grade 1B).
> In settings such as burn, cardiac surgery, lung resection surgery and patients with Do-Not-Intubate orders, NPPV use for postextubation respiratory should be individualized (Recommendation 1C).

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Noninvasive Ventilation in Postextubation Respiratory Failure

45

Ritesh Agarwal

45.1
Introduction

Endotracheal intubation and mechanical ventilation is a lifesaving intervention used in patients with respiratory failure. Weaning, the entire process of liberating the patient from the endotracheal tube, must balance the risk of complications not only due to unnecessary delays in extubation but also due to premature discontinuation and the need for reintubation [1]. In the vast majority, once there is improvement of the underlying indication, mechanical ventilation can be withdrawn abruptly [2, 3]. Even once successfully extubated, the need for reintubation in the next 48–72 h ranges from 13% to 19% because of postextubation respiratory failure [4–6]. Patients who require reintubation have been noted to have a significantly higher rate of complications than those who are successfully extubated on the first attempt.

Noninvasive ventilation (NIV) is an effective tool in preventing endotracheal intubation and improving the clinical outcome of patients with different etiologies of acute respiratory failure, especially exacerbations of chronic obstructive pulmonary disease (COPD) [7] and cardiogenic pulmonary edema [8, 9]. Noninvasive positive pressure ventilation (NIPPV) has been tried for facilitation of weaning and extubation [10]. A meta-analysis by Burns et al. suggested that NIPPV can facilitate weaning in mechanically ventilated patients, especially the subgroup of patients with chronic obstructive lung disease [11]. The aim of this chapter is to specifically review the role of NIPPV in the management and prevention of respiratory failure after extubation.

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45.2
Pathophysiology of Postextubation Respiratory Failure

Postextubation respiratory failure is defined as the appearance of signs of respiratory distress within 48–72 h after planned extubation. It is broadly identified by one or more of the following features: increase in respiratory rate more than 50% from baseline with use of accessory muscles of respiration or abdominal paradox, pH less than 7.35 with $Paco_2$ more than 45 mmHg, pulse oximetric saturation less than 90% or Pao_2 less than 80 mmHg on Fio_2 more than or equal to 50%. It is obviously different from weaning failure in which a patient develops signs of respiratory or hemodynamic intolerance during a spontaneous breathing trial. Postextubation respiratory failure can arise from airway and nonairway causes, with the latter more common, and is associated with increased mortality [12, 13]. Airway causes include upper airway obstruction, aspiration, and excess pulmonary secretions; nonairway causes are congestive heart failure, encephalopathy, and others. Importantly, reintubation due to extubation failure is an independent risk factor for nosocomial pneumonia and increased hospital length of stay and hospital mortality [14, 15]. Certain risk factors are associated with increased propensity for extubation failure and include neurological impairment; older age; severity of illness; more than one comorbid illness. including cardiac failure; long duration of ventilation prior to extubation; use of continuous sedation; anemia; obesity; and others [14, 16–18].

45.3
Physiological Basis for the Use of NIV in Postextubation Respiratory Failure

During a spontaneous breathing trial, there is an increase in respiratory frequency and a decrease in the tidal volume. This causes alveolar hypoventilation and ventilation–perfusion mismatch [19]. Further, patients who fail weaning develop a decrease in mixed venous oxygen saturation due to an increase in oxygen extraction by tissues and failure to increase the cardiac output; this is in contrast to patients who tolerate a spontaneous breathing trial when it is associated with increased cardiac index [20]. Hence, it can be hypothesized that similar events would occur during the process of respiratory failure following extubation.

NIV augments the inspiratory and expiratory flow and pressure, thereby increasing the tidal volume and unloading the inspiratory muscles [21, 22]. This leads to accomplishment of an efficient breathing pattern and improvement in hypoxemia and hypercapnia [23]. Furthermore, it has been shown in mechanically ventilated patients that pressure support is associated with prevention of ventilation–perfusion mismatch while weaning patients from positive pressure ventilation [24]. Finally, in ventilator-dependent patients with chronic respiratory disorders, invasive and noninvasive pressure support are equally effective in decreasing the work of breathing and improving the arterial blood gases, but the breathing pattern and the respiratory pump improve better with NIPPV [25].

Thus, based on indirect evidence, one can hypothesize that NIV would be effective in management of postextubation respiratory failure and could potentially be tried in two

different scenarios: management of established postextubation respiratory failure and prevention of postextubation respiratory failure in patients at high risk for reintubation following successful extubation.

45.4
Noninvasive Ventilation in Postextubation Respiratory Failure

NIV has been beneficial in weaning, that is, in patients receiving mechanical ventilation who fail a successful spontaneous breathing trial, are systematically extubated, and who receive NIPPV [26–29]. In fact, Burns et al., in a meta-analysis, demonstrated that, compared to invasive ventilation, weaning using NIV decreased mortality, ventilator-associated pneumonia, and the total duration of mechanical ventilation, but all the studies were mainly of patients with COPD [30].

NIV was considered a promising modality for postextubation respiratory failure in the international consensus conference [31], primarily based on results of observational studies [32, 33]. In a study of 30 patients with COPD with postextubation hypercapnic respiratory failure insufficiency, the use of NIV was compared conventional treatment of 30 historically matched control patients. NIPPV was effective not only in correcting gas exchange abnormalities but also significantly reduced the need for endotracheal intubation (20/30 [67%] in the control group vs. 6/30 [20%] in the NIV group) [32]. In 15 patients without COPD patients after prolonged mechanical ventilation (more than 72 h) with acute respiratory insufficiency after early extubation, NIPPV improved pulmonary gas exchange and breathing pattern, decreased intrapulmonary shunt fraction, and reduced the work of breathing [33]. In another observational study of 43 patients with postextubation failure after cardiac surgery, NIPPV relieved hypoxemia and helped avoid reintubation in 75% of patients who already met standard intubation criteria at study entry [34].

However, two randomized controlled trials (RCTs) have not shown benefits from NIV in preventing reintubation in patients with postextubation respiratory failure (Table 45.1) [35, 36]. The first trial by Keenan et al. included 81 patients randomized to receive standard medical therapy (SMT; supplemental oxygen to maintain oxygen saturation by pulse oximetry more than or equal to 95%) alone or NIPPV by face mask plus SMT. The study found no difference in the rate of reintubation (28/39 [72%] NIV vs. 29/42 [69%] control), hospital mortality, duration of mechanical ventilation, or length of intensive care unit (ICU) or hospital stay. The other trial included 221 patients with postextubation respiratory failure randomly allocated to receive NIPPV (114 patients) or standard therapy (107 patients). There was no difference between the two groups in the need for reintubation (48% in both groups). The ICU mortality was higher in the NIV group than in the standard therapy group (25% vs. 14%), and the time from respiratory failure to reintubation was longer in the NIV group. If we combine the two studies, there is no benefit with NIPPV in decreasing either the reintubation rates (relative risk [RR] 1.03, 95% confidence interval [CI] 0.84–1.25) or ICU mortality (RR 1.14, 95% CI 0.43–3.0) [37].

Does this mean that NIPPV should not be used in postextubation respiratory failure? Before rejecting NIV completely in patients with postextubation respiratory failure, one

Table 45.1 Randomized controlled trials employing noninvasive positive pressure ventilation (NIPPV) in post-extubation respiratory failure

Study	IPAP/EPAP	Patient characteristics	Inclusion criteria	Exclusion criteria	Reintubation criteria
Keenan et al. [35], single center	$10.2 \pm 2/5.1 \pm 1.2$	81 patients, heterogeneous population (cardiac – 28, COPD – 9, others); APACHE II (NIPPV – 22.5 $\pm$ 7.1; control – 24 $\pm$ 7.9)	Respiratory rate above 30 or more than 50% increase from baseline, use of accessory muscles of respiration, or abdominal paradox	DNR order, prior obstructive sleep apnea, cervical spine injury, upper airway obstruction, language barrier, respiratory distress outside intensive care unit	Cardiac or respiratory arrest, apnea, respiratory distress in extremis, inability to protect airway, psychomotor agitation requiring sedatives, heart rate less than 50/min, SBP less than 70 mmHg
Esteban et al. [36], multicenter	Titrated to achieve a tidal volume more than 5 mL/kg body weight and patient comfort	221 patients: acute respiratory failure (pneumonia, sepsis, postoperative respiratory failure, trauma, cardiac failure, ARDS, others) 187 patients; acute-on-chronic respiratory failure (COPD, asthma) 27 patients; and neuromuscular disease 7 patients; SAPS II (NIPPV 37 $\pm$ 13, control 36 $\pm$ 10)	Two or more of the following: pH below 7.35 with $Paco_2$ more than 45 mmHg, respiratory muscle fatigue or increased respiratory effort, respiratory rate more than 25/min for 2 h consecutively, Sao_2 less than 90% or Pao_2 less than 80 mmHg on Fio_2 more than 0.5	–	At least one of the criteria for 1 h or less: lack of improvement in pH or $Paco_2$; altered mental status with patient unable to tolerate NIPPV; Sao_2 less than 85% despite high Fio_2; lack of improvement in respiratory muscle fatigue; SBP less than 90 mmHg for more than 30 min despite adequate volume challenge, vasopressors, or both; copious secretions associated with acidosis, or hypoxemia

APACHE Acute Physiology and Chronic Health Evaluation, *ARDS* acute respiratory distress syndrome, *COPD* chronic obstructive pulmonary disease, *DNR* do not resuscitate, *EPAP* expiratory positive airway pressure, *IPAP* inspiratory positive airway pressure, *SAPS* Simplified Acute Physiology Score, *SBP* systolic blood pressure

should also understand the limitations of the individual trials. There was a limited experience with the use of NIPPV by the physicians in the trials by Keenan and Esteban et al., and both the trials used different definitions for postextubation respiratory failure [35, 36]. Also, in the study by Esteban et al. [36], 28 patients in the standard therapy group crossed over to receive rescue NIPPV. If these patients are considered to have had treatment failure and included with the other patients in that group who were reintubated, then the standard therapy group had a significantly higher risk of a need for reintubation than the NIPPV group. Finally, there is also the criticism that the trial was stopped early [38]. Another approach to use NIPPV in all patients after extubation in a single study also showed no benefit with the use of NIPPV [39]. Thus, NIPPV should be used judiciously when likely to benefit, such as for those with COPD or hypercapnic pulmonary edema. The trial of NIPPV should not exceed 2 h. There should be close monitoring of respiratory, cardiovascular, and arterial blood gas parameters with facilities for intubation and invasive ventilation readily available. However, because of paucity of data, more studies are required to precisely identify the patients likely to benefit from NIPPV in this setting.

45.5
Noninvasive Ventilation in Patients at Risk for Respiratory Failure After Extubation

NIV may be more beneficial in patients who are "at risk" for postextubation respiratory failure in contrast to established postextubation respiratory failure. Two RCTs [40, 41] (Table 45.2) and one observational study [42] investigated the use of NIPPV in patients at high risk for postextubation respiratory failure. In the observational study, 62 patients with a body mass index if 35 kg/m^2 or more were assigned to NIV via nasal mask immediately following extubation and were compared to 62 historical controls treated with conventional therapy. Compared to conventional therapy, the institution of NIV resulted in significant reduction (10% vs. 26%) in the rate of respiratory failure and the ICU and hospital lengths of stay. Subgroup analysis of hypercapnic patients showed reduced hospital mortality in the NIV group compared to the control group [42].

In the first multicenter RCT, 97 consecutive patients requiring more than 48 h of mechanical ventilation and considered at risk of developing postextubation respiratory failure were randomized to receive NIV (8 h or more a day in the first 48 h) or SMT. Compared with the SMT group, the NIV group had a lower rate of reintubation (4/48 vs. 12/49) and reduced ICU mortality [40]. In the other RCT, 162 patients were randomly allocated after extubation to receive NIV for 24 h ($n = 79$) or SMT ($n = 83$). In the NIV group, postextubation respiratory failure was less frequent (13/79 vs. 27/83), the ICU mortality was lower, but the reintubation rates were similar [41]. Pooled analysis of the two RCTs showed that NIPPV, when compared to conventional therapy, significantly decreased the reintubation rates (RR 0.46, 95% CI 0.28–0.76) and the ICU mortality (RR 0.26, 95% CI 0.1–0.66) but not the hospital mortality (RR 0.71, 95% CI 0.42–1.20). The number needed to treat (NNT) (95% CI) was 9 (5–29), 9 (6–21), and 16 benefit (32 harm to 7 benefit) for reintubation rates, ICU, and hospital mortality, respectively [37].

From these studies, it can be inferred that the use of NIPPV following extubation decreases the reintubation rates and ICU mortality in patients who are at risk for postextubation respiratory failure but not once they develop respiratory failure. Several reasons

Table 45.2 Randomized controlled trials employing noninvasive positive pressure ventilation (NIPPV) in patients at high-risk for post extubation respiratory failure

Study	IPAP/EPAP	Patient characteristics	Inclusion criteria	Exclusion criteria	Reintubation criteria
Nava et al. [40], multicenter	$13.2 \pm 4.5/5.3 \pm 1.6$	97 patients: acute respiratory failure (pneumonia, postoperative respiratory failure, trauma, cardiac failure, ARDS, others) 57 patients; acute-on-chronic respiratory failure (COPD) 32 patients; neurosurgery 8 patients; APACHE II (NIPPV 22.5 ± 7.1, control 24 ± 7.9)	Patients intubated more than 48 h with successful weaning plus one or more of the following: more than one consecutive failure of weaning trial, chronic heart failure, $Paco_2$ 45 mmHg or more after extubation, more than one comorbidity (excluding chronic heart failure), weak cough, stridor at extubation	Coma, inability to protect the airways, cervical spine injury, neuromuscular diseases, lack of informed consent, agitated or uncooperative state, anatomical abnormalities interfering with the mask fit, uncontrolled cardiac ischemia or arrhythmias, failure of more than two organs, BMI 30 or above, sleep apnea, home NIPPV	At least one major (pH < 7.35 with $Paco_2$ > 45 mmHg or if hypercapnic $Paco_2$ increase more than 15%); (Sao_2 < 90% on Fio_2 > 50%) or two minor criteria (increase in respiratory rate more than 20% or more than 35 breaths/min); clinical signs of respiratory muscle fatigue; severe dyspnea; inability to remove secretions; coma, cardiac, or respiratory arrest; severe hypotension
Ferrer et al. [41], two centers	$14 \pm 2/5 \pm 1$	162 patients: chronic respiratory failure 82, chronic heart disease 53, diabetes mellitus 32, immunosuppression 17, neoplasms 18, cirrhosis 7, chronic renal failure 14; APACHE II (NIPPV 14 ± 3, control 13 ± 3)	Patients intubated for 48 h or longer who tolerated a spontaneous breathing trial plus at least one of the following: age above 65 years, cardiac failure as the cause of intubation, APACHE II score more than 12 on the day of extubation	Facial or cranial trauma or surgery, recent gastric or esophageal surgery, active upper gastrointestinal bleeding, excessive respiratory secretions, lack of cooperation, do-not-resuscitate order	Any of the following: respiratory or cardiac arrest, massive aspiration, apnea with loss of consciousness, psychomotor agitation, persistent inability to remove respiratory secretions, heart rate below 50/min with loss of alertness, severe hemodynamic instability without response to fluids and vasopressors

APACHE Acute Physiology and Chronic Health Evaluation, *ARDS* acute respiratory distress syndrome, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *EPAP* expiratory positive airway pressure, *IPAP* inspiratory positive airway pressure, *SAPS* Simplified Acute Physiology Score, *SBP* systolic blood pressure

may explain these differences. First, whereas the studies by Keenan [35] and Esteban et al. [35] applied NIPPV after patients had developed respiratory failure, the two studies by Nava [40] and Ferrer et al. [41] applied NIPPV immediately after extubation in high-risk patients. Because longer time from extubation to reintubation is associated with worse outcome [13], the delay in reintubation correlates with worse survival rates in patients who received NIPPV for established postextubation respiratory failure [35, 36]. Second, a significantly higher proportion of patients with chronic respiratory disorders were included in at-risk studies (145/383), whereas the postextubation respiratory failure trials enrolled only around 10–11% of patients with chronic pulmonary disease, the etiology shown to have the best response to NIPPV [43].

45.6
Conclusions

The use of NIPPV following extubation, compared to standard therapy, decreases the reintubation rates and ICU mortality but not the hospital mortality in patients who are at risk for postextubation respiratory failure but not once respiratory failure following extubation is established. In fact, there is a trend toward worse outcomes with application of NIPPV in patients with postextubation respiratory failure. NIPPV should be used judiciously in patients with established postextubation respiratory failure (Table 45.3). A protocol needs to be developed by which NIPPV is used prophylactically in patients who are at high-risk for developing postextubation respiratory failure. Early application of NIPPV seems crucial to avoid respiratory failure after extubation and consequently reintubation.

Table 45.3 Practical approach to the use of noninvasive positive pressure ventilation NIPPV in the postextubation setting

NIPPV in "at-risk" patients for postextubation respiratory failure
• Preferred approach for the use of NIPPV in the postextubation setting
• Identify high-risk features
– Elderly patients
– More than one consecutive failure of weaning trial
– Chronic heart failure
– Pa_{CO_2} more than 45 mmHg after extubation
– More than one medical/surgical comorbid illness
– Poor cough reflex
– Upper airway stridor at extubation not requiring immediate reintubation
– Higher severity of illness
– Severely obese patients (BMI > 35 kg/m^2)
NIPPV in established postextubation respiratory failure
• Use judiciously
• Likely to benefit in selected patients (acute COPD, hypercapnic pulmonary edema, etc.)
• Trial of NIPPV for 2 h with close monitoring of respiratory, cardiovascular, and arterial blood gas parameters
• Facilities for intubation and invasive ventilation readily available

COPD chronic obstructive pulmonary disease

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Section IX

Intraoperative and Postoperative Indications for Noninvasive Mechanical Ventilation

Intraoperative Use of Noninvasive Ventilation

46

Fabio Guarracino and Rubia Baldassarri

46.1
Introduction

Noninvasive positive pressure ventilation refers to the delivery of assisted mechanical ventilation without the need for an invasive artificial airway. In the last decade, noninvasive ventilation (NIV) has been recognized as useful for treatment of patients affected by moderate-to-severe respiratory failure [1]. This technique has been largely used for long-term treatment of patients with advanced chronic obstructive pulmonary disease (COPD). If NIV is performed in the very early phase of pulmonary impairment, it can reduce morbidity and mortality, avoiding more aggressive interventions such as endotracheal intubation and mechanical ventilation.

NIV can also be appropriate for treatment of acute respiratory failure due to either pulmonary or cardiac dysfunction or in patients with severe hypoventilation secondary to neurodegenerative or metabolic affections. For all these reasons, this kind of ventilatory support has been expanding.

A few studies have reported on the application of NIV for intraoperative airway management [2–5]. In patients who are at high risk for mechanical ventilation or general anesthesia due to pulmonary disease (i.e., COPD and recurrent pneumothorax) and in patients affected by respiratory failure, who can suffer from prolonged mechanical ventilation as well as from general anesthesia, intraoperative NIV can be beneficial.

46.2
The Rationale

Avoiding intubation should be an important objective in the management of patients with respiratory disease to prevent complications from tracheal intubation and mechanical ventilation, and NIV may help achieve that goal. Patients who are severely debilitated due to

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cardiac and respiratory disease are often scheduled for palliative surgery for conditions such as persistent pneumothorax and recurrent pleural or pericardial effusions, for surgery for malignancies, or for percutaneous cardiac procedures. Surgery and anesthesia in these sick patients can be fatal. When surgery under these circumstances is highly desirable, every effort must be made to minimize the significant risks.

The respiratory depression associated with the most common anesthetic agents and the high airway positive pressure related to mechanical ventilation and endotracheal intubation can worsen a preexisting pathologic condition and, above all, can determine prolonged or difficult weaning from mechanical ventilation in the postoperative phase. Although improving peripheral anesthetic procedures used with more confidence have given a chance to these high-risk patients, respiratory function can be worsened by neural block in regional anesthesia techniques.

NIV provides an adequate respiratory performance through the operation even when a supine position is necessary for the surgery and allows these patients to maintain spontaneous breathing, normal swallowing, and cough mechanisms.

The surgical procedure can be safely performed combining NIV and peripheral anesthetic technique, and the use of NIV can also significantly reduce either the perioperative respiratory complications or the risks associated with prolonged mechanical ventilation.

46.3
Technical Aspects and Clinical Intraoperative Scenario

Intraoperative NIV also presents limits and risks that must be considered for any single patient. Among the complications, the most common are the damage to facial tissues caused by the local pressure of the mask, the gastric distension due to air insufflation, and eye irritation. Also, the patient's tolerance to the face mask should be taken into account; each patient's adaptability to the rhythmic air insufflations cannot be the same and can even change in time. Some patients require mild sedation to accept ventilation until the end of the surgical procedure.

Continuous monitoring of the respiratory parameters to assess the adequacy of ventilation is mandatory. The setting of the ventilator must be adapted to the patient's body characteristics and clinical features and eventually modified on the bases of the functional parameters and monitoring information. The ventilator is usually connected with conventional tubing to a full-face mask with an inflatable soft cushion seal. The mask is safely secured with head straps. A hydrocolloid sheet can be applied over the nasal bridge. For patients with a nasogastric tube, a seal connector in the dome of the mask is used to minimize air leakage.

Pressure support is increased to obtain an exhaled tidal volume of 8–10 mL/kg, a respiratory rate below 25/min, and the disappearance of accessory muscle activity. Positive end-expiratory pressure (PEEP) can be increased in increments of 2 cmH_2O up to 10 cmH_2O until the FiO_2 requirement is 0.6 or less to maintain an SaO_2 above 95% on pulse oximetry. Ventilator settings are adjusted based on continuous oximetry and measurements of arterial blood gases.

NIV is reduced progressively and is discontinued once the patient maintains a respiratory rate of less than 30/min and a PaO_2 greater than 70 mmHg with an FiO_2 of 0.5 without ventilatory support.

Fig. 46.1 Noninvasive ventilation (NIV) during endovascular aortic valve implantation in a patient unsuitable for surgical treatment. Note the transesophageal echo (TEE) probe through the mask

We use NIV intraoperatively in patients submitted to endovascular aortic valve implantation in the catheterization lab (Fig. 46.1) and for palliative thoracic surgery.

In 2008 at our Institution, 53 patients affected by severe aortic stenosis, classified as III–IV, according to New York Heart Association (NYHA) classification, and at very high risk for an open heart surgical procedure according to the EUROSCORE system, were scheduled for the minimally invasive percutaneous technique. Among them, there were patients for whom severe respiratory dysfunction contraindicated mechanical ventilation even for the relative short period of the percutaneous procedure. In orthopneic patients, NIV was started and maintained for 15 min in the sitting position. Subsequently, this allowed the patients to move to the supine position and, still under NIV, to tolerate it for the duration of the procedure.

In some cases, we managed to introduce a transesophageal echo (TEE) probe through a hole in the mask to guide the implantation procedure by echocardiography (Fig. 46.1) [6]. Careful hemodynamic and respiratory monitoring was performed during the surgical procedure. In all cases, the NIV was successful, and no perioperative complication occurred.

We have applied NIV in patients with severe respiratory insufficiency undergoing palliative thoracic surgery. In those cases, we combined NIV with peripheral anesthesia or light sedation. This allowed us to operate on patients for whom general anesthesia and mechanical ventilation would place them at risk for major perioperative complications.

46.4 Conclusion

In conclusion, this approach may be applicable to a number of different surgical procedures on the chest and abdomen in patients who are considered to have conditions that are inoperable due to severe respiratory insufficiency or to contraindications to tracheal intubation and mechanical ventilation. The administration of NIV is well tolerated and allows

prevention of respiratory complications. We suggest that surgical and anesthetic programs should therefore consider NIV in the treatment of such high-risk and sick patients.

Key Recommendations

> It should be supported in patients with respiratory contraindications to general anesthesia and mechanical ventilation and in high-risk patients who have conditions that are considered inoperable due to respiratory insufficiency.
> Preoperative adequate patient information and a comprehensive explanation of how the NIV will work (i.e., by showing the patient the mask and allowing the patient to try it on his or her face) are important for intraoperative feasibility.
> Intraoperative NIV is feasible only for a cooperating patient.
> In orthopneic patients, NIV should be started in the sitting position.
> Intraoperative interaction between the anesthetist and the surgeon is pivotal during thoracic procedures.

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Noninvasive Ventilation in Adult Liver Transplantation

47

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47.1
Introduction

Noninvasive ventilation (NIV) with positive pressure, consolidated treatment of both acute and chronic respiratory failure, has proven effective in the management of numerous medical and surgical diseases.

Clinical experience has shown that intubation and reintubation, rather than the total duration of respiratory support, are determinants for the risk of lung complications. NIV, considered a "gentle," nonaggressive method of airway management, is therefore increasingly applied to avoid the side effects of conventional invasive methods.

A growing interest has emerged in adoption of NIV for ventilatory assistance in immunocompromised patients, such as those undergoing bone marrow, liver, lung, cardiac, and kidney transplantation.

The obligatory immunosuppression consistently increases the risk of ventilator-associated pneumonia (VAP) in "invasively" ventilated liver transplant patients. Nosocomially acquired infections in these recipients have an important effect on the early outcome since they increase morbidity, length of the intensive care unit (ICU) stay, and mortality.

47.2
Pathophysiology of Respiratory Failure in Liver Recipients

Some degree of respiratory failure and abnormalities of pulmonary gas exchange are common findings of end-stage liver disease. Causes of gas exchange abnormalities following orthotopic liver transplantation (OLTx) are numerous and include the persistence

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of preoperative intrapulmonary shunting, postoperative ventilation–perfusion mismatching, failure of the hypoxic vasoconstrictor response, and left ventricular failure. Almost 70% of patients undergoing pretransplant assessment of pulmonary function present a widened A-a (alveolar–arterial) oxygen gradient. Unpredictable changes in the neural drive to the respiratory muscles may be induced by the intraoperative anesthetics, poor recovery of the graft, and various drugs administered in the immediate postoperative period. Hypoventilation in liver recipients may be a consequence of decreased overall activity and lack of coordination of respiratory muscles. In addition, pleural effusions, abdominal distension, interstitial lung disease, and pneumonia are often responsible for restrictive respiratory disorders.

Liver transplant patients frequently have reduced lung volumes, elevation of both hemidiaphragms, and lower-lobe atelectases. These conditions consistently increase the work of breathing, making it difficult to achieve and maintain postoperative ventilatory autonomy.

47.3
NIV as a Tool to Facilitate Early Extubation After OLTx

The persistence of preoperative neurologic disorders, patchy lung infiltrates, lung imbibition, pleural effusion, sputum retention, and unsuccessful weaning attempts sometimes require prolonged tracheal intubation and mechanical ventilation after OLTx.

Rapid weaning from mechanical ventilation is highly recommended in liver transplant patients for at least the following reasons: (1) the augmented risk for ventilatory-induced complications, (2) the potential negative hemodynamic effects of a high intrathoracic pressure on graft perfusion, and (3) the need for rapid avoidance of sedatives.

Early removal of the endotracheal tube in the posttransplant course is essential in preventing tracheal mucosa injuries, impairment of airway ciliary function, bacterial colonization, sinusitis, and development of nosocomial pneumonia; a prolonged dependence on invasive airways is, in fact, associated with ventilator-associated complications and increased mortality. However, lack of improvement of preoperative ventilatory disorders along with postoperative respiratory muscle dysfunction, poor nutritional status, and suboptimal chest X-ray images make rapid discontinuation of mechanical ventilation sometimes challenging.

The introduction of noninvasive mechanical ventilation in the postoperative care of liver transplant patients has been of great help to clinicians during this transition phase often critical for the removal of artificial airways. Rapid extubation followed by prompt NIV application should be considered in this setting as a means to shorten and accelerate the weaning process.

A noninvasive technique, "prophylactically" applied soon after withdrawal of invasive airways, represents a method of ventilatory assistance particularly effective in those recipients who do not completely fulfill the criteria for safe extubation.

Noninvasive pressure support (PS) mode plus a continuous positive end-expiratory pressure (PEEP) could prevent severe lung derecruitment and the loss of vital

capacity following removal of the endotracheal tube. Since NIV with PEEP avoids the additional respiratory resistance imposed by the tracheal tube, it contributes to reduce inspiratory effort.

By limiting diaphragm elevation, NIV will also prevent basal atelectases in case of abdominal distension.

Prolonged invasive ventilation in the postoperative period may also negatively affect graft perfusion. Since mechanical ventilation decreases the extra–intrathoracic venous pressure gradient, it may increase inferior vena cava pressure and decrease portal vein flow. Lowering the intrathoracic pressure by rapid avoidance of positive pressure ventilation is an important strategy to reduce the backflow pressure to the liver and promote better oxygen delivery during early recovery of the graft.

Noninvasive techniques are associated with more favorable intrathoracic hemodynamic balance compared to conventional invasive methods. This is likely due to the fact that the lung inflation pressure reached with NIV is lower than when a patient is ventilated through an endotracheal tube.

This advantage makes NIV particularly suitable for ventilatory assistance of hemodynamically unstable transplanted patients. Less need, or no need, for sedatives along with a more physiologic venous return may decrease the use of inotropic and vasoactive agents, thus improving splanchnic circulation and graft perfusion.

Major benefits after extubation are observed when NIV is applied continuously rather than intermittently. Discontinuing NIV several times a day may result in limited clinical efficacy.

The success of NIV in preventing alveolar collapse and microatelectases and maintaining respiratory system compliance has been diffusely demonstrated.

In case of moderate sedation, sometimes necessary for agitation or invasive procedures, the recipients may experience a decrease in inspiratory muscle strength, some degree of lung derecruitment, loss of lung volumes, and impairment of gas exchange. NIV should always be considered in these circumstances to prevent hypoventilation.

Nocturnal ventilation in NIV is frequently indicated for moderately hypoxic liver recipients who require sedatives to facilitate night sleep.

An increase in intrathoracic blood volume and interstitial lung water, often unavoidable consequences of massive intraoperative fluid loading, can at times lead to respiratory fatigue and hypoxia. If lung congestion is responsible for ventilatory distress, an early NIV plus PEEP is useful to reduce extravascular lung fluid when diuretics alone are ineffective.

NIV can be maintained for as long as the patient requires it. Once the patient no longer requires the NIV-PS mode, intermittent CPAP (continuous positive airway pressure) by facial mask or a helmet system can be safely applied to preserve the patency of peripheral airways in spontaneous ventilation.

In the beginning of its use in solid organ transplantation NIV was mainly delivered with a full facial mask. However, there are numerous side effects associated with prolonged use of a full facial mask, such as erythema, ulcerations of the nose and face, conjunctival irritation, discomfort on speaking, claustrophobia, and air leaks. Now we prefer the helmet system, more suitable for long application of NIV. Antonelli et al. [1] demonstrated that the helmet system is associated with a lower failure rate than the facial mask.

47.4
NIV in the Prevention of Posttransplant Infectious Diseases

Prolonged anesthesia and surgery may impair the function of lung cells, which could increase susceptibility to postoperative infections.

The risk of postoperative pneumonia is greatly influenced by the time to extubation. In a study by Meduri et al. [2] the persistence of the endotracheal tube emerged as the single most important predisposing factor for VAP. After abdominal sepsis, VAP represents the most important cause of morbidity and mortality following OLTx, with a high cost in terms of economic resources and time demands on medical personnel.

As mentioned, an early extubation followed by rapid implementation of NIV should be considered to prevent VAP in case of inadequate ventilatory autonomy.

Nourdine et al. [3] reported a lower incidence of pulmonary and extrapulmonary infections as well as a lower mortality in patients treated noninvasively compared with patients intubated and conventionally ventilated. Hilbert et al. [4] compared early NIV with standard treatment in immunosuppressed hematological patients. NIV-treated patients had a significantly lower death rate in the ICU, and fewer individuals developed infections; pneumonia and sinusitis occurred only in patients who required intubation.

The first application of NIV in solid organ transplant recipients was described by Antonelli and coworkers [5]. They randomized patients with respiratory failure following transplantation to receive either NIV or standard therapy. Patients assigned to NIV showed a trend toward fewer VAPs and a significant reduction of severe sepsis or septic shock episodes.

NIV is particularly attractive in preventing posttransplant infectious diseases as it leaves the upper airways intact, reduces bacterial colonization and nosocomially acquired infections, and avoids the bleeding complications of invasive airways in such immunosuppressed thrombocytopenic recipients.

47.5
NIV in the Prevention of Tracheal Reintubation After OLTx

Reintubation often becomes necessary in the postoperative period of a complicated liver transplant, either within the first few days or at any time later. Respiratory distress can occur because of pulmonary edema, aspiration pneumonia, inadequate cough, excessive respiratory secretions, encephalopathy, infectious diseases, and cardiac dysfunction.

Patients who develop severe respiratory failure in the posttransplant course have been generally managed with tracheal intubation and mechanical ventilation. However, many respiratory disorders following OLTx may respond to specific treatments, such as hemofiltration, pleural drainage, bronchial toilette, abdominal drainage, and so on and are expected to improve over a period of hours or days. Intubation, deep sedation, and mechanical ventilation may lead to muscle weakness in such debilitated patients, therefore increasing the susceptibility to additional episodes of ventilatory failure.

It has been recognized that the immunocompromised recipients with hypoxemic respiratory insufficiency are at high risk of pulmonary infections and sepsis while intubated.

If the severity of ventilatory failure does not require immediate intubation, NIV may be cautiously attempted before proceeding to invasive airways.

NIV represents an effective means of ventilatory assistance especially when the need for respiratory support will presumably be short lived. Supporting the failing recipient with a noninvasive technique may reduce the work of breathing and maintain gas exchange while awaiting an improvement in spontaneous ventilation.

Instituting this strategy at a more advanced stage may imply the application of both an increased level of pressure support and a long time of dependency on NIV. This may increase patient discomfort and side effects.

Clear advantages of NIV in severe immunodepressed or transplanted patients suffering from acute respiratory failure have already been demonstrated [5]. In the study by Antonelli and colleagues [5], patients who received NIV (vs. standard treatment) had a reduced need for reintubation and a lower ICU mortality rate.

NIV does not seem to be beneficial in avoiding reintubation when these patients have developed overt respiratory failure associated with life-threatening hypoxemia, and it does not represent a replacement for endotracheal intubation in recipients who require airway protection.

A long delay in NIV institution, frank muscle exhaustion, very low arterial blood pH, and a marked alteration of the patient's mental status reduce the likelihood of success. In the presence of severe abnormalities in respiratory mechanics, neurologic disorders impairing respiratory drive, and severe comorbid conditions, NIV may be futile in trying to avoid reintubation.

47.6
Conclusion

NIV and CPAP by a helmet system have gained increased acceptance in posttransplant ventilatory assistance.

Recognition of serious complications associated with prolonged intubation and standard mechanical ventilation, a better understanding of respiratory failure in this setting, and the development of ventilatory modalities that allow more patient–ventilator synchrony strongly promote NIV following OLTx.

Clinical experience has shown that properly delivered NIV mostly benefits moderately dyspneic recipients in acute respiratory failure, while it appears less promising and efficient in the weaning process of patients ventilated for extended periods of time.

The improvements in arterial oxygenation, decreased ventilatory demand provided with an inspiratory support, as well as the scarcity of hemodynamic repercussions are among the major benefits of this method.

Numerous studies and multicenter trials will be needed to verify whether NIV has a clear positive impact on a large scale in reducing postoperative morbidity, graft complications, length of ICU stay, costs, and mortality following OLTx.

Key Recommendations

> The introduction of NIV in the postoperative care of liver transplant patients has been of great help to clinicians during the transition phase, often critical, of the removal of artificial airways.

> Rapid weaning from mechanical ventilation is highly recommended in liver transplant patients for at least the following reasons: (1) the augmented risk for ventilatory-induced complications, (2) the potential negative hemodynamic effects of a high intrathoracic pressure on graft perfusion, and (3) the need for rapid avoidance of sedatives.

> Lowering the intrathoracic pressure by rapid avoidance of positive pressure ventilation is an important strategy to reduce the backflow pressure to the liver and promote better oxygen delivery during early recovery of the graft.

> NIV is particularly suitable for ventilatory assistance of hemodynamically unstable transplanted patients. Less need, or no need, for sedatives along with a more physiologic venous return may decrease the use of vasoactive agents, thus improving splanchnic circulation and graft perfusion.

> NIV is particularly attractive as it leaves the upper airways intact, reduces bacterial colonization, decreases the incidence of VAP, and avoids the bleeding complications of invasive ventilation in such immunosuppressed thrombocytopenic recipients.

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Noninvasive Positive Pressure Ventilation in Patients Undergoing Lung Resection Surgery

48

Christophe Perrin, Valérie Jullien, Yannick Duval, and Fabien Rolland

48.1
Introduction

Lung resection surgery is often complicated by significant pulmonary dysfunction that persists for a few days after surgery [1–3]. Alteration of ventilatory function is multifactorial, with all factors contributing (Fig. 48.1): reflex inhibition of the phrenic nerve, depression of the respiratory drive by narcotics, chest pain, closure of distal airways, and the loss of functioning parenchyma [2, 3]. Pleural air leaks may further deteriorate pulmonary gas exchange and increase the work of breathing [2, 3]. Finally, hemodynamic instability may occur and participate in gas transfer decrease within the lungs and oxygen transport to tissues [2, 3]. This pulmonary function impairment may lead to postoperative pulmonary complications such as sputum retention, atelectasis, pneumonia, and respiratory failure [4].

Postoperative mortality and morbidity after lung resection surgery remain important. A study found 30-day mortality and morbidity rates of 4% and 23.8%, respectively, after lobectomy and of 11.5% and 25.7%, respectively, after pneumonectomy [5]. Postoperative pulmonary complications remain the leading cause of death; for example, acute respiratory failure after lung resection may be fatal in up to 60–80% of cases [6]. These high mortality and morbidity rates are mainly linked to complications of endotracheal mechanical ventilation [7]. Indeed, prolonged invasive mechanical ventilation increases the risk of bronchial suture disruption, bronchopleural fistula, persistent air leakage, and pneumonia [8, 9].

Noninvasive positive pressure ventilation (NPPV) is applied using a mask or mouthpiece rather than an endotracheal or tracheostomy tube. Although NPPV is often used for long-term nocturnal or continuous support in patients with chronic respiratory failure,

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Fig. 48.1 Factors of alteration of ventilatory function following lung resection and postoperative complications
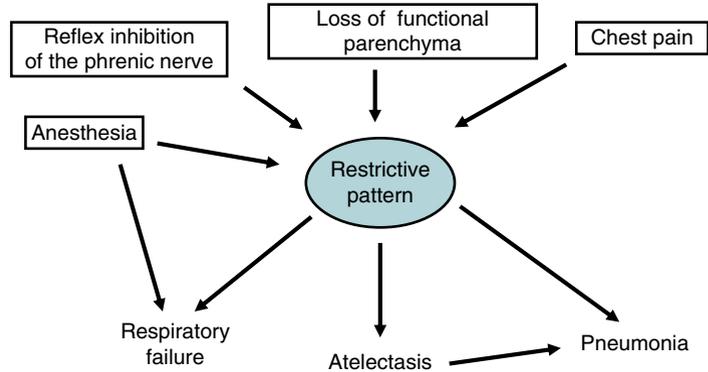
NPPV is also useful in patients with acute respiratory failure [10]. Indeed, NPPV improves gas exchange in patients with various cause of acute respiratory failure [10–13]. Furthermore, NPPV is safe and may avoid endotracheal mechanical ventilation in patients with acute respiratory failure from various causes [14–19]. As a consequence, NPPV reduces the risk of lower respiratory tract infection and pneumonia, thereby reducing in-hospital morbidity and mortality [13, 14, 17].

On the other hand, continuous positive airway pressure (CPAP) has also been demonstrated to be useful in the prevention [20, 21] and treatment [22] of pulmonary atelectasis after upper abdominal surgery.

Taking all of this into account, whether NPPV may be useful in patients undergoing lung resection surgery has been assessed. Although few articles have been published on the topic, this chapter reviews contrasting approaches of NPPV in this field.

48.2
NPPV Improves Gas Exchange After Lung Resection Surgery

Regarding mechanisms of postoperative pulmonary function impairment in patients who are candidates for lung resection surgery, NPPV may improve arterial blood gases by opening previously closed lung units [11, 12]. On the other hand, NPPV may cause adverse side effects, such as increasing the ratio of dead space to tidal volume (VD/VT) and the pulmonary-to-pleura air leaks. Further, by decreasing venous return, NPPV may reduce cardiac output [23] and interfere with oxygen transport.

Aguilo et al. [24] designed a prospective, randomized, controlled, and parallel trial to investigate the short-term effects of NPPV on pulmonary gas exchange, ventilatory pattern, systemic hemodynamics, and pleural air leaks in 19 patients submitted to elective lung resection. Medical therapy, including chest physiotherapy, was standardized for all patients. Ten subjects received NPPV with a nasal ventilator support system (study group). The remaining nine individuals constituted the control group. In the study group, NPPV significantly increased PaO_2 and also significantly decreased alveolar-to-arterial oxygen pressure gradient ($P[A-a]O_2$). By contrast, PaO_2 and $P[A-a]O_2$ remained unchanged

throughout the study. Pa_{CO_2}, the ventilatory pattern, and systemic hemodynamics did not change significantly throughout the study in any group. NPPV did not increase the ratio of dead space to tidal volume or significantly worsen pleural air leaks.

48.3
NPPV Reduces Mortality in Acute Respiratory Failure Following Lung Resection

Pulmonary complications are the leading cause of postoperative death in patients following lung resection. Auriant et al. [25] conducted a randomized controlled trial of usual care with or without NPPV in 48 patients with acute hypoxemic respiratory failure after lung resection. Patients were enrolled if they met at least three of the following criteria: dyspnea at rest (respiratory rate > 25 breaths/min), active contraction of the accessory respiratory muscles, ratio of Pa_{O_2} to fraction of inspired oxygen (Pa_{O_2}/Fi_{O_2}) below 200 mmHg, and chest X-ray abnormalities (alveolar consolidation, atelectasis, or interstitial pulmonary edema). Usual care consisted of oxygen supplementation to achieve an arterial oxygen saturation above 90%, bronchodilators, patient-controlled analgesia, and chest physiotherapy. The primary outcome variable was the need for endotracheal mechanical ventilation, and the secondary outcome variables were in-hospital and 120-day mortality rates, duration of stay in the intensive care unit, and duration of in-hospital stay. Half of the patients assigned to the no-NPPV group required intubation versus only 5 of 24 patients (20.8%) in the NPPV group ($p = 0.035$). Of the 17 patients who required intubation, 9 in the no-NPPV group and 1 in the NPPV group were started on endotracheal mechanical ventilation during the first 48 h after lung resection. Nine patients in the no-NPPV group died (37.5%) compared to only three (12.5%) in the NPPV group ($p = 0.045$). The other secondary outcomes were similar in both groups.

48.4
Prophylactic Use of NPPV Following Lung Resection

Although surgical resection is the treatment of choice for non-small-cell bronchogenic carcinoma, a significant number of patients cannot undergo surgical resection because of associated comorbidities that increase operative mortality and postoperative morbidity [26]. Potential patient-related risk factors that may contribute to the risk of postoperative pulmonary complications include smoking, poor general health status, older age, obesity, and chronic obstructive pulmonary disease (COPD) [4]. Furthermore, it has been suggested that a major risk of postoperative complications may be associated with a preoperative impairment of pulmonary function defining "the marginal patient" [26]. The marginal patient has a forced expiratory volume at 1 s (FEV_1) of less than 1.2 L/min; a maximum voluntary ventilation of 35–40% predicted; a forced expiratory volume of 0.6 to 1 L/min; a diffusion capacity for carbon monoxide of 30–40% predicted; and a Pa_{CO_2} greater than 45 mmHg [26]. Although CPAP has been tested in a prophylactic manner after abdominal surgery and seems to be more effective than routine chest physiotherapy [27], its benefits are unfortunately not sustained, and functional residual capacity deteriorates a few minutes

after interruption of CPAP [28]. In comparison to CPAP, relatively high inspiratory pressure is used with NPPV. As a result, NPPV may strongly improve the distribution of ventilation by recruiting zones of alveolar collapse [29]. Thus, prophylactic use of NPPV may promote better recovery of arterial blood gases and pulmonary function after lung resection and perhaps may avoid postoperative pulmonary complications.

In a retrospective study, Lumbierres et al. [30] studied 20 stable patients on NPPV for chronic respiratory failure secondary to kyphoscoliosis (8), morbid obesity (6), thoracoplasty (4), and neuromuscular diseases (2) who underwent surgical procedures with general anesthesia. These patients were compared to subjects without respiratory disease who were submitted to the same type of surgical procedures (gastroplasty, mastectomy, septoplasty, hip prosthesis, cholecystectomy, Gasserian ganglion thermocoagulation, hysterectomy, endoscopic retrograde cholangiopancreatography). The mean postoperative intubation time was 3.8 ± 3.2 h, and only one patient remained intubated for more than 12 h. The mean stay in the postsurgical reanimation unit was 19 ± 9 h (vs. 19 ± 6 h in the general population, p not significant).

Perrin et al. [31] examined the prophylactic use of NPPV administered pre- and postoperatively associated with chest physiotherapy for reducing postoperative pulmonary function impairment. Thirty-nine patients with a preoperative FEV_1 below 70% of the predicted value scheduled for elective lobectomy related to lung cancer were enrolled. Seven patients were excluded after enrollment. A randomized, controlled, and parallel trial was designed. Patients were required to follow standard treatment without (control group, $n = 18$) or with NPPV (study group, $n = 14$) for 7 days preoperatively at home and for 3 days postoperatively in the hospital. Standard treatment included chest physiotherapy, performed with the same regimen during the pre- and postoperative period, twice a day. NPPV was provided via a facial mask, in the spontaneous mode, for 1 h five times a day. The primary outcome variable was the change in arterial blood gases on room air. Pulmonary function testing, lobar or supralobar atelectasis requiring a fiber-optic bronchoscopy, and duration of in-hospital stay were also recorded. This study demonstrated that preventive NPPV therapy used pre- and postoperatively in patients with a preoperative FEV_1 below 70% of the predicted value submitted to elective lung resection improves the overall perioperative evolution of arterial blood gas values and pulmonary function parameters. Also, this study showed that the preoperative use of NPPV may reduce the immediate postoperative hypoxemia and pulmonary function impairment. The hospital stay was significantly longer in the control group than in the study group. The incidence of major atelectasis was 14.2% in the NPPV group and 38.9% in the no-NPPV group, but the difference was not significant.

48.5
Conclusions

Indeed, short-term postoperative use of NPPV improves the efficiency of the lung as a gas exchanger without associated unwanted side effects in patients submitted to lung resection surgery. Furthermore, NPPV may be recognized as a safe and effective means of reducing the need for endotracheal mechanical ventilation and improving survival in patients with acute respiratory failure after such a surgery. Although prophylactic use of NPPV reduces

pulmonary dysfunction after lung resection, further studies are required to assess the real impact of NPPV in a preventive manner on postoperative pulmonary complications.

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Section X

Noninvasive Mechanical Ventilation in Neonates and Children

Equipment and Technology for Continuous Positive Airway Pressure During Neonatal Resuscitation

49

Georg M. Schmölzer and Colin J. Morley

49.1
Introduction

Immediately after birth, the lungs of newly born infants have to clear lung liquid, create a functional residual capacity (FRC), and establish regular spontaneous breathing [1, 2]. However, many preterm infants do not achieve this without assistance. The lungs of preterm infants are immature, are surfactant deficient, are prone to collapse at end expiration, and have difficulty establishing and maintaining FRC [1]. Current guidelines do not provide recommendations about the initial respiratory support of very preterm infants [3]. However, there is a growing body of evidence that continuous positive airway pressure (CPAP) and positive end-expiratory pressure (PEEP) might be beneficial during initial respiratory support in the delivery room (DR) [4–7]. CPAP is a continuous pressure delivered through a mask or nasal interface. PEEP is an end-expiratory pressure applied during positive pressure ventilation. When CPAP or PEEP is used, a distending pressure is applied to the airways to enhance lung expansion, promote a residual lung volume, prevent alveolar collapse and preserve endogenous surfactant, reduce ventilation–perfusion mismatch and airway resistance, improve oxygenation and lung compliance, reduce the work of breathing, and stabilize the breathing pattern [8, 9].

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Despite this information, the role of CPAP and PEEP in the resuscitation of very preterm newborn infants is yet to be precisely defined. This chapter describes different equipment and techniques for the administration of CPAP in the DR.

49.2
CPAP Interface

There are numerous devices available to deliver nasal CPAP, but none of them has been identified as the optimal interface. For practical reasons, both nasal prongs and face mask are used to deliver nasal CPAP in the DR. Interfaces such as a head box with seal, a negative pressure box, or a nosepiece are used in the neonatal intensive care units but are not applicable for DR resuscitation.

49.2.1
Nasal Prongs

Nasal prongs are the most effective technique of delivering nasal CPAP. One or two prongs inserted a short distance into the nostrils and attached to a pressure-generating device can be used to deliver CPAP [8, 10]. Neither double prongs nor a single prong has been shown to be superior in applying nasal CPAP in the DR, although it has in the neonatal intensive care unit [11]. During stabilization in the DR, a single nasal prong can be inserted easily into one nostril to deliver nasal CPAP (see Fig. 49.1). This is usually a less than 5-cm cut down 2.5- or 3-mm endotracheal tube that is passed 1–2 cm into one nostril [8, 10]. Application of CPAP by a single nasal prong needs constant attention because the prong becomes easily dislodged or kinked, resulting in loss of pressure. The contralateral nostril and the mouth have to be occluded to reduce any leak, and the gas flow has to be high enough to maintain the level of PEEP (see Fig. 49.1) [8, 10]. However, the Columbia experience has shown that bilateral nasal Hudson prongs can be easily used to apply CPAP and PEEP immediately after birth [12]. Application of binasal prongs needs constant attention because they can easily dislodge, resulting in loss of pressure.

49.2.2
Face Mask

A face mask will deliver CPAP to the entire airway, not limiting it to the nose. No loss of pressure through the mouth is an advantage of this interface, although achieving a good face mask seal is difficult (see Fig. 49.2). Every time the face mask is lifted to assess the infant, the pressure is lost. In addition, the gas flow has to be high enough to prevent loss of PEEP during inspiration (see Fig. 49.3) [8, 10] and to compensate for leaks.
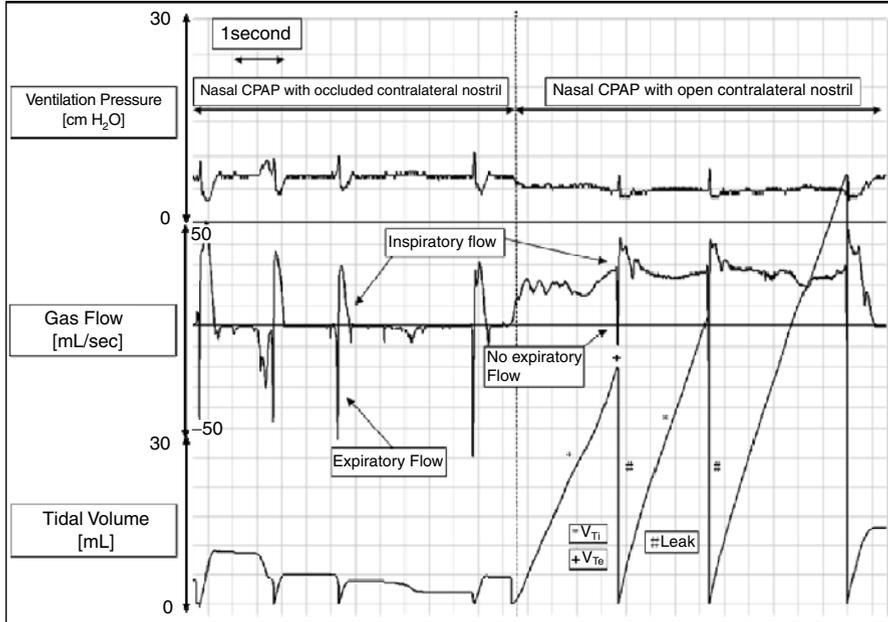
Fig. 49.1 Continuous positive airway pressure (*CPAP*) with single nasal prong and a T-piece device. Expiratory breath holds in a spontaneous breathing infant with nasal prong CPAP support of 7 cmH$_2$O. After inspiration, the infant holds his breath between 1 and 2 s before expiration occurs. Initially, the contralateral nostril is occluded. This is reflected in the gas flow pattern and tidal volume curve and no leak. Suddenly, the resuscitator releases the occlusion and 100% leak occurs

49.3
CPAP Device

Currently, there is little evidence to guide clinicians' choice of CPAP pressure-generating device. However, to facilitate the development of FRC immediately after birth, to improve oxygenation, and to prevent lung collapse, the device must provide continuous PEEP or CPAP. A range of devices is available [13–15]. A self-inflating bag does not provide PEEP or CPAP (see Fig. 49.4) [16]. An attached PEEP valve provides inconsistent PEEP during positive pressure ventilation but cannot deliver CPAP [15–17]. Variable and operator-dependent PEEP is provided by a flow-inflating bag [15, 16]. It cannot be used to provide CPAP. T-piece devices allow operators to deliver a predetermined and measured level of PEEP and CPAP [14, 16]. A neonatal ventilator in CPAP mode could be used to provide CPAP, and in ventilator mode also provides PEEP.
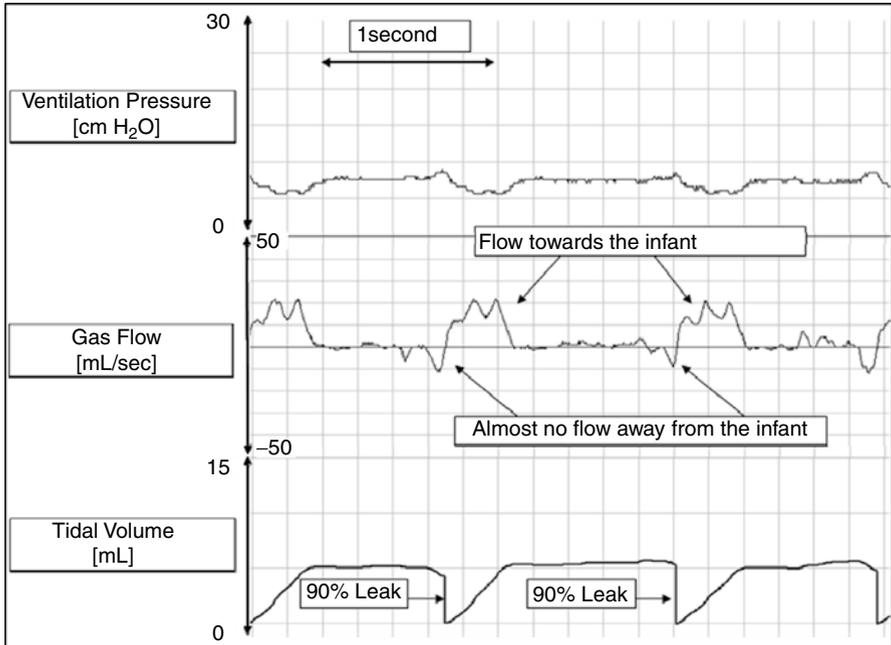
Fig. 49.2 Leak during (continuous positive airway pressure) CPAP with a face mask and a T-piece device. Spontaneously breathing preterm infant with CPAP support of 9 cmH$_2$O through a T-piece device. The area underneath the inflation flow curve is greater than that under the expiratory flow curves. Leak is displayed as a *straight line* in the tidal volume curve

49.4
Problems with the Use of CPAP

A major problem during DR CPAP is face mask leak. During stabilization, a good mask seal is essential to maintain the pressure (see Figs. 49.2 and 49.3). In our experience, operators are often unable to achieve adequate mask seal during mask CPAP and tend to lift the mask from the face to assess the infant; hence, the pressure is lost. In comparison, a single nasal prong might be more reliable to deliver leak-free CPAP while occluding the other nostril (see Fig. 49.1); however, this still needs to be studied.
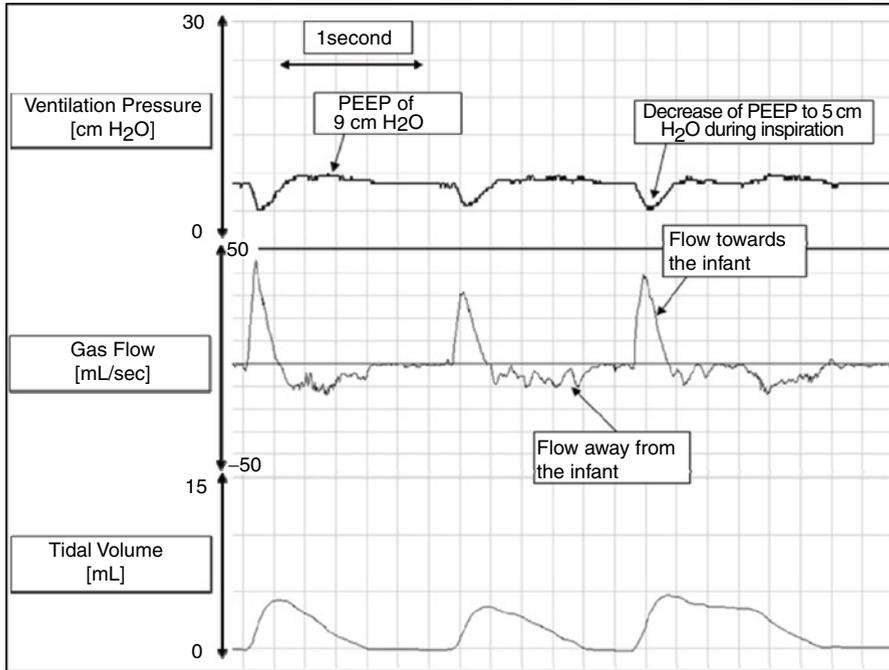
Fig. 49.3 Continuous positive airway pressure (CPAP) with a face mask and a T-piece device. Spontaneously breathing preterm infant with CPAP support of 9 cmH_2O through a T-piece device. The pressure curve shows a drop to 5 cmH_2O during inspiration. The tidal volume curve shows an equal volume of gas entering and leaving the lung and no leak

49.5
Limitations of CPAP and PEEP in the Delivery Room

Despite the frequent use of CPAP and PEEP in the DR, a number of significant gaps in our knowledge remain unanswered: (1) What is the optimal device to deliver CPAP or PEEP? (2) What pressure is optimal during transition? (3) How do we identify infants most likely to benefit from CPAP and PEEP?
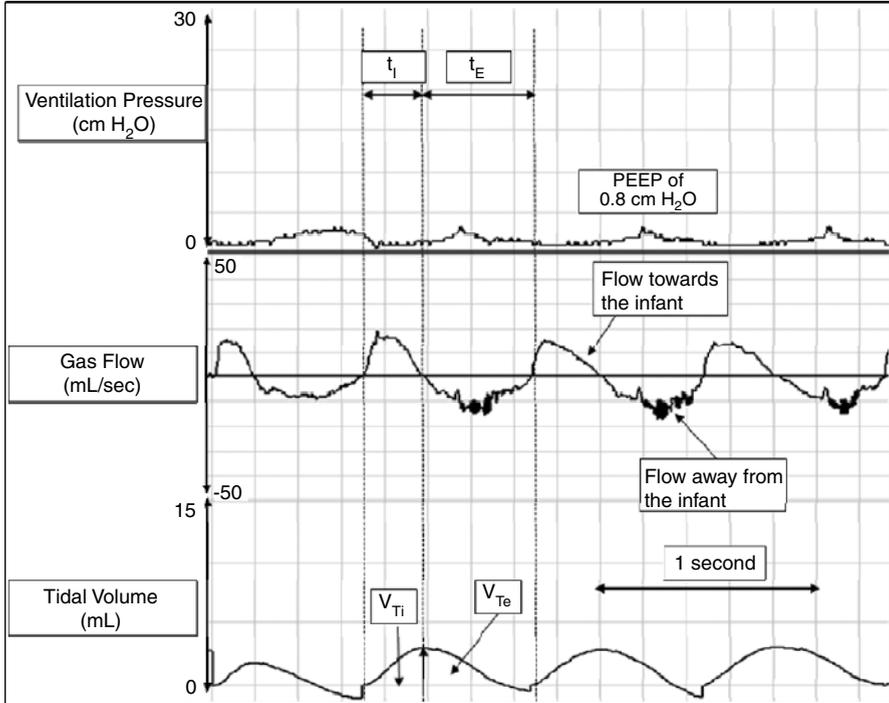
Fig. 49.4 Continuous positive airway pressure (CPAP) with a face mask and a self-inflating bag. Spontaneously breathing preterm infants with CPAP support through a self-inflating bag. The self-inflating bag does not deliver positive end-expiratory pressure (*PEEP*). The tidal volume curve shows an equal volume of gas entering and leaving the lung and no leak

Key Recommendations

> CPAP or PEEP should be delivered to facilitate the early development of FRC, reduce atelectrauma, and improve oxygenation during the transition from intrauterine to neonatal life in preterm infants immediately after birth.

> Both nasal prongs and face mask can be used as interfaces to deliver CPAP and PEEP. The nasal prong provides better access to the infant face during stabilization.

> Currently, a T-piece device delivers more reliable CPAP and PEEP compared to a flow-inflating bag. A self-inflating bag does not provide consistent PEEP and does not provide CPAP.

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Air Leakage During Continuous Positive Airway Pressure in Neonates

50

Gerd Schmalisch

50.1
Introduction

Since the implementation of continuous positive airway pressure (CPAP) technology by Gregory and colleagues in 1971 [1], CPAP has been increasingly used as a mode of noninvasive respiratory support for neonates worldwide to assist in the treatment of a broad range of neonatal respiratory diseases (e.g., respiratory distress syndrome, apneas of prematurity, and tracheomalacia). CPAP helps to stabilize airways and the diaphragm, to decrease dead space ventilation, to increase compliance and functional residual capacity leading to a rise in arterial oxygen pressure (Pao_2), and to prevent alveolar collapse at the end of expiration. Several studies have shown that, in neonates, CPAP decreases the risk of adverse outcomes compared to intubation and mechanical ventilation [2–4]. Even in mechanically ventilated infants, CPAP reduces the incidence of adverse clinical incidents (apnea, respiratory acidosis, increased oxygen requirement, and reintubation) after extubation [5].

CPAP was initially used in the endotracheal mode, and a variety of commercial CPAP systems and interfaces became available [6, 7]. CPAP can be applied via a facial mask or head box, using mono- or binasal prongs, or via pharyngeal or endotracheal tubes employing either a constant or a variable driving flow [8]. Independent of which interface or flow driver is used, some degree of air leakage occurs, caused by leakage flow between the patient and interface or in tubing within the patient, which may reduce treatment efficacy and cause adverse effects (e.g., impairment of the nasal or upper airway mucosa [9]). Especially, oral air leakage that occurs with the use of nasal prongs can lead to highly variable leakage flows.

Although the effect of air leakage on CPAP treatment has been widely investigated in adults [9–12], only a few studies have examined the effect of such leakage in neonates [13, 14] because of the technical difficulties associated with air leakage measurements. In neonates, leakage measurements depends mainly on the interface used, as shown in Fig. 50.1.

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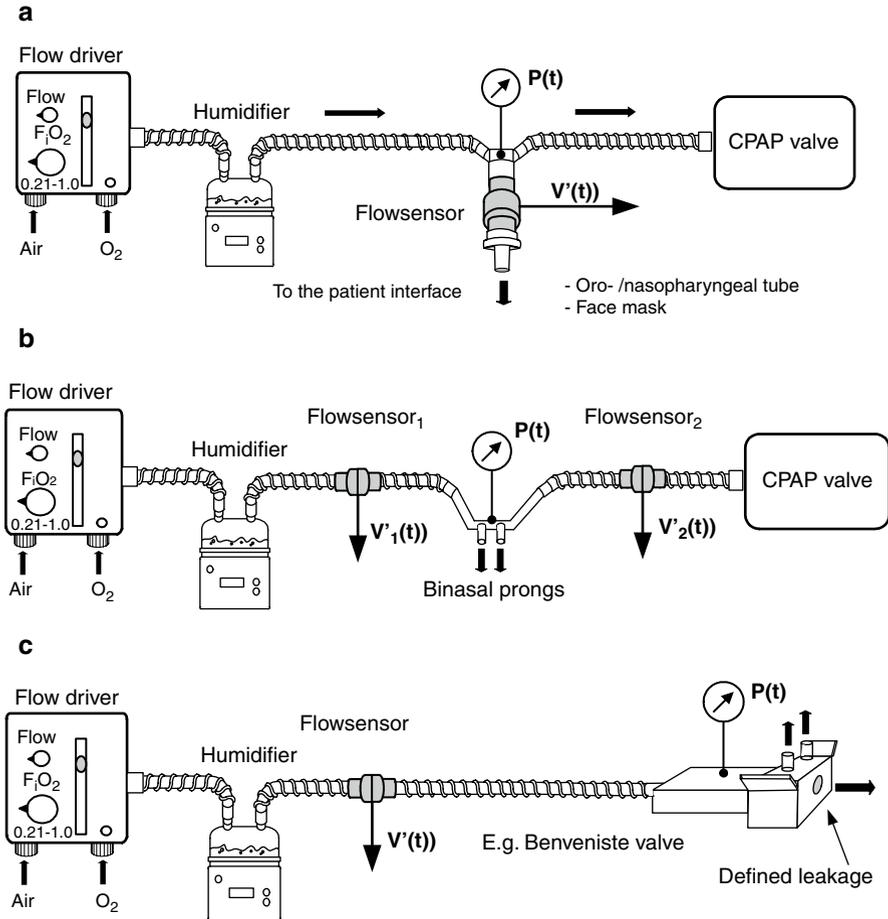
Fig. 50.1 Methods of ventilatory measurement during continuous positive airway pressure (*CPAP*) in neonates using tubes or face masks (**a**), binasal prongs (**b**), or special CPAP devices with defined leakage at the interface (**c**). If there is no air leak, the baseline of the measured flow (**a**) or flow difference (**b**) is zero, whereas in the method in **c** the baseline is permanently shifted by flow through the defined leakage in the interface

Furthermore, air leakage is mostly characterized by leakage flow per se in adults [15], whereas in neonates air leakage is usually characterized by leakage flow related to patient flow and is represented as a percentage. Depending on which measure of patient flow is used, different leakage definitions are possible [14].

The air leakage given as a percentage is not easy to interpret, and the use of different leakage definitions makes comparisons between studies difficult. Therefore, the aim of this study was to theoretically investigate the relationship between air leakage and leakage flow using different leakage definitions and to validate the modeling by in vitro measurements using a commercially available CPAP device.

50.2
Air Leakage Measurements During CPAP Treatment of Neonates

50.2.1
Theory of Air Leakage Measurements During CPAP

In adults, air leakage during CPAP is commonly characterized by the leakage flow derived from the flow of the blower that aims to keep the CPAP of the face mask constant. An unintended leakage flow is compensated by an increase in flow generated by the blower so that blower flow gives information on air leakage [16]. In neonates, however, a constant driving flow is commonly used, and air leakage is usually calculated as the difference between inspired and expired volume, related to the measured volume. Three different definitions are possible:

$$\text{Leak}_1(\%) = 100 \cdot \frac{V_{\text{insp}} - V_{\text{exp}}}{V_{\text{insp}}} \tag{50.1a}$$

$$\text{Leak}_2(\%) = 200 \cdot \frac{V_{\text{insp}} - V_{\text{exp}}}{V_{\text{insp}} + V_{\text{exp}}} \tag{50.1b}$$

$$\text{Leak}_3(\%) = 100 \cdot \frac{V_{\text{insp}} - V_{\text{exp}}}{V_{\text{exp}}} \tag{50.1c}$$

where V_{insp} and V_{exp} are the measured inspiratory and expiratory volumes, respectively.

If there is no air leakage, V_{insp} and V_{exp} should be identical. However, if there is any air leakage at a flow resistance R_{Leak} between the patient's lung and the flowmeter, the measured airflow of the patient

$\dot{V}_{\text{Pat, meas}}$ will be reduced (using the current divider rule) by

$$\dot{V}_{\text{Pat, meas}} = \frac{R_{\text{Leak}}}{R_{\text{CPAP}} + R_{\text{Leak}}} \dot{V}_{\text{Pat}} \tag{50.2}$$

where $\dot{V}_{\text{Pat}}$ is the real airflow of the patient, and R_{CPAP} is the flow resistance of the CPAP system (interface + flowmeter). R_{CPAP} is defined as the maximal flow through the CPAP interface:

$$\max \dot{V}_{\text{CPAP}} = \frac{\text{CPAP}}{R_{\text{CPAP}}} \tag{50.3}$$

provided that the flow driver allows such a high flow. For the leakage flow, we obtain

$$\dot{V}_{\text{Leak}} = \frac{\text{CPAP}}{R_{\text{Leak}} + R_{\text{CPAP}}} \tag{50.4}$$

Assuming that the leakage resistance is constant during the breathing cycle and that the inspiratory and expiratory volumes of the patient are equal,

$$\int_0^{T_{insp}} \dot{V}_{Pat} dt = - \int_{T_{insp}}^{T_{insp}+T_{exp}} \dot{V}_{Pat} dt = V_T \tag{50.5}$$

and we obtain the measured inspired and expired volumes using Eqs. 50.2–50.5:

$$V_{insp,\,meas} = \int_0^{T_{insp}} \dot{V}_{meas}(t) \cdot dt = \left(1 - \frac{\dot{V}_{Leak}}{\max \dot{V}_{CPAP}}\right) V_T + \dot{V}_{Leak} \cdot T_{insp} \tag{50.6a}$$

$$V_{exp,\,meas} = -\int_{T_{insp}}^{T_{insp}+T_{exp}} \dot{V}_{meas}(t) \cdot dt = \left(1 - \frac{\dot{V}_{Leak}}{\max \dot{V}_{CPAP}}\right) V_T - \dot{V}_{Leak} \cdot T_{exp} \tag{50.6b}$$

where $\dot{V}_{meas}$ is the flow measured by the flow sensor. Thus, $\dot{V}_{Leak}$ can be measured breath

by breath by

$$\dot{V}_{Leak} = \frac{V_{insp,\,meas} - V_{exp,\,meas}}{T_{insp} + T_{exp}} \tag{50.7}$$

With a definition of the minute ventilation $\dot{V}_E$ of the patient as

$$\dot{V}_E = \frac{V_T}{T_{insp} + T_{exp}} \tag{50.8}$$

we obtain the following for the three leakage definitions:

$$Leak_1(\%) = 100 \frac{\dot{V}_{Leak}}{\left(1 - \frac{\dot{V}_{Leak}}{\max \dot{V}_{CPAP}}\right)\dot{V}_E + \dot{V}_{Leak} \cdot \frac{T_{insp}}{T_{insp} + T_{exp}}} \tag{50.9a}$$

$$Leak_2(\%) = 200 \frac{\dot{V}_{Leak}}{2 \cdot \left(1 - \frac{\dot{V}_{Leak}}{\max \dot{V}_{CPAP}}\right)\dot{V}_E + \dot{V}_{Leak} \cdot \frac{T_{insp} - T_{exp}}{T_{insp} + T_{exp}}} \tag{50.9b}$$

$$Leak_3(\%) = 100 \frac{\dot{V}_{Leak}}{\left(1 - \frac{\dot{V}_{Leak}}{\max \dot{V}_{CPAP}}\right)\dot{V}_E - \dot{V}_{Leak} \cdot \frac{T_{insp}}{T_{insp} + T_{exp}}} \tag{50.9c}$$

As shown by equations 50.9a-c, there is a nonlinear and complex relationship between the leakage given in percentage and leakage flow, patient ventilation, and the performance of the CPAP device as given by max $\dot{V}_{CPAP}$. However, if $\dot{V}_{Leak} \ll \max \dot{V}_{CPAP}$ and $T_{insp} = T_{exp}$, then the formulas are considerably simplified:

$$\mathrm{Leak}_1(\%) = 100 \frac{\dot{V}_{\mathrm{Leak}}}{\dot{V}_{\mathrm{E}} + 0.5 \cdot \dot{V}_{\mathrm{Leak}}} \tag{50.10a}$$

$$\mathrm{Leak}_2(\%) = 100 \frac{\dot{V}_{\mathrm{Leak}}}{\dot{V}_{\mathrm{E}}} \tag{50.10b}$$

$$\mathrm{Leak}_3(\%) = 100 \frac{\dot{V}_{\mathrm{Leak}}}{\dot{V}_{\mathrm{E}} - 0.5 \cdot \dot{V}_{\mathrm{Leak}}} \tag{50.10c}$$

and we obtain a simple relationship between the three leakage definitions:

$$\mathrm{Leak}_1(\%) = 100 \frac{\mathrm{Leak}_2(\%)}{100 + 0.5 \cdot \mathrm{Leak}_2(\%)} = 100 \frac{\mathrm{Leak}_3(\%)}{100 + \mathrm{Leak}_3(\%)} \tag{50.11}$$

However, this relationship breaks down with increasing leakage flow or uneven inspiratory and expiratory times.

50.2.2
Computer Simulation

To investigate the relationship between the three leakage definitions and to identify the most important factors influencing measured leakage, a computer simulation was performed using Mathcad 14 (MathSoft, Cambridge, MA).

The relationship between the displayed air leakage using the three leakage definitions and the leakage flow related to patient ventilation is shown in Fig. 50.2. For small leakages, the differences between the three leakage definitions are small, but they increase notably with increasing leakage flow. Both Leak_2 and Leak_3 rise to infinity before the maximal leakage flow is reached. Only Leak_1 is limited in magnitude and attains the final
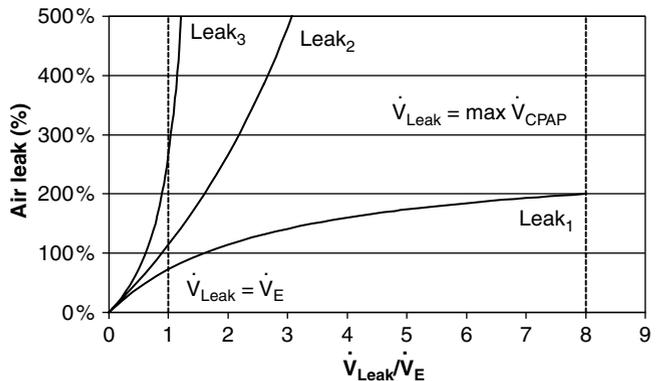
Fig. 50.2 Relationship between the displayed leakage and leakage flow related to the minute ventilation of the patient using the three definitions (Leak_{1-3})

value $100*(T_{in} + T_{ex})/T_{in}$ at the maximal leakage flow given by max $\dot{V}_{CPAP}$. Thus, for monitoring of high leakage flows, only the calculation of $Leak_l$ is useful, and this was considered in further investigations as discussed next.

A disadvantage of leakage monitoring using $Leak_l$ is the dependency of $Leak_l$ on breathing pattern. As shown in Fig. 50.3, the displayed leakage varies distinctly with the
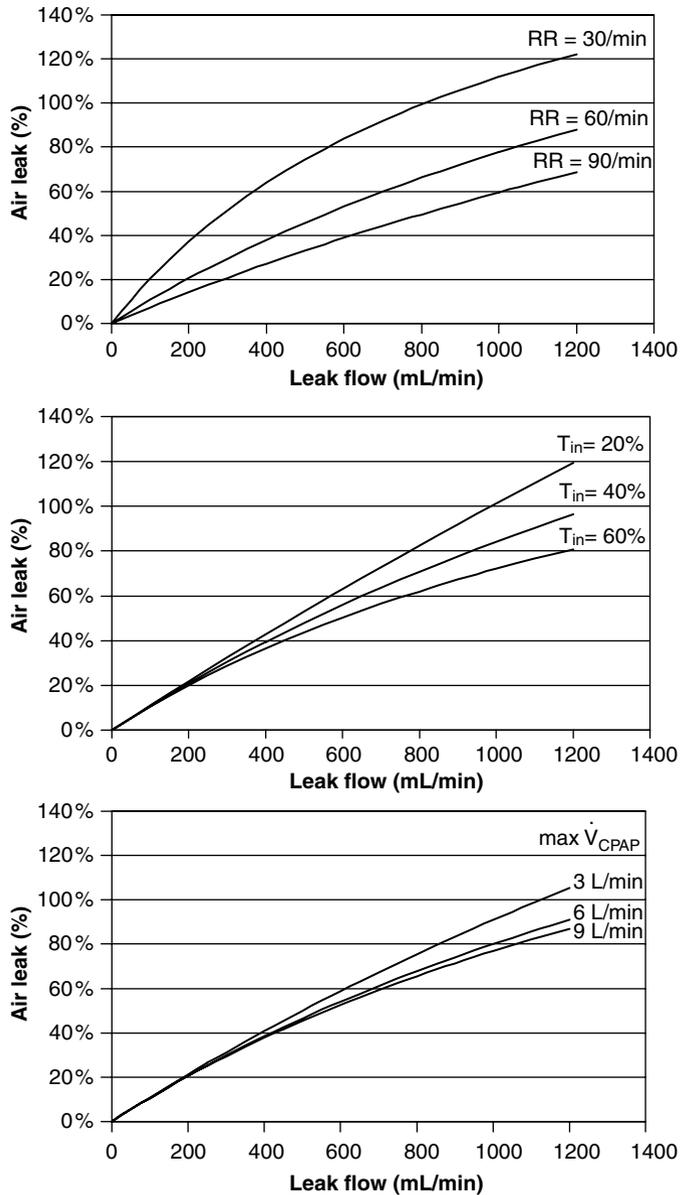
Fig. 50.3 Effect of respiratory rate (*RR*; *top left*), inspiratory time (*top right*), and maximal continuous positive airway pressure (CPAP) flow on $Leak_l$
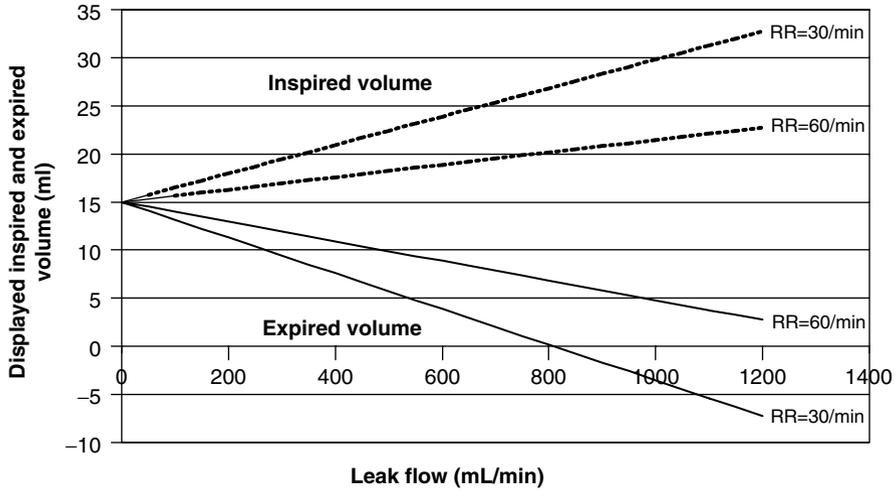
Fig. 50.4 Dependence of the measured inspiratory and expiratory volume on the leakage flow for different respiratory rates (*RR*s), assuming a tidal volume of 15 mL. Note that for high leakage flows and low respiratory rates the displayed expiratory volume can become negative

respiratory rate (RR). The influence of T_{in}/T_{ex} on the displayed leakage is small for leakage flows in the range of patient ventilation but increases continuously with rising leakage flow. Compared to the timing parameters of the breathing cycle, the measured leakage is only minimally affected by changes in max $\dot{V}_{CPAP}$ caused by changes in the CPAP.

A leakage flow leads to an overestimation of inspiratory volume and an underestimation of expiratory volume, and the volume error depends on the RR, as shown in Fig. 50.4. Depending on the RR with increasing leakage flow, the measured expiratory volume can even become negative, which may be difficult for a clinician to interpret. Therefore, in most devices, the measuring scale for air leakage is limited to less than 90% so that negative volume values are excluded.

50.2.3
In Vitro Experiments

To validate the modeling, in vitro measurements were performed using a commercial CPAP device (Leoni; Heinen & Löwenstein, Bad Ems, Germany) and a mechanical lung model (V_T = 15 mL) with an adjustable RR, as described by Fischer and colleagues [17]. Leaks were simulated using open silicon tubes (3.2-mm inner diameter) of varying lengths (16–170 cm) connected between the flow sensor and lung model. For all simulated air leaks, CPAP was varied between 3 and 9 cmH$_2$O, and the RR was in the interval 30–90/min. Leakage flow was measured using differential pneumotachography (the method shown in Fig. 50.1b), as described by Foitzik and associates [18].

The Leoni can provide CPAP therapy for premature babies, neonates, and infants and uses a hot-wire anemometer, located between the Y-piece, for airflow measurement. The displayed

volume of the Leoni is the measured expired volume V_{exp}, and the displayed leakage is calculated using the definition of $Leak_1$ given by Eq. 50.1a. The maximum displayed leakage of the device is set at 90%, and higher leakages cannot be measured. The Leoni does not display leakage flow. However, our modeling permits leakage flow to be calculated using Eqs. 50.6a, 50.8, and 50.9a by

$$\dot{V}_{Leak} = \frac{Leak_1}{100 - Leak_1} \frac{V_{exp}}{T_{in} + T_{exp}} \qquad (50.12)$$

As shown in Fig. 50.5, there was a strong correlation ($r = 0.984$) between measured leakage flow and that calculated using Eq. 50.12. The difference between the measurements was 16.5 mL/min; this is negligible from the clinical viewpoint. An Altman–Bland plot showed relatively wide measurement scatter, but the residuals were randomly distributed.
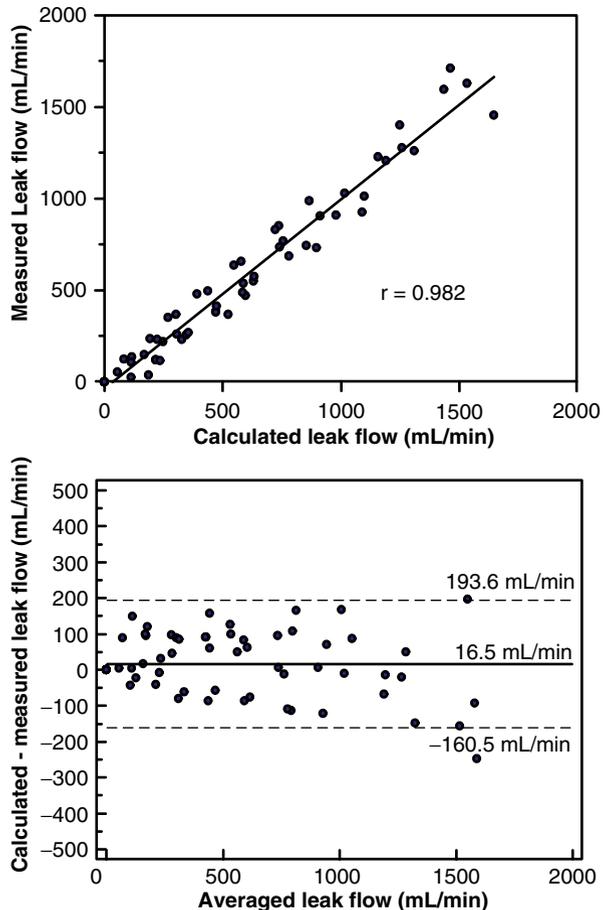
Fig. 50.5 Correlation between the calculated and the measured leakage flow (*left*) and the corresponding Altman–Bland plot (*right*) using the Leoni ventilator

Fig. 50.6 Relationship between the volume error of the Leoni ventilator and the size of the simulated air leak
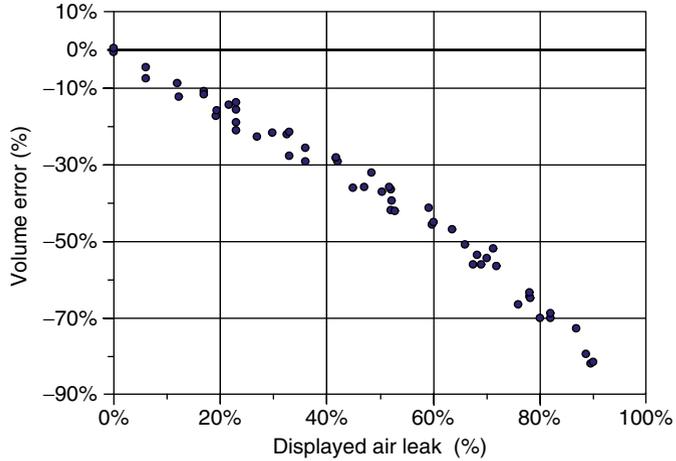
With increasing air leakage, the displayed volume decreased, as shown in Fig. 50.6. According to our modeling, the leakage-dependent volume error can be calculated using Eq. 50.6b by

$$\delta V_{exp}(\%) = 100\frac{V_{exp,\,meas} - V_T}{V_T} = -100\left(\frac{\dot{V}_{Leak}}{\max \dot{V}_{CPAP}} + \frac{\dot{V}_{Leak} \cdot T_{exp}}{V_T}\right)$$

$$\approx -100\frac{\dot{V}_{Leak} \cdot T_{exp}}{V_T}$$

(50.13)

where the approximation assumes that $\dot{V}_{Leak} \ll \max \dot{V}_{CPAP}$. The correlation between the calculated and the measured volume error is shown in Fig. 50.7. There was also a strong correlation ($r = 0.995$) between the measured and the predicted volume error, and the bias of 1.1% was very small. However, the Altman–Bland plot showed that, with increasing volume error, there was an overestimation of calculated volume error. This may be caused by neglect of some nonlinearities in our modeling of volume and air leakage measurements.

50.3
Discussion

The present study showed that, during CPAP, the display of an air leakage as a percentage of measured patient ventilation is not adequately informative because leakage depends not only on the size of the leak and the resulting leakage flow, but also on patient ventilation, that is, the tidal volume, RR, and inspiratory/expiratory time ratio. As shown in Fig. 50.3 for low RRs, even moderate leakage flows can cause the displayed leakage to rise to 90%, and this is commonly the upper limit of the measuring range [17]. For higher RRs, leakage measurements are still possible even with much more serious leaks. The dependence of

Fig. 50.7 Correlation between the calculated and the measured volume error of the Leoni ventilator (*above*) and the corresponding Altman–Bland plot (*below*)
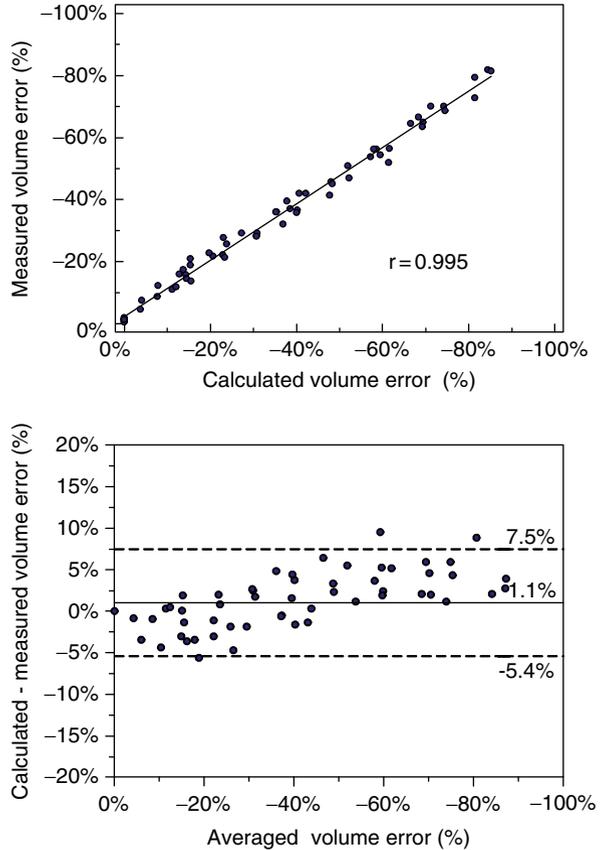
the displayed leakage on breathing pattern hampers monitoring of the air tightness of a CPAP system, especially considering that the breathing pattern of newborns with chronic lung disease may be very variable [19], thus causing highly fluctuating leakage displays.

Furthermore, the present simulation study showed large differences in leakage results depending on the various possible leakage definitions. This makes comparison of displayed leakages between different devices difficult because the leakage calculation used is often not described in detail by the manufacturers. If the leakage flow exceeds patient ventilation, only a calculation using $Leak_1$ will be of practical value because all other definitions can attain infinity.

However, the measuring range of air leakage is commonly limited (e.g., to <90% of monitored patient ventilation). This may be adequate for ventilated patients in whom endotracheal tube leakages are commonly relatively small [20], but not during CPAP, when air leakage is much higher. In particular, with nasal CPAP, oral leaks can cause leakage flows that clearly exceed patient minute ventilation [21].

In contrast to the display of air leakage as a percentage of the measured ventilation, a display of leakage flow in milliliters per minute may be better for comparisons and is commonly used in adult studies [15]. The leakage flow depends only on leak resistance and

the CPAP instrument employed and is generally independent of the breathing pattern of the patient. Adverse effects of leakage flow (e.g., irritation of the skin or impairment of the nasal or upper airway mucosa by mouth leaks [9]) are influenced by the magnitude of leakage flow and are independent of patient ventilation.

The effect of a leakage flow during CPAP is contradictory. Small leakage flows may improve alveolar gas exchange by CO_2 washout of airway dead space (including apparatus dead space) [22]. However, with increasing leakage flow, ventilatory measurements become more difficult because of a shift in flow baseline [18, 23]. Furthermore, the effective CPAP for the patient will be reduced by the pressure drop across the CPAP interface ($\Delta CPAP = \dot{V}_{Leak} \cdot R_{CPAP}$). A high leakage flow creates additional noise, which impairs the identification of the beginning and end of inspiration and expiration [23, 24]. This is an important point in the triggering of bilevel CPAP.

Large leaks also cause a high error in measurement of patient ventilation, as shown in Fig. 50.6. To what extent a faulty reading can be numerically corrected is still unknown. The present study showed good agreement between modeling and in vitro measurements, so that numerical correction of the displayed volume may indeed be possible. In a previous in vitro study, successful volume corrections were achieved when leakage was up to 90% [14], but this could not be confirmed by in vivo measurements [21]. Nevertheless, leakage flow measurement alone, which is independent of measurement of patient ventilation, may be helpful in assessment of CPAP treatment. Irrespective of which measuring principle of Fig. 50.1 is used, leakage flow means a shift in the measured flow baseline. For leakage monitoring during CPAP in neonates, new efforts are necessary to develop well-adapted algorithms to separate the baseline from the measured flow signal.

Currently, for devices used in neonates that present leakage as a percentage of patient flow, leakage flow measurements are possible only by numerical calculation using the displayed leakage and volume. The low bias between calculated and measured leakage flow and volume errors (Figs. 50.5 and 50.7) demonstrates the adequacy of the model used; however, the relatively wide scatter of the calculated leakage flows indicates the technical problems associated with leakage measurements based on the difference between inspired and expired volumes. Such leakage measurements are affected by several technical (e.g., differences in the transfer characteristics of the pneumotach between inspiration and expiration, quality of breath detection [24]) and physiological factors (e.g., instability of end-expiratory lung volume [25], changes in gas composition between inspiration and expiration [26]). Bubble CPAP is widely used and may be advantageous [8, 27]; however, the technique is associated with severe technical difficulties, mainly with respect to airflow measurements and breath detection as a result of the noisy flow signal [24].

Although the effects of air leaks on CPAP effectiveness [9, 16], side effects [15], triggering function, humidification, and inspiratory oxygen fraction [28] have been investigated in adults, few such studies have been performed in neonates because of the difficulties associated with ventilatory and leakage measurements during CPAP. In adults, leakages over 24 L/min are defined as excessive and can compromise the effectiveness of treatment [15]. If we assume a tenfold lower ventilation requirement in neonates, then an excessive leakage flow would be 2.4 L/min, which is commonly higher than patient ventilation and outside the measuring range of most devices. Such high leakage flows are not uncommon, especially during nasal CPAP. Hückstädt and colleagues [13] performed leakage flow

measurements in neonates during nasal CPAP using differential pneumotachography (the method shown in Fig. 50.1b). Leakage measurements were not possible in 49 of 69 infants as the leakage flow was higher than one third of the CPAP flow (4–6 L/min), which was the upper limit of the measuring range of the equipment used [18].

In conclusion, the display of air leakage as a percentage of measured ventilation is unsuitable for leakage monitoring during CPAP because such a measurement often fails for high leakage flows, which are not uncommon. Furthermore, the differences in results obtained with the use of various leakage definitions, and the dependence of the displayed leakage on breathing pattern, hampers comparisons between different measuring conditions and various CPAP devices. A superior method would be to display the leakage flow measured by a suitable technique so that the effect of air leakage on CPAP treatment of neonates can be investigated in more detail.

Key Recommendations

> Very little is known about the effect of air leakage on CPAP treatment of neonates, and new clinical air leakage studies are necessary. However, with the measurement equipment available today, only small leakages can be measured. High leakages are not uncommon, especially when the widely used nasal CPAP is employed, and measurement of such leakages requires new methodological and technical developments.
> The current display of air leakage as a percentage of measured patient ventilation has several disadvantages and should be replaced by direct measurement and display of leakage flow. New algorithms are necessary to reliably separate leakage from measured flow signal.
> The relationship between air leakage and volume error can be adequately described by modeling. However, to date, it remains unknown to what extent a numerical correction of measured patient flow and volume is possible in the presence of air leakage. This should be addressed in future clinical studies.

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The Use of Noninvasive Ventilation in the Newborn

51

Debbie Fraser Askin

51.1
Introduction

Noninvasive ventilation (NIV) in the form of nasal continuous positive airway pressure (CPAP) was first introduced for use in newborns in the early 1970s. When mechanical ventilation for infants became available in the late 1970s, the use of CPAP declined. More recently, recognition that exposure to mechanical ventilation significantly increases a premature infant's risk for developing chronic lung disease has resulted in renewed interest in the use of NIV.

There is a growing body of research supporting the use of NIV as a treatment for neonatal apnea and respiratory distress and for facilitating extubation following mechanical ventilation. There is a variety of devices and strategies for using NIV in newborn infants. The successful application of NIV relies on knowledgeable health care providers who are familiar with the equipment and benefits and limitations of various types of NIV.

This work provides a brief overview of the types of NIV available for use in newborns and summarizes the available research supporting its use in this population. A brief description of the care of newborns receiving NIV concludes this review.

51.2
Materials and Methods

This work is based on a search of PubMed, CINHAL (Cumulative Index of Nursing and Allied Health Literature), and the Cochrane databases. The following search terms were used: premature infant, newborn, CPAP, NCPAP (nasal continuous positive airway pressure), noninvasive ventilation, apnea, respiratory distress syndrome, and chronic lung disease.

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51.3
Types of NIV

There are two main types of NIV used in newborn infants: CPAP using either continuous-flow or variable-flow devices and phasic ventilation. CPAP is the application of continuous positive pressure across the respiratory cycle, while phasic ventilation provides continuous positive pressure with the addition of periods of increased airway pressure (or breaths) [1]. Continuous-flow CPAP may be delivered by a neonatal ventilator or through bubble CPAP, a simple device that provides a supply of fresh gas while submerging the expiratory tubing of the system under water. The amount of positive airway pressure is controlled by the level of water in the outflow chamber. In phasic NIV, breaths may be delivered at regular intervals or nonsynchronized (nasal intermittent positive pressure ventilation [NIPPV]) or may be synchronized with the infant's inspiratory efforts (synchronized nasal intermittent positive pressure ventilation or SNIPPV).

51.4
Benefits of NIV in Newborns

The use of positive pressure in newborns has been shown to provide a number of physiological benefits, including [2]

- Stabilization of the airways, diaphragm, and chest wall
- Increased lung volumes
- Decreased airway resistance and work of breathing

51.5
Indications for NIV

In newborn infants, NIV has been shown to facilitate extubation from mechanical ventilation [3]; reduce the incidence and severity of apnea and bradycardia [4]; and improve survival in infants weighing less than 1,500 g with respiratory distress syndrome (RDS) [5]. More recent research has examined the role of NIV in the prevention of bronchopulmonary dysplasia (BPD). While not as promising as was hoped, there is some evidence that NIV reduces the length of time on mechanical ventilation and in turn reduces the incidence of BPD [6]. What has emerged in the recent studies of NIV in newborns with RDS is the combined benefit of surfactant and NIV [7].

51.6
Comparison of Different Modes of NIV

Limited research has been done comparing various types of NIV. Some studies of bubble CPAP have shown that bubble CPAP generates chest wall vibrations similar to those seen in high-frequency ventilation that may increase gas exchange [8]. Studies comparing CPAP to NIPPV and SNIPPV have found that, in particular, both modes of phasic ventilation may confer additional benefits not seen in CPAP alone [9]. These include a greater decrease in work of breathing, greater reduction in apnea, and greater success in preventing reintubation.

51.7
Contraindications to NIV

Some newborns are not candidates for NIV. These include patients with congenital airway anomalies; gastrointestinal anomalies or significant gastrointestinal distension; significant central apnea; hemodynamic instability in conditions such as shock, patent ductus arteriosus, or sepsis; and untreated surfactant deficiency [10].

51.8
Side Effects

Reported side effects of NIV include gastric distension and feeding intolerance, damage to the nasal septum and mucosa, pneumothorax, and overdistension of the lungs [1]. In some cases, it may be difficult to determine if the symptoms of gastric distension are benign findings of NIV or more early signs of necrotizing enterocolitis. Necrotizing enterocolitis is more likely to be accompanied by other clinical findings, including skin discoloration over the abdomen, loss of bowel sounds, and signs of systemic illness [1].

51.9
Failure Criteria

Some infants cannot be successfully managed with NIV; however, criteria identifying those infants that require intubation and mechanical ventilation have not been defined. The infant's birth weight, gestational age, and underlying medical condition must be considered in determining when an infant has "failed NIV." Persistent and significant apnea, an arterial level of carbon dioxide exceeding 60 mmHg, and the need for more than 60% inspired oxygen suggests the need for mechanical ventilation [11].

51.10
Weaning from NIV

An evidence-based approach to weaning an infant from NIV has not been determined. It is generally accepted that a reduction in the number and severity of apneic spells, the level of supplemental oxygen required for acceptable saturation levels, and a return to normal work of breathing signals that an infant may be ready to wean. For infants on phasic NIV, the rate is usually reduced and the infant switched to CPAP. Once CPAP pressures are reduced to less than 5 mmHg, a trial without NIV may be considered. No published trials have supported these criteria [12].

51.11
Patient Care

The successful management of a newborn infant receiving NIV is dependent on attention to detail. Caring for a newborn on NIV requires time and attention as well as a thorough knowledge of the equipment used. The selection of appropriate prongs and careful positioning of the infant are critical in avoiding complications such as damage to the nasal mucosa. Short binasal prongs have been shown to be more effective than single or long prongs [13]. Selection of the appropriate size prongs and hat is also important. Excessive movement and tension of the prongs and tubing are associated with an increased risk of mucosal injury. Infants should be swaddled and, when monitored, placed prone with the neck slightly extended [12]. The delivery of positive pressure is enhanced when the infant's mouth is closed. A pacifier or chin strap may be used to facilitate delivery.

Key Recommendations

> NIV is an effective strategy for managing newborn infants with apnea or RDS and those being extubated from mechanical ventilation.
> Growing evidence suggests it may also help reduce the incidence and severity of BPD.
> The success of NIV in the clinical setting is dependent on attention to the details of care, including the selection of equipment, positioning of the infant, and ongoing patient assessment.

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Nasal High-Frequency Ventilation: Clinical Studies and Their Implications

52

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52.1
Introduction

During the last three decades, there has been an increase in the survival rate of infants with very low birth weight (VLBW) [1, 2]. However, this improvement in survival has been accompanied by the increased rate of long- and short-term morbidities, with bronchopulmonary dysplasia (BPD) one the most common adverse outcomes [3]. Introduction of surfactant and widespread use of antenatal steroids changed the clinical course of respiratory distress syndrome (RDS) as well as the histological picture and natural history of BPD. The incidence of BPD in the VLBW infants varies between centers, ranging from 3% to 43% even when using standardized definitions [1]. Severe cases originally described by Northway ("old BPD") are rarely seen now. The "new BPD" remains an important problem. The etiology of so-called new BPD is unclear and probably multifactorial. Available evidence suggests that BPD develops as a result of abnormal growth and repair of the immature lungs exposed to repetitive stress of mechanical ventilation (namely, volutrauma and barotrauma), especially via endotracheal tube, aggravated by recurrent infections and chronic inflammation [4]. It is believed that the mere presence of an endotracheal tube may contribute to the development of BPD by impairing natural airway defenses and increasing the risk of infection and inflammation of the upper and lower airways [5]. Yet, a large proportion of preterm and ill term infants requires respiratory support at some point during their hospital stay.

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52.2
Noninvasive Modes of Ventilation

Continuous positive airway pressure (CPAP), delivered by noninvasive means such as with nasal prongs, may be a gentler mode of respiratory support. CPAP is frequently used as an alternative therapy in an attempt to prevent or decrease the use of endotracheal intubation and mechanical ventilation. CPAP improves oxygenation by stabilizing surfactant-deficient alveoli. A meta-analysis published in the Cochrane database indicated that CPAP is effective in preventing extubation failure when compared to oxygen supplementation via a hood [6]. However, the effect of CPAP on the incidence of BPD is inconclusive. Avery et al. were the first ones to suggest that use of CPAP might be associated with decreased risk of developing BPD [7]. A retrospective analysis showed that, among eight centers, the lowest BPD rate was reported in the center that used CPAP preferably rather than intubation and mechanical ventilation. Many other retrospective studies have also suggested that CPAP may decrease the incidence of BPD. The published continuous positive airway pressure or intubation at birth (COIN) trial, which compared infants randomized at delivery to CPAP or intubation and mechanical ventilation, showed no significant difference in BPD/death at 36 weeks but a positive trend (CPAP group 34% vs. intubation group 39%, 95% relative risk [RR] 0.8, confidence interval [CI] 0.6–1.1) [8]. However, the rate of pneumothorax was threefold higher in the CPAP group. Other smaller randomized controlled trials of early CPAP (Finer, Thomson) also showed no significant reduction of BPD [9, 10]. However, a meta-analysis of relatively small studies comparing early surfactant administration and prompt extubation to CPAP versus selective surfactant and continued mechanical ventilation showed a significant reduction of BPD in the group with early CPAP (RR 0.51, 95% CI 0.26–0.99) [11].

Yet, many infants fail nasal continuous positive airway pressure (NCPAP) [6]. For those infants who fail CPAP, other forms of noninvasive ventilation, like nasal intermittent positive pressure ventilation (NIPPV), may be beneficial. Available data indicate that NIPPV improves alveolar ventilation and carbon dioxide (CO_2) elimination and is more effective than CPAP in treating apnea of prematurity [12]. A meta-analysis of three trials comparing NIPPV with CPAP showed that NIPPV significantly and consistently reduced extubation failure (RR 0.21, 95% CI 0.10–0.45) [13]. In the study of Bhandari et al., NIPPV was associated with a lower incidence of BPD at 36 weeks when compared to conventional ventilation (52% vs. 20%, $p < 0.05$) [14]. Also, when compared with CPAP, NIPPV seems to have a favorable effect on the incidence of BPD, as illustrated by the results of the retrospective case-control study conducted by Kulkarni et al. [15]. Data from the study of Garland et al. suggested that NIPPV may be associated with increased risk of gastrointestinal perforation, but in the most recent reports no clinically significant gastrointestinal side effects were observed [13, 16]. Currently, NIPPV is being used in about 50% of the neonatal intensive care units (NICUs) in England [15]. Even though NIPPV seems to be more effective than CPAP alone in preventing reintubation, a significant percentage of patients (45% in the study of Bhandari et al.) will fail because of CO_2 retention or worsening oxygenation. That group of patients may potentially benefit from nasal high-frequency ventilation (nHFV).

52.3
Nasal High-Frequency Ventilation

Nasal high-frequency ventilation is a less-well-studied noninvasive method of assisted ventilation, but there is some rationale supported by limited data that this mode of ventilation may decrease the need for intubation and incidence of BPD. Endotracheal HFV (high-frequency ventilation) is effective in eliminating CO_2, probably due to several mechanisms that enhance gas exchange [18]. Animal data suggest that when compared to intermittent mandatory ventilation, nHFV in preterm lambs promotes alveolarization by preserving the balance between mesenchymal cell apoptosis and proliferation [19]. Recent meta-analysis of 15 trials showed that high frequency oscillatory ventilation (HFOV) was associated with reduction of death or BPD of borderline significance (RR 0.93, 95% CI 0.86–1.00) [20]. However, there are limited data on nHFV.

Van der Hoeven et al. were the first to publish their experience treating neonates with nHFV. They reported a group of 21 patients who failed CPAP because of CO_2 retention (median value 62 mmHg), acidosis (median pH 7.24), or increasing oxygen requirement (median Fio_2 0.42) [21] and was treated with nHFV. This was an uncontrolled observational study that included patients with various respiratory diseases, including RDS, transient tachypnea of the newborn (TTN), air leak, or apnea. Nasal CPAP was applied via a single nasopharyngeal tube. The median (range) gestational age was 29 weeks (27–32 weeks) and median (range) birth weight was 1,010 g (750–2,170 g). Of the 21 patients, 15 (72%) were switched to nHFV early in the course of the respiratory disease (median age of 17 h; range 2–36 h), and in 6 (28%) nHFV was initiated late (median 9 days; range 9–21 days). nHFV was initiated with a mean airway pressure equal to or higher than that on CPAP, a frequency of 10 Hz, and an amplitude that was adjusted until the infant's chest showed adequate vibration. The mean airway pressures were significantly higher after initiation of nHFV. Median (range) amplitude was 37 cmH_2O (29–46 cmH_2O). Only five patients (23%; three with severe RDS in the early group and two in the late group, one with air leak syndrome and one with apnea associated with sepsis and necrotizing enterocolitis) failed nHFV (pH < 7.2, Pco_2 > 64 mmHg, Fio_2 > 0.8, or severe apnea) and subsequently required endotracheal intubation. The median duration of nHFV was 35 h (range 2–144 h) in the early group and 40 h (range 17–126 h) in the late group. After initiation of nHFV, small but significant reductions in Pco_2 were observed compared with values recorded before nHFV ($p < 0.01$). Thus, nHFV might be a valuable addition to the ventilatory management of the newborn infant and might reduce the need for subsequent mechanical ventilation.

Colaizy et al. reported the results of short-term use of nHFV in 14 VLBW infants requiring nasal CPAP support [22]. Just like van der Hoeven et al., they used a single nasopharyngeal tube to deliver both nasal CPAP and nHFV. Infants were switched from nasal CPAP to nHFV and ventilated with that mode for a fixed period of 2 h. The positive end-expiratory pressure (PEEP) during nHFV was the same as during nasal CPAP, and frequency was kept constant at 10 Hz. The amplitude was adjusted based on the presence of visible chest wall or upper airway (anterior neck) vibration. The amplitude, which ranged from 29 to 60 cmH_2O, was adjusted every 30 min by 4–6 cmH_2O as necessary to maintain an appropriate chest wall or anterior neck vibration. Median (range) gestational

age was 27 weeks (26–30 weeks), and median (range) birth weight was 955 g (438–1,374 g). All infants had a history of RDS early in the neonatal course but were studied at a median (range) of 30 days (18–147 days). nHFV resulted in a significant decrease in P_{CO_2} (from 50 to 45 Torr, $p = 0.01$) and a higher pH (7.37 to 7.40, $p = 0.04$). There was no effect on F_{IO_2} or oxygen saturation. Side effects were not reported. Chest X-rays obtained after 1 h of nHFV did not show evidence of gas trapping.

52.4
Discussion

Clinical studies suggested that CO_2 elimination during nHFV is superior to that during CPAP, and that nHFV decreases the need for endotracheal intubation and mechanical ventilation in patients with mild-to-moderate respiratory failure due to CO_2 retention. However, several limitations in both studies have to be considered. In the study of Colaizy et al., infants were relatively stable [22]. For many clinicians, blood gas values with P_{CO_2} in the range of 50 Torr and average pH of 7.37 that were used as entry criteria for the study would have been acceptable for the patient stable on CPAP. In the study of van der Hoeven et al., the P_{CO_2} and pH values before the intervention were probably closer to the widely accepted definition of mild-to-moderate respiratory failure, but it has to be pointed out that the study group was diverse [21]. For example, the age at the entry into the study ranged from 4 to 480 h. Values of P_{CO_2}, that would be considered as an indicator of impending respiratory failure early after birth might be acceptable and in line with a "permissive hypercapnia" protocol in an older infant.

The effects of nHFV on BPD or measures of lung injury were not studied, and the only controlled study had a crossover design with a short period of study. Randomized controlled trials are necessary to determine if nHFV improves pulmonary outcomes. Also, the effect of the nHFV on severe apnea in the premature infants needs to be investigated further.

It is important that neither of the two studies was designed to assess the side effects of nHFV. Even though randomized trials of NIPPV have not reported an increased risk of side effects, nHFV may present additional problems, like overdistention and gas trapping. In the study of Colaizy et al., chest radiographs taken 1 h after initiation of the study did not show evidence of gas trapping in any of the patients [22]. However, it is important to notice that the pressure amplitude used in both studies was relatively high. Although it is well known that the high-frequency signal is dampened by the circuit, nasopharyngeal tubes, and airways, the degree of dampening is variable and difficult to estimate clinically [19]. The presence of chest oscillations during nHFV observed in patients in both studies indicates that the delivery of the pressure to the alveoli was probably substantial, and there is concern about gas trapping and overdistention while using this mode of ventilation. With variable-pressure transmission secondary to leakage and varying airway patency, a sudden decrease or increase in the pressure delivered may put the patients at risk for acute loss of lung volume or air leak.

One potential advantage of nHFV over NIPPV is that synchronization is not necessary. Moretti et al. reported a very high rate of synchronization in their study [23]. However, outside the study protocol in the busy NICU, it may be difficult to achieve synchrony. The presence

of a variable inspiratory leak through the nasal prongs during NIPPV makes synchronization of the patient's respiratory effort with respirator cycling difficult, especially with the new ventilators that rely on inspiratory flow to trigger the ventilator. Yet, lack of synchronization may impair the ventilation and limit the benefits of noninvasive ventilation. During synchronized breaths, positive pressure ventilator breaths are delivered when the glottis is open. With nonsynchronized breaths, reflexes originating probably from bronchopulmonary receptors may sometimes cause partial closure of the glottis, resulting in increased airway resistance and variations in delivered tidal volumes [24]. Some authors postulated that this is one of the mechanisms designed to protect the lungs from overinflation. Thus, fine-tuning of the ventilator support, including noninvasive methods, is important [25].

Key Recommendations

> Nasal high-frequency ventilation can improve CO_2 elimination.
> Nasal high-frequency ventilation has a potential to decrease the need for endotracheal intubation and mechanical ventilation in the group of infants with mild-to-moderate respiratory failure.
> Further research on the effectiveness of nHFV in sicker patients is necessary.
> Before nHFV therapy can be recommended for widespread use, further studies of safety are required.

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Bubble Continuous Positive Airway Pressure

53

J. Jane Pillow

53.1
Introduction

Since the initial report from Gregory et al. describing the use of endotracheal continuous positive airway pressure (CPAP) to support the ventilation of spontaneously breathing newborn infants [1] and the subsequent development of a head box for noninvasive CPAP delivery, CPAP has gained widespread popularity for respiratory support of the nonintubated infant. Whereas these initial modes of delivery assumed that a leak-free application was essential for effective therapeutic delivery of CPAP, improved ease of application and access to infants was achieved when the method was subsequently successfully adapted to generate nasal CPAP [2].

Currently, there are three main forms of nasal CPAP commonly applied to infants with respiratory distress syndrome (RDS): Agostino's adaptation [2] uses a neonatal ventilator to generate a constant bias gas flow whilst CPAP was achieved through provision of a variable resistance to exhalation. This approach created constant positive pressure that fell below the desired value during spontaneous inspirations. The emergence of bubble CPAP, as described by Wung et al. in 1975 [3], represented a simple but significant change to this initial nasal CPAP circuit. Wung et al. supplied a heated and humidified constant flow to the baby and created the positive airway pressure by immersing the expiratory limb of the circuit in a column of water instead of a variable resistor. More recently, a third approach has utilized a variable-flow CPAP system (Infant Flow®, Viasys, USA). The proposed advantages of this latest approach include low extrinsic work of breathing [4], improved thoracoabdominal synchrony [5], and maintenance of constant pressure throughout the respiratory cycle (including during inspiration) aided by a unique fluidic flip action. A variation on the variable-flow CPAP system includes a biphasic CPAP (Infant Flow SiPAP™, Viasys), which facilitates alternating high and low levels of CPAP pressure whilst maintaining the other potential benefits of variable flow and the fluidic flip mechanics.

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Although used clinically for in excess of 30 years, it is only over the last decade that research efforts have focused on improving our understanding of whether bubble CPAP offers a specific physiological and clinical advantage over other forms of nasal CPAP and, if so, defining the mechanisms underlying that benefit. This review summarizes the evidence supporting the use of bubble CPAP with a specific focus on understanding the principles and application of bubble CPAP and how it may differ from the two other main modes of neonatal nasal CPAP.

53.2
Bubble CPAP Circuits, Lung Mechanics, and Their Influence on Delivered CPAP

The basic bubble CPAP circuit used first by Wung et al. in 1975 [3] (Fig. 53.1) remains in use around the world today, with a commercially marketed version (Fisher & Paykel Healthcare, Auckland, NZ) now available in some countries. Rather than achieving a constant pressure (ventilator-derived CPAP and variable-flow CPAP), bubble CPAP generates, at the nares, pressure waveforms with broadband frequency composition (up to ~60 Hz) and oscillatory amplitudes that are on the order of 4 cmH$_2$O around the mean pressure depending on the applied flow and physical properties of the expiratory limb. This noisy pressure waveform generated by the bubbles created when bias flow escapes from the distal end of the expiratory limb creates vibrations that are transmitted via the
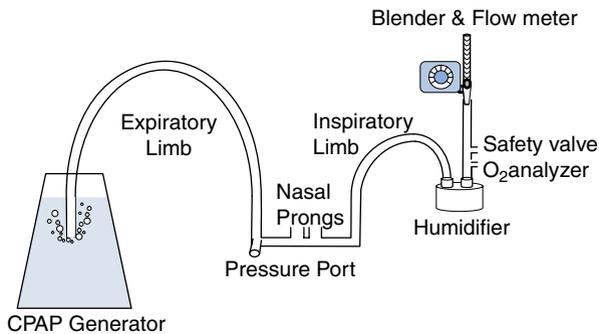
Fig. 53.1 Equipment required for bubble continuous positive airway pressure (*CPAP*). Medical oxygen and air are blended, and a flowmeter is used to generate a set inspiratory flow (6–10 L/min), which is heated and humidified prior to delivery to the nasal prongs. An oxygen analyser and pressure safety limit valve can be incorporated into the inspiratory limb to prevent the delivery of inadvertently high airway pressures in the event of blockage in the expiratory limb. The tip of the expiratory limb is submerged within a calibrated vessel (jar) filled with fluid (normally water). The depth to which the tip is submerged is the main determinant of mean pressure delivered to the nares. Flow is adjusted to ensure "bubbling" occurs, indicating that the circuit is free of significant leaks and that the desired mean pressure will be achieved. The bubbling creates pressure oscillations that are transmitted back through the expiratory limb to the patient's nares

nasal prongs to the infant's chest wall and lungs, providing the expiratory tubing is sufficiently rigid.

Adjusting the depth of insertion of the expiratory limb alters the average CPAP applied. It is important that the mean pressure measured at the nares may exceed the anticipated mean pressure estimated from the depth of the tip of the expiratory limb due to pressure drop between the nares and the submerged point at which flow escapes into the bubble-generating fluid [5]. The magnitude of this pressure difference increases with increasing applied bias flow [6], highlighting the importance of measurement of mean pressure at the nares to gain an accurate impression of delivered pressure.

Other factors may influence the frequency content and amplitude of the generated pressure waveform delivered to the nares. The geometry of the tip of the expiratory tube is an important determinant of both of these factors, with both factors reported greatest when a funnel with a 30-mm diameter and 90° angle relative to a normal line projected on the water surface is used [7]. A device incorporating a 135° angle in the terminal end of the expiratory limb was noted to increase amplitude and decrease frequency content of the pressure waveform [8]. This high-amplitude CPAP device was able to achieve acceptable gas exchange in healthy and saline-lavaged juvenile rabbits [9] and may have been associated with reduced work of breathing compared to conventional bubble CPAP [10], although equivalence of mean airway pressure was not shown. Increased viscosity and surface tension coefficient of the fluid at the air–fluid interface will result in larger bubbles and alter the speed of bubble formation [11].

Whereas flow magnitude may influence the amplitude of the pressure waveform at the nares, there is minimal effect of flow on the amplitude of the pressure waveform delivered to the lung. Rather, as shown previously for high-frequency oscillatory ventilation, there is marked damping of the pressure waveform between the nares and the lung during bubble CPAP [6, 12]. A major determinant of the extent of damping is lung compliance with transmission of the pressure oscillations to the lung decreasing exponentially with increasing compliance. Thus, the poorly compliant surfactant-deficient lung will experience much greater fluctuations in CPAP pressure than the highly compliant lung, in which pressure oscillations are minimal. In vitro studies further suggest that the poorly compliant lung also filters out less of the frequency content of the waveform delivered to the nares [13], likely due to higher corner frequency.

53.3
Clinical Studies

Bubble CPAP has attracted growing interest amongst neonatal practitioners over the last two decades following the reports of Avery [14] and, more recently, van Marter [15] highlighting the low incidence of chronic lung disease in preterm infants at the Columbia Presbyterian Medical Center. Avery showed that the reasons for low bronchopulmonary dysplasia (BPD) rates at Columbia Presbyterian Medical Center were multifactorial, including tolerance of permissive hypercapnea and minimal sedation, handling, and postnatal

steroid use. In addition, however, Wung et al. had included early use of bubble nasal CPAP as a primary focus of the clinical treatment strategy since their initial report in 1975 [3]. Despite the extended period, clinical data comparing the efficiency of bubble CPAP to other forms of nasal CPAP remain limited to anecdotal reports. In one of the more detailed historical comparisons following a change of clinical practice, Narendran and colleagues showed that delivery room intubations, days on mechanical ventilation, and use of postnatal steroids decreased after introduction of early bubble CPAP in infants with extremely low birth weight, while mean days on CPAP, number of babies on CPAP at 24 h, and mean weight at 36 weeks of gestation increased compared to historical controls [16]. Compared to a similar hospital instituting early ventilator-derived CPAP, bubble CPAP was associated with a trend towards decreased BPD [17].

The first prospective randomized controlled trial comparing bubble CPAP to an alternative nasal CPAP strategy was published in 2009 [18]. One hundred and forty preterm infants at 24–29 weeks of gestation or with birth weights of 600–1,500 g ventilated at birth for RDS were randomized to receive either variable-flow CPAP (Infant Flow Driver®, Viasys) or bubble CPAP. Although the proportions of infants who achieved successful extubation for 72 h and 7 days were similar between groups, the median duration of CPAP support was 50% shorter in infants on bubble CPAP. Analysis of the major subgroup (those ventilated for 14 days or less, $n = 127$) showed that infants managed with bubble CPAP had a significantly higher rate of successful extubation. This intriguing result suggested that, for subgroups of infants, advantages of the bubble-generated pressure oscillations outweigh any potential disadvantage of constant-flow CPAP generation when compared with a variable-flow device.

While the clinical data to support a potential clinical benefit of bubble CPAP over other forms of nasal CPAP therapy in neonates are clearly limited, they provide justification for research focused on understanding the relevance of the bubble oscillations in achieving the observed clinical effect.

53.4
Theory and Discussion

Current evidence suggests that bubble CPAP may enhance physiological responses through increased airway patency and recruitment, augmentation of gas mixing and CO_2 clearance, and consequent damping of the inflammatory cascade.

53.4.1
Airway Recruitment: Power Laws, Avalanches, and Stochastic Resonance

The avoidance of atelectasis and early establishment of an "open lung" via volume recruitment are now acknowledged as fundamental goals of noninjurious ventilation. The recruitment of terminal airspaces is governed by power law distributions, arising from avalanches of airspace opening events, as the applied pressure rises above airway pressure thresholds and propagates down the branching airway tree [19]. This recruitment

process benefits from the superimposition of noise on the applied driving pressure, exploiting a phenomenon known as *stochastic resonance* [19]. Pressure fluctuations above the mean pressure will promote greater lung volume recruitment than those pressure fluctuations falling below the mean pressure, provided the upper limit of the pressure fluctuations lies above the point of the lower inflexure of collapsed lung units on the pressure volume curve.

Stochastic resonance may partially explain the benefits of bubble CPAP in neonatal RDS [12, 13]: The oscillatory component of the bubble CPAP pressure waveform is superimposed on the desired mean CPAP and the low-frequency pressure fluctuations imposed by the subject's spontaneous respiratory efforts. While the net volume output of the superimposed oscillations is essentially zero because these are applied to a nonlinear dynamic system, the noisy nature of the pressure waveform generated from the bubbling in the expiratory line may actually promote airway-opening events and consequently lung volume recruitment if superimposed on subthreshold respiratory effort. Given that the transmitted pressure amplitude is greater in the presence of low compliance [12, 13], reopening of atelectic airspaces resulting from stochastic effects of the bubble CPAP waveform is likely to be greatest during neonatal transition when fluid must be cleared from the lung and functional residual capacity is established and in the presence of acute neonatal RDS when lung volume and compliance are low. This benefit, compared to ventilator-derived CPAP, was evident in self-ventilating preterm lambs with surfactant-deficient lung disease treated with bubble CPAP [12].

The principles of stochastic resonance suggest that the amplitude and frequency of the superimposed noise can be optimized to achieve the most favorable amplification (i.e., volume recruitment events). There was no evidence of significant short-term physiological consequences of 8 L/min versus 12 L/min in preterm lambs treated with bubble CPAP [12]. Increased amplitude of the generated pressure oscillations was associated with improved oxygenation in surfactant-deficient rabbits [10].

53.4.2
Gas Mixing and CO_2 Clearance

The noisy nature of the pressure waveform delivered to the airway opening during bubble CPAP may augment gas mixing in a similar fashion to mechanisms present during high-frequency oscillatory ventilation. Nekvasil and colleagues observed that high-frequency bubble oscillation achieved effective gas exchange when used to treat respiratory failure in three neonates weighing 1,250–2,700 g [7]. Subsequently, Lee and colleagues [20] randomized a group of infants ready for extubation to receive either bubble CPAP or ventilator-derived CPAP for 15 min prior to crossover to the alternative treatment. Whilst there were no differences in partial pressure of arterial carbon dioxide (Pa_{CO_2}) between treatment groups, babies had lower respiratory rates and lower minute volumes while on bubble CPAP compared to ventilator-derived CPAP, indicating more efficient ventilation. Likewise, bubble CPAP in preterm lambs is associated with lower Pa_{CO_2} and decreased ventilation inhomogeneity compared to ventilator-derived CPAP [12].

53.4.3
Inflammation and Surfactant Metabolism

There is some limited evidence to suggest that the use of bubble CPAP may reduce the inflammatory response to noninvasive ventilation. Preterm lambs treated with bubble CPAP tended to have lower levels of protein in bronchoalveolar lavage fluid compared to those treated with ventilator-derived constant-flow CPAP [12].

The superimposition of noise on the distending pressure waveform may also promote increased surfactant secretion. Preterm lambs treated with bubble CPAP tended to have higher saturated phosphatidylcholine levels in bronchoalveolar lavage fluid compared to lambs receiving ventilator-derived CPAP [12]. However, this difference was not statistically significant and remains to be proven.

53.5
Conclusions

The initial attraction of the bubble CPAP method related primarily to its simplicity and significant cost advantage, facilitating its use throughout the Western and developing world. Evidence is mounting that the use of bubble CPAP is associated with distinct clinical outcomes, including improved oxygenation, increased airway patency, improved lung mechanics and lung volume, reduced ventilation inhomogeneity, more efficient CO_2 exchange, increased extubation success, and possibly improved surfactant secretion and reduced inflammation. Future research needs to focus on the key recommendations presented next.

Key Recommendations

› Additional well-designed and adequately powered clinical trials are needed comparing bubble CPAP to other forms of nasal CPAP that include the outcomes of severity of lung disease and long-term neurological outcomes.
› There needs to be equipment development to further evaluate the benefits or otherwise of specific frequencies and amplitudes of bubble-generated pressure oscillations and how this may be optimized to meet the needs of the individual patient.
› It must be established whether application of bubble CPAP impedes the magnitude of the inflammatory response in the setting of acute respiratory distress.
› Discovery must be made regarding whether similar oscillations present during positive end-expiratory pressure in routine mechanical ventilation may provide clinical and physiological benefits in the intubated infant.
› It should be found if there are relevant applications of bubble CPAP in older paediatric and adult patients.

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Noninvasive Mechanical Ventilation with Positive Airway Pressure in Pediatric Intensive Care

54

Giancarlo Ottonello, Andrea Wolfler, and Pietro Tuo

54.1
Introduction

In recent years, the use of noninvasive positive pressure ventilation (NIPPV) in pediatric intensive care units (PICUs) has been increased. Although its use is widely accepted for chronic respiratory conditions such as neuromuscular weakness and obstructive sleep apnea [1–3], the use of NIPPV in the acute setting in pediatric patients is still uncommon. Because of the lack of adequate devices and of trained staff, several PICUs do not yet consider NIPPV among their strategies for ventilation [4, 5].

Few reports have addressed the use of NIV (noninvasive ventilation) in patients with acute respiratory failure (ARF) in the PICU [6], and additional studies are needed to evaluate the specific indications, contraindications, and possible adverse effects of this type of ventilation.

The use of NIPPV can be beneficial or not, depending on the etiology of respiratory failure. In some cases, it might cause a delayed time to intubation. In other specific situations, such as for immunocompromised children and those affected by cystic fibrosis (CF), it offers major benefits by avoiding tracheal intubation, which may be counterproductive in these particular diseases, and potentially could improve the survival rate [7–9].

54.2
The Equipment

Different manufacturers have created different equipment to connect the mechanical ventilator to the patient; these minimize air leaks, improve patient comfort, and allow patient synchrony with mechanical ventilation [10].

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54.2.1
The Masks

Unlike results in adult studies, pediatric studies showed that nasal masks seem to be preferred for NIPPV in children, both in the chronic and acute settings, despite the fact that children enrolled in these studies were often past the age of obligatory nose breathing [11, 12]. In the clinical setting, it is recommended to have available different models and types of masks to find the best fit for each patient [13].

54.2.2
The Helmet

Although the mask is the most common interface used to deliver NIPPV, at the same time it may be responsible of a certain number of NIPPV failures. These are related to pressure necrosis of the skin, air leaks, and discomfort associated with the mask. A helmet represents an alternative with better acceptance in the acute setting [14]. A helmet is currently available for continuous positive airway pressure (CPAP) and for bilevel positive airway pressure (BiPAP) ventilation. For CPAP use, a continuous fresh gas flow of at least 35 L/min is needed to achieve washout of exhaled CO_2 from the system. The helmet for NIPPV is smaller than that used for CPAP and can be connected to the mechanical ventilator. The volume of the helmet may decrease the sensitivity of the inspiratory triggering mechanism of the mechanical ventilator, causing asynchrony between the patient and the ventilator [15]. The helmet is transparent, which allows the child to see and interact with parents, nurses, and the environment (Fig. 54.1). In children, the helmet can minimize air leaks, and three different sizes fit a large portion of the pediatric population older than 1 month [10]. A number of studies have reported the role of helmet CPAP and helmet ventilation in the PICU. Codazzi and colleagues reported a small series of 15 young children (from 1 month to 5 years) with ARF treated with CPAP ventilation with a helmet. No adverse events related to the device were reported, and the authors described an increase in oxygenation

Fig. 54.1 The helmet: treatment of bronchiolitis

above baseline after 2 h. They concluded that the helmet is a suitable device for CPAP delivery to infants and preschool children with hypoxic ARF [16].

54.3
The Choice of the Mechanical Ventilator

None of the ventilators available today is perfect and able to adequately ventilate all the different patient types who could need NIPPV. The sensitivity triggering inspiration of most of the ventilators is insufficient for infants [17]. For NIPPV, the mechanical ventilator must have

1. A blender for FiO_2 up to 1
2. The ability to compensate for large air leaks
3. A high maximal inspiratory flow
4. The possibility to silence alarms of apnea, low exhaled tidal volume, high inspiratory volume (because in infants the presence of air leaks often causes zeroing of expired tidal volume)
5. The availability of different modes of ventilation, including time cycled, pressure limited

54.4
Humidification

NIPPV with unidirectional flow increases the need for humidification due to the high flow of fresh air used by the ventilator. The nasal mucosa loses water delivered to the inspiratory gas, leading to an increase in nasal airway resistance, which in adults has been shown to increase up to six times the baseline value [18]. Because the older child is no longer an obligatory nose breather, this could lead to mouth breathing and associated air leaks [18].

Heated humidifiers are the only type useful for NIPPV. The presence of a humidifier will add resistance to that of the circuit and will tend to interfere with triggering and possibly pressure delivery.

54.5
Timing of NIV Initiation

There are no clear indications about the best timing for the beginning of NIPPV in children affected by ARF, but NIPPV should be anticipated in critical patients. Since NIPPV requires patient effort, waiting too long to begin the therapy risks having a fatigued patient who cannot effectively use NIPPV and may lead to treatment failure and need for conventional ventilation.

54.6
Monitoring

NIPPV often requires more monitoring and care than invasive mechanical ventilation. Since the possible failure of NIPPV has to be promptly detected to avoid the delay in starting conventional ventilation, close bedside assessment of its effectiveness by the respiratory care team is essential. Qualified professional staff must observe children treated with NIPPV through the use of cardiac and respiratory monitors, pulse oximetry, and, when necessary, blood gas analyses.

54.7
Contraindications

The main contraindications for NIPPV are acute neurological impairment, inability to protect the airway, hemodynamic failure with shock, massive hemoptysis, facial or airway abnormalities, facial trauma or burns, and upper gastrointestinal surgery due to the risk of gastric distension. Although the inability to handle airway secretions is listed as a relative contraindication to NIPPV in adult patients, children with cerebral palsy and spastic laryngeal dysfunction have been treated successfully with NIPPV.

54.8
Side Effects

54.8.1
Gastric Distension

Gastric distension due to air is common and might increase the risk of acute emesis of gastric contents into the nasal–oral mask. For this reason, use of nasal–oral masks requires careful attention to feeding practices and a highly monitored setting.

54.8.2
Skin Injury

Skin injury is very common. The spectrum of this problem can range from transient erythema to skin necrosis [19].

54.8.3
Major Complications

Major complications are unusual. Tension pneumothorax, depressed cardiac output, and progressive hypercarbia have been described in acutely ill children. Other

described complications are secretions obstructing the upper airways and severe gastric distension [20].

54.9
Factors Predicting Success or Failure

The lack of clear clinical improvement after the first hours of treatment should make the physician think about changing the technique of respiratory support. An FiO_2 greater than 0.8 after 1 h of treatment has been associated with the failure of the technique [20]. A PcO_2 value higher than 55 mmHg during the first 24 h may correlate with an increased risk of failure [21].

54.10
Application of NIV in the Acute Setting

In the acute setting, NIPPV is effective in improving hypoxemia and the signs and symptoms of ARF of different origin (asthma, bronchiolitis, lung contusion, pneumonia, etc.). The use of NIPPV has reportedly led to a reduced need for intubation [22]. The largest series of pediatric patients with ARF treated with NIPPV to date has been reported by Essouri et al. [23]. Success in the use of NIPPV was largely dependent on the cause of respiratory failure as well as on severity of illness, as reflected by their Pediatric Risk of Mortality (PRISM) and Pediatric Logistic Organ Dysfunction (PELOD) scores on day 1 of PICU stay. The worst results were found in patients with acute respiratory distress syndrome (ARDS) [23]. In a population of children with ARF mainly related to parenchymal lung disease, NIPPV enabled decreased oxygen requirement, PcO_2 levels, respiratory rate, and need for intubation [21]. Even among children with acute moderate hypercapnic respiratory insufficiency, NIPPV was able to improve clinical outcome. It allowed an increase in tidal volume and minute ventilation and a decrease in esophageal and diaphragmatic pressure time product, reducing the mean partial pressure in carbon dioxide [24].

54.10.1
Cystic Fibrosis

NIPPV is used in patients with CF, mainly during acute exacerbation of chronic respiratory failure. It avoids intubation and its possible catastrophic consequences. Nevertheless, NIPPV is not uniformly used in CF centers, and poor patient tolerance and increased incidence of side effects, when compared to other treated diseases, have been reported [25, 26]. To enhance tolerance and compliance to NIPPV for CF patients, some authors have suggested the use of invasive methods, like measuring esophageal pressures, to define optimal settings of the mechanical ventilator [27].

54.10.2
Lower Airway Obstruction

Asthma and bronchiolitis are among the most common causes of hospital admissions in infancy and childhood. Patients with more severe forms need tracheal intubation and mechanical ventilation, which is often a difficult task and is associated with significant complications, such as barotrauma, hemodynamic instability, infections, and increased length of hospital stay [28].

NIPPV has been evaluated to reduce intubation rate and to improve clinical scores of asthma and bronchiolitis. Thill et al. reported data from 20 children aged between 2 months and 14 years with acute lower airway obstruction. They found that the children receiving NIPPV had a significantly decreased respiratory rate and a lower Clinical Asthma Score (CAS) [29]. Beers et al. analyzed retrospectively a group of 73 patients aged 2–17 years with status asthmaticus and indication for admission in an intensive care unit (ICU). The use of NIPPV improved oxygenation, and only two patients progressed to tracheal intubation and mechanical ventilation [30]. Airflow limitation is always associated with severe asthma exacerbation. If severe gas trapping occurs, the application of NIPPV might increase the amount of gas inspired during each breath, but the low expiratory flow will prevent the exhalation of the entire inspired volume. In this condition, invasive ventilation with very long expiratory time may be required [31].

Nasal CPAP improves the clinical score and the CO_2 elimination in infants with refractory bronchiolitis. These positive effects are significantly enhanced when nasal CPAP is combined with heliox instead of air and oxygen. Both techniques are noninvasive, seem safe, and may reduce the need for endotracheal intubation [32].

54.10.3
Upper Airway Obstruction

The presence of upper airway obstruction is a common challenge in the PICU. Laryngomalacia, tracheomalacia, tracheal hypoplasia, and Pierre–Robin sequence are common congenital causes, while croup is the most frequent acquired condition. NIPPV has been used in these patients, but the problem of synchronization is common since patients with obstructed airways often fail to trigger the mechanical ventilator [33].

54.10.4
Acute Respiratory Distress Syndrome

Very few studies have evaluated the role of NIPPV in ARDS in pediatric patients. Essouri et al. treated less-severe ARDS ($PaO_2 / FiO_2 > 150$) with NIPPV as the more severe patients were systematically intubated and mechanically ventilated. Nevertheless, they reported a very low success rate of NIPPV in their group of patients with the diagnosis of ARDS: 78% were eventually intubated. Multivariate analysis showed that a diagnosis of ARDS

was an independent predictor for NIPPV failure [23]. The absence of clinical improvement after 1 h of NIPPV in ARDS patients should indicate the need for intubation and mechanical ventilation to avoid dangerous delays [34].

54.10.5
Postextubation Respiratory Failure/Weaning from Extubation

The largest series of pediatric patients was that of Essouri et al. Nevertheless, the population was too small to draw clear conclusions. They reported that 33% of patients treated with NIPPV after extubation required reintubation, and 11% of these patients died. They excluded those deaths that were related to the use of BiPAP or to delayed reintubation. This finding is similar to those for the adults. It has been shown that a requirement for reintubation after failed extubation in adults is associated with a poor outcome and a higher mortality rate [35].

54.10.6
Immunocompromised Patients

ARF in immunocompromised patients offers an interesting opportunity for the use of NIPPV. There are different pediatric case reports on the successful utilization of NIPPV in hematological malignancies with ARF. These encouraging results could be effectively related to a reduction in infectious and bleeding complications due to invasive ventilation together with the reduction in sedation and length of ICU stay and increase in the use of enteral nutrition [36, 37]. Moreover, the avoidance of a translaryngeal device allows the patient to maintain the ability to communicate verbally, to cough, and to swallow [38].

54.11
NIV in Patients Under 1 Year of Age

It is difficult to synchronize spontaneous breathing with mechanical ventilators, particularly in the presence of large leaks and the high respiratory rate in children less than 1 year of age. The mechanical ventilator must be set in a time-cycled, pressure-controlled mode, with a respiratory rate moderately higher than the spontaneous respiratory rate of the child. Bilevel home ventilators might be inadequate since they do not reach respiratory rates higher than 30/min. Few masks are available for small infants, and sometimes custom circuits and interfaces are needed for particular situations [39]. Critical situations secondary to cardiac surgery, such as paralysis of the diaphragm, may require prolonged periods of mechanical ventilation, which could be treated with NIV [40].

Key Recommendations

› NIPPV has a key role in the PICU. For some patients who are immunocompromised and patients with CF and neuromuscular diseases, it should be available because its use offers a possible reduction in mortality and an improvement in quality of care and of life.
› Specific training is needed to achieve satisfactory use and outcome of the technique. Training must involve all the staff: physicians and nurses.
› Mechanical devices and equipment are crucial. Most mechanical ventilators are suited for NIPPV in adults, but only a few can be applied in the pediatric population.
› Great attention must be given to the selection of the mask; all the possible interfaces must be available: nasal, oronasal, nasal prongs, helmets.
› NIPPV is an important treatment option, but in the presence of worsening of, or the absence of, clinical improvement, it may cause a delay in the institution of tracheal intubation and mechanical ventilation.

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Home Mechanical Ventilation in Children with Chronic Respiratory Failure

55

Sedat Oktem, Refika Ersu, and Elif Dagli

55.1
Introduction

Use of noninvasive ventilation (NIV) in the treatment of chronic respiratory failure advanced rapidly in the paediatric population. This may be due to further advances in technology and increasing reports of success with NIV. The major advantages of NIV, compared to invasive ventilation with tracheostomy, include greater patient comfort; simpler application, use, and care; and reduced incidence of complications, hospital cost, and sedation requirement. NIV provides a technique more amenable to domiciliary use. But, the use of NIV can be problematic in children because of the difficulties in finding proper size, well-accepted masks and synchronizing the patient with the ventilator [1, 2].

55.2
Methods of NIV

55.2.1
Negative Pressure Ventilation

Negative pressure ventilation was the first mode of delivering NIV; however, now it is only available in a few centers in the world. Negative pressure can be applied to the lungs using a specially designed airtight rigid chamber that encloses the thorax and upper abdomen. There are a number of factors that limit the use of these devices in the home, including the cumbersome nature of the equipment, significant restrictions placed on the sleeping position, difficulty in performing personal care, the noise disturbance to the household, and problems with upper airway collapse [2].

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55.2.2
Positive Ventilation via Mask

NIV is based on the cyclical application of a positive pressure (or volume) to the airways. Volume-targeted ventilators deliver a set flow to the users' airways for a timed interval and at a specified frequency or in response to an inspiratory effort. This terminates when a preset volume has been delivered. Using a pressure-targeted respiratory assist device, the ventilation achieved from a preset airway pressure varies with user effort and the mechanical characteristics of the respiratory system, such as compliance, resistance, autopositive end-expiratory pressure, the ventilatory frequency, and potential leakage. When applying respiratory assist, the trigger function, usually sensed as either pressure or flow changes in the system, is of fundamental importance. In the case of a small or weak child, inspiratory flows generated by the child may be insufficient to activate the trigger. This is further complicated by the volume added by the humidifier, which in children is often interposed. For this reason, some authors have chosen protocols by which the setting of the rate of the ventilator is slightly higher than the child's spontaneous rate, thus effectively instituting a controlled mode of ventilation.

55.3
Clinical Scenarios for Home Noninvasive Ventilation with Positive Pressure

Long-term NIV at home has been used in a wide range of paediatric conditions (Table 55.1).

55.3.1
Obstructive Sleep Apnea Syndrome

Obstructive sleep apnea syndrome (OSAS) is not a single entity but is a spectrum of disorders ranging from primary snoring without impairment of gas exchange to chronic respiratory failure with nocturnal hypoxaemia and hypoventilation. Enlargement of the adenoids and tonsils is at least one important mechanism of OSAS in children, but it is not unusual for children with OSAS to have nocturnal derangements in respiratory gas exchange following adenotonsillectomy. It has been shown that treatment of these children with supplemental oxygen alone is safe but does not prevent hypoventilation associated with upper airway narrowing. Nasal continuous positive airway pressure (nCPAP) has been found to be highly effective in school-age children and even some toddlers with OSAS complicated by hypoxaemia but with normal CO_2 elimination. Noninvasive positive pressure ventilation (NPPV) is indicated for the older child with OSAS complicated by both hypoventilation and hypoxaemia. The sleep laboratory is an ideal site to initiate NPPV or CPAP as a means both to initiate the appropriate pressure settings and to assess the benefit or lack thereof of adenotonsillectomy in the child with complicated OSAS [3]. The American Academy of Pediatrics published guidelines on the diagnosis and management of childhood OSAS, recommending the following: All children should be screened for snoring, complex cases

Table 55.1 Clinical conditions associated with the use of long-term noninvasive ventilation at home

Common indications
Obstructive sleep apnea or hypopnoea
Craniofacial syndromes
Obesity hypoventilation disorders
Metabolic disorders
Cerebral palsy
Neuromuscular disorders
Kyphoscoliosis
Possible indications
Cystic fibrosis
Bridge to transplantation
Tracheobronchomalacia
Central hypoventilation
Congenital central hypoventilation syndrome
Down syndrome
Myelomeningocoele
Chronic lung disease of infancy

should be referred to a specialist, polysomnography (PSG) is the diagnostic gold standard, and adenotonsillectomy is the first-line treatment. NPPV is an option for those who are not candidates for surgery or who do not respond to surgery [4].

55.3.2
Neuromuscular Diseases

The most common indication for long-term NIV in children is respiratory failure due to neuromuscular disorders [5]. Most children with neuromuscular disease (NMD) eventually require assistance with airway clearance and breathing, especially during sleep. The onset of pulmonary symptoms in children with NMDs depends in large part on the type of underlying disease. Children with Duchenne muscular dystrophy may not experience any respiratory problems until midadolescence, whereas an infant with spinal muscular atrophy type I is likely to develop respiratory compromise within the first year of life. In either case, there is a typical sequence of events that leads to respiratory insufficiency and ultimately to respiratory failure. Firstly, respiratory muscle weakness leads to impaired airway clearance and cough, so these patients are prone to recurrent atelectasis and chest infections. Secondly, progressive inspiratory muscle weakness causes nocturnal respiratory

dysfunction, which is manifested by frequent arousals, sleep fragmentation, and sleep-related hypoventilation. Finally, hypercapnia extends into the daytime, and frank respiratory failure ensues. The duration of this timeline can be expanded by interventions such as assistance with clearance of respiratory secretions and nocturnal mechanical ventilation.

The criteria for home mechanical ventilation (HMV) of children with neuromuscular weakness have evolved since PSG became available. Before this, patients who were candidates for HMV were generally those with frequent, prolonged, or severe episodes of lower respiratory tract infection or those who had complications secondary to chronic hypoxaemia or hypoventilation. PSG allows for the early detection of patients who have hypoxaemia or hypoventilation during sleep and provides opportunities to initiate HMV before serious complications.

The appropriate time to introduce NIV depends on what one is attempting to achieve. For example, there are a number of potential pathophysiological problems in NMD one might wish to tackle.

These possibilities include

- Prevention of respiratory decompensation
- Reduction in frequency of chest infection, physiotherapy use
- Facilitation of pulmonary rehabilitation and exercise programs
- Control of nocturnal hypoventilation, symptoms
- Alteration of chest wall and lung characteristics
- Treatment of established hypercapnic ventilatory failure [6]

NIV, applied intermittently and preferably during sleep, relieves respiratory muscles from the work of breathing and augments alveolar ventilation.

However, NIV therapy is problematic in patients with severe bulbar weakness leading to aspiration, if arterial blood gas tensions can no longer be controlled, if there are insuperable interface difficulties, or if there is failure to thrive. In these situations, a transfer to ventilation via tracheotomy is a next step. However, some individuals with progressive conditions elect to continue with NIV therapy and cough assistance and forgo invasive ventilation.

55.3.3
Central Hypoventilation

Congenital central hypoventilation syndrome (CCHS) is a failure of automatic control of breathing. Patients have absent or negligible ventilatory sensitivity to hypercapnia and hypoxaemia during sleep and wakefulness. Management consists of ventilatory support whilst asleep to overcome the lack of central drive. Traditionally, this has been supplied via a tracheostomy and positive pressure ventilation, especially for infants and younger children. As tracheostomy is viewed unfavourably by many family members of children with CCHS, there is a trend towards utilization of NPPV as an alternate means of nocturnal ventilatory assistance [7]. There is growing interest in the possibility of using noninvasive means to deliver this nighttime support and free the child of a tracheostomy during the day

when the respiratory drive is voluntary. Some centers in the United States also offer supplemental diaphragmatic pacing to be applied during the day as an adjunct to mechanical ventilation at night. There are some instances when NPPV alone is used as the primary treatment of CCHS as a means of avoiding tracheostomy. The success of this approach must be checked by careful observation and sleep studies along with regular assessments of the child's developmental progress and echocardiography of the status of the pulmonary hypertension.

The role of NPPV in other disorders characterized by central mechanisms of hypoventilation is also evolving. NPPV has been useful in mild hypoventilation associated with the Arnold–Chiari malformation, such as in children with myelomeningocele. The important principle in the use of NPPV in these disorders is to be sure that the device used can function in a timed mode to deliver backup machine-delivered inflations in the event of a prolonged central respiratory pause.

Anecdotal reports of the successful introduction of mask support from diagnosis in infancy are emerging, although they are not universally encouraging. More encouraging is increasing experience in the successful transfer of older children or adolescents from an invasive to a noninvasive interface. Some studies demonstrated beneficial effects from the long-term use of NIV in CCHS, including children from the age of 7 weeks to teenagers, who in the latter case were converted from invasive ventilation. In general, NIV is best started after 5–6 years of age, when the clinical course of CCHS is usually more stable [8] (Fig. 55.1).

55.3.4
Cystic Fibrosis

Several short-term physiologic studies found that NPPV improves gas exchange in children, both awake and asleep, with cystic fibrosis (CF) [9]. Treatment of nocturnal hypoxaemia in CF with supplemental oxygen alone may aggravate hypoventilation, a complication

Fig. 55.1 Child with congenital central hypoventilation syndrome receiving noninvasive ventilation (NIV) with a nasal mask

prevented by NIV. NIV efficiently unloads the respiratory muscles in CF patients with a comparable level of lung function.

Lung transplantation is an effective treatment option for selected CF patients with end-stage respiratory failure. In advanced CF, NPPV has been successfully used as a "bridge" treatment to facilitate survival before lung transplantation or at least helped these individuals to be discharged from the hospital in countries where lung transplantation is not an option [10].

The indication for long-term NIV is diurnal hypercapnia or sleep disturbance. Data from the French national CF Observatory were the first to indicate that NIV is associated with stabilization of lung function decline in patients with severe CF lung disease [11].

55.4
Relative Contraindications

Contraindications have not been defined. However, there are a number of clinical situations in which NIV may not be suitable. Severe craniofacial malformations, severe laryngomalacia or tracheomalacia, inadequate nasal passages, ventilatory support for 24 h a day, severe learning disabilities, marked bulbar impairment, profuse secretions, inability to ventilate sufficiently, and the child's or parents' inability to cooperate would seem to be possible contraindications [2].

55.5
The Interface in NIV

55.5.1
Nasal Versus Full-Face Mask

Full-face masks minimize leakage; however, they also have significant drawbacks, including increased risk of gastric distension with air, difficulties in feeding, worsening gastroaesophageal reflux, and even aspiration. Nonetheless, some children prefer the full-face masks, and they can be used safely provided there can be a reasonable level of monitoring. In the acute setting, full-face masks have clear advantages over nasal masks in reducing oral leaks.

55.5.2
New Masks

The desirable characteristics of an interface should include low amount of dead space, adequate transparency, easy adaptability, good seal with low pressure on skin, and low cost. The correct size should be chosen considering a balance among patient's physiognomy, the least dead space possible, and the possibility of avoiding leaks. Newer interfaces designed to provide NPPV to children include the helmet device, nasal pillows or plugs, and modified wide-bore soft nasal tubing systems. Whereas these newer interfaces show promise in the paediatric population, experience with them is preliminary.

55.6
Complications of NIV via Mask

Two important factors in patient adherence with NIV are the fit and comfort of the interface. Complications are poor mask fit, skin irritation, mucosal drying, airflow-induced arousals, dyssynchrony, carbon dioxide retention associated with large dead space, aspiration, abdominal distention, and midfacial deformity.

55.6.1
Poor Mask Fit and Skin Irritation

The interface is a crucial determinant of the success of NIV because the patient cannot tolerate and accept NIV in the case of facial discomfort, skin injury, or significant air leak. Often, because of poor-fitting interfaces or inadequate headgear, nasal masks are placed firmly on a child's face, and injury to the underlying skin occurs. Some headgear systems have been adapted for smaller children so the systems can fit adequately into systems designed for adults. The prophylactic use of tape or hydrocolloid dressing to protect the skin and changing of mask design may relieve the affected area and aid recovery.

55.6.2
Midfacial Deformity

There is evidence that the chronic use of tight-fitting masks may affect facial growth, resulting in midfacial hypoplasia in some children [1]. This seems more likely if the child starts NIV before the age of 8 years and has weakness of the facial muscles. Regular evaluation of facial development is advisable. Alternation among face masks, nasal masks, and nasal plugs, together with the use of customized masks, may distribute pressure more widely over the facial skeleton in the long term, thereby reducing this problem.

55.7
Initiation of Home Ventilation

The primary indication for the use of NIV is chronic alveolar hypoventilation with associated respiratory failure as indicated by hypoxaemia and hypercapnia. *Hypoxaemia* is defined as one of the following:

- Hypoxemia three standard deviations below normal whilst breathing room air and adjusted for age in a steady state in an infant or young child
- Nocturnal hypoxia, defined as SpO_2 below 90% for more than 5% of night
- The presence of pulmonary hypertension or right ventricular hypertrophy or polycythemia due to chronic hypoxaemia as cited

Hypercapnia is defined as Pa_{CO_2} above 45 mmHg. Indications for elective NIV include symptoms of nocturnal hypoventilation (such as sleep disruption, night sweats, fatigue, morning headaches, and daytime sleepiness) in patients with OSAS, CF, and NMD.

Other symptoms such as severe dyspnoea, right heart failure, and arterial pulmonary hypertension or other conditions such as transition from a tracheostomy to NIV could also justify NIV in patients with restrictive disorders [5, 10, 12].

55.7.1
Initial NIV Adjustments in Children

NPPV should be based on specific goals, such as to assist the respiratory muscles, decrease nocturnal hypercarbia, improve daytime respiratory gas exchange, prevent atelectasis, and improve upper airway patency. The peak inspiratory pressure (PIP) should be set at a level sufficient to unload the respiratory muscles, increase tidal volume, and restore alveolar ventilation [3]. Children may get uncomfortable at PIP settings above 20 cmH_2O, although this may vary. A reasonable starting PIP in the clinical setting is 8 cmH_2O, with the expectation to raise this in increments as necessary to reduce the work of breathing. PIP levels of 8–18 cmH_2O suffice for most children. The positive end-expiratory pressure (PEEP) setting generally adjusts in the range of 4–10 cmH_2O with NIV, dependent on the specific process involved [3].

55.8
Discharging the Pediatric Patient on NIV

Several important aspects of successful application of long-term NIV in children include careful preparation of the patient and family, comfortable interface selection, and a strong commitment by both the physician and family towards the success of the intervention.

A child may be considered suitable for discharge on long-term NIV at home if

1. The medical condition is stable; this would be a clinical decision and would generally imply

   - The presence of a stable airway
   - Stable O_2 requirements (if required), usually less than 40%
   - P_{CO_2} levels that can be maintained within safe limits on ventilatory equipment that is operable by the family in their home
   - Nutritional intake adequate to maintain expected growth and development
   - All other medical conditions well controlled

2. Parents understand the long-term prognosis and are willing and capable of meeting the special needs of their child in the home setting.
3. It is practical to provide the level of support and intervention that the child requires at home [13, 14].

55.9
Follow-Up

Children treated with NIV on a long-term basis should be followed by a team of clinicians experienced in the assessment and management of paediatric respiratory diseases. Respiratory gas exchange, pulmonary function, state of mask, lateral projection of the skull, blood pressure, developmental milestones, growth, and patient satisfaction should be monitored carefully. Echocardiography for pulmonary hypertension should be performed annually. Each patient should have an annual sleep study that includes a brief period of unassisted breathing and titration of relevant ventilator pressures and oxygen. Depending on the condition, follow-up could take place typically every 3–6 months. Generally, at the beginning of the NIV at home, the younger or the more unstable the child is, the shorter the intervals should be between hospital visits [10].

Key Recommendations

> The major advantages of NIV, compared to invasive ventilation with tracheostomy, include greater patient comfort; simpler application, use, and care; and reduced incidence of complications, hospital cost, and sedation requirement.

> Common indications for the use of NIV in children include OSAS, NMDs, CF, and central hypoventilation.

> There are no contraindications for NIV. However, there are a number of clinical situations for which NIV may not be suitable. Severe craniofacial malformations, severe laryngomalacia or tracheomalacia, inadequate nasal passages, ventilatory support for 24 h a day, severe learning disabilities, marked bulbar impairment, profuse secretions, inability to ventilate sufficiently, and child's or parents' inability to cooperate would seem to be possible contraindications.

> The interface is a crucial determinant of the success of NIV because the patient cannot tolerate and accept NIV in the case of facial discomfort, skin injury, or significant air leak.

> Common complications are poor mask fit, skin irritation, mucosal drying, dyssynchrony, aspiration, and midfacial deformity.

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