Noninvasive Mechanical Ventilation

Theory, Equipment, and Clinical Applications

Antonio M. Esquinas
Editor

Third Edition

Springer

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ISBN 978-3-031-28962-0 ISBN 978-3-031-28963-7 (eBook)
https://doi.org/10.1007/978-3-031-28963-7

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

The 3rd edition of **"Noninvasive Ventilation, Theory, Equipment and Clinical Practice**" was born 6 years ago as a written reference on the three fundamental aspects that define an adequate and complete vision of noninvasive ventilation. This book has been able to achieve a 3rd edition, thanks to all the researchers and scientific contributions that continue to confirm that noninvasive ventilation remains one of the major advances in clinical practice, of a multidisciplinary scope and of major contribution to the improvement of the most common and atypical situations of chronic acute respiratory failure in the pre-hospital, hospital and home care setting.

In this 3rd edition, there is a selection of the most important controversial top topics of the past two years, since together with a valuable panel of authors, the concept of noninvasive ventilation in a wide variety of situations has been analyzed.

The reader who is new to noninvasive ventilation and a senior of this technique can find a solid and well-defined reference on the definition, equipment advances (ventilatory modes, interpretation of noninvasive ventilation-asynchrony; mask interfaces technology), advances in monitoring, indications, classes and emerging indications of noninvasive ventilation.

The book encompasses and structures the concepts in specific sections and chapters, linked for a correct conclusion of noninvasive ventilation.

The index offers a sequence of concepts and applications from physiology and pathophysiology, physical basis of the equipment and ventilatory modes. In the section on clinical indications, there is a logical sequence of all possible indications in the hospital setting. Finally, the book concludes with a section on prognosis, ethical aspects, and quality of life of the patient, which allows a global vision and application of noninvasive ventilation.

Murcia, Spain — Antonio M. Esquinas

Acknowledgements

To all the authors who gave their time and made this 3rd edition possible.
To our patients, the essence of the realization of this book.
To our families

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Abbreviations

ACPE	Acute cardiogenic pulmonary edema
ACRF	Acute on chronic respiratory failure
AHI	Apnea-hypopnea index
AI	Asynchrony index
ALS	Amyotrophic lateral sclerosis
ANN	American Academy of Neurology
ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
AVAPS	Average volume-assured pressure support ventilation
Bilevel NPV	Bilevel negative pressure ventilation
BiPAP	Bilevel positive airway pressure
BMI	Body mass index
BPAP	Bilevel positive airway pressure
CARDS	Covid-19 acute respiratory distress syndrome
CNAPV	Continuous negative abdominal pressure ventilation
CNPV	Continuous negative pressure ventilation
CO	Cardiac output
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
COT	Conventional oxygen therapy
COVID-19	Coronavirus disease 2019
CPAP	Continuous positive airway pressure
CPPV	Continuous positive pressure ventilation
ENPV	External negative-pressure ventilation
EP	Expiratory port
EPAP	Expiratory positive airway pressure
ERV	Expiratory reserve volume
ETI	Endotracheal intubation
FF	Full face
FiO_2	Fraction of inspired oxygen
FOSQ	Functional Outcomes of Sleep Questionnaire
FRC	Functional residual capacity
FVC	Forced vital capacity
HF	Heart Failure

HFNOT	High flow nasal oxygen therapy
HFOT	High flow oxygen therapy
HRQoL	Health related quality of life
I:E	Inspiration to expiration ratio
IBW	Ideal body weight
ICU	Intensive care unit
IHT	Intra-hospital transport
IMV	Invasive mechanical ventilation
IPAP	Inspiratory positive airway pressure
IPPV	Intermittent positive pressure ventilation
ITPP	Intra-thoracic positive pressure
iVAPS	Intelligent volume assured pressure support
LV	Left ventricle
MIP	Maximal inspiratory pressure
MV	Mechanical ventilation
NIPPV	Non-invasive positive pressure ventilation
NIV	Noninvasive ventilation
NRS	Noninvasive respiratory support
OHS	Obesity hypoventilation syndrome
ON	Oronasal
OSA	Obstructive sleep apnea
OSAS	Obstructive sleep apnea syndrome
$PaCO_2$	Partial carbon dioxide pressure
PaO_2	Partial oxygen pressure
PaO_2/FiO_2	Arterial oxygen pressure/inspiratory fraction of oxygen ratio
PEEP	Positive end expiratory pressure
Pres-NIV	Pressure-preset noninvasive ventilation pressure
PS	Pressure support
PSV	Pressure support ventilation
Ptm	Trans-mural pressure
pts	Patients
PVA	Patient–ventilator asynchrony
PVR	Pulmonary vascular resistance
QOL	Quality of life
RCT	Randomized controlled trial
REM	Rapid eye movement
RV	Right ventricle
SNIP	Sniff nasal inspiratory pressure
SpO_{2-}	Pulse oxygen saturation
SRI	Severe respiratory insufficiency
T_e	Expiratory time
T_i	Inspiratory time

TLC	Total lung capacity
TPP	Trans-pulmonary pressure
TST	Total sleep time
TV	Tidal volume
Vol NIV	Volume-preset noninvasive ventilation
VR	Venous return
V_T	Tidal volume
VTPCV	Volume-targeted pressure-controlled ventilation
WOB	Work of breathing

Part I

Physiology

Rationale of Noninvasive Ventilation

1

Teresa Michi, Tommaso Rosà, Michael C. Sklar, and Domenico Luca Grieco

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_1

Noninvasive ventilation is a form of respiratory assistance that delivers positive pressure ventilation without bypassing the upper airways.

It was first proposed in the 1980s to manage hypercapnic respiratory failure [1, 2] and was subsequently suggested as feasible treatment of acute cardiogenic pulmonary edema [3–5] and acute hypoxemic respiratory failure [6–13]. In recent years, it has been employed in the peri-operative setting, in the weaning process, and in chest trauma [14]. Moreover, delivering ventilatory assistance noninvasively is crucial in certain contexts, such as for immunocompromised patients [7, 8, 11] and palliative care [15]. Currently, it plays a leading role in preventing and treating respiratory failure of different etiologies in the acute care setting [16].

1.1 The Physio-Pathological Mechanism Underlying NIV

To understand why NIV is effective regardless of etiology and severity of pulmonary disease, a basic explication of the physiologic mechanisms involved is required.

1.1.1 NIV and Gas Exchange Improvement

The main physiologic effects of applying positive airway pressure are tidal volume and minute ventilation (V_M) augmentation [17].

Despite an increased dead space (V_D) due to interface and breathing circuit, alveolar ventilation (V_A) is improved: $V_A = V_M - V_D$. The mathematical relations of gas exchange are as follows:

$P_AO_2 = PIO_2 - (VO_2/V_A) \times k$

$P_ACO_2 = (VCO_2/V_A) \times k$

P_AO_2 and P_ACO_2 are, respectively, oxygen and carbon dioxide alveolar partial pressure. PIO_2 is inspired oxygen pressure, VO_2 is total body oxygen consumption, and VCO_2 is total body CO_2 production. Consequently, when alveolar ventilation increases, additional oxygen is provided, and additional CO_2 is removed from the alveolar gas mixture. Then, gas transport across the alveolar–capillary membrane is facilitated by membrane diffusing properties and gas tension gradients between alveolar and venous blood.

Gas exchange also depends on the ventilation–perfusion matching relationship (*V*/*Q*), which is affected by respiratory compliance, regional resistances, body position, and inspiratory muscle activity [18]. In fact, CO_2 is very soluble in blood and CO_2 content is essentially linearly related to P_ACO_2, falling steadily as V_A is increased by NIV. In contrast, O_2 is poorly soluble in blood and mainly carried by hemoglobin. Thus, raising P_AO_2 in high *V*/*Q* alveolar units cannot compensate low *V*/*Q* ones and it minimally affects O_2 content, which then depends principally on hemoglobin and *V*/*Q* ratio. In severe parenchymal lung disease, alveolar inflammation, swelling and collapse result in *V*/*Q* mismatching and shunt, impairing O_2 exchange. NIV-delivered tidal volume can recruit collapsed and atelectatic alveoli, while setting a positive end-expiratory pressure (PEEP) may stabilize the recruitment [19]. The net

consequences are minimization of V/Q mismatch, improvement of gas exchange, and enhancement of respiratory system compliance (C_{rs}) [20]. Preventing alveolar de-recruitment, PEEP may also mitigate atelectrauma, that is, the lung injury due to cyclic opening and closing of alveoli [21].

Injured lung parenchyma is typically heterogeneous, making it hard to set optimal PEEP. In fact, a certain level of PEEP may recruit collapsed alveoli in diseased regions and at the same time over-distend previously recruited alveoli in healthy regions [22].

1.1.2 NIV and Work of Breathing Reduction

According to the simplified equation of motion, ventilation relies on generating a pressure (P_{tot}) able to create a flow (F) in a system of given resistances (R_{aw}), to create a volume change (ΔV) in a system of determined compliance (C_{rs}). P_{tot} is the sum of a resistive component (P_{res}) required to overcome airway resistance and an elastic component (P_{el}) to overcome the load of respiratory system elastic recoil.

$P_{tot} = P_{res} + P_{el}$

$P_{tot} = (R_{aw} \times F) + (\Delta V/C_{rs})$

P_{tot} is supplied entirely by the ventilatory muscles (P_{mus}) during spontaneous unassisted breathing and by the mechanical ventilator (P_{mv}) during controlled mechanical ventilation. During interactive assisted breathing, P_{tot} is a combination of P_{mus} and P_{mv} [23].

In several lung diseases, muscles lose the ability to generate the P_{mus} necessary for the patient's ventilatory needs, a condition known as ventilatory failure. In this circumstance, respiratory assistance is required to fully or partially provide P_{tot}, reducing patient work of breathing (WOB).

NIV reduces patient WOB in two ways. First, a positive pressure inspiratory support, when applied, increases transpulmonary pressure and unloads inspiratory muscles, decreasing WOB in direct proportion to the assisted level set [24].

Second, PEEP counterbalances intrinsic PEEP and increases respiratory system compliance, mitigating both the elastic threshold and the elastic load to inspiration [25].

Improving gas exchange and reducing muscle loads, in turn, can reverse fatigue, mitigate dyspnea, and reduce neural drive, resulting in a more normal ventilatory pattern [26].

1.1.3 Cardiovascular effects of NIV

NIV has potentially remarkable hemodynamics effects, according to the level of positive pressure applied and to the underlying cardiovascular disease. In general, increasing mean intrathoracic pressure results in venous return decrease and right ventricular afterload augmentation. Consequently, cardiac output and pulmonary perfusion decrease. It should be noted that increased intrathoracic pressures reduce

left ventricular afterload, improving left ventricular function. Thus, NIV reduces cardiac output up to 20–30% in healthy subjects, whereas it improves cardiac function in patients with left heart failure [27].

Of note, inadequate NIV setting can lead to dyspnea, anxiety, and discomfort resulting in stress-related catecholamine release, which increases myocardial oxygen demand and risk of dysrhythmias.

1.2 Clinical Benefits and Negative Effects of NIV

1.2.1 Clinical Benefits of NIV

In addition to its efficacy in managing respiratory diseases, NIV offers several clinical advantages. The main benefit of using NIV is to avoid side effects and complications associated with endotracheal intubation (e.g., laryngeal and tracheal trauma) and invasive ventilation [28].

Specifically, preserving airway defense mechanism (e.g., cough and clearance of secretions) and facilitating mobilization, NIV may prevent infections and ventilator-associated pneumonia [6].

Furthermore, avoidance of sedation and neuromuscular paralysis may mitigate the risk of diaphragm dysfunction, ventilator induced lung injury, delirium, and ICU-acquired weakness [29, 30].

Noninvasive respiratory supports are affordable, easy to use, and available outside the ICU, permitting the prompt and effective management of a wide variety of pulmonary diseases in different settings.

1.2.2 NIV Side Effects

NIV has some inherent side effects. Noninvasive devices, in fact, apply pressure to the esophagus as well as to the trachea, leading to possible gastric distention, despite the presence of the gastroesophageal sphincter. A distended stomach impairs ventilation and exposes the unprotected airway to aspiration risk.

Despite sophisticated leak-compensation systems, air leaks are an inherent problem of NIV interfaces, leading to several issues in terms of accurate delivery of tidal volume and triggering of respiratory cycles. In addition, CO_2 rebreathing is a potential problem, especially with some interfaces and breathing circuits [31].

Moreover, during NIV, accurate respiratory monitoring to deliver protective mechanical ventilation may be harder to obtain. Maintenance of spontaneous breathing, especially in the most severe scenarios, carries the risks to exacerbate lung injury and to delay protective invasive mechanical ventilation, with detrimental effects on mortality [32–34].

Several factors are involved in NIV failure. Selection of patient and treatment monitoring are crucial, since severity of illness and lack of improvement are associated with high risk of NIV failure [35–37].

In this regard, tolerance to treatment and patient comfort are key factors to ensure treatment compliance.

Understanding physiological aspects inherent to the various interfaces and their ventilator settings can improve patient-ventilator interaction, favoring NIV success and favorable outcomes.

1.3 Mode of Ventilation

In clinical practice and in the great majority of clinical trials, NIV is delivered as biphasic positive airway pressure (mainly PSV = PEEP + pressure support) or continuous positive airway pressure (CPAP): unlike PSV, CPAP does not provide any inspiratory support on top of a positive end-expiratory pressure. Although ICU ventilators can administer CPAP–NIV, the use of high flow generators with oxygen/air blenders and O_2 reservoirs are needed to adequately meet the patients' flow demands (often very high during inspiration) and keep the set pressure constant over the entire respiratory cycle. Continuous high flows are necessary during helmet CPAP and should also be encouraged when oro-nasal and total-face masks are utilized [38, 39].

Both CPAP and PSV-NIV delivers a PEEP which helps improve arterial oxygenation, increase end expiratory lung volume (thereby reducing intrapulmonary shunt and dynamic strain) [40–42], and improve cardiac function in case of concomitant heart failure by reducing left ventricular afterload and right ventricular preload [43, 44]. PSV NIV (but not CPAP), through inspiratory pressure augmentation, also decreases inspiratory effort and work of breathing [40, 45]. This may partially explain why CPAP was able to improve oxygenation and dyspnea only transiently, with no effects on intubation rates in a mixed population of patients with AHRF of different etiologies [13].

Other ventilatory modes include proportional assist ventilation and neurally adjusted ventilatory assist (NAVA), created to optimize patient–ventilator interaction and tolerance during NIV [46–48]. However, their use has not been widely applied and no large RCTs are available to definitively evaluate their characteristics when compared to more "classic" modalities.

1.4 Interfaces

Although the same ventilatory modalities can be utilized with various NIV interfaces, the specific features of each of them must be known by physicians to optimize treatment efficacy and tolerability. Choice and setting of the right interface are crucial to support patient's breathing minimizing air leaks and avoiding excessive pressure on the face, to reduce the risk of skin ulcers. NIV can be delivered with face masks (oro-nasal, full-face) and helmets.

Face masks are capable of reducing a patient's work of breathing [40, 45] and improve the feeling of dyspnea in the acute setting, with applied pressure support,

low instrumental dead space, and CO_2 rebreathing. PSV–NIV delivered through face masks increases airway pressure, ameliorates arterial oxygenation, increases end-expiratory lung volume [26, 40–42], and improves cardiac function by reducing left ventricular afterload and right ventricular preload [43, 44]. However, air leaks are common (especially with the use of higher pressure), skin ulcers may develop, and wearability is sometimes problematic due to the patient's face contour.

Differently from face masks, helmets seem to improve patient's comfort (they do not contact the patient's face), reduce air leaks, and permit the application of higher PEEP for longer treatment cycles, which represents a crucial advantage in the setting of AHRF. Specific settings are necessary to optimally deliver NIV through the helmet, in order to minimize the risk of CO_2 rebreathing, pressurization delays, and improve work of breathing [38, 39, 49–56].

For these reasons, the choice of the interface appears crucial for NIV success and should be carefully tailored based on patients' underlying conditions and treatment objectives.

1.4.1 High-PEEP Helmet NIV

Helmets allow the application of high PEEP (10–12 cm H_2O) with minimal air leaks for prolonged treatments with minimal interruptions [50, 57–59]. High PEEP, favoring lung recruitment, reduces lung strain and atelectrauma, may reduce the driving pressure and convincingly improves mortality in intubated patients with early ARDS [58, 60–62]: similar effects may occur in spontaneously breathing patients [63, 64]. Higher PEEP renders lung insufflation more homogeneous, and reduces inspiratory effort. This is a key-aspect for the prevention of patient self-inflicted lung injury (PSILI) [65]. Helmet NIV was capable of reducing endotracheal intubation rates in patients with AHRF as compared to face mask NIV [66], and high flow nasal oxygen [59], through improvements in oxygenation and dyspnea, an effect probably mediated by higher PEEP.

Delivery of high PEEP is difficult during face mask NIV while it appears feasible when helmets are used, with the possibility of exploiting all the benefits of the non-invasive approach. Future studies are needed to make conclusive statements regarding the potential superiority of one interface over the other in this setting, but data concerning the benefit of administering high PEEP in continuous sessions with improved comfort appears promising and consistent with physiology, warranting further investigations.

1.5 Ventilators and Humidification

Turbine-based NIV ventilators best minimize asynchronies related to air leaks (i.e., autotriggering and delayed cycling) [67, 68]. In addition, in a bench model of invasive ventilation, newer generation turbine ventilators, as compared to servo-valve gas-based ventilators, seem to minimize trigger delay and optimize

pressurization capacity [69], but no data clearly tell us to what extent this affects NIV. Indeed, no clinical trials clarify whether and to what extent the choice of the ventilator may affect NIV outcome, and compressed gas-based ventilators were used to administer PSV-NIV in almost all the published randomized controlled trials.

During CPAP therapy, oxygen, mixed with compressed medical air, is delivered at high flow rates. When a compressed-gas system is used, dry and cold air is delivered to the patient, but 15 mg/L of water in the inspired mixture is necessary to prevent airway dryness and promote comfort and tolerance during oro-nasal and total-face NIV treatments: to achieve this goal, heat and moisture exchangers (HME) and heated humidifiers (HH) are utilized. Efficacy of these two humidification systems is similar, but HME's is reduced in the case of air leaks [70]. Indeed, HH were able to reduce work of breathing, respiratory rate, and $PaCO_2$ better than HMEs during full-face NIV, especially in hypercapnic patients [70–72]. Another randomized controlled trial (RCT) instead failed to demonstrate the superiority of HH as compared to HME in preventing ETI during oro-nasal PSV-NIV. Data from this RCT showed a trend toward a higher failure rate in hypoxemic patients treated with HH, it seems wise to suggest that HH use requires caution in these category of patients [73].

These data cannot be applied to helmet NIV, as gas heating and humidification are also performed by the patients themselves, due to the high-volume chamber (18 L). In one recent study, a double-tube circuit with no humidification allowed adequate conditioning of inspired gas, optimized comfort and improved patient–ventilator interaction. Use of HHs or HME in this setting resulted in increased discomfort due to excessive heat and humidity in the interface, which was associated with more intense dyspnea [74]. However, humidification may be necessary when fresh gas flows above 40 L/min are utilized [75].

1.6 Pharmacological Agents

Pharmacological agents may represent one strategy to improve comfort during NIV and at the same time reduce respiratory effort and therefore the risk of P-SILI. Indeed, 13% of patients experience discomfort during NIV and up to 10% may fail NIV due to intolerance [76, 77]. In limited reports, mild sedation with opioids has been advocated to improve comfort without affecting respiratory pattern and hemodynamics [78], while dexmedetomidine appears less effective [79]. On the other hand, only propofol and benzodiazepines are able to reduce respiratory effort [80, 81], while opioids primarily reduce respiratory rate with mixed effects on tidal volumes and inspiratory effort [82, 83]. Obviously, sedatives carry inherent risks and their use should always be accompanied by strict monitoring by experienced personnel. Partial neuromuscular blockade has been utilized in one experimental study and was shown capable of reducing inspiratory effort, but this strategy cannot be used in non-intubated patients for safety reasons and should nevertheless be better studied in future investigations [84].

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Part II

Interface, Ventilatory Modes and Ventilators

2 Interfaces for Noninvasive Mechanical Ventilation: Different Types and Mask Ventilation

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2.1 Introduction

The interface distinguishes noninvasive ventilation (NIV) from invasive ventilation [1]. Choosing the correct interface is a major step before starting noninvasive ventilation. In all techniques, an interface is needed to connect the patient to a ventilator

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_2

tube, providing a direct entry of pressurized gas. Using the wrong interface is a common reason for NIV intolerance. There are several types of interfaces, and choosing the right one for each situation is sometimes a major challenge. Interfaces deliver positive pressure either through the mouth, the nose, or both. Although there is no perfect recipe, knowing the advantages and disadvantages of each type helps us to make the best choices according to different situations. In this chapter, we will go through the current available interfaces and analyze which one is more suitable to your patient.

2.2 Interface Selection

Seven main classes of interfaces, with different sizes, are available (Table 2.1). This vast number allows several different options for each patient. The interface choice is mainly influenced by the patient's facial anatomy and comfort. It is almost impossible to achieve a successful NIV for long periods if the patient is totally uncomfortable. Other aspects, such as staff experience with the equipment or patient's breathing pattern, are also of major importance [2, 3]. Choosing the correct size of mask and headgear with several attachment points helps to distribute the pressure [4]. Straps hold the interface in place and can be adjusted to avoid excessive leaks or pressure on the face. Leaving enough space to allow two fingers underneath the strap helps avoid excessive pressure. The interface is usually made of a stiff transparent material hooked together with a cushion of soft material, mainly hydrogel, to seal the frame against the patient's face [5].

Studies have shown that, despite the heterogeneity in mask internal volume and compliance, the dynamic dead space and the clinical efficacy of different interfaces are on average remarkably similar, revealing the importance of patient's tolerance [5].

Although a "perfect mask" does not exist, some aspects, such as ventilator compatibility, reduced air leak, comfort, minimal resistance to airflow, not producing trauma, cost-effectiveness, and a good securing system, are essential.

Table 2.1 Different interface types

Interfaces for noninvasive ventilation
Oronasal
Nasal
Total face/Full face
Nasal pillow
Helmet
Mouth piece
Custom-built

2.3 Facial Interface

2.3.1 Oronosal Mask

An oronasal (ON) mask covers the mouth and nose. It increases minute ventilation and reduces $PaCO_2$ more effectively than nasal in acute respiratory failure and should be the first-line strategy in this situation, along with a full-face mask [1, 6]. In acute situations, patients usually do not collaborate and an ON mask avoids the mouth leaks seen with nasal masks. In these patients, an ON mask improves alveolar ventilation and prevents the increase in nasal resistances observed with the nasal mask in the case of mouth leaks [7]. It is important to notice that in long-term ventilation, this interface can cause claustrophobia in some patients. Also, this type of interface reduces patient's ability to communicate or to clear secretions and increases the risk of aspiration. Another major problem of long-term ventilation with an ON interface is the creation of nasal ulcers because it is placed over the nose [2]. A good interface adaption to patients naïve to NIV is especially important and a major predictor of ventilation success (Table 2.2).

The choice of ON mask type is influenced not only by the patient's face anatomy but also the available NIV circuit. If constant monitoring of the patient is not possible, the mask should have an anti-asphyxiation valve to prevent asphyxiation in case NIV accidently stops. If a single-limp circuit is being used, an exhalation port is mandatory. Usually, this port is attached to the mask but can also be added to other parts of the circuit. If a double limb circuit is being used, the mask should not have an exhalation port.

2.3.2 Total-Face/Full-Face Mask

As mentioned before, ON and full-face (FF) masks (Fig. 2.1) are the best option for acute patients. This type of interface covers the whole face and creates an air seal using a silicon gasket around the perimeter of the face, thus eliminating discomfort over the nasal bridge [8]. As FF masks are well tolerated, they may become an alternative in

Table 2.2 How to maximize oronasal interface adaptation

"Tips" for oronasal interface success
1. First adapt the superior cushion to the nose and then the inferior one between the inferior lips and chin. Do not adapt the mask in the teeth.
2. Adjust the strap allowing two fingers to avoid excessive pressure. If leak persists, consider changing interface size or type.
3. In men, consider shaving the beard to reduce leaks and discomfort.

Fig. 2.1 Full-face mask

cases in which mask intolerance is the primary reason for NIV failure [6]. FF masks are designed as one size that should fit most patients, making mask fitting easier in acute settings. It is a good alternative for patients that develop nasal ulcers; however, skin trauma may occur in other parts of the face [5]. Eye irritation due to positive pressure should be monitored and treated, if needed, with artificial tears [2]. This interface cannot deliver aerosolized medications and could also be a problem for more claustrophobic patients [1]. As mentioned before in this chapter, although the larger volume of the FF mask has raised concerns about increased dead space, studies have not demonstrated an increase in effective dead space compared with ON masks. This fact seems to be related with air streaming within the FF mask [8].

2.3.3 Helmet

The NIV helmet covers the entire head without coming in direct contact with the face. It is made of a transparent hood fixed around the neck or shoulders. It is available in different sizes, according to neck circumference and ventilation mode. The helmet can be connected to a ventilator or directly to a high flow air-oxygen source together with a positive end expiratory pressure (PEEP) valve. The helmet allows more autonomy to the patient, making it possible to read, eat, and talk. Also, a major advantage of the helmet is that it can be used in difficult anatomic situations, such as patients with face trauma. It is more appropriate to use a helmet with continuous positive airway pressure (CPAP) or high flow because the increased dead space may generate asynchrony with traditional ventilators and there is a risk of asphyxia. The

helmet interface could expose patients to a high level of noise and earplugs could be of great use in this situation [1, 5].

This interface is extremely useful in severe hypoxemia, especially for patients with acute respiratory distress syndrome (ARDS). During ARDS, high levels of PEEP are needed to improve oxygenation. At this high level of pressure, air leaks and mask intolerance are major problems to achieving ideal oxygenation. The helmet's design allows increased PEEP without substantial leaks. Some studies have showed that helmet use could reduce intubation rates in patients with ARDS [9]. Also, this interface makes it easier to turn patients to the prone position, a maneuver used in patients with ARDS. Helmet devices were a major contributor to the good results seen in patients with severe acute hypoxemia and showed very low air leaks (thus reducing aerosolization) during the novel coronavirus (COVID 19) pandemic in 2020. Recent studies have shown promising results of this interface usage for COVID-19 patients [10].

2.4 Nasal Interface

2.4.1 Nasal Mask

This mask is designed to entirely cover the nose (Fig. 2.2). A nasal mask is the first option in chronic patients, as they appear to be more comfortable than facial interfaces. A nasal mask allows the patient to eat, talk, cough, and is less claustrophobic.

Fig. 2.2 Nasal mask

In acute settings, the improvement in gas tension appears to be slower than with facial interfaces; therefore, the use of a nasal mask in the intensive care unit (ICU) for acute settings is not recommended. Patient's collaboration is important to avoid nonintentional leaks through the mouth. Nasal congestion or obstruction might cause failure of this interface. Chinstraps may be used to reduce air leaks via the mouth in selected patients, but they are not always tolerated, and in those cases, an interface change is recommended [2, 5, 6]. Some studies have shown better results in treating obstructive sleep apnea syndrome (OSA) with nasal masks over oronasal masks in patients under continuous positive pressure [11].

2.4.2 Nasal Pillow

As an alternative to nasal masks, nasal pillows can be used to reduce the risk of pressure sores over the nasal bridge. Nasal pillows are cushions that are directly inserted into the nostril and held in place with a flexible strap around the back of the head. They are often used for adults with OSA. This interface is the least invasive mask available.

2.5 Other Interfaces

2.5.1 Mouthpiece

A mouthpiece is placed between patients lips and delivers pressure directly into the mouth. Nasal clips could be used to avoid nasal leaks. There is limited data about the use of this interface in acute respiratory failure because it demands a lot of patient collaboration to reduce nasal leaks and asynchrony. Positive results for this interface have been reported in patients with chronic respiratory failure who need nearly continuous ventilatory assistance. Patients suffering tetraplegia or neuromuscular disease are the perfect candidates for this interface [5, 7]. A flexible support arm can fix a flexed mouthpiece to the mouth and make air delivery more convenient. Some centers use open-circuit mouthpiece NIV for daytime ventilatory support and other masks for nocturnal ventilation or mouthpieces fixed by a lip-covering flange. As a mouthpiece is associated with less risk of pneumonia and respiratory complications, it has been replacing ventilatory support via tracheostomy for chronic ventilated patients [12].

2.5.2 Custom-Built

A personalized mask is made for an individual patient to overcome the lack of an adequate interface. There are several different methods for making custom-built interfaces. Some of the materials used are thermoformable plastic individually adjusted; acrylic masks from plaster models of the face and facial scanning to create

Fig. 2.3 Regular oronasal mask and non-vented mask (blue elbow)

3D models. Limited studies have compared the efficiency of these models, but they appear to be well tolerated and with reduced skin injury or eye irritation [13].

2.5.2.1 Mask Ventilation

The dead-space volume of masks is an important factor that must be considered. Physiological dead space is increased with any type of mask [7]. As mentioned earlier, NIV can be applied via open single limb circuit or a closed double-limb circuit. In the first type, if a non-vented mask is used, an additional exhalation valve, to allow carbon dioxide removal, must be added to the circuit. Several types of valves can be used: whisper swivel, simple swivel, or plateau valve. It is especially important that all the staff know these valves, and they should not be obstructed. Non-vented masks are identified with a blue elbow (Fig. 2.3). These masks are good options in patients with infectious diseases to reduce aerosolization, but they require close monitoring. "T pieces" could be added to the circuit to allow oxygen support.

2.6 Conclusion

Choosing the right interface is crucial to maximize the efficacy and patient's tolerance during NIV. As discussed in this chapter, facial masks are more effective and better tolerated in acute settings, making them the first treatment option for those situations (Table 2.3). Patients suffering from severe hypoxemia respond well to CPAP delivered through a helmet interface, and recent studies have shown a delay in patient's intubation rate with this interface. Also, the helmet interface is a major ally in pandemic situations. Nasal masks are comfortable and a first option in chronic patients. Mouthpiece and custom-built interfaces are less used than other interfaces, but several studies have proven their efficiency, especially for chronic patients.

Skin injury and eye irritations are common complications of most interfaces, and clinicians should be aware of them. An ideal interface should combine comfort, efficiency, price, and easy application. Although the perfect interface does not exist,

Table 2.3 Advantages and disadvantages of various types of interfaces

	Oronasal	Total face	Helmet	Nasal	Nasal pillow	Mouthpiece	Custom built
Acute setting	✓✓	✓✓	✓✓	✓		✓	
Claustrophobic patient				✓✓	✓✓	✓✓	✓✓
No pressure nasal bridge		✓✓	✓✓		✓✓	✓✓	✓✓
Secretion clearance				✓✓	✓✓	✓	✓✓
Speaking and eating			✓✓	✓✓	✓✓	✓	✓✓
Chronic setting	✓	✓		✓ ✓	✓✓	✓✓	✓✓

✓✓ frequent, ✓ less frequent

the best approach in any ventilation unit is to have a wide variety of interfaces, with different types and sizes, and staff should be trained to select the best one for each individual patient.

Key Major Recommendations

- Using the wrong interface is one of the most common reasons for NIV intolerance.
- Periodic assessment of the skin, air leaks, and skin-protective strategies should be done to reduce discomfort and tissue damage; two important reasons for NIV intolerance.
- The ideal interface should be easy to wear, comfortable, efficient, and have few complications. No perfect model exists, and each interface should be chosen according to patient's face anatomy, clinical situation, staff experience, and ventilation mode.
- Facial interfaces are preferred for acute situations where less patient collaboration is expected. Nasal interfaces, mouthpieces, and custom-built are usually more comfortable and should be considered for chronic patients.
- A wide choice of interface types and sizes is advisable in ventilation units, and staff should be trained to choose the best option in each situation.

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3 Ventilatory modes of Noninvasive Mechanical Ventilation: Technology and Clinical Implications

S. Aneesa Shahul and Nishant Kumar Chauhan

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_3

Modalities for mechanical ventilation have seen paradigm shifts and evolution over the past seven decades ever since the introduction of the first volume controlled mechanical ventilator, Engstrom 100, in 1951. Based on the trans airway pressure gradient required to generate gas flow, ventilators are classified as positive pressure ventilators and negative pressure ventilators [1]. Two classical devices used for negative pressure ventilation are the iron lung and chest cuirass. With the advent of positive pressure mechanical ventilators, the chest cuirass is currently being used only in selected home care settings.

During positive pressure ventilation, positive pressure is applied at the airway opening which generates an inspiratory flow due to the transairway pressure gradient. Positive pressure ventilation can be provided either by invasive modes such as endotracheal intubation or tracheostomy or by noninvasive modes. Noninvasive ventilation is the modality where positive pressure ventilation is delivered without the use of an artificial airway. It has revolutionized acute respiratory failure management in many clinical scenarios, avoiding unnecessary intubation and the sequence of complications related to it. In this chapter, the basic details of noninvasive modes of ventilation will be described (Fig. 3.1; Table 3.1).

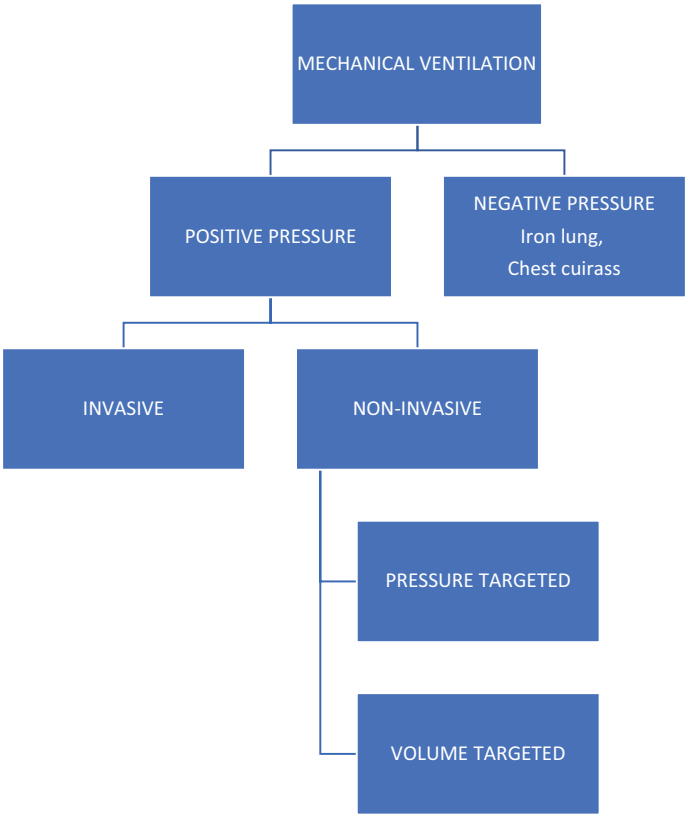

Fig. 3.1 Flow diagram showing classification of noninvasive ventilators [1]

Table 3.1 Indications of NIV [1]

Acute hypercapnic respiratory failure	Neuromuscular diseases
Obstructive sleep apnea	Central sleep apnea
Obesity hypoventilation syndrome	Refractory cardiogenic pulmonary edema

3.1 Contraindications for NIV

1. Severe facial deformity
2. Facial burns
3. Fixed upper airway obstruction
4. Facial trauma
5. Copious secretions
6. GCS < 8
7. Cognitive impairment
8. Claustrophobia

3.2 Advantages

1. It does not require an artificial airway
2. Numerous interfaces available as per patient choice and comfort
3. Lower risks of complications than invasive ventilation

3.3 Modes of Noninvasive Ventilation

There are two basic modes of providing mechanical ventilation.

1. Volume-targeted ventilation
2. Pressure-targeted ventilation

In volume-targeted ventilation, the operator sets the tidal volume to be delivered and the duration of inspiration (T_i). The ventilator generates whatever pressure is necessary to deliver the set volume within this time.

In pressure-targeted ventilation, the operator sets the inspiratory and expiratory pressures. In this mode, the volume of air the patient receives is a function of the impedance to inflation of the lungs and chest wall and the inspiratory time. The T_i should be of sufficient length to achieve an adequate volume and at a frequency that allows time for the patient to fully exhale [2].

3.4 Advantages of Pressure-Targeted Ventilation

1. Constant pressure is delivered which avoids sudden, uncomfortable rise in pressure as opposed to volume control.
2. There is provision for compensation for air leaks.

3. EPAP flushes out exhaled carbon dioxide from the mask and distal ventilator tubing and also aids in triggering.
4. EPAP prevents upper airway collapse during expiration.

3.5 Ventilator Modes

3.5.1 Continuous Positive Airway Pressure Ventilation (CPAP)

As the name suggests, in CPAP mode, single continuous positive pressure is delivered during inspiration and expiration. It delivers a constant pressure as long as the patient makes a spontaneous respiratory effort. It does not actively support the respiratory muscles. It is not effective in the absence of a respiratory effort. CPAP mode has been of great benefit in treatment of obstructive sleep apnea and cardiogenic pulmonary edema refractory to medical therapy.

3.5.2 Bilevel Positive Pressure Ventilation (BiPAP)

As the name suggests, there are two pressure levels in BiPAP: inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP). IPAP is the positive pressure applied on the airway during inspiration and EPAP is the one applied during expiration. IPAP is similar to peak airway pressure in invasive mechanical ventilation, whereas EPAP is similar to the PEEP/CPAP during mechanical ventilation. EPAP keeps the upper airway patent and improves oxygenation by recruiting alveoli [1]. The difference between IPAP and EPAP forms the pressure support, and this pressure support assists the patient's inspiration. It reduces the load on the respiratory muscles, increases tidal volume, and thereby increases minute ventilation [1, 2].

3.5.2.1 Spontaneous Mode

In the Spontaneous (*S*) mode (also known as assist mode), the ventilator delivers assisted breaths in response to patient inspiratory effort. If the patient fails to make adequate inspiratory effort, no ventilator support is delivered.

3.5.2.2 Control Mode

In the control (*T*) mode (also known as timed mode), the ventilator delivers breaths at a rate set by the operator regardless of patient inspiratory effort. In this mode, the operator also decides the inspiratory time (T_i) and breath cycling. The ventilator is triggered into inspiration at the preset time. Once the T_i has elapsed, the ventilator cycles into expiration. The triggering and cycling occurs independent of patient effort and hence has the disadvantage of discomfort and poor tolerance [1, 2].

3.5.2.3 Spontaneous/Timed Mode

S/T mode is also known as assist control mode. It is the NIV mode most commonly employed in treating acute hypercapnic respiratory failure. Here, a backup rate is set by the operator. The ventilator delivers breaths if the patient's respiratory rate is

slower than the backup rate. (i.e., controlled ventilation). Also, if the patient breathes faster than the backup rate, no machine determined breaths will be delivered and all breaths will be triggered (or assisted). The proportion of controlled and assisted breaths depends on the patient's level of alertness and respiratory drive [3, 4].

3.5.3 Proportional Assist Ventilation

In this mode of ventilation, the ventilator generates pressure support in proportion to the patient's spontaneous effort. Here, positive pressure is delivered by the ventilator in response to the flow generated by the patient in a way that an increased demand or increased effort from the patient leads to increased support from the ventilator in the form of flow assist and volume assist. Though this ventilatory strategy reduces patient ventilator asynchrony, studies have not shown significant benefit over the traditional BiPAP mode [2].

3.5.4 Volume Preset Ventilation/Volume Targeted Ventilation

The tidal volume or minute volume is preset instead of pressure. The ventilator delivers fixed tidal volume and inspiratory flow with each breath. Here a spontaneous mode cannot be set and there is poor leak compensation.

3.5.5 Volume Assured Pressure Support (VAPS)

In this hybrid mode of ventilation, a minimum level of minute ventilation is delivered by varying levels of pressure support provided by the ventilator. Named variably by different brands, various VAPS modes exist such as AVAPS and iVAPS where the clinician sets target minute ventilation or alveolar ventilation. The basic principle is that adjustments are made on inspiratory pressure to match the respiratory impedance and ensure the set minute ventilation. This modality has the advantages of provision of stable ventilation, better patient comfort, and fewer side effects such as gastric distension. Though there is a lack of studies in the acute setting, this approach is beneficial in patients who require long-term NIV who do not tolerate high inspiratory pressures [3, 4].

3.5.6 Adaptive Servo Ventilation

This is a form of non-invasive ventilatory therapy that provides variable IPAP to support inspiration when breathing amplitude is reduced, ensures sufficient respiration when respiratory effort is absent, and provides fixed or variable end-expiratory PAP (EPAP) to maintain upper airway patency.

SERVE-HF was the first multicentric randomized, controlled trial designed to investigate the effects of adding ASV to guideline-based medical management compared with medical management alone (control) on survival and cardiovascular

outcomes in patients with symptomatic HF [5]. The ability of ASV therapy to significantly reduce the apnea–hypopnea index (AHI) and improve oxygen saturation and other sleep-disordered breathing (SDB) parameters was confirmed in SERVE-HF.

3.6 Clinical Implications of NIV

3.6.1 Hypercapnic Respiratory Failure

In hypercapnic respiratory failure due to exacerbation of COPD or bronchiectasis, NIV has a good track record of success. Several trials have proven that use of NIV was associated with reduction in endotracheal intubation, increased survival, reduced complication rates, and decrease in length of hospital and ICU stay [2–4].

3.6.2 Obstructive Sleep Apnea

CPAP forms the mainstay of therapy in adults with OSA. The mechanism of continuous positive airway pressure involves maintenance of positive pharyngeal transmural pressure so that the intraluminal pressure exceeds the surrounding pressure, thereby preventing upper airway collapse. Another explanation is the possible stimulation of mechanoreceptors, which leads to an increase in airway tone [6].

3.6.3 Obesity Hypoventilation Syndrome

In patients presenting with obesity hypoventilation syndrome, NIV is the preferred mode of ventilatory support. Application of NIV overcomes the upper airway obstruction and also unloads the overburdened respiratory muscles. In 60–80% of OHS patients, application of optimal CPAP eliminates respiratory flow limitation and hypoxemia. In 20–50% of patients with OHS, hypoxemia and hypercapnia persists despite CPAP therapy. BiPAP is considered as the next step in management. Sleep laboratory titration is done to determine optimal IPAP and EPAP to ensure sufficient chest wall expansion and to optimize respiratory mechanics, respectively. Alveolar ventilation and nocturnal gas exchange are corrected by the same.

3.6.4 Central Sleep Apnea

CPAP is the preferred first-line therapy for symptomatic patients with hyperventilation-related central sleep apnea. CPAP reduces the frequency of central apneas, probably by preventing pharyngeal airway narrowing and occlusion during a central apnea.

The CANPAP trial demonstrated greater improvement in the Apnea–Hypopnea Index from baseline in patients of CSA treated with CPAP. They also had improved

mean nocturnal oxygen saturation (and longer 6-minute walk distance) compared with the control group. However there were no differences in quality of life, transplant-free survival, or hospitalizations [7].

3.6.5 Pulmonary Edema

In patients with cardiogenic pulmonary edema refractory to standard medical therapy, CPAP has an important role. Application of CPAP reduces pulmonary congestion, improves respiratory mechanics and cardiac output as evidenced by many studies and trials.

3.7 Limitations

1. Close monitoring of patient in high dependence unit is required.
2. When a patient shows any signs of respiratory distress or persistent hypoxia, the patient should be intubated and mechanically ventilated.
3. Patients may initially find it difficult to tolerate the pressure delivered and drying of the upper airway is a common problem.

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Noninvasive Ventilation-Leaks Compensation and Clinical Implications

4

Beatriz Ferraz, Bruno Gomes, and Antonio M. Esquinas

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4.1 Introduction

Noninvasive ventilation (NIV) has an important role in the treatment of acute and chronic respiratory failure. During the ventilatory treatment, it is crucial not only to monitor the effectiveness but also the presence of complications that would prevent achieving the setup pressure.

It is estimated that 31% of the patients under oronasal masks suffer from major air leaks and 80–100% under NIV suffer from minor air leaks [1].

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_4

NIV is a non-hermetic system; therefore, leaks are an expected component of the system. There are two types of air leaks: intentional and unintentional. The first are due to the presence of an exhalation system; the second occur between the mask and the face of the patient – these prevent the proper functioning of the NIV [2].

When NIV is started, the clinician should identify if unintentional air leaks are present or not. If they are present, the clinician should try to find their origin and correct them, as they can completely thwart an effective treatment.

4.1.1 Air Leaks

During NIV therapy, the intentional air leaks are an integrant part of the therapy due to the presence of the exhalation ports to avoid CO_2 rebreathing. On the other hand, unintentional leaks between the mask and the patient's face and through the mouth can be one of the most critical points to determine the efficacy of the therapy [2].

Leaks can arise from passive mouth opening ("primary leaks") or because of an increase in airway resistance ("secondary leaks" or "reflex obstruction during ventilation").

4.1.2 Mouth Leak

A mouth leak is a major issue when using a nasal face mask. They can easily exceed 0.6–1.0 L/s [3]. These leaks commonly arise from masseteric hypotonia or from the inability of the soft palate and mouth musculature to counteract the insufflation pressure [4]. This leak will affect three main elements of the ventilator synchrony—the inspiratory trigger, the pressurization capacity, and the end of support [3].

During sleep, air leaking is associated with arousals that will contribute to sleep fragmentation and decrease sleep quality [5]. At the same time, sleep disruption will decrease the response to hypercapnia and hypoxia—which will create a vicious cycle [3].

There are several options to reduce or neutralize leaks—chin traps, adhesive tapes, or other devices that can support the chin will ensure mouth closure [6]. Adding to the system humidifiers may help to reduce the nasal resistance, thus reducing the patient's propensity to open their mouth. If these devices are not enough to reduce mouth leaks it may be necessary to change to a face mask.

4.1.3 Internal Air Leaks

When high pressures are being used, 15–20 cm H_2O, the ventilator will overcome superior esophageal sphincter pressure [7]. It is estimated that aerophagia occurs in 5–40% of the patients under NIV—and the air is being distributed between the lungs and the stomach [4]. Some risk factors from the patient and from ventilatory

therapy will predispose to aerophagia such as low respiratory system compliance, high airway resistance, and short inspiratory time.

These result in gastric distention that will compress the lung—decreasing lung compliance and demanding a higher airway ventilation pressure. All factors will promote the occurrence of a vicious cycle [1].

In extreme cases, gastric insufflation may result in vomiting and inspiration of gastric content that ultimately can cause aspiration pneumonia.

Aerophagia can be an important complication that can remain unnoticed by most clinicians. To avoid this problem, pressures higher than 20–25 cmH_2O should not be used [1].

4.2 Air Leaks Clinical Implications

4.2.1 Volume vs Pressure Ventilators

Volume ventilators are not capable of compensating for the air leaks of NIV—because inspiratory flow and duration are fixed [8]. When there is an air leak, the volume that the patient will receive will be diminished [3]—this will be shown as an associated desaturation in the oximetric trace.

On the other hand, pressure support ventilators will compensate unintentional air leaks by increasing turbine speed—with an increase in inspiratory flow and sustaining target inspiratory pressure and time. They will be effective until a leak of 0.4 L/s [4].

Because it delivers a similar tidal volume at a lower peak inspiratory pressure, it will increase the air leaks between the mask and the patient's face, which will increase the discomfort and cause sleep disturbances, conjunctivitis, and throat dryness [1].

Large air leaks have an important impact on the efficiency of NIV therapy as they can decrease the O_2 delivered to the patient and unsettle the ventilator auto triggering capacity. The impact that air leaks have on arterial oxygen saturation is not well defined—some studies have shown that they have no impact [9] but Lujan et al. show that they have an important effect [8].

The fraction of inspired oxygen obtained by the patients will depend on the system capacity of mixing air supplied by the system and the oxygen given to the circuit, if there is a large air leak, a higher FiO_2 will be needed to deliver the same amount of oxygen to the patient.

Another potential clinical implication of increasing inspiratory time is the inversion of the ratio I:E; this will result in an inadequate expiratory time that will make CO_2 excretion difficult and increase air trapping. Furthermore, the patient will need to activate expiratory muscles to cycle into EPAP. All these factors contribute to patient discomfort and NIV intolerance [10].

Pressure-targeted ventilators will be a better option to compensate air leaks than volume-targeted; as they have a high and sustained maximal inspiratory flow capability, and adjustable I:E ratio so that the ratio inversion can be avoided.

4.2.2 Asynchrony

During invasive mechanical ventilation, the most frequent cause of asynchrony is associated with ineffective effort. In opposition, during NIV asynchronies are mostly associated with the presence of leaks around the interface between the patient and the mask—reflected as delayed cycling and auto-triggering [11].

Auto triggering will prevail in flow-triggered ventilators—in the presence of a large air leak the ventilator may interpret the decrease of the flow as the onset of the inspiration and start a new cycle [10].

On the other hand, in the presence of a major air leak, the ventilator may not detect the patient's inspiratory effort leading to a delayed trigger or a mandatory cycle.

In both cases, these alterations will result in interrupted respiratory cycles, increased respiratory effort, a higher number of arousals, and asynchrony—which thwart an effective ventilatory therapy [3].

Key Major Recommendations

- Intentional air leaks are an integrant part of NIV therapy. Large unintentional air leaks can be the cause of the intolerance of NIV.
- Mouth air leaks are common in patients using nasal interface masks—chin traps, adhesive tapes, and system humidifiers can help to reduce this leak.
- Large unintentional air leaks are the base of ventilatory asynchronies—delayed cycling and auto triggering—that will result in higher inspiratory effort and a higher number of arousals.
- Air leaks should always play a central role in the assessment of a patient under NIV—clinicians should try to minimize them without increasing the patient's discomfort.

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New Ventilatory Modes of Noninvasive Mechanical Ventilation

5

Umberto Vincenzi

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5.1 Positive + Negative Synchronized Ventilation

This is a new ventilatory modality and was created to try to overcome the limits found in mechanical ventilation, to increase clinical benefits, and to reduce side effects. The idea came from our long experience in the Intensive Respiratory Care in Foggia, with positive pressure ventilators and negative pressure ventilators (including Iron Lungs).

It consists in the combination and the synchronization of two pulmonary ventilators: the first, at positive pressure, acting directly in the airways (in noninvasive or invasive mode) and the second, at negative pressure, acting externally on the chest (always in noninvasive mode).

The characteristic of this type of ventilation is based on the concept of compensating, between the two machines, the intrathoracic pressures derived from the mechanical ventilatory act, the recruiting of a greater lung volume, the avoiding of

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_5

the risks due to barotrauma, the lowering of the ventilatory frequency and an increase in the possibility of intervention on the part of the operating doctor. With the exception of the ventilatory frequency, which is synchronized per se, a peculiar feature of this mode of ventilation is that both machines allow full control over their respective command panels in order to leave ample room for the intensivist doctor to find the best "driving pressure" to deliver.

The advantages but also the limitations of pulmonary ventilators have long been known.

As far as negative pressure ventilation is concerned, the advantages consist of compliance with normal respiratory physiology, noninvasiveness, a demonstrated reduction in the use of intubation [1], a low incidence of airway infections and pneumonia [2], the possibility of leaving the head completely free, the potential of providing ventilatory support, even intermittently, and the assistance of chronic patients even for very long periods of time [3–5]. In addition, the "pneumowrap" or "poncho" and of the "cuirass" offer the possibility to have arms and legs completely free.

Regarding the iron lung, the disadvantages are the size and weight of the ventilator (now reduced with the most recent machines, such as the "porta lung") and the impossibility of assisting the very obese. Disadvantages common to other negative pressure ventilators, such as the "cuirass" and/or the "poncho," are more evident with ventilation at high pressures, which consist in the possibility of apnea phenomena and occlusion of the upper airways, due, generally, to the posterior fall of the tongue and soft palate, especially when the patient is in the supine position. These symptoms are less evident if the patient is positioned with a trunk elevation of at least 30°, which is only possible with the "poncho" and "cuirass." Very rarely, if the patient is ventilated for a long time with high negative pressures, "ex vacuo" pulmonary edema may arise.

As for positive pressure ventilators (in a noninvasive way), the most obvious advantages are the small size of the equipment and the relative ease of use. Furthermore, in recent years, a proliferation of machine–patient interfaces of various sizes, materials and shapes, consisting of nasal, oro-nasal, total-face, and helmet masks, have helped facilitate noninvasive ventilation. Invasive ventilation, generally delivered by ventilators of greater size and complexity, has seen the birth of new interfaces such as tracheal tubes made of more flexible and ductile materials, tubes with suction probes for secretions, laryngeal masks made of softer material and tracheostomy tubes of various lengths and curves, all of which help to better adapt the interface to the patient's somatic characteristics. Additional advantages, which can be found with noninvasive positive pressure ventilation, are the reduction of infectious phenomena and pneumonia, the possibility of easily interrupting and resuming ventilation and the reduction of mortality compared to invasive mode. The major advantages of invasive positive pressure ventilation (IPPV) are greater safety in ensuring preset pressures, flows and volumes, little chance of air leakage in intubated or tracheostomized patients, greater ventilator–patient interaction and the ability to ventilate patients in deep sedation and/or curarized.

The disadvantages of noninvasive positive pressure ventilation are the easy possibility of air leaks, the onset of skin lesions from bedsores, the patient's intolerance to endure the interface, the possibility of inadequate ventilation and related problems from pulmonary barotraumas [6, 7]. The latter are mostly found in invasive positive pressure ventilation where high pressures have to be used. With invasive IPPV, episodes of encumbrance of the airways by bronchial secretions, phenomena of bronchial obstruction, and greater onset of pneumonia can occur more easily.

5.1.1 Ventilatory Mechanics

To obtain an inspiratory act one can intervene in two distinct and opposite ways.

1. Reducing the pressure at the level of the alveoli and sucking air from the external environment toward the alveoli, as occurs in normal physiological ventilation and in negative pressure ventilation (NPV).
2. Increasing the pressure in the upper airways and pushing air from the outside to the inside of the chest, as it occurs in positive pressure ventilation (PPV).

Therefore, the ventilatory mechanics of extrathoracic negative pressure ventilation, which simulates the normal muscular inspiratory act, differs substantially from positive pressure ventilation.

By observing, during inspiration, the transairway pressure ($P_{TA} = P_{awo} - P_A$), that is the difference in pressure between the one measured in the upper airways in contact with the outside and the alveolar pressure (P_A), it is possible to observe:

1. In the physiological ventilation of a healthy individual and in the ventilation determined by a negative pressure ventilator, a lowering of the pleural (P_{pl}) and alveolar (P_A) pressure compared to the one present in the upper airways (P_{awo}) with the consequent aspiration of air from the outside to the inside;
2. In positive pressure ventilation, on the other hand, an increase in pressure in the upper airways (P_{awo}) which, by pushing air from the outside to the inside of the chest, will cause an increase in alveolar pressure (P_A) and an expansion of the chest.

The expiratory act, in general, is a passive act with elastic return towards the initial positions of the chest and lungs.

When applying this new type of mechanical ventilation, it is necessary to bear in mind the variations in the forces and pressures caused by both ventilation modes.

In fact, Positive + Negative Synchronized Ventilation (PNSV) is based on the combination and synchronization of these two methods.

We know that a normal ventilatory act in a healthy individual is due to the contraction of the respiratory muscles which determine a force or pressure (P_{rs}) such as

to overcome the pressures present inside the lungs (P_L) and the rib cage (P_{cw}) according to the formula:

$$P_{rs} = P_L + P_{cw} \tag{5.1}$$

These pressures, which can also be expressed as resistances, consist of:

1. Elastic pressures of the thoraco-pulmonary system (P_{el}), which depend on the elastance of the entire system (E_{rs}) and increase with the expansion in lung volume,
2. Pressures necessary for the production of an air flow (P_{res}), which are influenced by the air resistance present within the bronchial tree and by the extent of the flow to be delivered,
3. Inertial pressures (P_{in}), which increase with the acceleration of the thoraco-pulmonary movement, that is, with the variation of the air flow in the unit of time. The inertial resistances are, however, negligible.

At this point the formula (5.1) can also be written in another way:

$$P_{rs} = P_{el} + P_{res} + P_{in} = \left(E_{rs} \times \Delta V\right) + \left(\text{Raw} \times V'\right) + P_{in} \tag{5.2}$$

This second formula is commonly called the Equation of Motion of the Respiratory System.

Considering the total elastance of the respiratory system (E_{rs}) as the sum of the lung elastance (E_L) and the elastance of the rib cage (E_{cw}), that is:

$$E_{rs} = E_L + E_{cw} \tag{5.3}$$

we can rewrite number 5.2 as follows:

$$P_{rs} = P_L + P_{cw} = \left(\left(E_L + E_{cw}\right) \times \Delta V\right) + \left(\text{Raw} \times V^{`}\right) + P_{in} \tag{5.4}$$

This subdivision of the elastance can be useful for us in analyzing the behavior of the two ventilators when they determine an inspiratory act. In fact, in the positive + negative synchronized ventilation (PNSV) the two machines, in a synchronous way, place their force of action on two opposite sides of the chest. The negative pressure ventilator (NPV) acts first on the rib cage, in which the E_{cw} is present, and then on the pleural space, the lung parenchyma and the airways, while the positive pressure ventilator (PPV) acts first on the airways and the lung parenchyma, in which the E_L is present, then on the pleural space and the rib cage. Both, of course, must overcome all the remaining forces present within the thorax to perform the ventilatory act. Analyzing what happens inside the airways and alveoli, we see that with the NPV there is an enlargement of the caliber of these structures by a concentric stretching toward the outside, while, with the PPV it is the pressure force of the air introduced into the thorax which first dilates the airways, then the alveoli and finally the rib cage. In the first case, the negative alveolar pressure draws air from the outside; in the second case, the positive pressure of the air introduced by the ventilator first dilates the airways and alveoli until the chest expands.

The combined use of both ventilators causes an increase in airway pressure created by the PPV to be counterbalanced by the negative pressure created by the

Table 5.1 Example of pressures detectable inside the chest, in the single moments of a ventilatory act, during a positive pressure ventilation (*P*), an external negative pressure ventilation (*N*) and a ventilation equivalent to the positive + negative pressure (*P* + *N*)

	End of expiration			Inspiration			End of inspiration			Expiration		
	P	*N*	***P + N***	*P*	*N*	***P + N***	*P*	*N*	***P + N***	*P*	*N*	***P + N***
$P_{TA} = P_{awo} - P_A$	0	0	**0**	−5	−5	**−10**	0	0	**0**	2	2	**4**
P_{awo}	0	0	**0**	10	0	**10**	10	0	**10**	4	0	**4**
$P_A = P_L + P_{pl}$	0	0	**0**	5	−5	**0**	10	0	**10**	6	2	**8**
$P_L = P_A - P_{pl}$	5	5	**10**	7	7	**14**	10	10	**20**	8	8	**16**
$P_{pl} = P_A - P_L$	−5	−5	**−10**	−2	−12	**−14**	0	−10	**−10**	−2	−6	**−8**
P_{cw}	−5	−5	**−10**	−2	−2	**−4**	0	0	**0**	−2	−2	**−4**
P_{neg}	0	0	**0**	0	−10	**−10**	0	−10	**−10**	0	−6	**−6**
$P_{rs} = P_L + P_{cw}$	0	0	**0**	5	5	**10**	10	10	**20**	6	6	**12**

NPV. We can verify this data in the example shown in Table 5.1, which shows, in the individual moments of a ventilatory act, the various intrathoracic pressures relating to positive pressure ventilation (*P*), extrathoracic negative ventilation (*N*), and to the positive + negative synchronized ventilation (*P* + *N*).

As you can see, the alveolar pressure (P_A), throughout the inspiratory act, has remained equal to zero. And this despite the fact that the forces or pressures of the two ventilators have literally been added together or the transairway pressure (P_{TA}), the transpulmonary pressure (P_L), and the pressure of the entire respiratory system (P_{rs}) have been doubled, expressing the necessary energy to mobilize the entire thoraco-pulmonary system. Of course, nothing prevents proportionally reducing the power of the individual ventilators, so as to equal the one expressed by a single ventilator, with the consequence of an overall reduction of all intrathoracic pressures while always maintaining the alveolar pressure at 0 during inspiration.

Maintaining the alveolar pressure at this value throughout the inspiratory act is an important fact because it is during inspiration, usually shorter than expiration, that the ventilator delivers all its power and can create lung damage resulting from pressure peaks. The exhalation is, normally, a passive act where the elastic return of the thoraco-pulmonary structures is exploited.

Therefore, being able to bring the alveolar pressure to zero during inspiration becomes a fundamental fact.

The idea of being able to combine positive pressure ventilation (NIPPV or IPPV) with extrathoracic negative pressure ventilation (NPV) was based precisely on these physiological considerations.

The greatest difficulty in creating this "positive + negative synchronized ventilation" (PNSV) consisted in being able to completely synchronize the two ventilators and in choosing which machine was the master and which one the server. Given the greater sensitivity of the flow triggers and the possibility of being able to detect volumes, pressures and flows in the patient circuit on the part of the positive pressure ventilator, this machine was chosen as the master and the extrathoracic negative pressure machine as the server. Both, however, kept all their commands with the exception of the duration and the ventilatory rate which was synchronized. From a

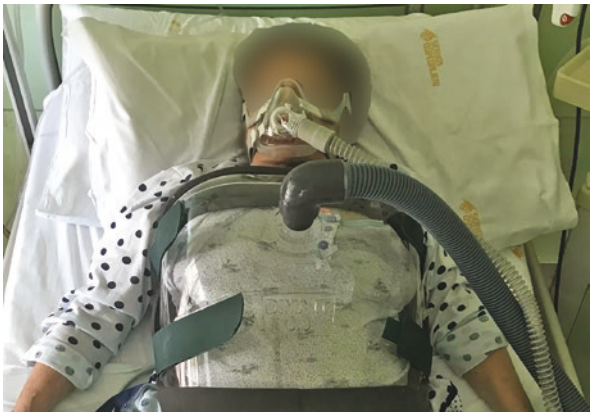

Fig. 5.1 Patient subjected to positive + negative synchronized ventilation (PNSV) where positive ventilation is delivered through a face mask, while external negative pressure ventilation is delivered through a cuirass

technological point of view, this PNSV ventilation was designed to work both in a completely noninvasive and in an invasive way. In the latter case, the positive pressure ventilator was connected to the patient with tracheal tubes or cannulas.

To verify the operational capacity and functionality of the PNSV, as well as the onset of any side effects, this new ventilatory modality was applied to eight patients suffering from severe respiratory failure resulting from COPD.

Figure 5.1 shows how the face mask of the positive pressure ventilator and the cuirass of the extrathoracic negative pressure ventilator are positioned on the patient undergoing PNSV.

The PNSV was compared, for each individual patient, to both NIPPV and NPV, administered individually, on different days and in a random manner.

The evaluation of this study and a more detailed analysis of this new ventilatory modality (PNSV) was published by Vincenzi U. in 2021. [8].

In this study, the pressures delivered by individual ventilators were those normally used to treat each patient prior to the study. After 1 h of ventilatory treatment with the three ventilatory modalities (NIPV, NPV and PNSV), it was clearly visible that the PNSV showed very significant improvements in pH ($p = 0.0008$) and in $PaCO_2$ ($p = 0.002$), while less significant ($p = 0.02$) was the change in $PaCO_2$ with NIPPV alone.

In reality, with the PNSV, while keeping the settings of both machines unchanged, during inspiration the alveolar pressure (P_A) was zeroed, while the transairway pressure (P_{TA}) and the transpulmonary pressure (P_L) were doubled, being the sum of the pressures delivered by each ventilator. Therefore, it was logical to expect such an evident improvement in blood gas analysis. However, simply due to the balancing of the pressures inside the chest, obtained from the action of the two machines, there were no side effects, changes in blood pressure or heart rate.

These encouraging data prompted us to test PNSV, with invasive ventilation, also on intubated or tracheostomized patients, inpatients in our ICU. However, with the onset of COVID-19, the study was interrupted and it was not possible to make statistical calculations. In any case, the possibility of using PNSV in these patients has been demonstrated, with benefits comparable to noninvasive ventilation.

An important aspect to underline is that all patients were awake and cooperative enough. This made it possible to use the "pressure support" mode on the positive pressure ventilator with the possibility for the patient to activate the inspiratory "trigger" and, consequently, also the ventilatory rate. Exhalation occurred when the positive pressure ventilator reached the set level of expiratory "trigger" or, voluntarily, by the patients themselves. The entire ventilatory act was completely synchronized between the two machines. The pressure delivered by the negative pressure ventilator was equal to the one set on the positive pressure ventilator to counterbalance the intrathoracic pressures.

During the application of PNSV, pulmonary mechanics were also monitored by electrical impedance tomography (EIT) using a Draeger PulmoVista® 500 device.

Comparing the images detected with the application of PNSV (Fig. 5.3) compared to those detected with only positive pressure ventilation (Fig. 5.2), it was possible to find an evident reduction in the ventilatory rate, but also an evident increase in the surface of the ventilated lung, i.e., a greater alveolar recruitment.

This, of course, explained the remarkable success, in terms of blood gas analysis, achieved by the PNSV in this study.

The first fact that is immediately evident and present in almost all the individuals examined is the reduction in the spontaneous ventilatory rate during PNSV. This data is easily explained by the greater overall ventilated lung volume, due to the application of a force (P_{TA} or P_L or P_{rs}) which, compared to that of a single ventilator, had literally doubled and significantly improved gas exchange. Patients

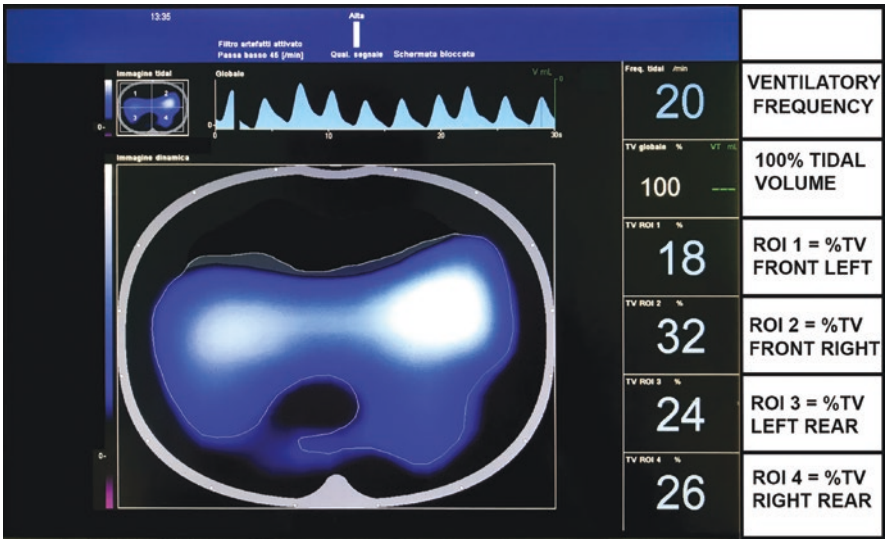

Fig. 5.2 Electrical impedance tomography (EIT) detected in a patient receiving positive pressure ventilation only. In the column on the right you can find the percentages of the tidal volume values corresponding to the following quadrants: ROI 1 = front left quadrant; ROI 2 = right anterior quadrant; ROI 3 = left rear quadrant; ROI 4 = right rear quadrant

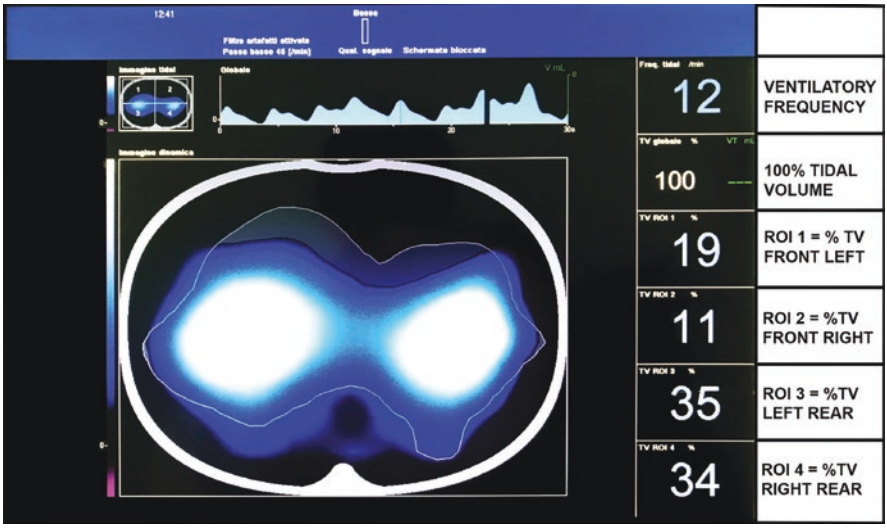

Fig. 5.3 Electrical impedance tomography (EIT) detected in the same patient undergoing synchronized positive + negative ventilation. Note the reduction in ventilatory rate and an increase in pulmonary recruitment in the posterior areas of the thorax where the values of ROI 3 and ROI 4 have increased

ventilated in "pressure support," when faced with an improvement in their respiratory insufficiency, instinctively reduced the ventilatory rate, adjusting it to their metabolic respiratory needs.

The increase in the pulmonary alveolar surface due to this new ventilatory modality, observable in Fig. 5.3 also at the level of the posterior portion of the thorax (ROI 3 and ROI 4), explains the greater recruitment of the lungs and, therefore, the greater exchange capacity of respiratory gases. Furthermore, the same increase in the surface and in the alveolar–capillary exchange time is favored by a prolongation of the expiratory time due to the slowing of the ventilatory rate.

This is of greater importance when the patient is of higher severity and is in the supine position where, as we know, alveolar recruitment is very difficult.

A pathology we can refer to is ARDS, where we know the great number of difficulties encountered in finding the right "driving pressure," since the ventilable parenchyma could be greatly reduced (the so-called baby lung) and inhomogeneous [9]. Hence, the easy onset of important local stress and pulmonary tension [10].

The difficulties due to this pathology require great care in setting the right "driving pressure," that is, in establishing pressures, flows, volumes, and frequencies to be used, and in setting a PEEP based on the measurement of the so-called stress-index [11].

In addition, the danger of barotrauma is higher in the treatment of patients suffering from ARDS due to COVID-19 [12], with increased difficulty in obtaining sufficient lung recruitability [13].

The control of the pressures delivered by the ventilator is very important when you are faced with an inhomogeneous lung parenchyma, in which areas with

different time constants (τ) occur, some of which are subject to hyperventilation or to significant increases in pressure [14]. Barotrauma is always possible when only a positive pressure ventilator is used, while, in my opinion, a PNSV, where there is a reduction or zeroing of alveolar and airway pressures, a recruitment of previously unventilated areas and a slowing of the ventilatory rate, would offer an extra weapon in the treatment of this pathology. It is logical that, in this case, the ventilatory pressures being used, when added together, be equivalent to those of a single positive pressure ventilator, but with the benefit of an evident greater intrathoracic pressure balance due to the careful regulation of the two ventilators.

We should also bear in mind that with the PNSV, with the exception of the ventilation frequency which is synchronized, it is possible to adjust, on each machine, the flows, volumes and pressures to be delivered and to maintain all the ventilation modes of the individual machines.

Furthermore, the PNSV could, in the near future, be integrated into a system that sees an external negative pressure machine synchronized with a positive pressure ventilator using neurally adjusted ventilatory assist (NAVA) [15]. The sensitivity of the inspiratory and expiratory neuronal triggers and the early detection of the PEEPi level given by NAVA, would allow a rapid synchronization between the patient and the machines and an earlier and better adaptation of the patient to the ventilatory treatment.

A still new aspect to explore is that concerning cardio-circulatory hemodynamics and heart–lung interaction in the course of this new ventilatory modality.

We know that positive pressure ventilation can lead to a reduction in venous return (VR), stroke volume (SV), and cardiac output (CO) [16, 17], while the effects of NPV are less known.

Some studies performed with negative extrathoracic pressure have shown that the stroke volume index (SVI) and cardiac index (CI) were significantly increased [18, 19]. Other authors have shown that biphasic cuirass ventilation allowed a reduction in pulmonary mean arterial pressure (mPAP), an improvement in pulmonary artery occlusion pressure (PAOP), cardiac index (CI), and serum NT-proBNP levels compared with baseline [20].

At this point it can be assumed, even if everything has yet to be demonstrated, that the positive + negative synchronized ventilation (PNSV) can allow a greater balance in intrathoracic pressures and ensure that the possible negative effects of one mode can be compensated for by the other ventilatory mode.

5.2 Intermittent Abdominal Pressure Ventilation (IAPV)

This type of ventilation has been designed to offer patients, with neuromuscular weakness and diaphragmatic paralysis, conditions present in all individuals suffering from neuromuscular pathologies, the possibility to perform a valid expiratory act and along with this, the capacity to speak as well.

This ventilatory mode, with intermittent abdominal pressure, is a modern reinterpretation of the old “Pneumobelt.” This device, in turn, was inspired by the Bragg-Paul pulsator conceived in 1935 which, however, acted on the chest and not on the

abdomen. The ventilatory efficacy of the "Pneumobelt" was demonstrated in numerous studies concerning the daytime treatment of neuromuscular patients, but, following the diffusion of noninvasive mechanical ventilation through masks applied to the face and invasive ventilation through tracheostomy, which supported the patient for the whole day, it had a sharp decline until it disappeared altogether.

With IAPV, which features innovative electronic equipment and a specific software, the possibility of interfacing with the patient has definitely improved. The principle of IAPV is based on the study of these neurological patients, who, if placed in a sitting or semi-sitting position, having poor strength in the abdominal muscles and diaphragm, do not have the necessary power to produce a valid exhalation and, with it, an impossibility of the patient to be able to make sounds.

By applying the IAPV in a neurological individual in a sitting position, after an inhalation that sees, by gravity, a downward fall of the diaphragm, we witness the swelling of a belt placed around the abdomen with an increase in intra-abdominal pressure and, with it, a valid exhalation. The device used (LunaBelt), by means of special software, allows to detect the individual phases of the ventilatory acts and to intervene in the expiratory phase, adapting to the patient's needs. Abdominal pressures are adjustable not only in volume, but also in the delivery time of the air. Furthermore, the IAPV allows the individual with diaphragmatic paralysis to have sufficient expiratory time to formulate complete sentences and actively relate to other people. This type of noninvasive extra-thoracic ventilation does not use masks or other devices to be placed on the patient's face, and thus it does not produce bedsores or skin lesions, improving the quality of life.

The efficiency depends on the surface of the chest and abdomen covered by the pneumatic band and the inclination of the patient's trunk, having its maximum effectiveness in a vertical position or with an inclination of a few degrees (30°–45°) Trained patients can learn to close the glottis during the expiratory act and then suddenly open it in order to make an effective cough, taking advantage of the increase in the created chest pressure. Moreover, having the head completely free from facial prostheses, not only are patients able to speak freely but they also retain the olfactory and gustatory functions and a better spatial visual orientation.

A limit to this application may be with very obese or severely scoliotic individuals.

In any case, IAPV is a valid alternative to other ventilatory modes when the use of daytime ventilatory support is required, and it is gaining a prominent place in the world of noninvasive mechanical ventilation.

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Ventilators for Noninvasive Mechanical Ventilation: Theory and Technology

6

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6.1 Introduction

The use of positive-pressure noninvasive ventilation (NIV) to treat both acute respiratory failure (ARF) and chronic respiratory failure (CRF) has been tremendously expanded in the past three decades in the spectrum of diseases that can be successfully managed, as well as in its field of application in terms of the achievable goals. This is due to the advantages of choosing NIV, when feasible, over conventional

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_6

invasive ventilation in terms of avoidance of artificial airway-related complications (i.e., VAP, VIDD, VILI, weaning failure). Noninvasive respiratory support modalities (NIV, CPAP, and high flow nasal cannula—HFNC) represented the first choice therapy in the recent COVID-19 pandemics [1–4].

The choice of a ventilator is a "crucial ingredient" to achieve the success of NIV in acute and chronic settings. Technical properties of the ventilator (i.e., type of circuit, efficiency of trigger and cycling systems, speed of pressurization, air leak compensation, CO_2 rebreathing, blender for O_2, monitoring accuracy, and transportability) play a key role in reaching the goals of mechanical ventilation in ARF (by unloading respiratory muscles, improving gas exchange) and CRF (by improving gas exchange, sleep quality, quality of life, and survival) [5–7].

With the growing implementation of NIV, a wide range of ventilators have been produced to deliver noninvasive support both in randomized controlled trials and in real-life scenarios. This chapter will examine the key points concerning the technology of ventilators for NIV and their main impact in the clinical practice.

6.2 Classification of Ventilators

Even if any ventilator can theoretically be used to deliver NIV both in ARF and in CRF, the chance of targeting a successful application is greater if the ventilator is able to (a) adequately compensate for unintentional air leaks; (b) provide an accurate continuous monitoring of patient–ventilator synchrony and ventilatory parameters due to a display of pressure–flow–volume waveforms and software algorithms; (c) adjust the fraction of inspired oxygen (FiO_2) with a blender to assure stable oxygenation in more demanding patients; and (d) adjust inspiratory trigger sensitivity and expiratory cycling, inspiratory pressurization and other parameters as an aid to prevent and solve patient–ventilator asynchronies and meet changeable patient ventilator needs [5–7].

Ventilators may be "arbitrarily" classified into four categories, whose features are briefly summarized in Table 6.1 [5–7].

1. *Volume-controlled home ventilators* were the first machines used to deliver NIV, mostly for domiciliary care; even if well equipped with alarms, monitoring system, and inner battery, their usefulness to apply NIV is largely limited by their inability to compensate for air leaks. Consequently, their NIV application today has practically disappeared, often restricted to very select home-based cases of neuromuscular disorders (i.e., air stacking function, mouth-piece ventilation); also their role as a safe invasive support of ventilatory-dependent tracheostomized patients has been taken over by hybrid modalities of ventilation.
2. *Bilevel ventilators* evolved from home-based continuous positive airway pressure (CPAP) devices and derive their name from their capability of supporting 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

Table 6.1 Technological features of different categories of Ventilators for NIV

	CO_2 rebreathing	Blender O_2	Adjustment of trigger and cycling	Modality of NIV	Monitoring	Air leak compensation	Alarms	Battery	Transportability	Costs
Volume-target ventilators	–	No	+	Volumetric	+	–	++	Yes	++	++
Older Bilevel ventilators	+++	No	–	Pressometric	–	+++	–	No	+++	+
Newer Bilevel ventilators	+/–	No	+++	Pressometric, Volumetric, Hybrid	++	+++	++	Yes	+++	++
Intermediate ventilators	+/–	Some	++	Pressometric, Volumetric, Hybrid	++	++	+++	Yes	++	++
Conventional ICU ventilators	–	Yes	++	Pressometric and Volumetric	+++	–	+++	Yes	+/–	+++
New ICU ventilators	–	Yes	+++	Pressometric and Volumetric	+++	+++	+++	Yes	+/–	+++

designed to deliver NIV thanks to their efficiency in compensating air leaks. Due to their easy handling, transportability, lack of alarms and monitoring system, and low cost, the first generation of bilevel ventilators match the needs for nocturnal NIV in chronic patients with a large ventilatory autonomy. However, traditional bilevel ventilators showed important technical limitations (risk of CO_2 rebreathing in single-limb circuit machines with inefficient dispersion expiratory devices; inadequate monitoring; lack of alarms and O_2-blending, limited generating pressures; poor performance in response to the increase in respiratory system load; lack of battery), which have been largely overcome by more advanced and sophisticated machines that have been introduced in the commercial market over the past decade. These newer generations of bilevel ventilators have gained popularity in clinical practice to apply acute NIV, especially in higher levels of care settings, as well as to invasively support ventilatory-dependent chronic patients at home. These new devices are capable of delivering a large range of more advanced pressometric modalities of ventilation, including hybrid modes such as volume-target pressure-preset ventilation (i.e., volume-assured pressure support ventilation—VAPS), which could dynamically change the level of pressure assistance depending on the measured tidal volume according to different algorithms. More recently, some ventilators have algorithms to dynamically change EPAP level according to the degree of patency of upper airway aiming at dynamically managing obstructive events in patients with coexisting sleep disordered breathing disorders. Despite their physiological benefits, the real clinical advantages of these hybrid modes must still be demonstrated in comparison to the traditional pressometric modalities. Due to the expanding indications of acute HFNC in hypoxemic and, even to a lesser extent, in hypercapnic patients, both alone or in combination with NIV, newer bilevel ventilators have implemented this type of respiratory support together with NIV modalities with the possibility of switching the same patient from NIV to HFNC by using the same device. Moreover, some patients with residual persistent respiratory failure may be potential candidates to be adapted to home-based HFNC devices.

3. *ICU ventilators* were initially designed to deliver invasive ventilation through a cuffed endotracheal tube or tracheal cannula to either ICU patients or to allow surgery procedures in the theatre room. Despite a good monitoring of ventilatory parameters and of flow–pressure–volume waves as well as a fine setting of FiO_2 and of ventilation, performance of conventional ICU ventilators to deliver NIV was poor because they were not able to cope with leaks. Therefore, a new generation of ICU ventilators have been developed in the past decades to efficiently assist acute patients with NIV, using the option of leak compensation (i.e., "NIV module"), which allows a partial or total correction of air leak-induced patient–ventilator asynchrony, even if with a large inter-machine variability. Newer ICU ventilators have been up-graded with modules for delivering HFNC as well as NIV modalities in acute critically ill patients [5, 7].
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). Hybrid modes of ventilation such as VAPS are available in the great majority of newer intermediate ventilators. These new machines represent a good choice to support complex acute and chronic respiratory patients managed in different settings (i.e., ICU, respiratory high dependency care units, emergency department, weaning units, nursing home residencies, home) as well as to safely transport critically ill patients both within an intra-hospital (i.e., radiology, endoscopy, ICU, operating room) and extra-hospital context. Similar to newer ICU ventilators, more recent versions of intermediate/hybrid devices also have built-in modules and circuits for switching from NIV modalities to HFNC.

6.3 Technologic Issues

(Table 6.2) [7].

6.3.1 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 types of intermediate ventilators are provided with either a compressor or an electrically supplied turbine pump to pressurize room air, which may not assure a constant stability in the

Table 6.2 Technological performance of ventilators for NIV

Source of gases	-Compressed medical gases (High pressure source) -Compressed or electrically supplied (turbine pump)
Oxygen supply	- Blender (High pressure source) - Supplementation at ventilator-circuit-mask (Low pressure source)
Circuit	-Double limb (non vented) -Single limb with anti-rebreathing valve (non vented) -Single limb with exhalation system at circuit or mask (vented)
Inspiratory trigger	- Sensitivity changeable or not - Pressure or flow or volume dependent ; mixed mechanism
Expiratory cycle	- Flow or time dependent - Automatically set
Pressurisation	- Speedy changeable or not
Back-up rate	- Frequency Changeable or not
Leak compensation	- Activated in ventilated with NIV module

(continued)

Table 6.2 (continued)

Humidification	-Heated systems -Heat-moisture exchangers -Hybrid systems (i.e Booster)
Battery	-Absent -Available (internal or additional external)
Alarms	-Absent, minimal (disconnection) , advanced
Monitoring system	-Inspiratory numeric parameters -Inspiratory and expiratory numeric parameter -Flow, volume and pressure curves
Modes of ventilation	-Spontaneous modes (PSV, bilevel S-ST-T) -Mandatory modes (PCV, VCV) -Volume-guaranteed or hybrid modes (VAPS)
Interface	-Nasal, full-face or total-face mask -Helmet -Mouth-piece -Hybrids (nasal pillow and oral mask)

Notes. PSV Pressure support ventilation, PCV: pressure control ventilation; VCV: volume controlled ventilation
VAPS: volume-assured pressure support; S: spontaneous; T: timed; ST: spontaneous-timed;

pressurization, especially in more demanding patients (i.e., high minute ventilation). These machines do not usually have a blender; therefore, O_2 is delivered from low-pressure sources and the FiO_2 during NIV 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 enrichment, breathing pattern, and amount of unintentional leaks. 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 [8]. Assuring a pre-set, precise FiO_2 is a great help in managing acute hospitalized patients suffering from either severe hypoxemia (i.e., request of high FiO_2s) or hypercapnic decompensated CRF (i.e., avoidance of CO_2 rebound due to inappropriately high O_2 supplementation) [5–7].

6.3.2 Circuit

Ventilators with a single-limb circuit offer two possibilities of CO_2 wash-out depending on the type of exhalation system: (1) intentional leak or "vented circuit" and (2) anti-rebreathing expiratory valve or "non-vented circuit" (7). The original Respironics BiPAP and the following bilevel ventilators were provided with a "vented" single-limb circuit; with this device, the exhalation of expired air occurs through the whisper swivel—a fixed resistance, variable flow leak port situated either in the circuit proximally to the interface or within the interface itself. According to the first physiologic bench studies, this type of equipment may theoretically expose the patient to the risk of CO_2 rebreathing, which may be detrimental

when treating hypercapnic patients [5–7]. 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 mask with the exhalation port in the circuit and a total face mask with the exhalation port inside. The options that the clinician has for preventing this risk are: (a) keep the conventional whisper swivel and apply high EPAP levels, such as 8 cm H_2O, which may therefore be poorly tolerated or detrimentally increase dynamic hyperinflation in obstructed patients; (b) use of specific devices such as the plateau exhalation valve, which thanks to its diaphragm limits air leaks during inspiration and allows a unidirectional air flow during expiration. However, it should be remarked that the clinical impact of the potential risk of CO_2 rebreathing using ventilators equipped with a vented single-limb circuit is probably overestimated, especially with newer machines equipped with highly performing turbine which are able to generate high flow rates (>60 L/min) [5–7].

6.3.3 Pressurization rate or inspiratory flow

It is known that severely dyspneic COPD patients cope better with higher inspiratory flow and neuromuscular patients do better with lower inspiratory flow (i.e., pressure rise time of 0.05–0.1 s and 0.3–0.4 s, respectively) [7]. In the first generation bilevel ventilators, this parameter is unchangeable; conversely in the following developed and more advanced bilevel ventilators, as well as in the intermediate and ICU ventilators, the rise time may be set with a potentially 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 NIV tolerance even though the diaphragmatic effort was greatly 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 a good tolerance and to minimize unintentional air leaks, keeping a relatively high pressurization rate [5–7].

6.3.4 Back-Up Respiratory Rate

First generation bilevel ventilators do not have the option of setting a back-up 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 back-up f. This option is particularly advantageous in sicker patients with unstable respiratory drive, as it prevents the phenomena of apneas and of periodic breathing such as Cheyne–Stokes in chronic heart failure. Back-up f may also be useful when a cautious sedation is administered to improve patient compliance to NIV in expert intensive acute care settings [7].

6.3.5 Air Leak Compensation

Due to the intrinsic properties of NIV, air leaks are almost a constant feature of this ventilator technique and when excessive may interfere with patient's comfort, patient–ventilator synchrony and, eventually, the likelihood of success both in acute and chronic patients [5–7, 9]. During NIV delivered by ventilators equipped with a vented single-limb circuit, we have to consider both intentional (due to the presence of the exhalation system) and unintentional leaks (throughout the mouth during nasal ventilation and/or between the interface and the face with both nasal and oronasal mask) [7]. Excessive unintentional leaks are strongly correlated with NIV failure as a consequence of alveolar hypoventilation, discomfort, patient–ventilator asynchronies, and sleep fragmentation. On the other hand, tightly fitting headgear straps to reduce air leaks should be avoided because this may reduce the patient's tolerance and predispose them to skin damage [7]. Consequently, it is important to have a ventilator capable of largely compensating air leaks well during NIV. Air leak compensation is greater during use of bilevel than volume-target home ventilators; in the latter, a fall in tidal volume (VT) > 50% is more likely. Conversely, the fall in VT is <10% and in IPAP <8% with bilevel ventilators during leaks, owing to an adequate increase in the inspiratory flow and in the T_i. However, the effects of air leaks during NIV are more complex than the simple fall in IPAP and VT, due to the role played by further variables such as T_i, expiratory cycling, and inspiratory trigger sensitivity. Mathematical models that analyze the complex interaction between unintentional air leaks and PSV during obstructive conditions and their potential clinical implication have been recently implemented [5–7]. Even though all bilevel ventilators and most intermediate and newer ICU ventilators equipped with NIV modes were able to compensate air leaks, their performance was not uniform [7]. Therefore, adaptation of the same patient to a different ventilator (i.e., switching from ICU/intermediate ventilator to bilevel ventilator) may be challenging for the heterogeneous properties of the machines.

6.3.6 Battery

For both acute and chronic patients with a high level of dependency on NIV, a battery power source is mandatory in case of electricity supply failure at home and in case the patient must be transferred within the same hospital or to another hospital. However, clinicians must be aware that battery duration differs greatly among portable ventilators and may be shorter than that reported in the operator's manual. Moreover, portable ventilator battery duration is affected by the setting, lung impedance characteristics, and the ventilator features [7]. In alternative or in addition to internal batteries for NIV ventilators, it is also possible to use external batteries which guarantee a prolonged autonomy of the ventilator in case of electricity unavailability. It must be considered that external batteries may make the ventilator too heavy for transportation. For high risk demanding patients (i.e., advanced neuromuscular disorders with NIV dependence >12 h a day), prescribing a back-up ventilator is highly recommended [7].

6.3.7 Alarm and Monitoring System

The need for sophisticated alarms and monitoring systems during NIV is essentially based on clinical practice, since up to now there has been no scientific evidence of their clinical utility. In the acute context, the safe management of critically ill patients at risk of NIV failure requires the identification of an expert and highly monitored setting where the switch from NIV to invasive ventilation is quickly available. Concerning patients adapted to home ventilation, care must be taken when setting the alarms on the ventilator to ensure that they will only function when a genuine need arises because frequent spurious alarms can significantly disturb sleep and adherence to the scheduled therapy of the patient. The prototype of Respironics BiPAP did not have an alarm or monitoring features, with an advantage in costs and transportability during 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, VT, f, FiO_2, leaks) and monitoring graph (i.e., flow, VT, pressure curves) may be useful in terms of safety and in improving patient–ventilator interaction [4, 5]. Conversely, elaborate and overly sensitive alarms may be counter-productive in the clinical practice since they frequently indicate very minor air leaks during NIV [7].

In the context of patient–ventilator interaction, even if some asynchronies may be suspected at bedside by a careful observation of chest and abdomen movements during NIV, the interpretation of ventilator curves is helpful to noninvasively assess patient–ventilator interaction (Fig. 6.1) [9, 10]. The correct identification of the type of asynchrony during NIV is helpful in choosing the best strategy to improve the

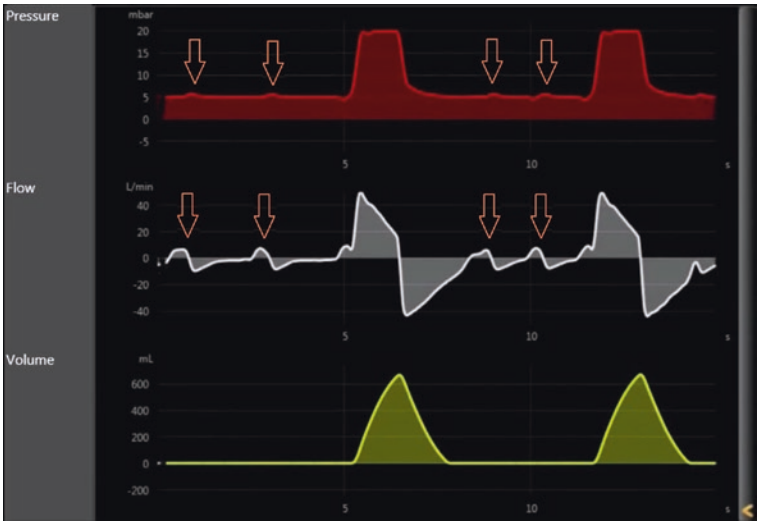

Fig. 6.1 A typical patient-ventilator asynchrony pattern due to ineffective effort during NIV delivered in pressure support mode that may be easily suspected looking at the flow and pressure curves built in advanced ventilators

degree of patient–ventilator interactions (e.g., choose a different interface to reduce leaks and/or change the setting of the ventilator). A randomized controlled trial clearly demonstrated that a curve-driven setting of the ventilator is capable of achieving a correction of acidosis in a shorter time as compared to a traditional setting based only on numeric ventilator monitoring in severe COPD exacerbations [11].

The key parameters to be monitored during NIV are expiratory VT and f, the determinants of the breathing pattern. Concerning the former, excessive unintentional air leaks may cause a significant discrepancy between inspiratory and expiratory VT. Expiratory VT assessment is adequate with ventilators equipped with a dual-limb circuit where expiratory VT is obtained by subtracting leaks from inspiratory VT. With these ventilators, monitoring expiratory VT is more reliable with machines that take measurements at the level of the expiratory branch of the Y-tube than with those which measure at the inlet of the expiratory tube into the ventilator. Behavior of ventilators with a single limb depends on the type of exhalation system. In the presence of an anti-rebreathing valve built in a non-vented circuit, the ventilator gives an inspiratory VT value that is always an actual measurement of volume delivered by the ventilator itself. The values are computed at the beginning of inspiration, so that in the presence of unintentional leaks, the leaks are considered as part of the delivered inspiratory VT. In this case, the ventilators are not able to accurately measure the exhaled VT but could only to provide an estimation of leaks and of expiratory VT. In the presence of vented circuits or circuits connected to vented masks, the ventilator provides an estimation of expiratory VT that should be the real volume inspired by the patient without the intentional leaks. In this case, the ventilator is able to provide an accurate estimation of leaks. The leak value displayed may be the total value of leaks (intentional + unintentional) or only the unintentional leaks according to the algorithm used by the ventilator. Unfortunately, for a very large leak, its estimation, as well as the estimation of expiratory VT, may become unreliable (Fig. 6.2) [11].

It should be remarked that with a single limb circuit non-vented ventilator, there is a risk of under-assistance of a patient under volume-target PSV modalities in case of excessive air leaks [12].

Concerning f assessment during NIV, there might be a gap between the rate of ventilator-assisted and patient-triggered breaths. Looking at the ventilator-f, ineffective efforts and auto-triggering may cause, respectively, under-estimation and over-estimation of the *patient's effective f*. [10].

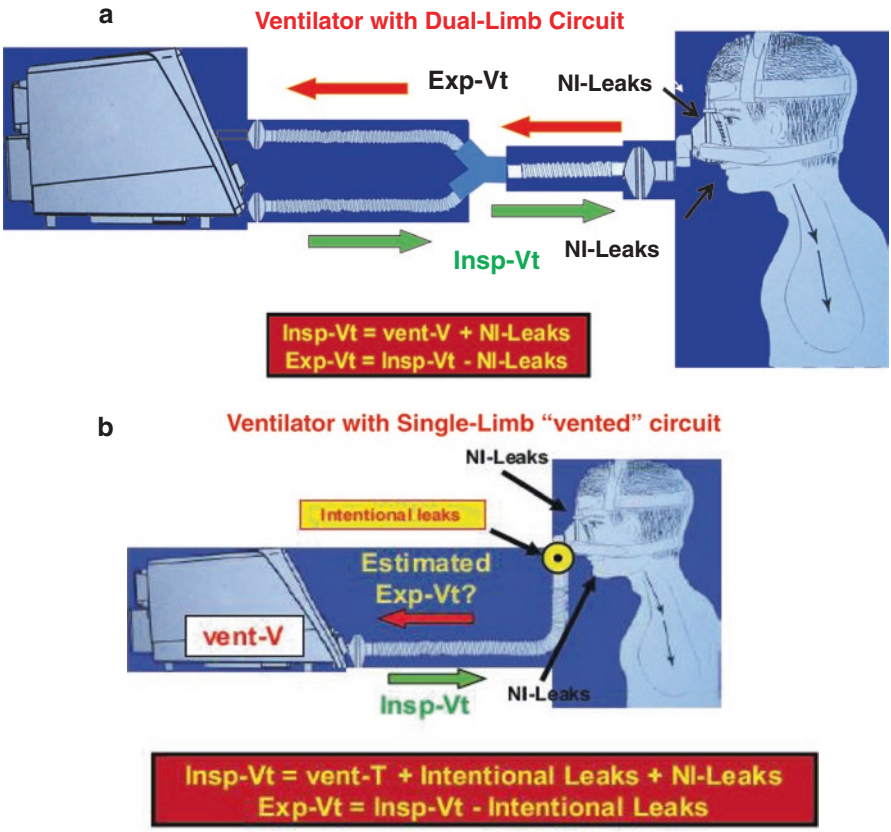

Fig. 6.2 Differences in Vt monitoring during NIV delivered by means of ventilators equipped with double-limb circuit (**a**), single-limb circuit provide with a "non-vented system" (**b**) or single-limb circuit with a "vented exhalation device" (**c**)

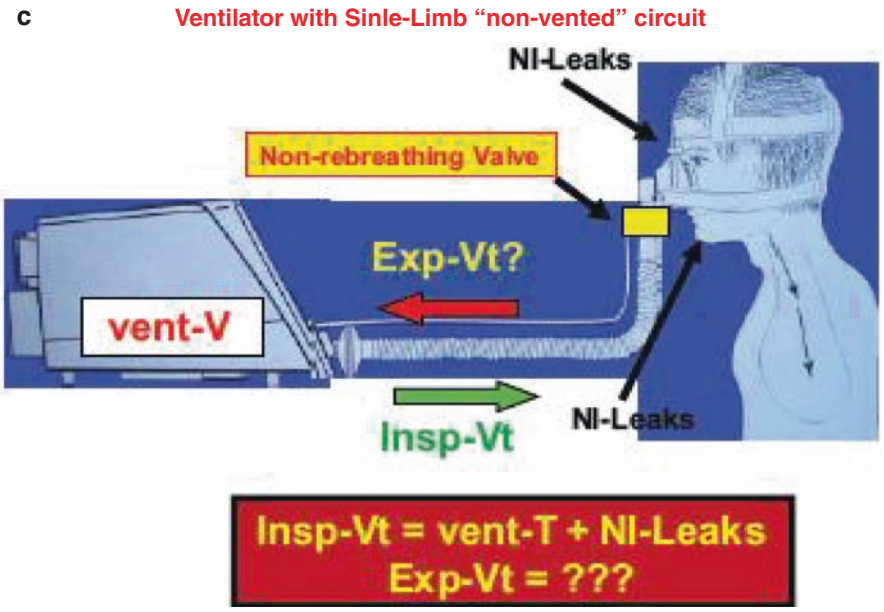

Fig. 6.2 (continued)

6.4 Controversial Issues

Due to the huge gap between the increasing number of commercially available, newer ventilators and their physiologic and clinical careful evaluation, we do not have published data about several sophisticated ventilators routinely used in the clinical practice. A part from *very few studies "*in vivo,*" the majority of the published data about the performance of these newer ventilators are based on studies "*in vitro*" conducted on lung models*. Therefore, some doubts remain about the real clinical significance of the technical differences observed in the bench studies of various types of ventilators. Consequently, every extrapolation of these experimental data to the clinical ground 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 must be applied to acute patients under NIV in the presence of excessive unintentional leaks.

Based on published data, despite a wide heterogeneity found in each category of machines, several bilevel ventilators demonstrated better performance than several ICU ventilators. However, no study has shown greater NIV clinical success for either type of ventilator, both in acute and chronic settings. Nevertheless, some points should be clear when clinicians choose a ventilator:

- Since excessive air leaks are correlated with treatment failure, the clinician should choose *ventilators designed for NIV with leak compensation capability*

(i.e., bilevel, some intermediate and new ICU ventilators). In addition, the chance to set several parameters and look at flow-volume-pressure waveforms with newer ventilators may be helpful in improving patient–ventilator synchrony, comfort, gas exchange, and clinical outcome.

- The choice of ventilator should be tailored to the *pathophysiology and the severity of acute and chronic respiratory failure*. For hypoxemic patients in acute settings, ventilators with an O_2 blender are recommended. For patients with hypercapnia, ventilators with a dual-limb circuit have an advantage in lowering $PaCO_2$. In patients with mild COPD exacerbation, the use of home ventilators may be appropriate, particularly if the patient is already on home NIV; by contrast, patients with life-threatening ARF at risk of intubation should be treated with more sophisticated machines. In chronic settings, conditions where respiratory drive is good (i.e., COPD) could benefit from a simple ventilator that works in a spontaneous mode, whereas conditions where respiratory drive is impaired require mandatory back up rate. Conversely, for patients with fast-progressing neuromuscular diseases, a more sophisticated ventilator with adequate monitoring equipment and an inner battery is recommended. The clinical superiority of new "hybrid modes" of NIV (i.e., VAPS) over the traditional pressometric modes must still be demonstrated both in acute and chronic settings, considering the potential detrimental effects of this modality in excessive air leaks.
- The selection of a ventilator should also take in account *costs and staff experience*. The more sophisticated a ventilator is, the longer 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 NIV setup with positive repercussions in costs and workload.
- Clinicians should be aware of the *multiple interferences of the accessories for NIV* (interfaces, exhalation systems, pressure settings, and humidification devices) with the performance of the different categories of ventilators. Take, for example, the issue of humidification during NIV: 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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Continuous Positive Airway Pressure (CPAP)

7

Giovanni Ferrari, Elena Rindone, Roberta Di Tria, and Roberto Prota

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7.1 Introduction

Continuous positive airway pressure (CPAP) refers to application of positive pressure into the airways (above the atmospheric pressure), through an interface, during the entire breathing cycle. CPAP can be applied in spontaneously breathing patients, either invasively or noninvasively.

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_7

CPAP is not a real ventilation mode, but it is universally included in the field of noninvasive ventilation (NIV). We consider "noninvasive respiratory support" (NRS) High Flow Oxygen Therapy (HFOT), CPAP and NIV.

CPAP therapy can be applied only if patients have an intact respiratory drive and if they are able to start and complete each respiratory act. During spontaneous breathing in CPAP, pressure may vary of ±2 cm H_2O as a result of breathing work. The ideal CPAP device should maintain the pressure constant throughout the entire respiratory cycle.

7.2 Devices to Deliver CPAP

CPAP may be delivered by means of different devices; regardless of the device used, we must be sure to deliver a flow sufficient to meet the patient's need. Conventional oxygen therapy (COT) systems may not always be able to provide either adequate inspiratory fraction of oxygen (FiO_2) or adequate flow, required in acute hypoxemic respiratory failure when patients need high inspiratory gas flows. For example, a normal subject breathing at tidal volume of 400 mL is taking gas at a flow <30 L/m, instead for patients in respiratory distress, whose tidal volume may be greater than 500 ml, with a short inspiratory time and a high respiratory rate, we may assume that they need a flow >60 L/m.

CPAP is a ventilatory technique that requires the administration of a continuous positive pressure in the airways; this can be achieved by (Table 7.1):

- High flow generators, providing continuous flow;
- Ventilators.

Table 7.1 Comparison of CPAP devices

Type	Pros	Contra
Continuous high flow	– Requires only oxygen supply – Cheap – High inspiratory flow – Ease of use	– High oxygen consumption – Noisy – FiO_2 and PEEP are flow dependent – No alarms – Absence of respiratory monitoring
Boussignac® (Vigon, France)	– Requires only oxygen supply – Cheap – Compact – Low oxygen consumption – Ease of use – Ideal for patient transport	– Noisy – PEEP dependent by inspiratory flow – No alarms – Absence of respiratory monitoring
Mechanical ventilators	– Respiratory monitoring – Low noise – Possibility to switch to other modes of ventilation	– Expensive – Some models require oxygen and air

FiO_2 inspiratory fraction of oxygen, *PEEP* positive end-expiratory pressure

7.2.1 High Flow Generators

High flow CPAP systems may consist either of an oxygen and air blender, or use a Venturi flow generator, both able to generate an adequate flow that exits through a spring-loaded valve (i.e., PEEP valve). In both systems, to keep pressure constant in the circuit, the flow administered should be two–four times the patient minute volume or at least equal to the patient's peak inspiratory flow [1].

An old CPAP system (now disused) was powered by oxygen and air, variously combined by respective flowmeters, and a reservoir balloon in line with the circuit and a water valve to set the desired pressure. The limit of these systems was the low flow (often <50 L/m) dependent only on the flowmeter setting and the elastic return of the balloon, which, in the presence of high ventilatory demand was not performant to satisfy patients ventilatory needs.

More recently, an air-oxygen blender has been configured to deliver CPAP with a flow up to 80–100 L/m and with a FiO_2 ranging from 0.21 to 1.

More performant systems use the Venturi principle (demonstrated by Bernoullis' theorem and Poiseuille principle): briefly, the velocity of a fluid in a conduct is inversely proportional to the section of the conduct itself, and the fluid exerts, on the wall of the conduct, a pressure inversely proportional to the speed of the fluid. With the Venturi effect, O_2 delivered under pressure, passes through a narrow section of the conduct, increasing its speed and consequently determining a subatmospheric pressure that aspirates room air into the system through some openings placed in the duct, generating a high flow.

The Venturi CPAP system, mixing high flow oxygen with room air, obtains a high output flow (up to 140 L/m) with a FiO_2 ranging from 0.30 to 1. The device is small, does not require an electrical power supply, and generally has three switches: on-off, flow regulator, FiO_2 regulator (Fig. 7.1). The high flow is delivered to the airways by means of a circuit and an interface (oro-nasal mask or helmet); the high flow and a PEEP valve guarantee the administration of a positive pressure throughout the entire respiratory cycle of the patient. The PEEP valve, furthermore, allows eliminating the excess flow.

To meet patients' ventilatory demand, it is suggested to start by setting the system with the flow regulator open (flow 140 L/m) and the oxygen regulator closed (delivering a FiO_2 of approximatively 0.30). Afterwards FiO_2 can be increased, paying attention to the consequent flow reduction (due to the Venturi effect). If not integrated into the device, it is desirable to have an oximeter and a manometer available to check FiO_2 and the pressure delivered (Fig. 7.1).

As opposed to air-oxygen blenders, Venturi requires only an oxygen supply. Like any Venturi system, FiO_2 may be affected by flow rate. FiO_2 may also be influenced by PEEP level; with highest PEEP, flow reduces and FiO_2 may increase [2].

A particular device is the Boussignac CPAP system (Vygon, France) that consists of a simple pressure generator, cylinder shaped and open. The pressure generator that can be connected to interfaces such as face mask or tracheostomic cannulas has two connections: one for inflow of oxygen and one for pressure control, CO_2 monitoring or addition of medical gases. It does not need a device to generate flow

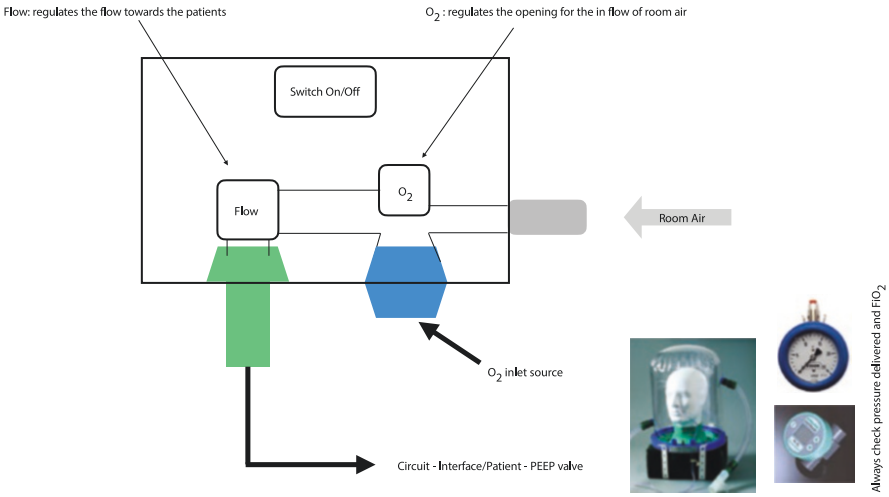

Fig. 7.1 Diagram of CPAP system with a Venturi type flow generator

because the gas molecules accelerated in the inlet device bumping between each other and against the wall of the device, create a turbulent flow, realizing a virtual diaphragm between the patient and the environment. The kinetic energy of gas particles creates a sort of "virtual valve" able to generate a positive pressure throughout the entire respiratory cycle. The pressure value of this virtual valve may eventually be adjusted by increasing or decreasing the amount of oxygen supplied to the patient.

The Boussignac device does not incorporate an air-entrainment input to supplement flow, but because the distal tube is open, the patient is allowed to inhale additional flow from ambient air [3]; however, as with Venturi devices, the efficacy of Boussignac CPAP can be reduced when the gas flow delivered by the system is lower than patient's gas flow requested [1].

Even if the Boussignac system has some advantages (low weight, low oxygen requirement, allows one to easily perform a fibreoptic bronchoscopy) it has some limits:

- It is not possible to adjust PEEP level and FiO_2 separately;
- If the patient has a high minute ventilation, gas flow administered by Boussignac may be insufficient to meet the patient's needs;
- Inspiratory flow is mixed with atmospheric air, causing a significant reduction in FiO_2 and in airway pressure.

The pressure obtained in the Boussignac system can be measured with a manometer; the pressure is dependent on patient's minute volume and from gas flow. This is the reason why the system is usually powered with a gas flow of at least 30 L/m that allows obtaining a pressure of 9–10 cm H_2O, while with a flow of 15 L/m PEEP level is about 5 cm H_2O.

If only oxygen is used for the gas supply, the Boussignac system delivers a high FiO_2 (>60–70%); the principal feature of the system is to deliver a high FiO_2, even in the presence of high minute ventilation: it has been observed, in experimental studies, that if ventilation is <15 L/m with a pressure of 10 cm H_2O, a FiO_2 of 100% may be guaranteed, while with a ventilation between 15 and 20 L/m, FiO_2 may fall to 59–80% and, finally, for ventilation >30 L/m, it is difficult to guarantee a $FiO_2 > 60\%$ [4]. Therefore, the performance of the device depends mainly on oxygen flow setting, raising the possibility that flow generated by Bousssignac may be inferior to flow generated by Venturi systems. To increase performance, additional flow from ambient air may be used, but because the system is open, ambient air dilutes the inspiratory concentration of oxygen, reducing FiO_2 [5]. As opposed to Venturi devices, Boussignac CPAP may have greater variations of pressure delivered [5]. Furthermore, when the patient inspiratory efforts or inspiratory flow increases, FiO_2 may have a significant decrease with Boussignac, raising the possibility to increase the work of breathing and increasing respiratory distress [3].

7.2.1.1 Mechanical Ventilators

In all modern ventilators (critical care, portable or noninvasive dedicate ventilators) it is possible to set CPAP modality, throughout a dedicated algorithm or with a specific function or setting equal pressure inspiratory and expiratory levels. However, using a mechanical ventilator to deliver CPAP may have some limits mainly due to the necessity of interaction between the patient and the ventilator itself. If a mechanical ventilator is used, the ventilator may superimpose an additional work of breathing to the patient caused by the need to activate an inspiratory trigger and cycling from the inspiratory to expiratory phase. Also the trigger delay (time to start the delivery of the inspiratory act) and the continuous flow delivered by the ventilator may further worsen the work of breathing [1, 3].

While not necessary for CPAP, patient–ventilator synchrony is fundamental in noninvasive pressure support ventilation because the ventilator must "know" which phase of the respiratory cycle the patient is in; and the work spent to trigger the ventilator is quite irrelevant as opposed to the benefits of pressure support ventilation.

Another problem that may arise with mechanical ventilators is that the flow delivered results proportional to the ventilatory need of the patient, mainly during the inspiratory phase, determining a delay in flow administration with a consequent reduction in the pressure delivered.

Nevertheless, the new generation of mechanical ventilators has a performance similar to continuous flow systems [1].

7.3 Respiratory and Cardiovascular Effects of CPAP

The application of a positive intra-thoracic pressure (ITP) (as occurs with CPAP) primarily affects cardiac function by changing lung volume and intrathoracic pressure.

Both spontaneous breathing and mechanical ventilation can induce change in intrapleural and intrathoracic pressure and also lung volume. Each one of these changes can independently act on cardiovascular performance. Intrathoracic pressure changes are transmitted to the other structures: heart, pericardium, and the great arteries and veins.

During spontaneous breathing, inspiration produces a negative pleural pressure that is transmitted to the heart chambers. Otherwise, applying positive pressure during the entire breath cycle can have important effects on lung volume and the cardiovascular system.

Positive ITP usually decreases cardiac output, except in after-load dependent patients because increased ITP hinders the filling of the right ventricle, reducing venous flow into the thorax and cardiac output (CO) [6]. The application of a positive pressure to the airways, increases lung volume by increasing upper airway pressure, lung and chest wall compliance.

In the following paragraph, we will summarize briefly, the main respiratory end hemodynamic effects of CPAP.

7.3.1 Respiratory Effects of CPAP

CPAP may have several effects on the respiratory system:

- Maintains alveolar pressure and prevents the alveolar collapse at the end of expiration improving gas exchange and oxygenation through the recruitment of alveolar units, counterbalance of hydrostatic forces leading to pulmonary edema, and maintenance of airway patency [7];
- Reduces respiratory muscle load and the work of breathing [8] and can improve lung function through lung inflation and maintenance of functional residual capacity;
- Prevents upper airway narrowing and collapse;
- Can attenuate the increase in total pulmonary vascular resistance (PVR) leading to an improved ventilation–perfusion ratio and better gas exchange if hypoxic pulmonary vasoconstriction occurs due to hypoxia in association with acute decompensated hearth failure (HF) or HF accompanied by chronic obstructive lung disease (COPD) and sleep-disordered breathing (SDB). Attenuation of increased PVR can be associated with improved hemodynamics [9].

7.3.2 Hemodynamic Effects of CPAP

Variation of ITP and lung volume can affect trans-mural pressure (Ptm) of cardiac chambers. Moreover, the variation in pressure and volume in one chamber of the heart can influence the other side of the heart itself.

During spontaneous breathing, inspiration produces a negative pleural pressure that is transmitted to the right atrium. Otherwise, applying positive pressure during the entire breath cycle (CPAP) can have important effects on lung volume and the cardiovascular system.

Heart–lung interactions are influenced by changes in ITP which affects P_{tm} (that is the difference between the inside and the outside of the heart). P_{tm} of the right atrium and of the left ventricle (LV) vary with changes in ITP. As right atrial pressure (P_{ra}) is the driving pressure for venous return (VR), any change in P_{ra} during increased ITP may change venous flow rate, reducing it and reducing, as a consequence, right ventricle (RV) end-diastolic volume. Changes induced by positive ITP on VR are fundamental in approaching the hypovolemic or septic patient, where the application of relatively small pressures can cause a large decrease in pre-load and in cardiac output (CO) [6].

On the right side of the heart, other effects of positive ITP and increased lung volumes are on the pulmonary vascular resistances (PVR). At low lung volumes, an increase in pulmonary volume reduces PVR due to an effect on extra-alveolar pulmonary vessels, which tend to dilate in relation to lung expansion. A further increase in pulmonary volume, however, determines compression of intra-alveolar pulmonary vessels, increasing PVR and causing an increase in right ventricle after-load.

Variation in ITP, of course, also have effects on the left side of the heart, mainly that of left ventricle (LV) pre and after-load. To understand the effects of positive ITP on LV, it should be remembered that during spontaneous breathing, the negative swings in pleural pressure led to an increase in LV P_{tm}, affecting LV contraction and LV after-load. If these effects are negligible in spontaneously breathing patients, they may become very important during acute respiratory failure, increasing LV after-load and venous return, intrathoracic fluid content, and eventually worsening pulmonary edema. Conversely, a reduction in intrathoracic inspiratory pressure swings (obtained increasing ITP) reduces LV P_{tm} and thus LV after-load and pulmonary congestion [9].

This is the reason why the application of positive ITP, besides improving pulmonary compliance and respiratory mechanics, optimizes LV function and is efficient in treating acute cardiogenic pulmonary edema (ACPE) [10].

While patients with acute heart failure may benefit from increased ITP, caution is needed in hypovolemic or pre-load dependent patients, in which a reduced RV filling due to decreased VR should be avoided (Fig. 7.2). It is common to observe hemodynamic improvement in pre-load dependent patients when CPAP is removed [6]. If a positive ITP is needed for alveolar recruitment, pre-load should be optimized before increasing pressure levels (Fig. 7.2).

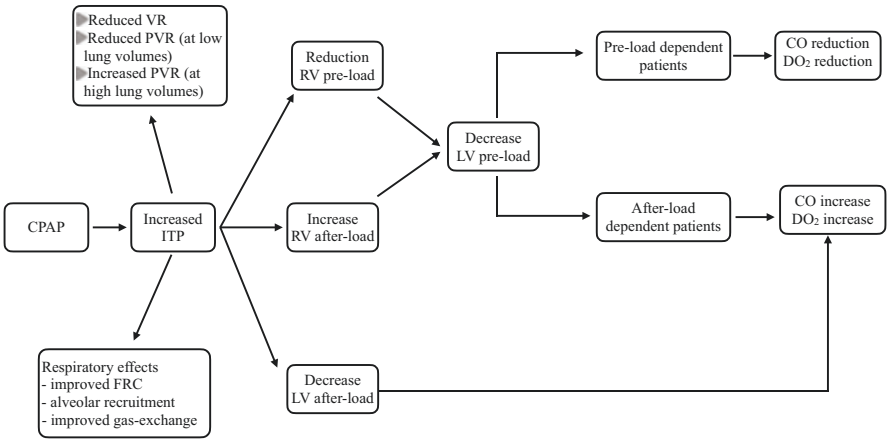

Fig. 7.2 Effects of CPAP on hemodynamics. Abbreviations: *CO* cardiac output, *CPAP* continuous positive airway pressure, DO_2 oxygen delivery, *FRC* functional residual capacity, *ITP* intrathoracic pressure, *LV* left ventricle, *PVR* pulmonary vascular resistance, *RV* right ventricle, *VR* venous return

7.4 CPAP Indications and Contraindications

An appropriate selection of the patient is the first step; a proper selection in the acute care setting should identify patients with compromised gas exchange ($PaO_2/FiO_2 < 250$ mmHg, despite optimized medical treatment), with an intact respiratory drive, able to breathe spontaneously throughout the complete respiratory cycle, not improving with conventional oxygen therapy (COT) or in which we considered probable COT failure.

Even if CPAP is not a mechanical ventilation technique, it reduces work of breathing, improves gas exchange and lung compliance. Furthermore CPAP may have, especially in patients with left ventricular dysfunction, positive hemodynamic consequences such as a reduction in pre-load and improvement in left ventricle after-load [9].

Criteria to start CPAP are the following [11]:

- Respiratory distress;
- Use of accessory respiratory muscles and/or abdominal paradox;
- Respiratory rate > 30/min;
- $PaO_2/FiO_2 < 250$ mmHg

In the acute setting, CPAP may find clinical applications in the following situations:

1. Acute Cardiogenic Pulmonary Edema (ACPE): CPAP is considered the first line intervention in ACPE [12]. Is affective also in ACPE patients presenting with hypercapnia, being comparable to pressure support ventilation in terms of length of ventilation and time to improve gas exchange [13].

2. Post-operative respiratory failure: surgery and anesthesia may worsen respiratory function, affecting gas exchange. Early application of CPAP may reduce intubation rate, nosocomial infections, ICU length of stay [14]. There is still insufficient evidence that CPAP may have effects on anastomotic leakage [14].
3. Immunocompromised: the rationale for using CPAP in immunocompromised patients is that the avoidance of endotracheal intubation may reduce mechanical ventilation side effects and nosocomial infections, reducing mortality. Early application of CPAP in immunocompromised patients may prevent respiratory impairment and ICU admission. Even if in a recent RCT intermittent noninvasive ventilation, compared to COT, failed to show benefits in terms of acquired infections, mortality, or ICU length of stay, ERS/ATS guidelines suggest early application of CPAP in immunocompromised patients [12].
4. Trauma: in chest trauma patients the main mechanisms involved in the development of respiratory failure are the direct involvement of the thoracic cage or lung parenchyma and the leakage of edema fluid into the lung and inflammatory cellular infiltrates associated with altered surfactant composition. Patients treated with CPAP had lower rate of pulmonary complications, nosocomial infections and a shorter hospital length of stay [15].
5. Pneumonia: even if there is uncertain evidence to recommend NIV (either bilevel ventilation or CPAP) for patients with "de novo" acute respiratory failure [12], a cautious trial with CPAP may be tried in patients with pneumonia. CPAP improves oxygenation in community-acquired pneumonia, as opposed to COT [16]; moreover, in an RCT, patients treated with CPAP, when compared to patients treated with COT, had a lower risk to meet endotracheal intubation criteria [17]. In the same study, patients treated with CPAP showed a faster improvement in gas exchange and respiratory distress.
6. CPAP during the Covid-19 pandemic: During the SARS-CoV2 pandemic there was a large use of CPAP for the management of acute respiratory failure. Coronavirus pneumonia can cause an inflammatory induced pulmonary vasculitis which leads to severe hypoxemia, dyspnea, impaired lung diffusion, formation of intravascular microthrombi hypoxic vasoconstriction, and intrapulmonary shunting [18] ending in acute distress respiratory distress syndrome (ARDS).

   We can describe two phenotypes of ARDS-COVID19 (CARDS):

- The early type L, characterized by low elastance, relatively high compliance, 50.2 ± 14.3 mL/cm H_2O), low ventilation to perfusion ratio, limited PEEP response and low alveolar recruitability;
- The late type H, characterized by high elastance, high right-to-left shunt, high lung weight, better PEEP responsiveness, and high alveolar recruitability.

The two types are not mutually exclusive and overlapping can occur during the course of the disease. CPAP can improve arterial partial pressure of oxygen (PaO_2) mediated by lung recruitment and by more uniform distribution of perfusion and prevent intubation and intensive care unit (ICU) admission.

It is difficult to assess the level of PEEP useful to improve oxygenation, the PEEP choice also depends on the phenotype (L or H).

Low PEEP values are suggested at the beginning of the treatment (5 cm H_2O and FiO_2 values assessed on patient's SpO_2) and can be raised considering the gas exchanges. Values higher than 15 cm H_2O can lead to complications as pneumomediastinum or pneumothorax.

In the COVID ARDS (CARDS), it is suggested to use preferentially helmet CPAP [19].

A correct management of CARDS with helmet CPAP includes:

- At least 40–50 L/min air flow to avoid secondary $PaCO_2$ augmentation due to rebreathing and to meet patients' ventilatory need;
- PEEP and anti-asphyxiation valves correct functioning;
- Correct size of helmet CPAP and good fit around the neck are essential to reduce air leaking. Helmet CPAP minimizes the risk of viral spreading to health care workers and other patients while offering the best comfort [19] and it can also be used outside of intensive care units (ICU).

7.4.1 Contraindications

Conditions once considered a contraindication for CPAP use such as thoracoabdominal surgery, agitation, or lack of cooperation are no longer an absolute obstacle for CPAP.

Also, the availability of different interfaces has overcome problems related to interface tolerance. In particular, helmet CPAP may have some advantages, decreasing leaks (an important issue during the Covid-19 pandemic), improving comfort, and reducing the probability to develop facial pressure skin ulcers.

7.4.2 Absolute

- Cardiac or respiratory arrest;
- Unable to tolerate the interface;
- Impaired sensorium;
- Multiorgan failure;
- Inability to protect the airways;
- Life-threatening arrythmias.

7.4.3 Relative

- Hemodynamic instability (systolic blood pressure <90 mmHg despite fluid challenge and/or amine infusion);
- Inability to clear secretions;

- Swallowing impairment;
- Gastro-intestinal bleeding;
- Pneumothorax not drained;
- Lack of cooperation.

7.5 Conclusions

CPAP is a mode of NRS. Several devices can be used to deliver CPAP.

The easiest, simplest, and most efficacious way to deliver a continuous flow is with a Venturi device, remembering to monitor FiO_2 and pressure delivered.

The last generation of mechanical ventilators can also deliver CPAP, with performance somewhat similar to continuous flow devices, and offer advanced respiratory monitoring.

Key Major Recommendations

- CPAP can be delivered with continuous flow systems or with mechanical ventilators.
- To achieve and maintain a constant pressure level, the system must deliver flows that at least meet the patient's inspiratory flow demands.
- Continuous flow CPAP are easy to set, cheap, and perform well, but lack respiratory monitoring.
- CPAP, increasing intra-thoracic pressure has either respiratory or hemodynamic effects.
- While CPAP has positive effects in after-load dependent patients (such as acuta cardiogenic pulmonary edema), cautious must be used in pre-load dependent (i.e., hypovolemia) patients in which a dangerous reduction in cardiac output and DO_2 can occur.

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Negative Noninvasive Mechanical Ventilation: External Negative Pressure Ventilation (ENPV)

8

Corrado Mollica and Umberto Vincenzi

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8.1 Introduction

In patients with acute respiratory failure (ARF), ventilation can be supported during the inspiratory phase either by inflating the airways (intermittent positive pressure ventilation, IPPV), or by external negative pressure ventilation (ENPV), applied around the thorax (and abdomen) by "*body ventilators.*" These ventilators include

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_8

the iron lung, portable lung (Portalung), pneumowrap, chest cuirass, pneumobelt, and rocking bed and should be reserved for patients with an intact upper airway.

In respiratory mechanics, the term "negative pressure" refers to the fact that the pressure in certain districts (pleuro-pulmonary) is slightly less positive than the atmospheric pressure although this does not imply that the pressure is always less than zero.

ENPV assists respiration by intermittently applying a sub-atmospheric pressure only around the thorax (when the cuirass is employed), or around both thorax and abdomen when it is performed by poncho or pneumowrap ventilator. It can be delivered also by a whole-body ventilator (i.e., "*iron lung*" or tank ventilator) (IL).

It should be taken into account, however, that ventilators acting externally to the chest can also act during the expiratory phase, hence the so-called biphasic ventilation.

Authoritative authors consider ENPV more physiological than IPPV because it comes closest to physical respiratory mechanics [1].

8.1.1 Operation of External Ventilators (ENPV)

The IL is an electrically powered pressure-controlled ventilator, which does not allow presetting of inspiratory flow or tidal volume, which – as mentioned above – depends on the interaction between the pressure (negative or positive) inside the ventilator and the mechanical properties of the patient's respiratory mechanics. The pressure inside the ventilator was initially provided by a mechanical system (cylinder/piston) and the frequency being regulated by a variator existing between the motor and the piston. This mechanical system was able to generate sine-like pressure waves.

The presence of two discharge valves (acting in the inspiratory and expiratory phases) of the air present inside the tank made it possible to vary said pressure waves, thus modulating the regime of sinusoidal waves both in relation to the pressure and to the time of execution of the inspiration/exhalation, and thus regulating the passage from the inspiratory phase to the expiratory phase. Therefore, this ventilation pattern could be called time-triggered and time-cycled. In more recent years, ventilators acting externally to the chest use air turbines with sufficient flow rates to create high pressures even in an entire chest, as in the so-called IL.

With the latest IL models (©C900 Iron lung. Officine Coppa Biella—Italy) (Fig. 8.1), it is possible to carry out not only controlled ventilation – by setting in-expiratory pressures and times – but also assisted ventilation, by means of two systems: either by a patient-generated negative pressure at the nares that triggers the machine or by patient activation of a thermistor trigger sensitive to T° differences at the nares between the in-expired air that triggers a breath.

This device allows patients to initiate the preset mechanical act according to their needs, considering that the response time of the device is in the order of a few milli-sec.

Fig. 8.1 Iron Lung C900 (®Officine Coppa, Biella, Italy)

The increased interaction between patient and ventilator by assisted ventilation has also facilitated "weaning" from the ventilator (at positive pressure) in the intubated patient [2]. It has been shown that a microprocessor-based iron lung capable of thermistor triggering was able to perform assisted ENPV with a marked reduction in diaphragm effort and a low rate of non-triggering inspiratory effort both in normal individuals and in patients with an acute exacerbation of COPD [3].

8.1.2 Ventilation "Mode"

As to delivered pressures, ENPV can be delivered by four modes: (1) *cyclical negative pressure ventilation*; (2) *negative/positive (or biphasic) pressure ventilation*; (3) *bilevel negative pressure ventilation (Bilevel NPV)*; and (4) *continuous negative pressure ventilation* (CNPV) (Fig. 8.2).

In *cyclical negative pressure ventilation,* negative pressure is applied *in the inspiratory phase only*, with exhalation being entrusted to the elastic return of the lungs ("*lung elastic recoil*") (i.e., *inspiratory Pressure:* iP = −30; *expiratory Pressure:* eP = 0).

With negative/positive pressure ventilation, the ventilator provides negative pressure ventilation in inspiration (i.e., iP = −30) and positive pressure ventilation in expiration (i.e., eP = + 30); the latter increases the lung elastic recoil in the expiratory phase.

With the Bilevel NPV, the ventilator can perform ventilation at two negative pressure levels, one higher in inspiration and one lower in expiration (i.e., iP = −35; eP = −10). In this ventilatory model, exhalation is entrusted to the pulmonary spring-back force.

During CNPV, the negative pressure delivered is of equal value in both inspiratory and expiratory phases (i.e., iP = −10; eP = −10). In this *ventilatory mode*, Insp/Exp acts are entrusted to the activation of the muscular forces (during inspiration

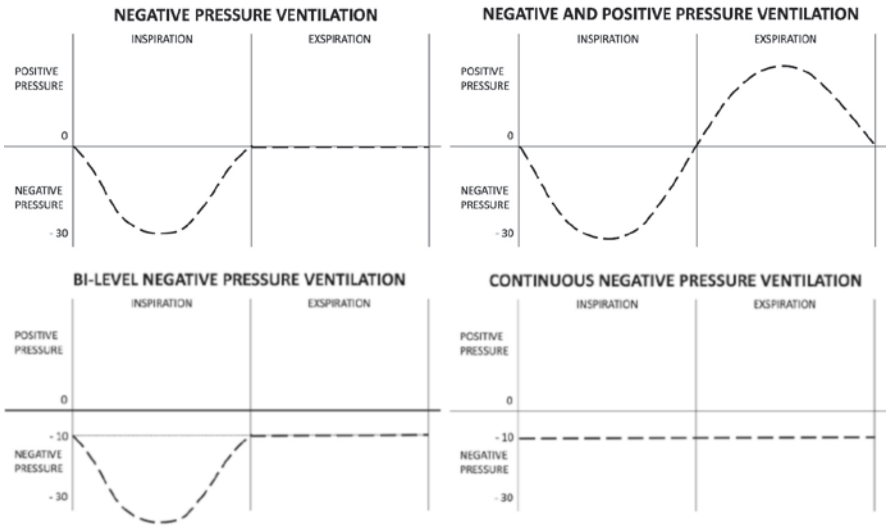

Fig. 8.2 External negative pressure ventilation: ventilation mode *(see text)*

phase) and elastic forces (in expiration phase) of the patient, which can be responsible for minimal oscillations of the pressure wave resulting from the afore-mentioned respiratory movements; in CNPV the continuous negative pressure facilitates inspiration.

As far as the flow is concerned, with ENPV it is ensured by the difference in pressure that is created between the mouth (outside the ventilator) and the alveoli, inside it. This difference in bucco-alveolar pressure is obtained by creating an area of negative peri-thoracic pressure inside the ventilator during the inspiratory phase that generates an increase in trans-pulmonary pressure (TPP) with a consequent entry of ambient air into the patient's airways, thus inflating the lungs, and increases lung volume[1].

Therefore, *in all external ventilators*, a flow of air from the mouth to the alveoli is created during inspiration due to the increase in intrapleural negativity that occurs with each inspiratory act. It follows that any event (foreign body or simple muscle spasm) acting along the mouth/airway pathway will impede flow.

Conversely, *the expiration phase* varies according to the type of ventilator used: with poncho (or pneumowrap) differently than with iron lung (IL) or cuirass.

Indeed, when using poncho or "pneumowrap," the *expiration occurs only passively (or mechanically non-assisted)* because of the elastic recoil of the lungs and

[1] The mechanism rests on Boyle's law, which establishes the relationship between pressure and volume: at a constant temperature, the volume of a given mass of gas is inversely proportional to the pressure. [P x V = constant, i.e., $P = 1/V$]. Therefore, during the application of ENPV, a reduction in peri-thoracic (but internal to the ventilator) pressure – as occurs in the inspiratory phase – corresponds to an increase in lung volume; the reverse occurs in the expiratory phase.

chest wall (as the pressure within the ventilator rises to atmospheric levels) (*cyclical negative pressure ventilation)*.

Vice versa by using tank (IL) or shell ventilators (cuirass) the *expiration can occur* both *passively* and *mechanically assisted*, as a result of applying positive pressure to the outside of the chest (*negative/positive pressure ventilation*) (Fig. 8.3).

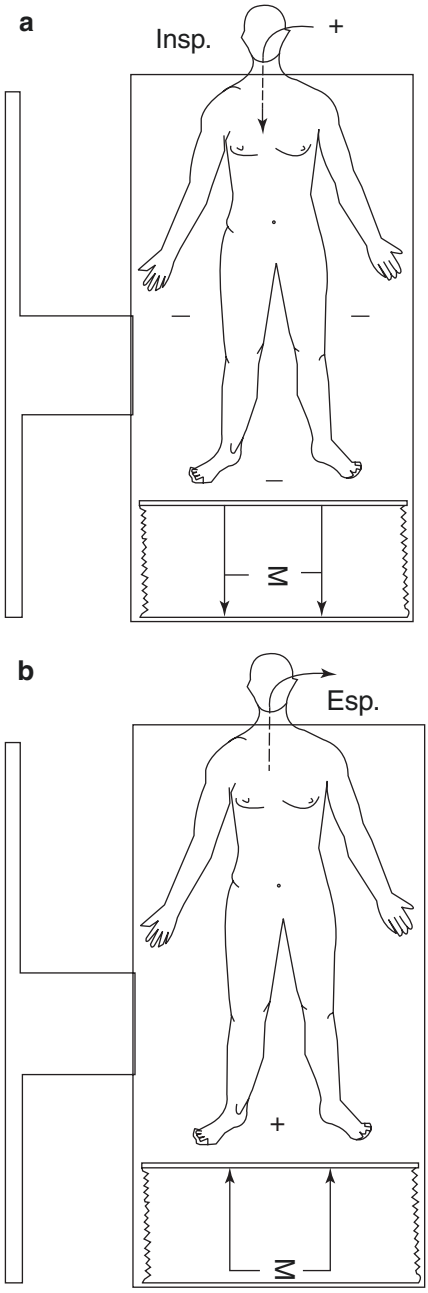

Fig. 8.3 Functional diagram of the "body respirator." The flow is ensured by the pressure difference (ΔP) between the mouth (outside the ventilator) and the alveoli. The pressure variations (ΔP) *inside* the respirator (but *outside* the rib cage) occur thanks to the oscillations of a piston (M); this creates, *at the top*, a negative pressure (−) which assists inspiration (**a**); while *at the bottom*, an area of perithoracic hyper-pressure is created which ensures *expiration* (**b**). *Credits: Del Bufalo C. (1997) Ventilatori agenti per via esterna. In: Del Bufalo C, ed., Intensivologia Respiratoria. Ravenna (Italia): Edizioni Cooperativa Libraria e di Informazione, 1997; 45 (Courtesy of the Author)*

This kind of ventilation mode in patients (pts) with rib-cage (chest wall) disorders increases tidal volume more than cyclical negative pressure alone [4].

Furthermore, a reduction in functional residual capacity (FRC) during the application of continuous positive (extrathoracic) pressure has been described in pts. with moderate airway obstruction [5].

Moreover, while controversial, the application of positive extra-thoracic pressure in expiratory phase in "flow-limited" pts. (chronic obstructive pulmonary disease, COPD) is meant to increase expiratory flow, and the finding in these patients of increased CO_2 concentration in expired air when this kind of ventilation mode is applied might be caused by increased alveolar ventilation [6].

8.1.3 Favorable and Adverse Side Effects of ENPV

The *advantages* include the already mentioned physiological nature of the method, which is preferable when it is necessary to ventilate for a prolonged period of time (sometimes for years) individuals in whom ventilatory autonomy has definitively ceased (like neuromuscular pts.), as well as the finding of an *improvement in hemodynamics* [7]. During ENPV, patient compliance is also reported to be better than the noninvasive positive pressure ventilation (NIPPV), via face mask or helmet [8].

Adverse side effects extend beyond organizational concerns; they also include difficulty of accessing the patient to carry out cardio-respiratory monitoring appropriate to the often very critical condition of patients (pts); this requires skillful ICUs staff trained in handling immobilized pts., as well as in managing arterial and venous lines, chest drains, and urinary catheters. Altogether, such expertise can only be found in a few centers.

Other adverse effects include the finding of a dynamic collapse of upper-airways, such as to determine "flow limitation," as in obstructive sleep apneas syndrome (OSAS), owing to the increased intra-thoracic negative pressure during the inspiratory phase; furthermore this results in the inability to protect the airway and/or high risk of aspiration as well as inability to clear secretions: conditions which altogether require endotracheal intubation (ETI).

8.2 Discussion and Analysis: Main Topic

8.2.1 Why and When ENPV Is to Be Used

ENPV is suitable for patients in need of mechanical ventilation (MV) for ARF who fail to adapt to NIPPV, owing to poor face mask compliance or to abnormal facial morphologies, excessive oropharyngeal secretions, as well as patients who experience anxiety and claustrophobia from a mask or helmet.

8.2.1.1 ENPV in COPD Pts

The role that mechanical ventilation itself plays in COPD exacerbations has long been accepted, both in the reduction of work of breathing (WoB) and in resting respiratory muscles, as shown by the improvement of muscular endurance, defined as muscle ability to carry a load along a given time [9].

In patients with a mild COPD exacerbation (PaO_2 range 49–78 mmHg; $PaCO_2$ range 38–57 mmHg) and chronic respiratory failure, Rochester et al. (*Am J Med 1977*) demonstrated the effectiveness of ENPV – during sleep and for short periods during the day – in WoB reduction and in diaphragm rest [10]; since then mechanical ventilation has been enriched with a further rationale of use.

On the other hand, in a double-blind study on 184 pts. with severe stable COPD treated with ENPV for 12 weeks at home, negative pressure ventilation was found difficult to apply and ineffective when used to let the respiratory muscles rest [11].

Furthermore, ENPV can be applied continuously for a long time although patient familiarization with the ventilator is necessary and improves blood gas exchange both in short [12] and in long-term studies [13]. In short-term studies, ENPV has been shown to improve the respiratory function of COPD pts. with hypercapnic failure and signs of inspiratory muscles dysfunction [14]. The significant fall in $PaCO_2$ is a result both of the increase in alveolar ventilation and in functional reserve of the inspiratory muscles [15] and in resting diaphragm and parasternal muscles [16].

In COPD pts. with acute on chronic respiratory failure (ACRF), ENPV applied by IL is useful in avoiding ETI even when performed on COPD pts. in coma status [17], and can also be considered as effective in avoiding ETI as a conventional approach [18], or as NIPPV [8]. In these pts., other beneficial effects due to ENPV on cardiopulmonary hemodynamics are described [19].

In fact, negative pressure applied to the chest wall increases venous return, thereby improving performance of a right ventricle overloaded by an acute rise in pulmonary artery pressure caused by hypoxic pulmonary vasoconstriction. It may also decrease left ventricular diastolic compliance by displacing the interventricular septum, due to an increase in right ventricular size. It follows that left ventricular ejection is inhibited [19].

On the other hand, in pts. with severe chronic airflow obstruction, a rehabilitation plus ENPV (with pneumowrap) does not result in increased benefit over that achieved by a comprehensive pulmonary rehabilitation program [20].

However, in a recent study of 129 patients with COPD, Hung-Yu Huang et al. (*Medicine, 2016*) showed that long-term (5 years) intermittent application of negative pressure ventilation combined with rehabilitation reduced the decline in lung function, hospitalizations, and healthcare costs [21].

8.2.1.2 ENPV in ARF- Other Than COPD Pts

In etiologies of ACRF other than COPD, such as kyphoscoliosis [22] or neuromuscular respiratory failure [23, 24], ENPV can avoid the need of ETI for the majority of pts.; in these illnesses, NEPV is also effective in weaning pts. from IPPV via ET tube [2].

8.2.2 In ARDS Patients

With some poncho models, it is also possible to maintain continuous negative pressure during CNPV, with physiological effects analogous to those of PEEP (i.e., to keep the pulmonary parenchyma relaxed) and applications in ARDS (*"Adult Respiratory Distress Syndrome"*) as well as in post-transplantation [25].

In the treatment of ARDS pts., the application of CNPV (−20 cm H_2O) increases TPP, thus generating an "*open lung effect*" similar to the one obtained by a PEEP of 15 cm H_2O [26].

Furthermore, CNPV differs from the positive pressure by increasing the venous return and the preload of the heart, and has no negative effects on cardiac performance [26].

As opposed to PEEP, where the increased TPP is associated with increased intrathoracic pressure, CNPV increases TPP by decreasing intrathoracic pressure, rather than by increasing airway pressure. Note that when the negative pressure is applied to the chest and upper abdomen only, as is the case when using a cuirass or a poncho device, the hemodynamic effects of the two approaches (PEEP vs. CNEP) can be expected to be different, due to the different effects on venous return and possibly transmural pressures [27].

Dynamic CT-scan showed that CNPV improved oxygenation compared to continuous positive pressure ventilation (CPPV) in patients with ARDS. This improved oxygenation due to CNPV, compared to CPPV, was not related to better lung perfusion, but to greater lung distension and better alveolar recruitment throughout the ventilatory cycle, as reflected by greater portions of the lung being ventilated and less lung atelectasis [27].

Analogous results have been obtained in pts. with ARDS by comparing 2 h CNPV in IL with 2 h CPPV. Tank pressures were −32.5 cm H_2O (minimum–maximum −30 to −43) at end inspiration and −15 cm H_2O (minimum-maximum −15 to −19 cm H_2O) at end expiration. CNPV improved gas exchange at lower transpulmonary airway and intra-abdominal pressures and, at least initially, improved hemodynamics [28].

In experimental lung injury[2] induced in Yorkshire pigs, continuous negative abdominal pressure ventilation (CNAPV) was applied to the external abdominal wall at constant negative pressure (−5 cm H_2O), to examine the effects on regional lung recruitment, gas exchange, and lung injury [30].

It is important to mention that the vertical gradient of pleural pressure is measured from the anterior to the dorsal part of the thorax in the supine position. In ARDS pts., the pressure gradient is increased; this is due to the greater presence of atelectasis and tissue imbibition in the dorsal part of the thorax. In this case, the poorly ventilated or atelectatic part of the lung is referred to as the "dependent lung," while the part of the lung that can still be ventilated, which is higher up, is

[2] In experimental lung injury, lung lavage is usually applied until the ratio of arterial partial pressure of oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) was <100 for 10 min, at PEEP of 5 cm H_2O [29].

referred to as the "non-dependent lung" [31]. Being reduced in ARDS, the total ventilable lung volume is called "baby lung" [32].

PEEP increases transpulmonary pressure in all lung regions, increasing pressure in the free airways and expanding the thorax non-selectively. This leads to increased pressures in the baby lung with possible damage. CNAPV, on the other hand, lowers pleural pressure in the "dependent" part, but not in the "non-dependent" part, leading to an expansion of the thorax without adversely affecting the well-ventilated part. Thus, CNAPV, in ARDS, reduces the vertical gradient of pleural pressure (i.e., the difference between dependent and non-dependent pleural pressure), improving oxygenation and lung compliance [33–35].

8.2.3 As a Bridge to Lung Transplant

For a select group of patients, ENPV applied by biphasic cuirass ventilator offers a less invasive respiratory support strategy as a bridge to lung transplant. ENPV applies alternate sub-atmospheric (negative) and atmospheric (zero) pressures on a control mode with an initial set of −15 cm H_2O synchronized to the patient's inspiration and +5 cm H_2O synchronized for expiration. Frequency, as well as inspiratory-to-expiratory ratio, was adjusted to synchronize patient efforts around the thorax and the abdomen facilitating airflow into the lung [36, 37]. Moreover, after total cavopulmonary anastomosis the application of negative extrathoracic pressure is described to be associated with large increases in pulmonary blood flow, which suggests that ENPV may be of particular benefit in patients subject to severe right heart overload [38]. In the context of hemodynamics, much is expected from the application of double positive + negative synchronized ventilation, in which two ventilators are applied simultaneously, synchronized with each other, one acting internally (at positive pressure) and one acting externally (at negative pressure). The most relevant effect found, due to the compensation of opposing pressures acting on the thorax, is that, during the entire inspiratory act created by the ventilators, the pressure in the airways and at alveolar level is equal to zero. This is also the case if the pressures delivered by the two machines are added together, i.e., if the transpulmonary pressure is doubled. Compensation of intrathoracic pressures should also allow, although this has not yet been demonstrated, an improvement in venous return, systolic output [39].

8.3 Conclusions and Take Home

- ENPV reduce diaphragm "fatigue" in patients with chronic respiratory failure; therefore, its use is reserved for the weaning from IPPV or the "long-term" treatment of ventilator-dependent patients;
- Its use is limited by difficulties in patient's monitoring, and when in the presence of "flow limitation" (that is in O.S.A.S. and in asthma patients);

- ENPV applications in ARDS and in post-transplantation patients are interesting, especially in terms of reducing side effects in the context of hemodynamics;
- The application of double positive + negative synchronized ventilation seems to be very promising in this respect.

Quiz

[Note: only 1 answer is correct: one in italics].

External ventilation using body ventilators (poncho, cuirasse, iron lung) is indicated:

1. In all forms of respiratory failure, even in hemodynamically unstable patients;
2. In patients with obstructive sleep apnoea or bronchial asthma;
3. *In the treatment of respiratory insufficiency due to COPD in patients who are hemodynamically stable and do not have obstructive sleep apnea or bronchial asthma.*

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Part III

Nasal High Flow

High Flow Nasal Oxygen Therapy

9

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9.1 Introduction

High flow nasal oxygen therapy (HFNOT) is becoming increasingly popular for the management of acute respiratory failure in various clinical settings [1, 2]. HFNOT has won its own place in the armamentarium of strategies employed to treat acute hypoxemia, representing an intermediate step between standard oxygen therapy and noninvasive positive airway pressure therapy [3]. The interest in HFNOT and its potential has been further increased during the current COVID-19 pandemic, which imposed significant demands on hospital resources, necessitating prudent patient prioritization and careful allocation of respiratory care equipment and intensive care unit (ICU) beds [4].

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_9

The rationale behind HFNOT stems from the need to deliver warm humidified air containing high fractions of oxygen (FiO_2) at a sufficiently high flow to meet the respiratory demands of the severely hypoxemic patient. In patients with acute respiratory failure, inspiratory flow increases significantly, ranging between 30 and 120 L/min [5]. Low flow oxygen treatment aims at correcting hypoxemia by delivering supplemental oxygen at flow rates that do not exceed 10–15 L/min. Therefore, the difference between patient inspiratory and delivered flow may lead to entrainment of atmospheric air which will dilute inspired oxygen, rendering oxygen therapy ineffective. Venturi masks can achieve higher inspiratory flows and relatively constant FiO_2; however, this advantage is lost when a $FiO_2 > 35–40\%$ is required [6, 7].

Importantly, as is the case with all medical gases, therapeutic oxygen is cold and minimally humidified. During normal breathing, inspired air passes through the upper airway, where it is warmed and humidified. Most of this conditioning process takes place in the nose and the nasopharynx. In normal individuals, when the inspired air has reached the nasopharynx, it has attained an end-inspiratory temperature of 34 °C, which increases further to 37 °C at the lower conducting airways [8]. At 5 cm below the bifurcation of the trachea, the inspired air has reached the "isothermic boundary" and is adequately humidified by airway mucosal fluid loss, attaining an absolute humidity of 44 mg H_2O/L and a relative humidity of 100% at 37 °C [9]. However, when the poorly humidified oxygen is administered at high flow rates, the ability of the airway mucosa to condition the inspired gas is superseded, resulting in complaints such as dry nose and throat and nasal pain. Importantly, the delivery of dry, cold air to the airways may cause bronchoconstriction, especially in patients with hyperreactive airways, as in asthma [10]. Unconditioned air also impairs mucociliary clearance [11], resulting in reduced lung compliance, higher work of breathing, and increased susceptibility to infections [12].

9.2 Design and Technology of High Flow Nasal Oxygen Therapy Devices

The purpose of HFNOT is to deliver an adequate FiO_2 (range of 0.21–1) at a sufficiently high flow to avoid dilution by ambient air. The inhaled gas should also be adequately warmed and humidified to improve patient tolerance and prevent complications due to bronchoconstriction and impaired mucociliary clearance. The standard HFNOT setup consists of a flow generator, a heated pass-over humidifier, a single-limb heated circuit, and the interface (Fig. 9.1).

High flows can be achieved by using three devices: air-oxygen blenders, built-in flow generators, and air-entrainment systems [13]. Air-oxygen blenders are commonly combined with a flow meter and receive oxygen directly from the high-pressure wall supply. Total gas flow is produced from a chamber that mixes oxygen and ambient air. In this way, the practitioner can directly dial the desired FiO_2 and titrate total gas flow according to the patient's needs (Fig. 9.1) [13, 14]. Build-in flow generators employ blowers and entrain room air to generate the required flow, while oxygen is supplied by low-pressure systems using standard Thorpe tubes

designed to provide oxygen at flows as high as 60 L/min. The practitioner can directly dial the desired total gas flow; however, actual FiO_2 is determined by the combination of current oxygen flow and total gas flow and is reported in real time on the machine's screen. When total flow is increased, more ambient air is entrained into the system, necessitating an increase in oxygen flow to achieve the desirable FiO_2 [13, 14]; specifically designed tables can assist the practitioner in the adjustment of settings. Air-entrainment systems employ the Venturi effect to generate high flows; total gas flow and FiO_2 are adjusted by different knobs and a build-in oxygen analyzer reports in real time the delivered FiO_2 [13, 14].

Heated pass-over humidifiers are the most common method for conditioning the delivered gas in HFNOT systems. They function by adding water vapor to the inspired air, as the latter is routed over a heated water chamber [15]. The temperature is set by the practitioner according to patient tolerance and can usually be increased up to 37 °C. Some systems (e.g., Vapotherm) provide humidification by using a bundle of filters with small pore size (0.005 μm). Single-limb circuits commonly incorporate a servo-controlled heated wire, which regulates the temperature inside the circuit, minimizing condensation and water vapor loss [13]. Silicone nasal cannulas are the most commonly used interface, and they come in small, middle, and large sizes. As a rule, the diameter of the prong should not be larger than half of the nostril diameter. Additionally, high flow oxygen therapy can also be delivered to patients with tracheostomies using special adaptors.

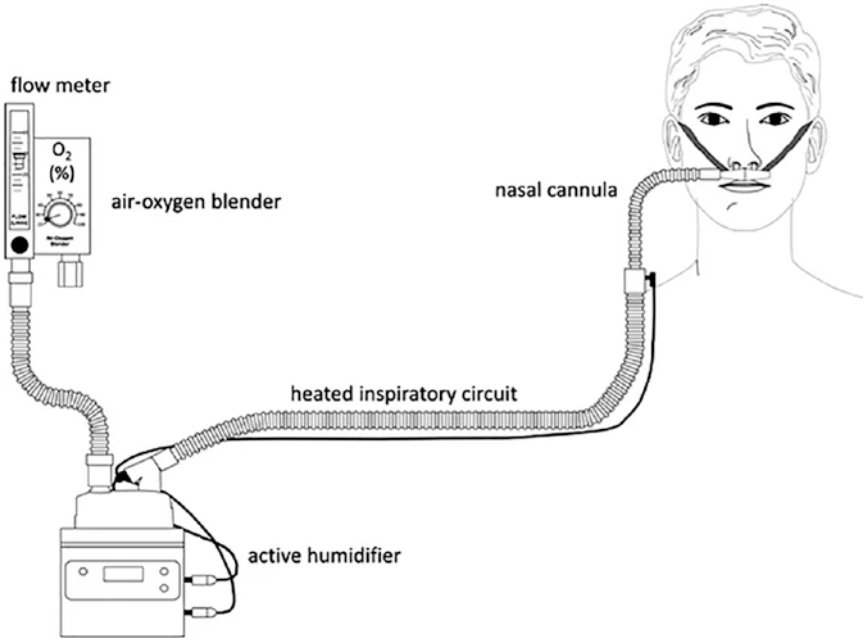

Fig. 9.1 High flow nasal oxygen therapy setup. High flow is generated by an air-oxygen blender (adapted from Ref. [1]). Available under http://creativecommons.org/licenses/by/4.0

9.3 Mechanisms and Physiologic Effects of High Flow Nasal Oxygen Therapy

Generally, the HFNOT nasal interface is more comfortable and better tolerated than standard oxygen masks and noninvasive ventilation (NIV) interfaces [3]. Heat and humidification also contribute to improved comfort by facilitating secretion clearance and reducing patient complaints related to dryness and low temperature [12, 16, 17]. In addition, high flows reduce the difference between the patient's native inspiratory flow and inspired gas flow, stabilizing FiO_2 delivery [18].

The physiologic mechanisms by which HFNOT exerts its beneficial effects have been the subject of extensive research. Among the various proposed mechanisms, the most important are dead space washout, reduction of the work of breathing, and improvements in lung volumes and ventilation. High nasal flows flush the nasal cavity and the nasopharynx, creating an oxygen reservoir and reducing carbon dioxide (CO_2) rebreathing [19]. HFNOT implementation also creates a small positive airway pressure which can be 3 cm H_2O when the mouth is closed but drops to 1 cm H_2O for mouth breathers and is flow dependent [20, 21]. This low-level positive pressure in HFNOT is associated with an increase in end-expiratory lung volume and lung compliance attributed to alveolar recruitment. The inspiratory work of breathing decreases leading to less breathlessness, lower breathing frequency, and lower minute ventilation without hypercapnia; oxygenation and ventilation homogeneity also improve [22–25]. It should be noted that, although the improvements in end-expiratory lung volume and oxygenation require high flows (e.g. 60 L/min), the effects on dead space, work of breathing, and respiratory rate can be achieved with lower flows (20–45 L/min) [23–25]. In addition, inspired gas conditioning may also contribute to less energy consumption [26].

9.4 Practicalities in the Implementation of High-Flow Nasal Oxygen Therapy

There exists no generally agreed approach on how HFNOT should be implemented in patients with acute respiratory failure. Initial flows for starting a patient on HFNOT vary widely in the literature [3]. Some authors suggest beginning with a relatively low flow (e.g., 35 L/min) to improve comfort, ease symptoms, and facilitate tolerance. Then, flow should be uptitrated in 5–10 L/min increments until oxygen saturation (SpO_2) improves, respiratory rate decreases, and the patient breathes comfortably. They recommend that hypoxemia should be initially corrected by increasing flow (thus decreasing room air entrainment), although increasing FiO_2 can achieve faster effects and should probably be preferred when hypoxemia is severe [3]. Ischaki et al. suggest starting HFNOT with an FiO_2 of 1 and a flow of 60 L/min and then adjust FiO_2 and flow to achieve a $SpO_2 > 88–90\%$ and a breathing rate <25–30 breaths/min [27]; this strategy might be preferable when treating patients with severe hypoxemia. In all cases, temperature should be adjusted to patient comfort.

9.5 Contraindications, Side Effects and Concerns Regarding High Flow Nasal Oxygen Therapy

The only absolute contraindication for HFNOT is any indication for invasive mechanical ventilation including shock, respiratory and cardiac arrest, bradycardia, severe arrhythmias, and impaired level of consciousness. Although NIV should be considered the primary treatment for patients with acute hypercapnic respiratory failure, not requiring intubation, less severe acidotic states (e.g., pH > 7.25) could be offered a cautious trial with HFNOT when NIV tolerance is a concern [28].

Face erythema and skin breakdown can also be observed in HFNOT users, although they represent less common complications compared to NIV [29]. Barotrauma can also occur and is attributed to the positive end-expiratory airway pressure build-up effected by HFNOT [30, 31]. Although HFNOT can be successfully used for the management of acute severe hypoxemia, failure is not uncommon (30–40%) raising concerns for delayed intubation and increased mortality [2].

9.6 Monitoring of High Flow Nasal Oxygen Treatment

The ROX index has been proposed by Roca et al. as a simple tool to predict the outcome of patients treated with HFNOT [32, 33]. It is calculated as the SpO_2/FiO_2 ratio divided by the patient's respiratory rare. In a prospective observational study of 175 patients with pneumonia, a ROX value ≥ 4.88 at 12 h post HFNOT onset had a positive predictive value of 89.4% and a negative predictive value of 42% in predicting treatment success [32]. In a subsequent study involving 191 patients with pneumonia, the same group demonstrated that a ROX index ≥ 4.88 was the best predictor of HFNOT success at 2, 6, and 12 h; a value <2.85 at 2 h, <3.47 at 6 h and <3.85 at 12 h predicted treatment failure; the SpO_2/FiO_2 ratio had a stronger influence on outcome prediction than the patient's respiratory rate [33]. More recently, in a study of 301 immunocompromised patients treated with HFNOT, the ROX index at 6 h was significantly lower in those who required intubation as opposed to those who did not (4.79 vs. 6.10); however, the previously used cut-off value (4.88) performed poorly in predicting treatment success [34]. Importantly, a recent physiologic study demonstrated that the ROX index is flow-dependent and may increase with flow, with more severe patients showing a better response [35].

9.7 Clinical Applications of High Flow Nasal Oxygen Therapy

There is strong evidence favoring the use of HFNOT in the management of severe acute hypoxemic respiratory failure. Robust data also support the use of HFNOT for the delivery of oxygen therapy in extubated critically ill patients and during airway procedures.

The beneficial effect of HFNOT in improving symptoms, oxygenation, respiratory rate, thoracoabdominal asynchrony, and in reducing the need for intubation in patients with acute hypoxemic respiratory failure has been assessed in several observational and cohort studies [2]. Frat et al. randomized 313 ICU patients with acute hypoxemic respiratory failure into standard oxygen therapy ($n = 96$), HFNOT ($n = 106$), and NIV ($n = 111$). This study observed a non-significant lower intubation rate at 28 days for the HFNOT group (38%) as compared to the standard oxygen (47%) and the NIV group (50%); however, this difference became significant when patients with a PO_2/FiO_2 ratio < 200 were analyzed separately. However, mortality at 90 days was significantly higher for the standard oxygen group and the NIV group as compared to the HFNOT group (hazard ratio 2.01 and 2.5, respectively). Additionally, the number of ventilator-free days at day 28 was significantly higher in the HFNOT group (24 days) compared to the standard oxygen (22 days) and NIV group (19 days). Complications did not differ between the three groups, but dyspnea scores at 1 h post-enrollment were significantly better in the HFNOT group than the two other groups [36]. Additionally, in a multicenter prospective cohort study involving patients with acute hypoxemia due to COVID-19 infection, HFNOT implementation as opposed to early intubation, was associated with significantly more ventilator-free days and a shorter ICU stay, but had no effect on mortality [37]. Regarding immunocompromised patients, a post-hoc analysis of a previous multicenter randomized controlled trial (RCT) [38] showed no benefit of HFNOT compared to standard oxygen treatment in reducing intubation and survival rates [39]. More recently, the HIGH RCT allocated 776 acutely hypoxemic adult immunocompromised patients to either HFNOT ($n = 388$) or standard oxygen therapy ($n = 388$) and failed to show any significant difference in 28-day mortality, rates of intubations, ICU and hospital length of stay, and rates of ICU-acquired infections [40]. A recent meta-analysis combining data from nine RCTs ($n = 2093$) which compared HFNOT to standard oxygen treatment for the management of acute hypoxemic respiratory failure showed no difference in mortality, although a significantly lower intubation rate (risk ratio 0.85) was observed for HFNOT [41].

Hernandez et al. conducted two RCTs to assess the efficacy and safety of HFNOT in preventing post-extubation respiratory failure in low- and high-risk patients. In the "low-risk" trial, 527 patients were randomized to HFNOT ($n = 264$) vs. standard oxygen therapy ($n = 263$). This trial observed a significantly lower proportion of all-cause re-intubation at 72 h and post-extubation respiratory failure for the HFNOT group as opposed to the standard oxygen group (4.9 vs. 12.2% and 8.3 vs. 14.4%, respectively). No difference was noted in crude ICU and hospital mortality and in the length of hospital stay [42]. In the "high-risk" trial, 604 patients were randomly allocated to either HFNOT ($n = 290$) or NIV ($n = 314$). This study showed no difference between the HFNOT and the NIV group in the rate of all-cause re-intubation at 72 h (22.8 vs. 19.1.%), although significantly fewer patients on HFNOT experienced post-extubation respiratory failure (26.9 vs. 39.8%). HFNOT patients spent significantly fewer days in the hospital (23 vs. 26 days), but otherwise no differences were noted in ICU length of stay and in ICU and hospital mortality. However, adverse effects necessitating withdrawal of therapy were observed in none of

HFNOT users vs. 42.9% in NIV users [43]. In another RCT involving cardiothoracic patients at high risk for post-extubation respiratory failure, again HFNOT was not associated with a higher rate of treatment failure compared to NIV [44]. More recently, Penissi et al. assessed the incidence of hypoxemia at post-operative day 4 in lung resection patients who were randomly assigned to either Venturi mask ($n = 48$) or HFNOT ($n = 47$). This study observed no significant difference in the incidence of post-operative hypoxemia, as well as in the rates of complications and subsequent requirement for standard oxygen therapy between the two groups; however, post-operative hypercapnia was lower in the HFNOT group [45]. Likewise, in a multicenter RCT of extubated chronic obstructive pulmonary disease (COPD) patients allocated to HFNOT ($n = 44$) or NIV ($n = 42$), no difference in intubation or treatment switch rates was observed between the two groups. However, treatment intolerance was significantly lower in the HFNOT group, with a risk difference of −50% [46]. In a recent meta-analysis of 8 RCTs (1594 patients), HFNOT was better than standard oxygen therapy and not inferior to NIV in reducing re-intubation and post-extubation respiratory failure, although it had no effect on mortality [47].

Other studies have evaluated the efficacy and safety of HFNOT in supporting oxygenation during airway procedures. Preoxygenation with HFNOT ($n = 51$) was compared to a non-rebreathing mask ($n = 50$) in a before–after quasi-experimental study of 101 ICU patients with mild-to-moderate hypoxemia for whom an intubation decision had been made. This study observed fewer episodes of severe hypoxemia for the HFNOT group as compared to the non-rebreathing mask group (2 vs.14%), although no significant difference was observed in the occurrence of cardiac arrest during intubation and in the ICU mortality [48]. Guiton et al. randomized 192 non-severely hypoxemic ICU patients requiring intubation to pre-oxygenation with HFNOT ($n = 95$) or standard bag-valve mask oxygenation. No difference was noted between the two groups in the lowest SpO_2, although the HFNOT group experienced significantly fewer adverse effects (6 vs. 19%) and fewer severe adverse effects (6 vs. 16%) [49]. In a recent RCT that compared gas exchange and oxygenation variables between HFNOT and bag-valve mask ventilation, the apnea phase was associated with a significant drop in SpO_2 in the bag-valve group, whereas no such change was noted in the HFNOT group [50]. Douglas et al. compared HFNOT ($n = 30$) to standard oxygen therapy ($n = 30$) in an RCT assessing the risk of desaturation in patients undergoing ultrasound bronchoscopy procedures. Desaturation occurred in 4 out of 30 patients in the HFNOT group as opposed to 10 out of 30 in the standard oxygen group, but this difference was significant only when a per-protocol analysis was performed [51]. In another RCT comparing HFNOT to NIV in hypoxemic critically ill patients undergoing bronchoscopy, NIV was associated with less desaturation than HFNOT [52].

The potential benefit of HFNOT in various other clinical settings is also currently being researched. These settings include acute infantile bronchiolitis [53], pediatric respiratory distress [54], chronic hypercapnic COPD [22], acute hypercapnic COPD exacerbation [28], administration of oxygen therapy during NIV breaks [55], and palliative care [56].

Conclusions and Key Major Recommendations

- HFNOT is an oxygen delivery modality which can administer high fractions of warm and humidified oxygen at flows close to the patient's inspiratory flow.
- The most common HFNOT setup includes a flow generator, a heated, pass-over humidifier, a single-limb circuit, and the nasal canula.
- HFNOT prevents entrainment of ambient air, improves patient tolerance, and facilitates mucociliary clearance. HFNOT implementation has been physiologically linked to increased dead space washout, reduction of the work of breathing and improvements in lung volumes and ventilation.
- The ROX index can be utilized for monitoring HFNOT, although further research is required.
- HFNOT reduces intubation rate for patients with severe acute hypoxemic respiratory failure, although current evidence does not support a survival benefit.
- HFNOT is better than standard oxygen therapy and not inferior to NIV in reducing re-intubations and post-extubation respiratory failure, but has no effect on mortality.
- When used for pre-oxygenation in ICU patients requiring intubation, HFNOT performs better than standard oxygen treatment or bag-valve mask ventilation in reducing desaturation episodes and averting complications.

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Part IV

Complementary Technologies in NIV

Humidification and Airway Secretions Management

10

Pinar Atagun Guney

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10.1 Introduction

Effective mucus clearance is necessary for lung health. Humidification and management of mucociliary activity are important elements of the application of noninvasive mechanic ventilation (NIMV). In addition to essential efficacy, the conditions affect patient tolerance and adherence. The respiratory tract normally provides an optimal temperature and relative humidity (RH) at the alveolar level to optimize the gas exchange and protect the lung tissue [1]. Normal respiration enables optimal mucociliary function at a temperature of 37 °C and 100% relative humidity [1, 2].

If the temperature and humidity conditions are inadequate, dehydration of mucus and decreased mucosal viscosity, as well as degradation of the pericellular layer

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https://doi.org/10.1007/978-3-031-28963-7_10

occur, leading to adhesion [3]. Mucociliary transport velocity and clearance is reduced and mucociliary function deteriorates. The application of mechanical ventilation can be invasive or noninvasive. While humidification is recommended for invasive mechanical ventilation (IMV) with 1A indications, the standard is not clear in cases of noninvasive mechanical ventilation (NIMV) [2]. NIMV provides the conduction of inspired gas from the upper airway to the respiratory tract, usually through a nasal or oronasal interface mask [4]. Ventilation with heated and humidified air similar to spontaneous breathing may be required to prevent the negative effects of dry, cold ventilated air, which can have various harmful effects [5].

Reduced mucosal viscosity and elasticity can lead to keratinization and structural disorders as a result of metaplastic changes in the upper airways. Increased nasal airway resistance, damage to the mucosa, increased breathing effort, difficulty in intubation, and poor compliance can result [4, 6, 7]. This is particularly true for patients using NIMV at home over a prolonged period of time.

10.2 Humidification Requirements in NIMV

NIMV can provide important treatment for patients with acute or chronic respiratory failure, especially critically ill patients. It is also used at home for chronic respiratory failure and sleep-related breathing disorders. During NIMV, the inspired gas is conditioned by the upper airways; however, this regulation system can be overwhelmed by the inhalation of cool, dry gas at a high rate of flow, especially in patients on intensive care ventilators. Several adverse effects can occur, including nasal congestion and upper airway dryness, which may lead to infection, inflammation, patient intolerance, and NIMV failure. The effects of insufficient gas conditioning during NIMV are defined by a clinical review and include nasal airway resistance, mouth dryness, damage to the mucosa, indirectly increased breathing effort, difficulty in intubation, mucus plug development, secretion retention, atelectasis, and airway obstruction [4].

Although it has been established that gas conditioning prevents adverse effects related to insufficient humidification, there is no clear consensus on whether additional humidification is always necessary in NIMV. It has been reported that humidification is typically insufficient in domiciliary NIMV and extended use can lead to structural and functional changes in the nasal mucosa and epithelium [6]. The current evidence regarding the need for humidification differs according to the patient population and the underlying disease. Recently, Esquinas et al. confirmed that structural changes and deterioration were seen in patients with acute respiratory failure treated for 7 days with NIMV. The same report emphasized the need for early humidification, even in short-term acute NIMV use [4].

Air leakage during NIMV is another factor that can lead to decreased effectiveness in humidification and increased labored breathing [8].

Although the association between humidification and pneumonia is controversial, a recent meta-analysis found a significant reduction in the incidence of ventilation-associated pneumonia in patients using humidified mechanical ventilation [9].

Increased mucosal secretion in patients with chronic obstructive pulmonary disease (COPD) or bronchiectasia is often an important factor affecting compliance and NIMV success. Several studies have demonstrated that humidification improved mucus clearance and reduced mucus viscosity and expectoration in patients with airway diseases. Hasani et al. observed that humidification improved lung mucociliary clearance in bronchiectatic patients [10]. Rea et al. reported that humidification was associated with shorter duration and less exacerbation in patients with COPD and bronchiectasis [11]. There are conflicting results on adding heated humidification to continuous positive airway pressure (CPAP). However, Sommer et al. found a significant reduction in mucus transport time and an increase in ciliary beat frequency after 8 weeks of CPAP use with humidification compared with CPAP without humidification in patients with obstructive sleep apnea (OSA) [12]. Boyer et al. also found that the addition of humidification during CPAP use significantly reduced nasopharengeal discomforts, including ear, nasal, and throat symptoms, in patients with OSA [13].

10.3 Types of Humidification in NIMV

Two types of humidifiers, a heated humidifier (HH) and a heat-and-moisture exchanger (HME), are used in both short- and long-term NIMV [14]. HME is usually used in cases requiring IMV because it is easily applied and less expensive than HH. However, HME is usually placed between the Y-piece and the interface, which can create a significant amount of dead space, compared with HH, which is placed in the inspiratory limb [5].

Previous studies by Jaber et al. and Lellouche et al. that compared the physiological effects of HME and HH found that HME was associated with a significantly higher partial pressure of carbon dioxide ($PaCO_2$), greater minute ventilation, and greater inspiratory effort than HH in NIMV patients [15, 16].

Based on the physiological and clinical evidence, HH is recommended during NIMV for acute respiratory failure, especially hypercapnic patients, to minimize work of breathing and maximize carbon dioxide clearance [5].

In contrast, some authors have suggested that HME should be the first humidifier option to be used because it is more cost effective. In long-term use, both methods have similar patient tolerance and adverse effects [17].

10.4 Problems of Humidification in NIMV

Several factors may influence the effectiveness of humidification during NIMV. Leaks through the mouth or the mask can be important, as they may lead to unidirectional airflow and cause a decrease in the humidity of the air in the respiratory tract and increased nasal resistance.

Other factors that influence the efficacy of NIMV humidification include the type of interface used, the appropriate fit and use of the mask, the level of fractional

inspired oxygen, ventilator setting, ventilation mode-pressure or volume control variables, the presence of a leakage compensation system, the type of humidifier, and the hydration and temperature of the inspirated air [4].

10.5 Management of Mucociliary Activity

Mucociliary clearance is an essential part of the respiratory defense system. Adequate humidification is directly related to mucociliary clearance, and while providing the optimal conditions for humidification may be difficult, delivering inspiratory gas under conditions that are less than optimal, including temperature (37 °C) and RH (100%), may lead to decreased mucociliary function and a reduced volume and quality of secretion [1]. In airway diseases characterized by hypersecretion, such as COPD and bronchiectasis, impairment of mucociliary activity with NIMV use can result in the development of secretion plugs, ventilator-associated pneumonia, and NIMV failure [11, 18].

10.6 Recommendations

Humidification is recommended for every patient receiving IMV (1A); however, there is currently no clear consensus regarding routine humidification for NIMV, regardless of the length of usage. The American Association for Respiratory Care (AARC) guideline recommends humidification during NIMV, as it may improve patient adherence and comfort [5]. The American Association of Sleep Medicine has also recommended the use of humidification as a measure to increase comfort and observance in OSA patients who used CPAP [19]. HH is recommended as AARC can increase compliance and comfort instead of HME in patients using NIMV due to the additional dead space created and increased respiratory effort and $PaCO_2$ (2B) [5].

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Aerosol Therapy

11

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11.1 Introduction

Aerosol therapy has an important role in the management of obstructive lung diseases [1]. However, many of these patients commonly develop chronic hypoventilation or are subject to exacerbations, both of which often require implementation of

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_11

noninvasive ventilatory support. Noninvasive ventilation (NIV) exerts its beneficial effect by reducing the work of breathing, resetting the respiratory center, and improving acid-base and gas exchange disturbances [2]. Although, when aerosol therapy is required, a patient can be temporarily disconnected from the NIV machine and connected back when treatment is finished, this method will increase nursing workload, is time-consuming, and could place the patient at a higher risk for respiratory deterioration in cases of acute severe respiratory failure. On the other hand, one might argue that, if these two treatments are combined, they can exert an augmented physiologic and clinical effect on the outcomes of patients with obstructive lung diseases [3, 4]. However, despite the fact that concurrent aerosol administration during NIV therapy is very common in clinical practice, the optimal strategy for combining these two modalities has not been clearly demonstrated. Issues that should be addressed when administering aerosol therapy, while maintaining NIV treatment, include the type of nebulizer, the optimal position of the aerosol exit port, ventilator settings, and how aerosol and NIV therapy may influence each other's performance. The main issues pertaining to the practice of aerosol therapy during NIV will be outlined in this chapter.

11.2 Aerosol Mechanics

Aerosols are liquid or solid particles suspended into a gas medium. The particle size can vary widely depending on the type of the substance, the method of delivery, and environmental conditions. Aerosols are commonly described according to their mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD). The former is expressed in micrometers (μm) and represents the diameter which separates the total aerosol mass into two halves, based on whether the particle size is higher or lower than MMAD. The latter quantifies the variability in particle size and is calculated as the ratio of MMAD to particle diameter at ±1 standard deviation, i.e., at 15.9 and 84.1% of the probability distribution scale. A perfect monodisperse aerosol has a GSD of 1 indicating that all particles have equal diameters. A polydisperse aerosol is defined based on a GSD > 1.22; as a rule, pharmaceutical aerosols are polydisperse with a GSD ranging between 2–3 [1, 5, 6].

Aerosol lung deposition (AD) can occur in three ways: inertial impaction, sedimentation and Brownian diffusion. Air velocity and turbulence, particle size, and bronchial branching hierarchy are among the most important variables influencing AD [1, 5–7]. Inertial impaction involves particles with a diameter >5 μm and is the predominant mechanism of deposition at the oropharynx and larger conducting airways (e.g., larynx, trachea), where air velocity and turbulence are higher. Particles with a diameter 1–5 μm are deposed at later generations of conducting airways mainly by sedimentation. Particles with a diameter <0.1–1 μm are more likely to reach the gas exchange zones by diffusion, where they collide with gas molecules and are finally deposed; however, a significant portion of these particles remain in suspension and eventually exhaled. The proportion of particles with a diameter

<5 μm represents the aerosol fine particle fraction (FPF) and as a rule therapeutic aerosols contain particles in the range of 1–5 μm which are more likely to travel beyond the upper airways and eventually reach the lungs [1, 5, 6]. Several other factors may also influence AD, including heterogeneities in the distribution of airflow across different lung regions, regional pathology, chronic inflammation, airway remodeling, inhalation technique, airway humidity, mechanical ventilation parameters, and the type of aerosol generating device [8].

11.3 Aerosol Generating Devices

Various types of aerosol generating devices are available for the delivery of inhaled drugs. Among these, pressurized metered dose inhalers (pMDIs) and different types of nebulizers (pneumatic jet, ultrasonic, and vibrating mesh nebulizers) are the ones most commonly used for the provision of inhaled therapy in patients receiving noninvasive ventilatory support.

A pMDI is a pressurized aluminum canister containing the inhaled drug in the form of ionized powder or aqueous solution combined with a volatile propellant. To deliver the drug, the canister is inverted and pressed toward an "actuator" that pushes the suspension into a metering chamber, which regulates the dose emitted through the inhaler's nozzle. The ejected suspension forms a plume moving at a very high speed; however, within a short time interval (0.1 ms), the propellant evaporates, reducing the size and increasing the velocity of the plume. pMDIs can be adapted to spacers or 1-way valve holding chambers, which slow down the aerosol plume even more and thus can improve aerosol delivery in patients with poor coordination [1, 5, 6].

A pneumatic jet nebulizer is driven by compressed air provided either by an oxygen source or a compressor. The high-pressure jet passes through a nozzle creating a lateral pressure drop which draws up the liquid drug solution into a capillary tube and entrains it into the gas stream creating droplets of various sizes. These droplets collide into one or more baffles forming smaller particles, which remain in suspension, and are inhaled by the patient, while larger particles fall back into the solution. The baffles are essential for optimal drug delivery because they reduce both particle size (MMAD) and their dispersion (GSD) [1, 9]. Jet nebulizers, however, produce aerosols with a larger GSD than pMDIs and thus their FPF is comparatively lower [10]. Breath-enhanced jet nebulizers increase aerosol delivery by 35–50% by entraining ambient air during inhalation, while breath-actuated nebulizers synchronize patient's breathing effort with aerosol delivery increasing AD (up to 3 times) and reducing drug waste [5, 11].

Ultrasonic nebulizers employ a piezoelectric crystal that vibrates at a frequency of 1.2–2.4 MHz. These sonic waves are transmitted to the drug container, creating oscillation waves and generating a fountain of droplets, which breaks into smaller particles to be inhaled by the patient. The higher the amplitude of the waves, the larger the nebulizer output with a frequency of 2.25 MHZ yielding particles with a MMAD of 2.5 μm [1, 9].

Vibrating mesh nebulizers can be either active or passive systems. Active systems consist of a domed plate with >1000 tapered apertures positioned under the drug solution container. These apertures are wider on the liquid side and smaller on the aerosol exit side. The mesh is connected to a piezoceramic system which vibrates at a frequency of 130 KHz forcing the apertures to move up and down by 1 μm. In this way, the liquid is pumped through the apertures yielding fine particles with a MMAD of 3–5 μm depending on the exit diameter of the aperture plate. In passive systems, the aperture plate is static and the liquid is forced through the apertures by the vibrations of a transducer horn connected to a piezoelectric crystal [1, 9]. Mesh nebulizers can deliver triple the dose of jet nebulizers, are less noisy, have minimal residual volume and faster treatment time, although they are more expensive [9].

11.4 Aerosol Therapy During Noninvasive Ventilation

Noninvasive ventilation is usually provided with either bilevel machines or intermediate type ventilators. Both systems consist of a single-limb circuit, an interface (which could be a nasal, oronasal, or a total face mask) and an exhalation device. In the case of bilevel machines, the exhalation device is usually a calibrated leak port which can be connected inline to the circuit or integrated into the interface. In bilevel machines, ventilation is provided in the pressure-preset mode which functions by switching from a lower pressure during expiration (expiratory positive airway pressure, EPAP) to a higher pressure during inspiration (inspiratory positive airway pressure, IPAP). Intermediate type ventilators allow the practitioner to choose from an array of different ventilatory modes, including pressure-preset, volume-preset and hybrid modes, while air exhaustion is achieved via a unidirectional exhalation valve. Modern intensive care unit (ICU) ventilators utilize double-limb circuits for ventilation provision and some of them also incorporate NIV modes that compensate for leaks in a manner similar to NIV-dedicated machines [12].

Although NIV implementation may theoretically favor AD by increasing tidal volume, reducing respiratory rate and particle size and exerting a bronchodilatory effect per se [3, 4], high flow rates and NIV-generated turbulent streams could counteract this effect [13, 14]. However, in a scintigraphic study of jet nebulization in 13 healthy volunteers, Maccari et al. observed no difference in AD between spontaneous breathing, continuous positive airway pressure (CPAP), and NIV [15]. No significant difference in AD between jet nebulization alone and jet nebulization coupled with NIV was also observed in another scintigraphic study of 21 individuals with asthma with moderate-to-severe exacerbation [16]. Nevertheless, a number of experimental and clinical studies have explored strategies that would optimize AD without interrupting NIV treatment.

11.4.1 Technical Aspects

Several bench and human studies have explored strategies to optimize AD with respect to the choice of the aerosol generating device, its position in the circuit, the

role of ventilatory mode, and the interaction between NIV and aerosol therapy. In a lung model study, in which 5 mg of albuterol (driven by a jet nebulizer at 8 L/min) were administered, Chatmongcolchart et al. evaluated AD according to the position of the aerosol exit port (distal or proximal to a Whisper-Swivel II port attached to a single limb circuit), at various combinations of IPAP and EPAP, and at two breathing frequencies (10 and 20 breaths/min). This study showed that AD was maximal (25% of the nominal dose) when the aerosol exit port was placed between the interface and the leak port with the breathing frequency set at 20 breaths/min; however, when the aerosol exit port was positioned proximally to the leak port, AD was optimal at 10/breaths/min. Importantly, a higher IPAP and a lower EPAP were associated with an improved AD [17]. More recently, Sutherasan et al. evaluated AD for bilevel and CPAP modes using three types of configurations: a vented mask and a non-vented mask with the aerosol exit port positioned either proximally or distally to the leak port (Whisper-Swivel II); 5 mg of albuterol were administered by a jet nebulizer driven at 8 L/min. AD was similar at CPAP levels of 5 and 10 cm H_2O, while in the bilevel mode the maximum AD was achieved at the 15/5 cm H_2O setting (as compared to 10/5 and 20/10 cm H_2O). In both modes and in all combinations of ventilatory settings, AD was minimum with the vented mask and maximum when the non-vented mask was used with the aerosol exit port placed distally to the leak port. Thus, at a bilevel setting of 15/5 cm H_2O, AD was 13.5% of the nominal dose with the vented mask, while when the non-vented mask was used, AD was 25.2% with the distal and 13.5% with the proximal configuration, respectively. At a CPAP of 10 cm H_2O, the respective numbers were 11.5, 23.9, and 32.8% [18]. Dai et al. used a jet nebulizer (delivering a nominal dose of 5 mg of albuterol at 8 L/min) to evaluate the role of the type of leak port in AD with respect to the position of the aerosol exit port in the circuit. They compared a single arch leak port (circumferential leak), a plateau exhalation valve, and a Whisper-Swivel II leak port. Among the various combinations, the highest AD was observed with the single-arch port with the aerosol exit port placed close to the ventilator outlet; the lowest AD was observed with the same leak port when the aerosol exit port was positioned between the lung simulator and the exhalation valve; a higher IPAP was associated with improved AD [19].

Branconnier and Hess conducted a bench study to evaluate AD during NIV treatment using either a jet nebulizer or a pMDI. This study tested two types of configurations, a vented mask with the leak port incorporated into the mask apparatus and a non-vented mask with a leak port attached to the circuit. For nebulizer studies, the aerosol exit port was positioned between the mask and the leak port and 5 mg of albuterol were delivered at 8 L/min; for pMDI studies, 100 μg of albuterol were given via a spacer placed between the mask and the circuit. This study demonstrated that AD did not differ between the pMDI and the jet nebulizer when the non-vented mask was used; however, AD was significantly lower for jet nebulizer with the vented mask, although no such interaction was observed with the pMDI. In addition, when the pMDI was used, AD was optimized when the canister was activated during inhalation [20]. Abdelrahim et al. also compared a jet and a mesh nebulizer in terms of AD; both devices effected a better AD when the aerosol exit port was placed between the lung simulator and the leak port; however, AD

was better for the mesh nebulizer because of its smaller dead volume [21]. Michottte et al. also evaluated the role of the aerosol exit port position on AD (500 mg of amikacin) by comparing three vibrating mesh nebulizers, one jet nebulizer, and one ultrasonic nebulizer. Overall, the highest performance was observed with the mesh nebulizers when the aerosol exit port was placed between the lung model and the leak port (Whisper-Swivel II); this position was associated with a higher inhaled dose and a low exhaled wasted dose. On the contrary, the ultrasonic nebulizer was associated with the highest total wasted dose regardless of the position in the circuit [22].

Some of these questions were also addressed by experimental studies in healthy volunteers and patients with obstructive diseases. Thus, in a study of 24 healthy volunteers, in which 5 mg of salbutamol were delivered by either a jet or mesh nebulizer connected to a single-limb circuit, Saeed et al. reported a better AD with the mesh nebulizer; while AD increased with both types of nebulizers with an increase in the fill volume, this effect was more pronounced with the jet nebulizer [23]. The same group examined these issues in a group of 12 patients with chronic obstructive pulmonary disease (COPD). In this study, a mesh nebulizer was associated with a higher systematic absorption of salbutamol, which was not influenced by the solution's fill volume and the circuit humidification status; however, the performance of the jet nebulizer improved when the filling volume was increased [24]. Hassan et al. used a single-limb bilevel ventilator to assess AD in 21 COPD patients with three types of aerosol generators: pMDI plus spacer (12 puffs of 100 μg of salbutamol), jet and mesh nebulizer (5 mg of salbutamol). This study showed that the pMDI plus spacer had a fourfold and sixfold higher AD (expressed as percentage of nominal dose) compared to mesh and jet nebulizer, respectively [25]. The influence of aerosol therapy on ventilator performance and accuracy has also been investigated in some studies. In the lung model study by Chatmongcolchart et al., the ventilator performance was not influenced by aerosol administration [17]. Conversely, in another bench study simulating chronic obstructive pulmonary disease (COPD) ventilation parameters, Xu et al. observed that jet nebulization influenced tidal volume monitoring both in NIV and ICU ventilators; however, trigger time and pressure were significantly higher with the ICU ventilators [26].

11.4.2 Lung Function Variables

The effect of aerosol therapy on lung function variables when delivered concurrently with NIV has also been investigated by several clinical studies. Pollack et al. prospectively randomized patients with acute asthmatic exacerbation to either jet nebulization alone ($n = 60$) or jet nebulization combined with NIV ($n = 40$); both groups received two doses of 2.5 mg of albuterol, 20 min apart and peak expiratory flow (PEF) was assessed at baseline and at the end of treatment. Although both groups exhibited significant improvements in average PEF, this effect was more pronounced in the NIV plus nebulization group as compared to the nebulization-only group [27]. Likewise, Brandao et al. randomized 36 patients with asthmatic

exacerbation to jet nebulization alone (control group), NIV plus nebulization with a low EPAP (IPAP 15 cm H_2O, EPAP 5 cm H_2O; group 1), and NIV plus nebulization with a high EPAP (IPAP 15 cm H_2O, EPAP 10 cm H_2O; group 2); all three groups were similar regarding the baseline lung function variables. At 30 min post-treatment, PEF, FEV_1 and FVC in group 2, but only PEF in group 1 were significantly higher compared to the control group. The difference in response between group 1 and 2 was attributed to the NIV bronchodilatory effect at higher EPAP levels [28]. In the previously mentioned trial by Galindo-Filho et al., higher improvements were observed in breathing frequency, minute ventilation, and spirometric variables in the NIV plus nebulization group compared to the nebulization-only group, despite similar scintigraphic AD [16]. Nava et al. recruited 18 stable COPD patients to assess differences in spirometric improvement between three types of treatment: pMDI plus spacer while on spontaneous breathing (400 μg of salbutamol); pMDI plus spacer on single-limb NIV (400 μg of salbutamol); and 5 mg of salbutamol by intermittent positive pressure breathing (IPPB). At 15 min post-treatment all modalities effected similar improvements in FEV_1 (10.8 ± 11.4% for spontaneous breathing; 9.6 ± 8.8% for NIV; and 7.9 ± 7.1 for IPPB) compared to control (placebo delivered by pMDI plus spacer). In a separate group of eight patients, they observed that although FVC increased significantly when NIV was coupled to either albuterol or placebo, FEV_1 increased only with albuterol [29]. Bodet-Contentin et al. also randomized COPD patients to NIV plus salbutamol (n = 21) vs. NIV plus placebo (n = 22); all treatments were administered using an ICU ventilator. This study observed no improvement in FEV_1 with salbutamol compared to placebo at 15 min (−20 mL vs. −35 mL); however, a minor improvement for the salbutamol group was noted at 55 min (30 mL vs. −50 mL) [30]. More recently, Avdeev et al. enrolled 30 NIV COPD patients, treated with NIV due to exacerbation, in a prospective, randomized, crossover study, which compared a jet and a mesh nebulizer in terms of short-term functional improvement. At 120 min following administration of 2.5 mg of salbutamol, significantly higher increases were noted with the mesh nebulizer in FEV_1 (165 vs. 116 mL) and in FVC (394 vs. 123 mL) [31].

11.5 Conclusions and Key Points

- Particles with a MMAD at the range of 1–5 μm represent the respirable portion of therapeutic aerosols.
- pMDIs and various types of nebulizers (jet, ultrasonic, and mesh nebulizers) are commonly used for the delivery of aerosol therapy in patients under NIV.
- Non-vented masks are associated with less drug loss compared to vented masks. When non-vented masks are used, the aerosol exit port should be placed between the interface and the leak port. A higher IPAP is associated with improved AD.
- Mesh nebulizers produce less noise, have smaller residual volume, and are very effective in providing aerosol therapy during NIV. Jet nebulizers are less effective and require a high fill volume to optimize their output. pMDIs when used

with a spacer and actuated during inspiration are very efficient in delivering aerosol therapy during NIV treatment.
- Close monitoring of ventilator performance during aerosol administration is warranted.
- The administration of aerosol therapy concurrently with NIV treatment may achieve higher acute improvements in functional variables than aerosol therapy alone, although this can be the sole result of the mechanical ventilation bronchodilatory effect.

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Part V

Methodology; Patient-Ventilator Interaction

How to Start Noninvasive Ventilation: Preparation of the Patient, Interface, and Primary Ventilator Setting

12

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12.1 Introduction

Over the past three decades the efficacy of noninvasive ventilation (NIV) has been proven for different clinical conditions (e.g., cardiogenic pulmonary edema, acute exacerbations of chronic obstructive pulmonary disease, and acute respiratory

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_12

failure [ARF] in immunocompromised patients) [1]. However, efficacy demonstrated in clinical research does not automatically imply clinical effectiveness in practice. Several premises have to be fulfilled to make the (first) NIV-session a successful one. Assuming that you have been adequately trained for this task (for further details see Chap. 80) and have chosen the right patient (see Chaps. 21 and 22), the following obstacles have to be considered when initializing VNI: (1) the appropriate choice of the ventilator and interface; (2) the preparation of the patient by means of a reassuring approach; (3) primary and secondary ventilator settings; (4) monitoring of the NIV session; and (5) how to deal with possible NIV failure.

Remarkable improvements in the management of NIV have been achieved, even though there were various prejudices and some real problems to overcome. Generally, minor side effects such as rhinorrhea or excessive dryness of the nose and mouth, conjunctivitis, and even anisocoria (in the case of anticholinergic drug nebulization) are quite frequent and have to be explained to the patient in advance. Provided that the patient is cooperative, a possible intolerance to the interface is addressed by careful choice of mask and appropriate initial ventilator setting (see below and Chap. 2). With increasing experience, even so-called difficult cases of ARF may be treated with NIV. In most cases, a short NIV trial is justified, but reasonable endpoints have to be defined and monitored accordingly (e.g., respiratory rate, pH, pCO_2, pO_2, $SatO_2$). A rapidly deteriorating clinical situation requires immediate oro-tracheal intubation [2, 3]. Thus, invasive mechanical ventilation must not be delayed under any circumstances. Another myth, claiming that NIV is a difficult and time-consuming procedure for nurses, has eventually been refuted. Indeed, if NIV may be a little more onerous in the first few hours of treatment, then this effect consecutively disappears and, at least in specialized environments, does not seem to affect the caregivers' overall workload. Minor sedation for increasing the patient's tolerance towards NIV is no longer absolutely contraindicated and may be used with close monitoring in appropriate settings.

In this chapter, we focus on the fundamental principles of how to start assisted NIV (leaving out controlled NIV) in the acute-care setting.

Finally, we would like to emphasize that not all issues depicted in this chapter are based on clear evidence. In this case, however, we tried to furnish best practice based on international guidelines and/or on the authors' plurennial clinical experience. We anticipate that some topics, addressed by ongoing studies, might become better defined in the near future. Nevertheless, guidelines are always just a framework of evidence and best clinical practice and have to be implemented according to individual patient factors, local preferences, and clinical judgement.

12.2 Ventilators and Interfaces

These two topics are thoroughly discussed in Chaps. 2 (*Interfaces for noninvasive mechanical ventilation*) and 6 (*Ventilators for noninvasive mechanical ventilation*). Some general and important remarks are outlined in this chapter, though.

Interfaces bridge the patient's airway to the ventilator circuit. All in all, six types of interfaces are commercialized for applying positive pressure to the upper airway: full-face (or oronasal) mask, total face mask, nasal mask, mouthpieces, nasal pillows or plugs, and the helmet. For the first NIV session in ARF, an oronasal mask is commonly used. In general, you should avoid too large a mask. Intolerance versus the oronasal mask does not automatically imply consecutive NIV failure; try another mask (e.g., total face mask or nasal mask).

We would like to stress the fact, that – in contrast to invasive mechanical ventilation – NIV is a somewhat "leaky" procedure that may result in two specific problems: unintentional air leaks and a variable resistance imposed by the upper airway. These intrinsic issues may compromise the delivery of an effective tidal volume and have to be considered and adequately handled.

Both, modern Intensive Care Unit (ICU) ventilators and specific home ventilators may be used to deliver NIV. Nowadays, they all have integrated modes that compensate for air leaks and sophisticated trigger systems to accomplish efficient and synchronized ventilation with minimal rebreathing of CO_2.

12.3 How to Approach the Patient

Fitting the mask, selection of appropriate ventilator settings, and patient coaching are of paramount importance to deliver NIV in a safe and effective way. The skills of the caregivers and their degree of experience are essential for the success of the technique. Collaboration among physicians, respiratory therapists, and nurses is crucial. The most important points are explained below and listed in Table 12.1.

Table 12.1 Synopsis of the crucial initial steps when starting the first NIV session

Equipment	Before addressing the patient, all necessary equipment is ready and you are familiar with each device
Patient	Usually awake, responds, gives informed consent
Explanation to patient	How NIV works and its goals, limits of care/ possible therapeutic options
First NIV session	Silence alarms, hold the mask in place (do not immediately apply straps)
	Titrate PS to patient comfort; check for accessory muscle use and respiratory rate
	Titrate PEEP for SpO_2, trigger effort and counterbalance of intrinsic PEEP (abdominal muscle contraction)
	Titrate FiO_2 for a $SpO_2 \geq 90\%$
	Fix the mask but avoid a too-tight fit; small leaks are acceptable
	Ask for a feedback (breathing more/less comfortable); continuously reassure the patient

NIV noninvasive ventilation; *PS* inspiratory pressure support; *PEEP* positive end-expiratory pressure; *SpO_2* peripheral capillary oxygen saturation

- *Instruction of patient*: the initial approach to the patient should consist in showing the various pieces of the equipment and illustrating briefly how they work [4]. The clinicians should reassure and motivate the patients to collaborate and instruct them to coordinate their breathing with the ventilator's cycles before starting and during NIV. Informed consent should be obtained whenever possible.
- *Hands on patient*: Once having placed the interface gently over the patient's face, it should be held in place manually for 1–2 min, with ventilator support delivered while adjustments are made. The mask should be secured with the straps only after being sure it fits comfortably and avoiding any excessive tightness (just enough to avoid major leaks). It should be possible to place two fingers easily between the straps and the patient's head.
- *Coaching*: fears and discomfort should be recognized and promptly addressed. To reduce stress and improve comfort, positioning the patient in the bed in an appropriate way is particularly important. Supportive devices such as pillows, rolls, and blankets can aid in providing comfort and safety. Attention should be paid to elevate the head of the bed to 60°–90°.
- *Pharmacologic support*: whenever possible, clinicians should manage patients without sedation. Sometimes it may be necessary to administer low doses of propofol, benzodiazepines, or opiates. In that case, caution is advised to prevent alveolar hypoventilation or loss of airway protection. Clonidine or dexmedetomidine could be an option that provides sedation without decreasing the respiratory drive [5].
- *What else*: if possible, an arterial catheter should be inserted for invasive blood pressure monitoring and measurement of arterial blood gases. NIV can be applied continuously or intermittently, depending on the patient's compliance and respiratory conditions. To avert NIV failure, continuous bedside care is needed during the first 1–2 h to assess patient's cooperation, the patient–ventilator interaction, the respiratory mechanics, the hemodynamic parameters, and the neurological status.

12.4 Primary and Secondary Ventilator Settings

Initial ventilator settings are paramount to ensure good patient tolerance and improved gas exchange. In the following, we will share with you our standard ventilator settings for the initial NIV session. A synopsis of the most important set parameters is listed in Table 12.2.

- *Inspiratory pressure support*: although the clinical conditions that require the use of NIV are manifold, one of the fundamental objectives is to put the inspiratory muscles to rest. We recommend choosing the initial inspiratory pressure support (PS) so that an exhaled current volume of 6–8 mL/kg (ideal body weight) may be achieved. Usually, this goal is easily realized within the first 5–10 min, starting with a low level PS (3–5 cm H_2O) and subsequent gradual increases by steps of

Table 12.2 Initial ventilator setting for the first NIV session

PS	3–5 cm H_2O
PEEP	3–5 cm H_2O
FiO_2	Titrate for $SpO_2 > 90\%$
Inspiratory trigger	Flow-based, very sensitive
Cycling	Flow-cycled; 50% for COPD and 20% for other forms of ARF
Pressurization rate	0.10 s
Alarms	Silenced for very first moments

ARF acute respiratory failure, *FiO_2* Fraction of inspired oxygen, *PEEP* positive end-expiratory pressure, *PS* inspiratory pressure support, *SpO_2* peripheral capillary oxygen saturation

2–3 cm H_2O at a time, collaterally evaluating air leaks (< 0.4 L/s or < 25 L/min) and patient tolerance. This procedure generally gives the patient time to become familiar with the treatment and the operator gradually evaluates the responses. PS is generally adjusted to render the inspiratory flow on the flow-time-curve as descending as possible.

- *Positive end-expiratory pressure*: The initial approach regarding positive end-expiratory pressure (PEEP) follows the logic described above, with a cautious start at 3–5 cm H_2O until it gradually reaches a clinically valuable target (adequate oxygenation, trigger effort, and counterbalancing of intrinsic PEEP). The summative evaluation of pressure applied to the airways requires subsequent selective variations of PS and PEEP, simultaneously observing what effect each altered variable has on the patient–ventilator interaction. When using a helmet, it is often recommended to use the highest PEEP and PS levels clinically indicated and tolerated by the patient to increase the elastance of the system and enhance the trigger sensitivity [6]. Ensure that for every increase in expiratory pressure you accomplish an equivalent increase in inspiratory pressure is achieved to maintain the same level of PS.
- *Fraction of inspired oxygen*: The fraction of inspired oxygen (FiO_2) should be titrated to achieve a $SpO_2 > 90\%$.
- *Inspiratory trigger*: The inspiratory trigger is primarily flow-based and is set as sensitive as possible (Cave: risk of auto-cycling) [7].
- *Cycling*: appropriate switching from inspiration to expiration should be flow-cycled and preferably match the end of the patient's inspiratory effort. We recommend a primary cycling setting of 50% peak expiratory flow for obstructive lung diseases and about 20% for other kinds of acute respiratory failure. Remember that retarded cycling (<20% peak flow) may increase inspiratory time, while faster cycling (>50% peak flow) in COPD patients is generally useful, as it reduces the risk of delayed cycling, intrinsic PEEP, and ineffective respiratory efforts.
- *Pressurization rate*: a correct pressurization rate (pressurization rise time) is important to decrease inspiratory effort and improve synchronization. However, this setting should be tailored to the patient's tolerance and comfort (check for changes in dyspnea, air leaks, double triggering, and work of breathing). An initial pressurization slope of 0.10 s might be suitable for most patients.

- *Ventilator alarms*: Initial priority ventilator alarm settings should be balanced to ensure high patient safety with little noise disruption and nuisance for care providers. Thus, for the very first minutes silence the alarms. Successively, reasonable alarm modalities are a disconnection alarm (for accidental removal of interface/ventilator circuit) as well as an appropriate backup rate or apnea alarm (in case of inadequate respiratory drive); low pressure alarm should be set above the PEEP level. Monitoring the patient's responses to NIV using low or high tidal volume, minute ventilation, and respiratory are also important.

12.5 Monitoring of the First NIV Session

To assure the success of NIV, the patient should be monitored carefully at the initiation of NIV and regularly thereafter. The aim of patient monitoring is to determine whether the initial goals are being achieved, including relief of symptoms, reduced work of breathing, improved or stable gas exchange, good patient–ventilator synchrony, and patient comfort. Close monitoring is compulsory, especially during the initial period and then every 15–30 min for the first 2 h of NIV therapy. Frequency of subsequent assessments will depend on the evolution of the patient status. When improvement is slow or if there is concern about deterioration, more frequent assessments should be made.

We recommend tight evaluation of:

- Subjective response of the patient (respiratory distress, dyspnea, anxiety, claustrophobia, mask discomfort, inadequate or excessive airflow, dryness of mouth or eyes). A good subjective response is important for NIV success and should be attained with all means. Alleviation of dyspnea depends on adequate provision of ventilator support and the ability of the patient to relax enough to allow the ventilator to assume some of the breathing workload. Some patients get very anxious when the mask is applied and need reassurance, coaching, or even sedation. Comfort is important as well and is related to the kind of interface, applied mask fit pressure, ventilator settings, and synchrony.
- Objective findings (respiratory and heart rate, blood pressure, level of consciousness, accessory muscle use, comfort, skin breakdown). Appropriate ventilator settings will result in a reduction of dyspnea, tachypnea, and the use of the accessory muscles of ventilation. Inspiratory activation of accessory muscles usually indicates insufficient PS, and activation of expiratory muscles may suggest inappropriate settings of cycling-off or of PEEP-level.
- Ventilator parameters (tidal volume, minute ventilation, leak under mask or through mouth, inspiratory/expiratory pressure setting, flow-pressure waveforms). After having unloaded the respiratory muscles from excessive work, you should start to reduce PS, accepting a level of respiratory activity compatible with muscle resources. Monitoring of tidal expiratory volume is important to assure adequate alveolar ventilation; a high tidal volume (>9.5 mL/Kg ideal body weight), in patients with moderate-to-severe hypoxemia, has been associ-

ated with NIV failure [8]. Patient–ventilator asynchrony and air leaking are assessed through patient bedside observation and flow/volume/pressure waveform analysis. Asynchronies should be managed by reducing the leakage, tuning the inspiratory trigger, adjusting the level of PS, pressurization rate, and cycling.

- Gas exchange (pulse oximetry, arterial blood gases at baseline and 30–60 min after initiation). Improvement of SpO_2, pH, and $PaCO_2$ within 1–2 h of ventilator support usually indicates NIV success. The HACOR score (Heart rate, Acidosis, Consciousness, Oxygenation, Respiratory rate) is a potentially useful bedside tool for the prediction of NIV failure in hypoxemic patients [9].

12.6 Preventing and Solving Problems

The success of NIV depends not only on the cause of ARF and patients' characteristics but also on when NIV is started and the setting in which the patient is treated [10]. Early use of NIV is advocated because the opportunity for a successful start might be lost if delay occurs and the patient's underlying disease progresses too far. Optimum staffing and location for delivery depend on the severity of illness, monitoring capabilities, and experience of the staff. The closely monitored intensive care setting allows safe application of NIV even in very sick patients. To manage such patients, a trained staff, familiar with the technique, is needed. The above-mentioned elements were critical in investigational trials and may constitute a significant limiting factor for NIV success.

Clinicians must be prepared to intubate promptly if goals are not met (i.e., adequate oxygenation, good cooperation, airway protection, hemodynamic stability). If a patient does not improve on NIV within 1–2 h of initiation, intubation should be considered. Delay in intubation runs the risk of respiratory or cardiac complications with related morbidity and mortality. Predictors of NIV failure are thoroughly discussed in Chaps. 21 and 22. NIV should not be used when patients are unable to protect their airway. For patients with impaired mental status, swallowing impairment, copious secretion and a weak cough reflex, orotracheal intubation should not be delayed.

Selecting the correct interface size is critical. A common mistake is choosing a mask that is too large. This results in air leaks, patient discomfort, and decreased effectiveness. Leaks through the mouth are not uncommon when using a nasal mask. When mouth leaks interfere with the effectiveness of ventilation, an oronasal mask or total face mask should be used.

Pressure sores on the bridge of the nose can be prevented by using soft silicone seals, lessening strap tension, and applying a hydrocolloid dressing or a nasal pad at the first sign of skin inflammation. Tightening straps excessively is strongly discouraged because of discomfort and risk of ulcers. Patients might tolerate the nasal mask better than the face mask if they have claustrophobia or a frequent productive cough. Treatment breaks of 30–90 min every 3–4 h, as tolerated, reduce the risk of skin necrosis, and provide an opportunity for oral intake.

Airway humidification improves comfort and tolerance of NIV. Heated humidifiers might reduce work of breathing and carbon dioxide accumulation compared with heat and moisture exchangers by reducing dead space and flow resistance [11].

Mild gastric distention commonly occurs during NIV but is rarely clinically significant as long as the airway pressures remain below the esophageal opening pressure (PS + PEEP ≤18–20 cm H_2O). Nonetheless, vomiting and aspiration are possible complications. Routine use of a nasogastric tube is not recommended because it may disrupt the seal in the interface and promote air leaks. Moreover, the likelihood of facial skin breakdown is increased.

Other complications related to positive pressure ventilation (e.g., barotrauma, hemodynamic instability) are rare during NIV compared with invasive positive pressure ventilation. Finally, several factors should be considered before a patient is transferred from the ICU to the ward: the patient should be hemodynamically stable, the actual nurse to patient ratio should be low (more than one to four), and the experience of the ward staff needs to be adequate to assess when NIV is required or whether it is failing. Patients should be able to call for help and have no need for high FiO_2 (<50%).

12.7 Conclusion

Fitting the mask, selection of appropriate ventilator settings, and patient coaching are of paramount importance to deliver NIV in a safe and effective way. The skills of the caregivers and their degree of experience are essential for the success of the technique. Close patient monitoring is compulsory to determine achievement of the initial goals or to timely avert possible NIV failure, respectively.

Key Major Recommendations

- Before starting the first NIV session, ensure that all necessary equipment is in place and fully functional.
- The patient has to be instructed regarding the technique and expected goals and usually gives informed consent.
- Silence alarms and initially just hold the mask on the patient's face (do not immediately apply straps).
- Titrate PS and PEEP to patient comfort and improved objective findings.
- Ask for feedback and continuously reassure the patient.

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Pressure/Airflow and Volume Waveforms

13

Laura Fagetti

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13.1 Introduction

Waveform representations of pressure, flow, or volume vs time are the three scalars that we can find on conventional mechanical ventilators.

Each scalar represents the entire breath from the beginning of inspiration to the end of expiration.

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https://doi.org/10.1007/978-3-031-28963-7_13

Ventilators measure airway pressure and airway flow. Volume is derived from the flow measurement. Pressure and flow provide most of the information necessary to explain the physical interaction between ventilator and patient [1, 2].

The analysis of the waves may allow the clinician to:

- Identify asynchrony between the patient and the ventilator during inspiratory phase
- Identify the control variables set
- Evaluate the correct setting of expiratory trigger
- Obtain an indirect estimate of the presence of eventual intrinsic PEEP
- Evaluate the presence of tracheobronchial secretions
- Evaluate if the patient is under- or over-assisted.

13.2 Pressure Versus Time Scalar

This curve represents the pressure in the airway as a function of time.

In the typical graphic displayed on the ventilator, the baseline pressure indicates the EPAP (PEEP) and the maximum pressure at the end of the curve indicates the peak of inspiratory pressure. This can be a fixed or variable amount depending on the mode of ventilation [1, 3, 4] (Fig. 13.1).

It is possible to divide a breath into four phases.

1. In the first part of a respiratory act in pressure support, the ventilator recognizes the inspiratory effort by the **inspiratory trigger.** In this phase, the effort of the respiratory muscles should be able to overcome the configured inspiratory trigger.

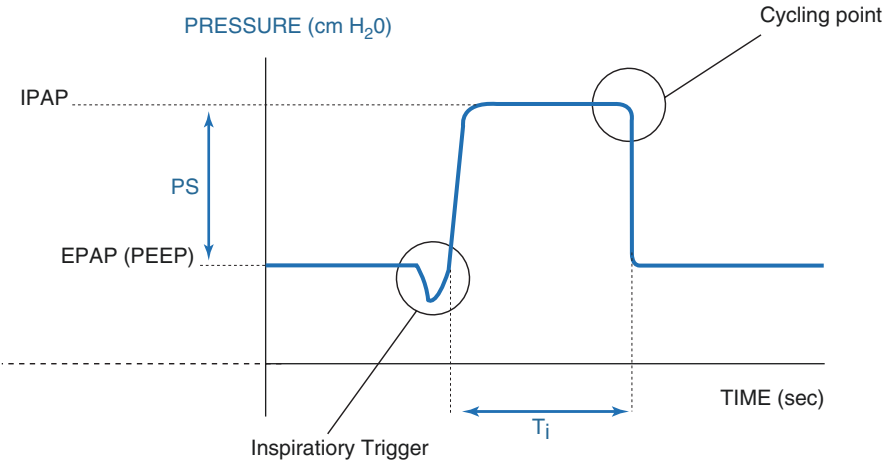

Fig. 13.1 Pressure versus time scalar

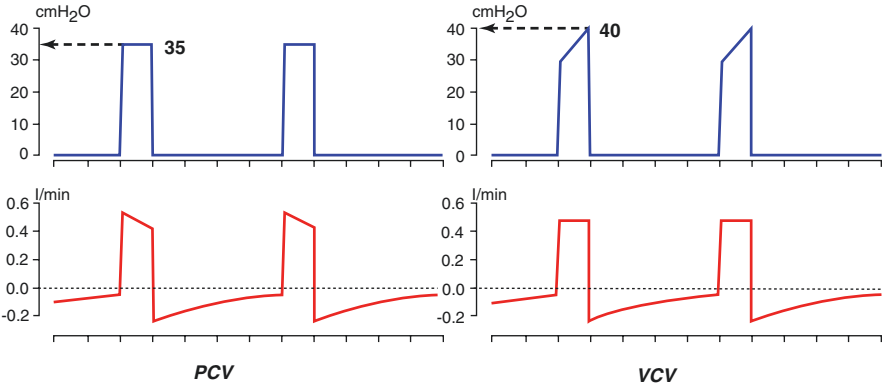

Fig. 13.2 Different waveforms for different modes of ventilation

2. Then the ventilator delivers an inspiratory flow until the configured pressure is reached (**pressurization phase**). During pressure control ventilation, when the configured pressure is reached, the pressure delivered is constant and the pressure scalar is square-shaped. In volume control ventilation, the pressure scalar is ascending due to the rise in pressure with a constant flow pattern (Fig. 13.2) [1, 4, 5].

The *inspiratory plateau level* is the pressure in the airway under static conditions, or when there is no airflow. It gives us information about reaching the limit between the phase variables and inspiratory pressure reached in the airways.

3. When the flow reaches a set value (cycling point), there is cycling from inspiration to expiration, that is, the **end of inspiration**. Ideally, the ventilator terminates inspiratory flow in synchrony with the patient's neural timing, but frequently the ventilator terminates inspiration either too early or too late, relative to the patient's neural timing. During volume-controlled ventilation, we can adjust variables that affect inspiratory time (e.g., peak flow, tidal volume). During pressure-controlled or pressure-support ventilation, we can adjust variables that affect the end of inspiration (e.g., inspiratory time, expiratory sensitivity).
4. **Expiratory phase.** The pressure returns to baseline.

13.3 Flow Versus Time Scalar (Fig. 13.3)

This curve represents the flow in the airway as a function of time.

Inspiratory flow is a positive value on the graph, whereas expiratory flow is a negative value. The area under the curve represents the volume involved during the phases of breathing [1, 4, 6].

The shape of the inspiratory limb of the curve depends on the mode of ventilation (see Fig. 13.2).

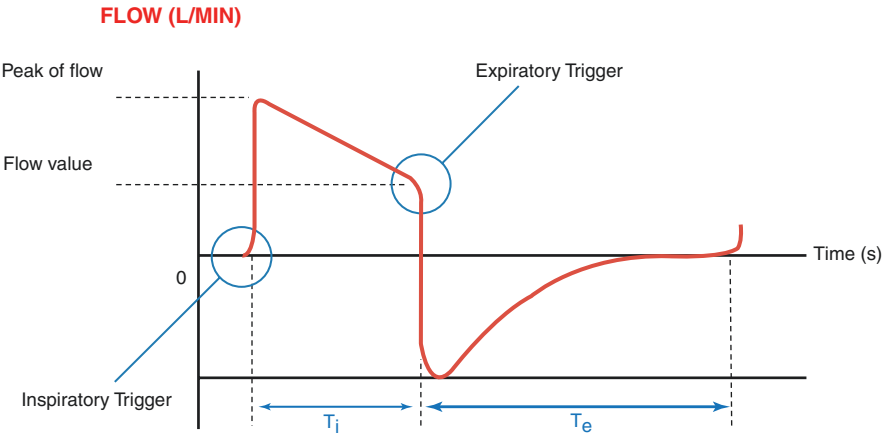

Fig. 13.3 Flow versus time scalar

In pressure-targeted modes, the peak inspiratory pressure (PIP) and inspiratory time are set and the flow is variable. The shape of the inspiratory flow is decreasing at the beginning of the breath, flow is delivered at a high rate but thendecreases during inspiration, resulting in a descending shape of the curve. Decreasing inspiratory flow is the consequence of inspiration with constant pressure. Pressure-supported modes may also have a sinusoidal flow curve.

In volume-targeted mode, the tidal volume, inspiratory time, and inspiratory flow are set, resulting in a constant flow or square shape to the flow scalar. Then there is a constant inspiratory flow and pressure in the airway increases during inspiration.

13.4 Volume Versus Time Scalar (Fig. 13.4)

The volume versus time scalar is the graphical representation of the amount of gas delivered into the lungs by the ventilator over time. It is calculated from the measurement of flow.

The ascending curve is the inspiratory volume and the descending curve is the expiratory volume [1, 3]. In a ventilation pattern without problems, inspiratory and expiratory volumes should be similar.

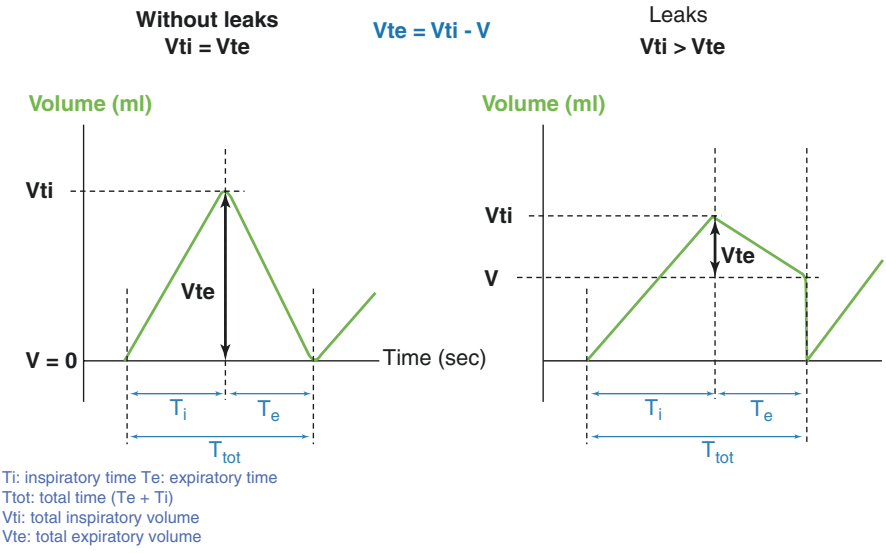

Fig. 13.4 Volume versus time scalar

13.5 Monitoring Noninvasive Mechanical Ventilation Using Ventilator Waveforms

The pressure and flow scalars provide the clinician with a wealth of information to identify problems with the phases of the ventilation. Following the sequential phases of the respiratory act, different problems can be encountered [2, 7, 8].

13.5.1 Ineffective Triggering or Ineffective Effort

It is possible to obtain much important information about the critical phase of the supported ventilatory act, that is, the activation of the inspiratory trigger by the patient.

An ineffective triggering is a decrease of pressure with an increase in flow not followed by a ventilatory cycle. In this case, the respiratory rate detected by the ventilator is lower than the real respiratory rate of the patient that is under and poorly attended [9–11] (Fig. 13.5).

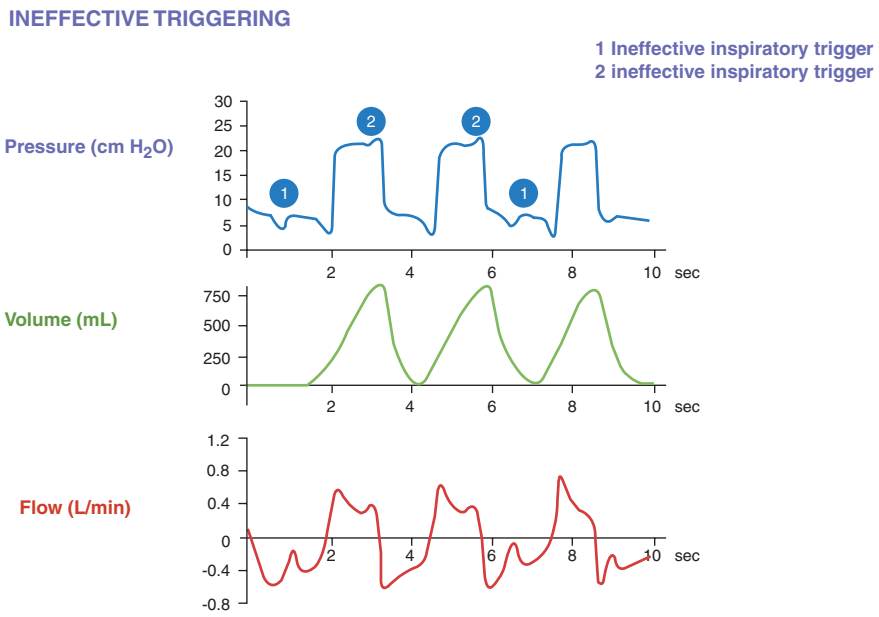

Fig. 13.5 Ineffective triggering

Cause:

- Intrinsic PEEP if the inspiratory trigger is correct
- Incorrect settings: inspiratory trigger, cycling… If we set an inspiratory trigger too strong we will ask the patient for a hard muscular effort that he/she will not be able to sustain and there will be ineffective inspiratory efforts
- Excessive inspiratory support: the high tidal volume generated does not allow a complete emptying of accumulated air

13.5.2 Autotriggering

In this case, the ventilator perceives the inspiratory trigger threshold is satisfied even when it is not due to inspiratory efforts but to artifacts. The respiratory rate of the ventilator is higher than the real respiratory rate of the patient that is poorly attended [12] (Fig. 13.6).

13.5.3 Double Trigger

In this situation, there is a sustained inspiration followed by another sustained inspiration after a very short time (<500 ms) [13] (Fig. 13.7).

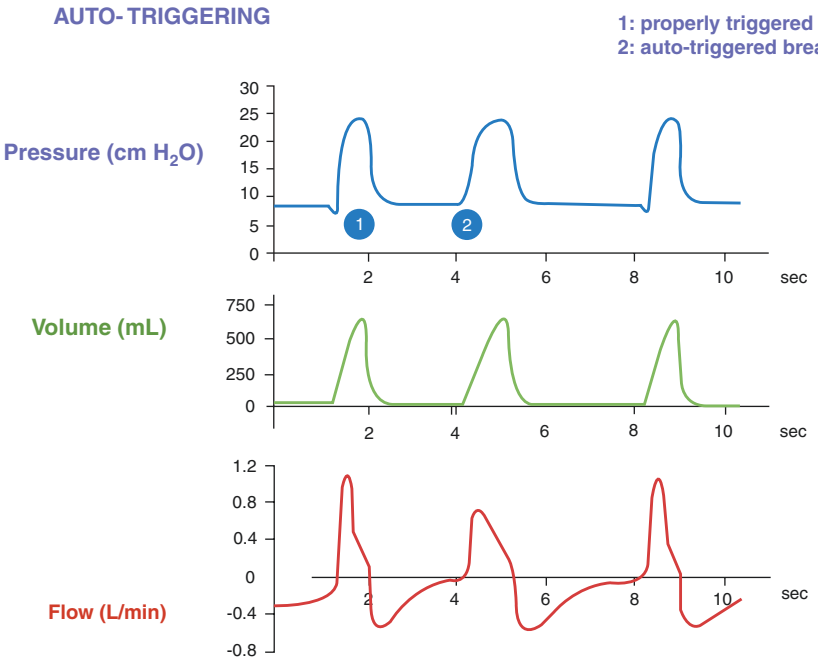

Fig. 13.6 Autotriggering

Cause:

- Secretions in the upper airways of the patients
- Secretions in the circuit
- Water in the circuit when there is a heated humidifier (especially with the pressure trigger)

13.5.4 Rise Time

Once the inspiratory trigger is started, it begins the phase of pressurization of the airway. During this time, it is possible to modify the "***pressure rise time***" In acute respiratory failure, most patients need to be supported in the ventilatory act with the lowest possible latency and as fast as possible modifying the ramp before increasing inspiratory support [11] (Fig. 13.8).

13.5.5 Hang-Up

Another classical problem with NIV is hang-up, that is, a prolonged inspiration due to leaks of the circuit. In the flow wave, there is an initial fall of the flow and then a plateau where the patient does not reach the fixed expiratory flow point to move to expiration.

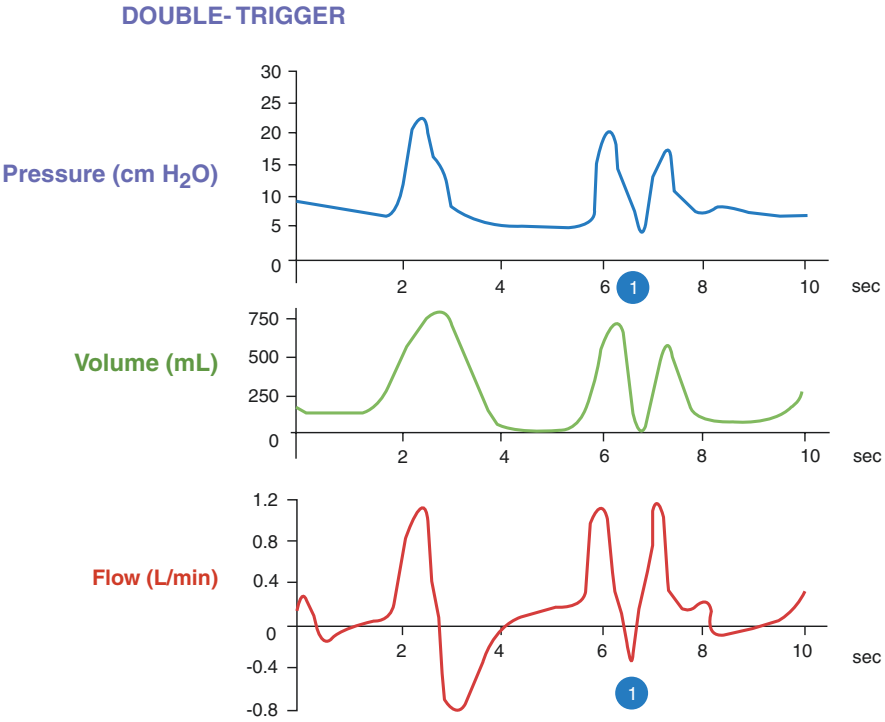

Fig. 13.7 Double trigger

Cause:

- Too high inspiratory flow
- Extremely high expiratory trigger

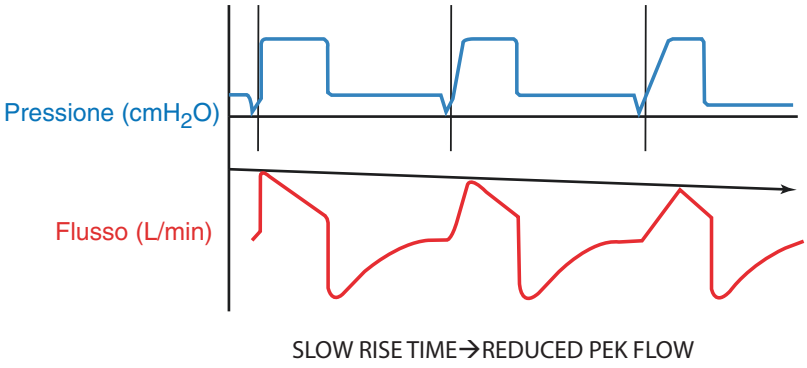

Fig. 13.8 Rise time

Cause:

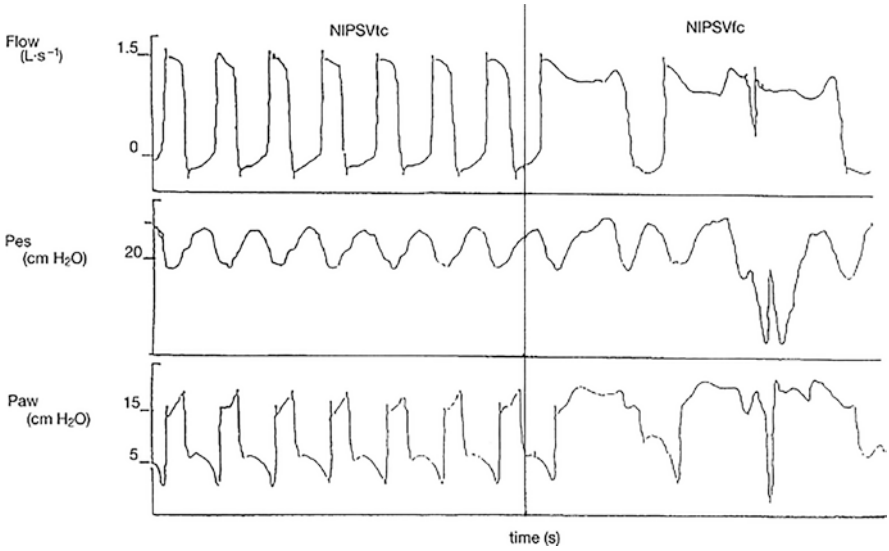

Fig. 13.9 Hang-up

- Leaks of the interface that interfere with the algorithm of the ventilator [4, 11] (Fig. 13.9).

13.5.6 Expiratory Cycling

At the end of inspiration, the analysis of waveforms can provide information about the correct configuration of expiratory cycling.

Cycle asynchrony usually occurs when there is a mismatch between the patient's inspiratory time (i.e., neural time) and the ventilator's inspiratory time.

If we set a percentage of expiratory flow too high, the neural time could be greater than the ventilator's inspiratory time (Fig. 13.10).

Consequently the ventilator ends flow delivery, but the patient's inspiratory effort continues. Premature cycling leads to a transient inversion of flow in the expiratory portion of the flow waveform. If the patient's effort exceeds the trigger threshold, it can activate another breath, generating a double trigger. The risk is the fall of tidal expiratory volume because of an excessive reduction of inspiratory time (Fig. 13.11).

If we set a percentage of expiratory flow too low, the patient initiates the exhalation while the ventilator is still delivering flow (prolonged or delayed cycling). Delayed cycling leads to a spike in pressure in late inspiration on the pressure scalar waveform. The airway of the patient remains pressurized for too long with side effects on comfort and expiratory time and dynamic hyperinflation [11, 14, 15].

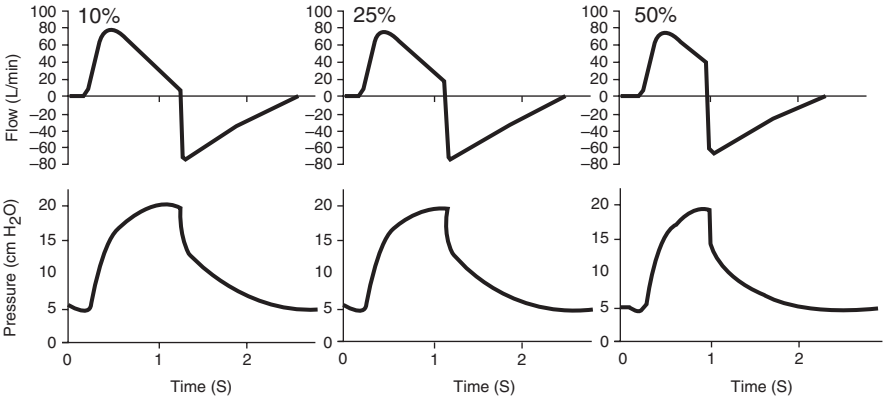

Fig. 13.10 Cycling

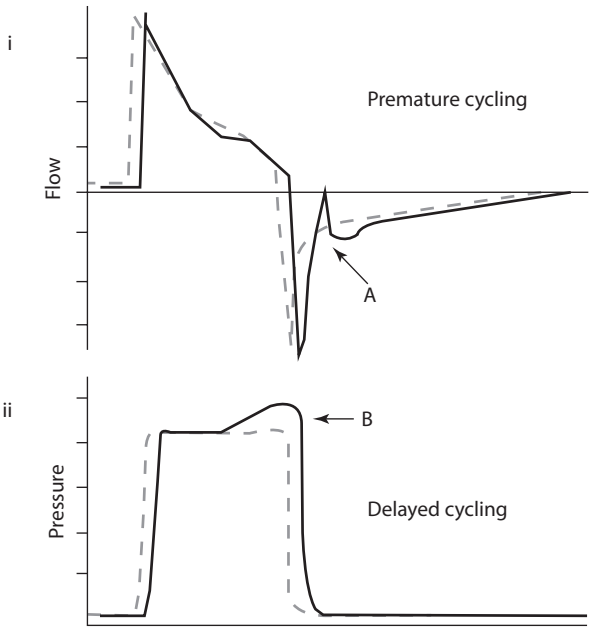

Fig. 13.11 Cycling asynchrony

13.5.7 Hyperdynamic Inflation

The shape of expiratory limb of the flow curve is affected by the resistance to airflow and the compliance of the lung. Under normal conditions, the expiratory limb of the curve returns to a baseline of zero flow prior to the next breath being initiated. However, if expiration of air is still ongoing when inspiration starts, then the lungs are not emptying completely and air trapping occurs. The persistence of flow at the end of the expiration shows that the pulmonary system is above the residual functional capacity and the flow is generated by positive elastic return of the respiratory

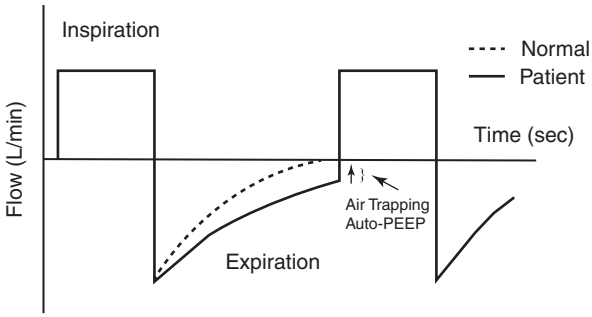

Fig. 13.12 PEEPi

system at the end of the exhalation (PEEPi). The analysis of the waves does not allow measuring PEEPi but provides an estimation of the possible presence of PEEPi [16] (Fig. 13.12).

13.5.8 Volume Scalar

The analysis of volume scalar is a completion of the analysis of pressure and flow scalar. It can be used to evaluate the volume of a patient's spontaneous breath and the effect that our adjustment of the ventilator settings can produce on volume.

In a ventilation pattern without problems, inspiratory and expiratory volumes should be similar. If there are differences between inspiratory and expiratory volume, there can be:

Air leaks in the system

Intrinsic positive end-expiratory pressure (i.e., auto-PEEP or air trapping). In this case, the downslope representing expiration decreases as expected but never reaches the baseline of zero volume before the next breath (see Fig. 13.4) [4, 11].

Key Major Recommendations

- The analysis of flow/pressure and volume waveforms is important to properly monitor the ventilated patient, to modify parameters of the ventilator, and reduce patient–ventilator asynchrony.
- At first, evaluate pressure and flow scalar; the analysis of volume scalar is a completion.
- The clinician should evaluate:
  - if respiratory acts are preceded by a normal activation of inspiratory trigger
  - if there are ineffective efforts or double efforts
  - if the ventilator generates autotrigger
  - if the pressure rises up properly
  - if the pressure is maintained properly or if there are signs of leaks
  - if cycling from inspiration to expiration is correctly configured
  - if there are signs of hyperdynamic inflation.

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Basic Patient Ventilator Interaction: Pressure–Volume–Flow

14

María Sevilla Martinez and Dionisio Guillamon Fernandez

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14.1 Introduction

The goal of noninvasive ventilation (NIV) is to improve gaseous exchange and to reduce the work of breathing by a complex process of interaction between the patient and ventilator. The application of pressure during the exhalation allows improving the alveolar recruitment and during the inhalation reduces the work of breathing.

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_14

The use of NIV in treatment of critical patients with primary and secondary lung injury has decreased mortality [1]. However, NIV presents complications; therefore, monitoring that allows controlling patients' interactions with the ventilator is essential. When this interaction is not correct asynchronism occurs, which we can study in the ventilator waveform [2].

14.2 Patient–Ventilator Interaction

The patient–ventilator interaction is synchronic when the ventilator is sensitive to patient's stress, the gas flow generated is enough to cover the demands, and the mechanic inspiration acts in phase with neural inspiration. Any variation or discrepancy in this process produces asynchronisms between the patient and ventilator. These asynchronisms are shown in ventilator waveforms [3].

To make an interpretation of the asynchronism in the waveform, first we will explain what a normal curve looks like (Fig. 14.1).

Phase 1 (Trigger): The pressure wave has a rectangular morphology preceded by a small negative deflection that corresponds to the onset of the inhalatory effort. The interval between the start of this wave and the beginning of the flow allow us to evaluate the trigger delay.

Phase 2 (Rise time): The rising part of that waveform must have an important gradient caused by the rise time programmed.

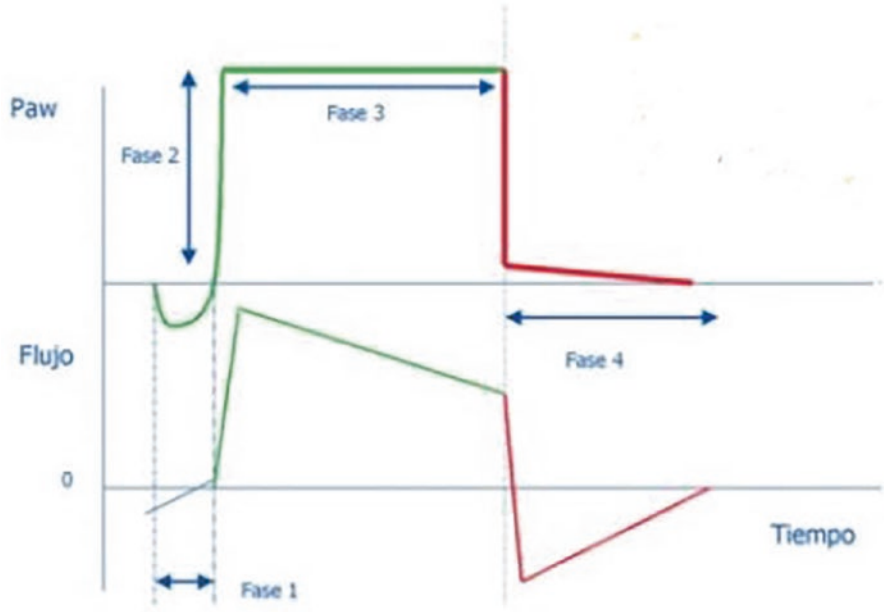

Fig. 14.1 Phases of a normal respiratory cycle

Phase 4 (Expiratory time): We have a waveform with an important inclination and a soft final part.

The morphology of the flow wave depends on the resistance in the airway and the compliance. The volume curve is dependent on the programmed pressure, the patients' effort, and their respiratory cycle.

Asynchronies can occur in any of the four phases of respiration [4]:

- At the beginning of the inspiration, which is determined by the sensibility of the ventilator, the effort of the patient and the valve.
- In the inspiratory phase, in which the flow is determined by the relationship between the ventilator flow and the effort of the patient.
- At the end of the inspiration, since the end of ventilator flow is not always simultaneous with the neural activity.
- In the expiratory phase. Auto positive end-expiratory pressure (PEEP).

14.3 Causes that Affect Asynchrony

- Sedation level, neurology/neuromuscular/respiratory or abdominal pathology, secretions, facial malformation, inspiratory effort, and determinants of autoPEEP.
- Trigger, flow pressure, flow curve, programming of sensibility, and time of incline.

14.4 Asynchrony Groups

14.4.1 Asynchrony in the Trigger Phase

Ventilator air delivery is activated by the patient's inspiratory effort when it reaches a programmed trigger. This trigger can be triggered by detecting changes in airway pressure, flow, volume or flow curve, diaphragmatic pressure and electrical activity of the diaphragm. The asynchrony due to the trigger phase can be expressed as [5]:

Autocycling: occurs when there is ventilator activation without the patient's effort. It is due to artifacts in the ventilator circuit, the presence of water in the circuit, leaks, and cardiac oscillations. It occurs in patients with low central inspiratory impulse, bradypnea, central hypoventilation, and high systolic volume.

It is identified in waveforms as the absence of an initial pressure drop below the end-expiratory pressure.

Solutions to this type of asynchrony: Increase trigger threshold, decrease sedation, and minimize leaks.

Trigger delay: there is a delay between the effort of the patient and when the ventilator supplies the gas.

Ineffective efforts: when there are muscular efforts of the patient that do not trigger the ventilator [6].

Causes of these asynchrony: dynamic hyperinflation, low inspiratory impulse, muscle weakness, and high assistance. The way to try to minimize them would be through reduction of auto-PEEP, external PEEP, increase expiratory time, and administer low volumes.

14.4.2 Asynchrony During the Pressurization Phase

It occurs when the demand for flow is higher than that provided by the ventilator, and rise time has a significant influence [7].

We should suspect it if any deviation in the shape of the flow curve under passive conditions occurs (a downward flow pattern) [8].

14.4.2.1 Possible Causes

- Insufficient flow: occurs when the effort of the patient does not trigger the ventilator, and therefore the demand is not supplied. It is due to tachypnea, incorrect programming, prolonged ramp, or short inspiratory time.
- To reduce this asynchrony, we must increase the IPAP (Inspiratory Positive Airway Pressure), reduce leaks, and program a faster ramp.
- Double trigger: occurs when the demand of the patient is very high and the mechanical inspiratory time is short. This situation occurs when there are leaks, in volume-controlled modes, and due to improper programming. One way to alleviate this asynchrony is to lengthen the inspiratory time and apply pressure-controlled modes.

14.4.3 Asynchrony of Cycling: Asynchronous Expiration

It occurs when the mechanical inspiratory time precedes or exceeds the neural inspiratory time.

Causes: excessive pressure support (PS), cycling toward low expiration (<25%), and constant prolonged time.

On the flow curve, after an initial decrease during expiration, we see a rise toward the baseline that indicates the sustained inspiratory effort of the patient [9].

At PS, a rapid drop in the inspiratory flow curve can be observed. In the pressure curve, during the inspiratory phase, we can observe a small elevation at the end of the same, which indicates sudden relaxation of the inspiratory muscles or contraction of the expiratory ones.

We can solve it increasing the cycling criteria in obstructive patients with prolonged time constants (> 25%) to reduce inspiratory time, avoid leaks, and decrease PS.

14.4.4 Asynchrony Related to Interfaces

The type of interface is decisive to achieve the therapeutic goal in NIV. Leakage is a very common problem, and although current respirators partially compensate for it, leaks produce asynchrony and reduce airway pressures. Leaks <0.4 L/s are considered acceptable.

It is therefore crucial to choose a suitable type and size of interface, as well as your harness, and to protect the patient with padding and hyperoxygenated oils [10].

14.5 Conclusion

A high rate of asynchrony has been shown to increase the duration of mechanical ventilation and complications. Therefore, knowing the waves of flow, pressure, and volume is crucial to correct phenomena that put the patient's life at risk or affect their prognosis, as well as their comfort.

Key Major Recommendations

- Proper monitoring is essential in the use of NIV to reduce complications
- Through the study of the ventilator curves, we can interpret the patient–ventilator interaction
- Asynchronies can occur in any phase of the respiratory cycle, and we must know how to act to minimize the undesirable effects.

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Non Invasive Ventilation Asynchrony: Diagnosis and Treatment

15

Rahul Roshan and Sanjeev Singhal

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_15

15.1 Introduction

The basic goal of noninvasive ventilation is to optimize gas exchange, reduce work of breathing (WOB) and improve patient comfort. Patient–ventilator interaction is dependent on multiple factors such as type of ventilator, ventilator settings, patient–ventilator interface and need of sedation. Optimization of synchrony between patient and ventilator improves patient comfort and outcomes [1]. Most of the earlier studies done on patient–ventilator asynchrony were on invasive ventilation. However, with the progressive rise in the use of noninvasive ventilation (NIV), it is vital to understand the unique characteristics of NIV-related patient–ventilator asynchrony (PVA) and its outcome. This chapter focuses on the diagnosis of asynchrony along with its impact on clinical management.

15.2 Diagnosis of Asynchrony

The method used to recognize asynchrony impacts the estimation of prevalence. The use of invasive methods such as monitoring of esophageal pressure and electrical activity in the diaphragm has led to more precise measurements of inspiration and expiration time along with patient efforts [2]. Subsequently, analysis of ventilator waveforms has led to underestimation or overestimation of PVA [3]. A thorough look at the influence of patient effort in the pressure and flow waveforms can be used to diagnose patient–ventilator asynchrony noninvasively. Patient efforts might be obscured from waveforms secondary to an accidental damping effect generated by leaky flow, which is quite common during NIV. Other noninvasive approaches such as computerized waveform analysis and surface EMG can be used to search for PVA. Breath-by-breath analysis has been used to detect asynchrony, but the sensitivity was poor, and the specificity was high, and it was unaffected by experience or location. A key question is to spot the severity of degree of patient–ventilator asynchrony at which the corrective action is effective (Table 15.1).

Asynchrony is usually detected using a combination of patient inspection (e.g. tachypnoea, auxiliary muscle usage, and nasal flaring), patient clinical status (e.g. dyspnoea), and waveform analysis (ineffective triggering, double-triggering, auto-triggering, premature cycling and delayed cycling) [4].

Asynchrony index is calculated to estimate the severity of PVA.

The number of asynchrony events are divided by the total respiratory rate, which was estimated as the sum of the number of ventilator cycles (initiated or not) and lost efforts:

$$\text{Asynchrony index}\left(\text{percentage}\right) = \text{number of asynchrony events / total respiratory rate} 100\%$$

Asynchrony indexes of more than 10% are usually considered serious.

Table 15.1 Severity of patient-ventilator asynchrony

Asynchrony between the patient and the ventilator falls into this group		Description
1	No breathing asynchrony—patient breathing in phase with ventilator	The patient appeared to be in good health. The patient's breathing attempts are matched by the ventilator
	Mild asynchrony of breathing—ventilator is occasionally out of phase with the patient.	Occasionally, there is a misalignment between the patient's breathing pattern and the ventilator Changes are not required when there is asynchrony
2	Moderate breathing asynchrony—ventilator frequently out of phase with patient	The patient appeared to be uncomfortable There appears to be a misalignment between the patient's breathing pattern and the ventilator The issue of asynchrony must be addressed
3	Severe breathing asynchrony—ventilator always out of phase with patient	Patient is uncomfortable The patient's breathing is out of sync with the ventilator Breathing is difficult to detect The asynchrony is severe enough to necessitate quick action

15.3 Ventilator Waveform Analysis and Terminologies in Asynchrony in NIV (Fig. 15.1)

Patient–ventilator asynchrony (PVA) is a common phenomenon which is under-recognized and under-reported. It can occur with any mode of ventilation and can affect any phase of respiration. A high prevalence of PVA has been reported with NIV. Trigger asynchrony is the most frequent PVA followed by double triggering and cycling asynchronies [5].

15.3.1 Ineffective Triggering

Ineffective triggering has been demonstrated to increase the amount of labour required to breathe, owing to the increased inspiratory threshold load associated with dynamic hyperinflation leaks, which have been proven to increase the trigger latency and the number of ineffective breaths.

15.3.2 Auto-Triggering

Leaks have been found as one of the main causes of auto-triggering. Leaks can reduce NIV efficiency, decrease patient tolerance, disrupt waking and sleeping patterns, and induce patient–ventilator asynchrony.

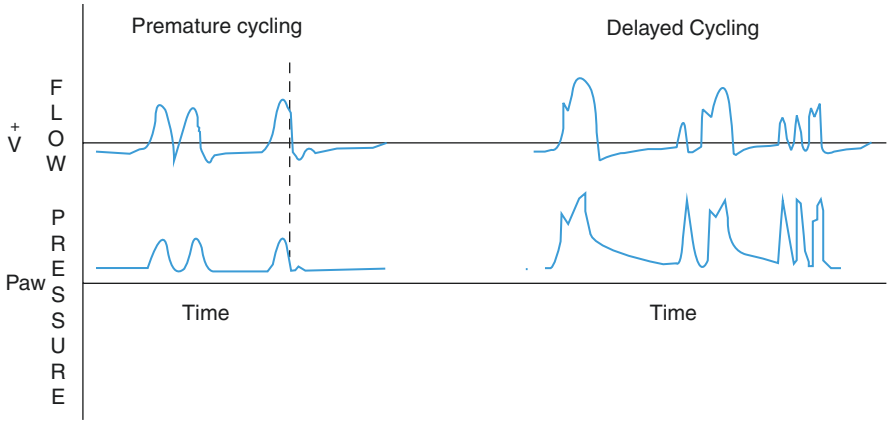

Fig. 15.1 Flowtime and pressure-time scalars showing premature and delayed cycling, respectively. There is the appearance of double triggering of breaths due to incomplete inspiration in remature cycling, while delayed cycling represents wasted efforts with the rise in peak pressures leading to trigger asynchrony

15.3.3 Double Triggering

Double triggering is frequently linked to insufficient pressure support. Inspiratory muscles continue to contract during premature cycling, causing the mechanical ventilator to sense a second effort, leading to a second breath, commonly called 'stacking of breaths' or 'double triggering'.

15.3.4 Premature & Prolonged Cycling

The presence of restricted respiratory mechanics is one of the key causes of premature cycling. Premature or short cycling occurs due to discordance between neural and ventilator inspiratory time (T_i). Premature cycling is the asynchrony seen when the neural inspiratory time is longer than the ventilator inspiratory time. Prolonged or delayed cycling happens when the ventilator inspiratory time is longer compared to the patient's neural inspiratory time. Both premature and prolonged cycling have significant adverse effects on patient outcomes.

Premature cycling leads to lower tidal volume, heightened inspiratory load and inaccurate depiction of respiration rate [6]. This asynchrony can also be seen when high flow termination criterion is utilized in patients with restrictive lung physiology. This results in higher incidence of double triggering and increased effort of breathing. Delayed cycling is classically seen in obstructive lung diseases such as chronic obstructive pulmonary disease (COPD) in which the inspiratory flow reduction is reduced due to dynamic hyperinflation, airflow resistance, and lung mechanics [7]. Intrinsic positive end-expiratory pressure (PEEP) may also cause trigger asynchrony.

15.3.4.1 Waveform Identification of Premature Cycling

- Flow-time scale – Positive inflection at end of expiration
- Pressure-time scale – Negative deflection 'notch' towards the end of expiration
- Double triggering or breath stacking due to incomplete inspiration

15.3.4.2 Waveform Identification of Delayed Cycling in Pressure Support

- Rapid fall in flow during inspiration
- Rise in airway pressure at the end of inspiration. It is due to inspiratory muscle relaxation with active contraction of expiratory muscle
- Missed trigger and trigger asynchrony are frequently seen

15.3.4.3 Clinical Identification of Cycling Asynchronies

- Identification of major leaks
- Use of high-pressure support
- Clinical features of asynchrony – increased WOB, paradoxical breathing

15.4 Determinants of Asynchrony in NIV

15.4.1 Patient–Ventilator Interface

The interface used with NIV plays a crucial role in patient–ventilator interaction and patient comfort [8]. Air leaks are common with NIV, and the interface encourages them. Leaks can lower NIV efficiency, lower patient tolerance, cause waking and sleep fragmentation, and increase patient–ventilator asynchrony. Clinicians and patients prefer the oronasal mask the most.

A single-limb circuit with a leak port adjacent to the patient is characteristic of NIV ventilators. The leak port serves as the patient's exhalation port as well as provides resistance against which the ventilator makes flow to generate pressure. The interfaces are now progressively including the leak port. Clinicians routinely mix interfaces from one manufacturer with ventilators from another to better tailor the interface to the patient [9]. Testing is paramount when moving to a mask with different leak characteristics in order to adjust the trigger sensitivity and pressure settings, as well as to confirm that no rebreathing occurs [8].

15.4.2 Rebreathing

Rebreathing during NIV has the potential to create asynchrony due to an increase in respiratory effort and dyspnoea leading to asynchrony [10, 11]. With bi-level ventilators, rebreathing is possible. Rebreathing is decreased if (a) the leak port is in the mask rather than the circuit [12], (b) oxygen is titrated into the mask rather than the circuit, (c) the expiratory pressure is higher, and (d) the plateau exhalation valve is used. Two important factors of rebreathing are the expiratory period and the flow

across the circuit during exhalation. Expiratory pressure is increased as flow is increased, which prevents rebreathing; many bi-level ventilators include a minimum expiratory pressure setting of 3–4 cm H_2O. When the ports on the interface are opened, the leak increases, increasing the flow through the hose and flushing the hose, causing the leak to decrease and rebreathing to occur.

15.4.3 Leaks

Variations in leaks induced by changes in inspiratory and expiratory pressures, as well as changes in breath-to-breath owing to interface fit, must be considered by leak detection algorithms. In contemporary bi-level ventilators, the redundant leak-estimation algorithm is applied. On the majority of the ventilators evaluated, leaks resulted in an increase in trigger delay and workload, as well as a loss of capacity to meet the pressure objective and delayed cycling.

According to Vignaux et al., NIV modes can sort out some or all of the leak issues that emerge with NIV, although there are significant differences in efficiency between machine trigger asynchrony [13].

Leakage may create trigger asynchrony with NIV, resulting in auto-triggering or ineffective triggers. Ineffective triggers might also be a result of the underlying sickness, such as auto-PEEP in COPD patients and insufficient inspiratory attempts in neuromuscular disease patients. Unlike in the past, while utilizing modern ventilators, trigger asynchrony is likely related to pathophysiology concerns rather than ventilator performance.

15.4.4 Humidification Devices

Supplemental humidification should be used during NIV and the selection of humidification device impacts work of breathing. The heat and moisture exchanger (HME) is linked with a significant increase in work of breathing as compared to heated humidifiers [14].

15.5 Key Practical Recommendations

Various guidelines have been published to provide a persistent level of support and guidance to clinicians about the management of patient ventilator asynchrony.

15.5.1 Type of Ventilator

Mechanical ventilators with NIV mode have long been utilized in critical care. The advantages are separate inspiratory and expiratory circuit limbs to avoid re-breathing, alarm systems and supply of adequate oxygen. Also, ventilator graphics

can help to identify the presence of any PVA. Dedicated NIV ventilators have been progressively employed which are at par effective as mechanical ventilators with NIV mode. Volume-preset and pressure-preset ventilators are usually equally effective in reducing PVA and improving patient compliance and tolerance [15].

15.5.2 Trigger

The sensitivity of the ventilator triggers the shift over from the expiratory to inspiratory phase by identifying effort by the patient. Methods to optimize trigger synchrony are:

(a) Adjust the sensitivity of the trigger to achieve the ideal balance of trigger effort and auto-triggering.
(b) To counteract auto-PEEP, increase PEEP (expiratory positive airway pressure).
(c) Reduce inadvertent leaks by properly fitting the interface.
(d) Address the root cause of the ailment (e.g. bronchodilators to decrease airways resistance and air trapping).

Both pressure and flow triggering have been used for years. However, in COPD patients, flow triggering offsets the amount of auto-PEEP by allowing a fixed flow by the circuit. Therefore, flow trigger is usually preferred over pressure trigger [16].

15.5.3 Flow Synchrony

(a) Depending on the patient's comfort, use pressure-targeted or volume-targeted ventilation.
(b) Use pressure-targeted ventilation to adjust inspiratory pressure.
(c) Use volume-targeted ventilation to adjust flow and tidal volume.
(d) Adjust the rising time (pressurization rate) to the patient's preference.
(e) Reduce inadvertent leaks by properly fitting the interface.
(f) Lower your respiratory drive (e.g. increase ventilation to treat acidosis)

15.5.4 Cycling

The criteria used for expiratory triggering can have a crucial impact on the efficiency of NIV and patient–ventilator synchrony.

(a) Reduce inadvertent leaks by properly fitting the interface.
(b) Rather than flow-cycled (pressure support), use time-cycled (pressure control) ventilation.
(c) Change the flow cycle's settings.
(d) Lower the support pressure.

(e) Address the root cause of the ailment (e.g. bronchodilators to decrease airways resistance).

A dip in inspiratory flow from peak to a threshold level (generally set at 25% of the peak flow) is the most frequent criteria used in pressure support ventilation, but recently, more advanced ventilators provide adjustable values. Patients with COPD or air leaks often have higher end inspiratory flow. Application of a high flow threshold of 25–40% of peak flow in these patients assists in reducing time for inspiration while allowing increased time for expiration. This avoids delayed cycling and intrinsic PEEP, thus improving patient compliance with NIV.

15.5.5 Patient–Ventilator Interface

Full oronasal face masks are associated with improved comfort and tolerance along with less PVA in patients with acute respiratory failure.

15.5.6 Humidification

Heated humidifiers have an advantage over heat and moisture exchangers as they lead to increased work of breathing.

15.6 Summary

Patient–ventilator asynchrony is a well-understood phenomenon during noninvasive ventilation. Correct identification and management of PVA is important to improve patient comfort and tolerance and subsequently positive clinical outcomes.

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Carbon Dioxide Rebreathing and Exhalation Ports During Noninvasive Mechanical Ventilation

16

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16.1 Introduction

The modern era of NIV began in the late 1990s with the publication by professional societies of clinical practice guidelines on the management of acute and chronic respiratory failure with NIV. The concept behind NIV is based not only on its noninvasive nature (without intubation) but also on the simplicity of its setting. In contrast to invasive mechanical ventilation (IMV), NIV can be applied outside the ICU using portable devices equipped with single-limb circuits. Undoubtedly, the phenomenon of CO_2 rebreathing is one of major concern, when the patient has to breathe in and out through the same tube. Exhaled CO_2 can escape from the

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_16

breathing circuit through either the exhalation ports (intentional leaks) or unintentional leaks from the mask–patient interface. Unintentional leaks are usually minimized by adjusting the interface to allow the delivery of the desired pressure assistance to the patient. Moreover, the mode of ventilation, the type of mask, the expiratory port, and the expiratory pressure level setting may also play a key role in modifying CO_2 rebreathing.

Many factors determine the performance of expiratory ports, CO_2 rebreathing and consequently the overall success of the NIV therapy. During the COVID-19 pandemic, a heated debate that often arose was whether mask NIV with a single-limb circuit could disperse infected aerosols into the environment, exposing healthcare personnel to danger.

In this chapter we aim to: (i) delve deeper into mechanisms governing CO_2 rebreathing, (ii) broaden our knowledge regarding expiratory ports, and (iii) discuss issues on the dispersion of infected aerosols during mask NIV via single-limb circuit in the midst of the COVID-19 pandemic.

16.2 General Mechanisms of CO_2 Rebreathing

CO_2 rebreathing is the phenomenon when a patient rebreathes part of the exhaled CO_2 which accumulates during the respiratory cycle inside the circuit. During IMV (endotracheal tube in place with inflated cuff, double-limb circuit with pneumatic valves built into the ventilator) the final part of the exhaled tidal volume has CO_2 concentration that does not differ from the respective value of mean alveolar CO_2 (i.e., the end-tidal CO_2). As a consequence, in this closed system, CO_2 does not escape from the aforementioned space, which is called "static" or "classic" dead space (proximal to Y-piece), except in cases where there is a bias flow for flow-based triggering purposes that promotes partial CO_2 clearance. Therefore, the rebreathing of the volume of "static" dead space does not significantly decrease the alveolar CO_2 and thus does not effectively remove CO_2 from the circuit [1, 2].

With NIV, mechanisms of CO_2 rebreathing differ depending on the interface, mask or helmet. During mask NIV the distal part of single-limb circuit and the inner volume of interface comprise the space where the inspiratory and expiratory flows meet each other. Thus, exhaled CO_2 fills this dead space and is pushed back to the patient during the next mechanical inspiration. In contrast with IMV (closed system), during mask NIV (open system) high expiratory flow through the expiratory port (EP) combined with potential air leaks around the mask significantly decrease CO_2 concentration of dead space below alveolar CO_2 value. This partially cleared dead space, called "dynamic," is different from the "static" dead space during IMV. In this context, mask NIV is not completely ineffective in removing CO_2 [2].

This is not the case with helmet NIV (semi-closed system). Exhaled gases from the patient are diluted in the inner space of helmet, which is much larger than the tidal volume (V_T). In addition, the high flow of gases provided inside the helmet reduces the CO_2 concentration. Thus, in contrast to mask NIV, during helmet NIV dead space does not contribute in any way to CO_2 rebreathing. The description of

mechanisms governing rebreathing during helmet ventilation is beyond the scope of this chapter.

16.2.1 CO_2 Rebreathing During Mask Ventilation

CO_2 rebreathing is generally considered a potential cause of treatment failure during NIV because it may enhance respiratory drive, overload the respiratory muscles, and increase the work of breathing (WOB) [3]. Since the first description by Ferguson et al. [4] in 1995, little has been published on this subject. The factors underlying the amount of CO_2 rebreathed during the respiratory cycle are the volume of "dynamic" dead space and its CO_2 concentration.

In this context, the issues influencing rebreathing during mask NIV include:

1. Type of circuit (double-limb or single-limb)
2. Type (non-vented or vented masks with exhalation port built-in on the mask) and size of masks
3. Devices attached to the circuit (conventional or nonrebreathing valves)
4. Level of expiratory pressure [positive end-expiratory pressure (PEEP) or expiratory positive airway pressure (EPAP)]
5. Mode of ventilation, ventilatory settings
6. Patient' s characteristics (breathing pattern, hypercapnic of normocapnic respiratory failure)

Notably, in double-limb circuits, the volume of dead space is limited to the inner space of the mask, which is added to the space proximal to the Y-piece (Fig. 16.1). In this setting, CO_2 rebreathing is negligible because the exhaled gases flow through the separate expiratory limb. It is also important to emphasize the role of bias flow in the double-limb setting. Very recently, in a lung model, Signori et al. [5] evaluated CO_2 rebreathing with a modified total face mask (with two different connectors to inflow and outflow gases) in comparison with a standard total face mask (with a single connector to the double-limb breathing circuit) during NIV (pressure support mode with bias-flow). The authors concluded that the modified mask could reduce CO_2 rebreathing during both continuous positive airway pressure (CPAP) and pressure support ventilation (PSV), while the addition of an adequate amount of bias flow enhanced this effect. A bias flow is a continuous flow circulating between the inspiratory and expiratory limbs independent from the ventilatory demands of the patient.

It is worth noting that in NIV ventilators using double-limb circuits, bias flow can be augmented only by modifying the flow-based inspiratory trigger sensitivity: reducing trigger sensitivity increases bias flow and thus enhances CO_2 washout [5]. Indeed, when unintentional leaks around the mask are reduced (after adjustment by the health-care provider), the patient's inspiratory effort might be insufficient to trigger the ventilator at the beginning of inspiration resulting in asynchronies. In line with this, some investigators argue that CO_2 washout by the bias flow should be

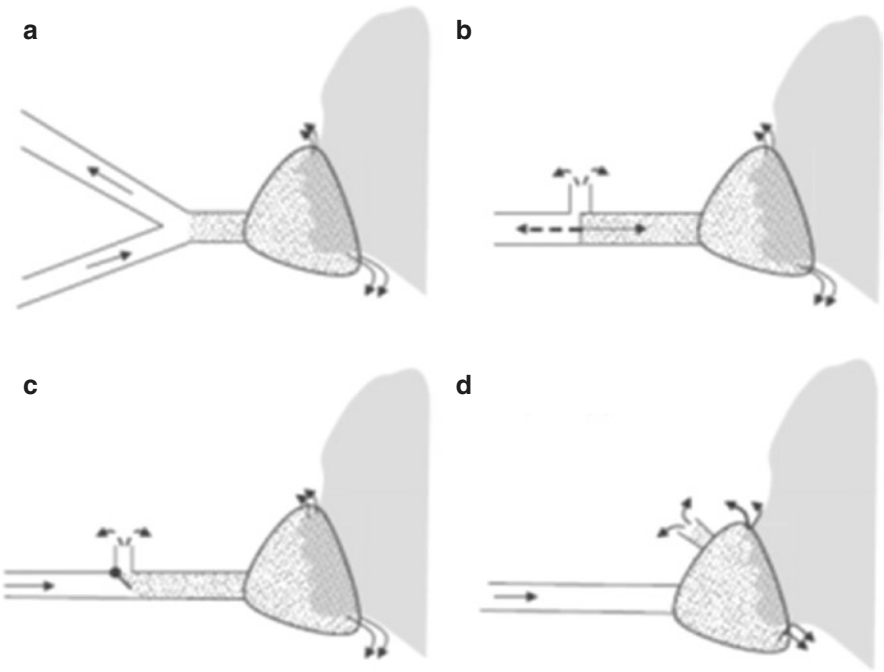

Fig. 16.1 Apparatus dead space (shaded area) in different settings during mask NIV. (**a**) Theoretically, in a double-limb circuit the dead space is limited to the volume distal to the Y-piece. The unintentional leaks around the mask result in lowering CO_2 content in this volume below the alveolar mean value (i.e., end-tidal CO_2). As a consequence, this volume is considered as "dynamic" dead space. (**b**) In a single-limb setting, with the EP on the circuit, the theoretical dead space is the volume distal to the EP. However, the actual volume of dead space is increased by large V_T of the patient and high resistance of the EP dashed arrows), whereas it is diminished by PEEP and prolonged expiratory time. (**c**) In a single-limb setting, an active (unidirectional) valve on the circuit can decrease dead space at the expense of increased resistance. (**d**) In a single-limb setting, an exhalation port on the mask can decrease dead space and thus CO_2 rebreathing. *EP* expiratory port, *PEEP* positive end-expiratory pressure, V_T tidal volume

balanced with the flow trigger sensitivity to achieve better patient–ventilator interaction. It has also been suggested that only the double-limb circuits can allow the bias flow to be set independently of the inspiratory flow sensitivity. Consequently, the challenge for the designers of next generation ventilators would be to allow the operator to set the bias flow independent of flow trigger sensitivity.

Single-lumen circuits are the most often used setting in every day practice. The design and position of EP, as well as the exhaled gas flow through them, can affect CO_2 rebreathing. It should be noted that different factors play a significant role during the expiratory phase of respiration. During the first part of expiration, as flow reaches its maximum value, the flow of exhaled gases is limited through the EP and thus it can extend to some distance beyond the EP. As a result, the actual dead space becomes larger than its theoretical size (between the patient's face and the EP) (Fig. 16.1b). Therefore, any factor that further compromises the flow through the EP

(i.e., type, small size, increased resistance) during early expiration can enhance CO_2 rebreathing.

During the second part of expiration, the intentional (through the EP) and the unintentional (around the mask) leaks prevail resulting in decreased dead space and CO_2 rebreathing. In addition, the use of PEEP or EPAP can effectively reduce dead space: dead space is reduced by the flow of fresh gases provided by the ventilator during the late expiratory phase to maintain PEEP or EPAP. Alongside a higher PEEP or EPAP, a long expiratory time, can promote the flow of fresh gas during late expiration limiting the dead space and thus CO_2 rebreathing.

Consistent with the previous mechanisms, the breathing pattern of the patient can also affect CO_2 rebreathing during mask NIV. If the expiratory flow (tidal volume divided by expiratory time, V_T/T_e) is lower than the flow of intentional leaks obtained through the EP, no exhaled gas remains in the circuit at the end of expiration and thus no rebreathing occurs. Accordingly, high V_T and short T_e enhance CO_2 rebreathing.

16.3 Expiratory Ports

During mask NIV with a single-limb circuit, EPs not only play a significant role in limiting CO_2 rebreathing but can also affect the performance of the ventilator. The factors determining the capability of EPs in CO_2 washout include their type and position on the circuit.

16.3.1 Types of Expiratory Ports

There are various types of EPs available on the market including (i) those which are built-in (in the form of small holes) on the mask or on the elbow connector, and (ii) those in the form of detachable devices on the circuit.

The built-in EPs offer the advantage of not needing an additional connector on the circuit. It is worth noting that the newly designed masks have built-in EPs rather than the conventional detachable EPs. It has been shown that intentional leaks through built-in EPs are enhanced with an increasing level of applied pressure during NIV and do not differ significantly from other types of masks (nasal or oronasal) with various EP (built-in on the elbow or the nasal bridge).

Conversely, detachable EPs have the advantage of being a separate piece of equipment that can be easily replaced and disinfected after use. There is a great variety of detachable expiratory devices taking the form of a single hole on the connector (Disposable Exhalation Port, Respironics Inc., Murrysville, PA, USA), a fixed valve connector with several narrow slits (Whisper Swivel, Respironics Inc., Murrysville, PA, USA), a connector with a circumferential leak design that allows the gas to escape along the direction of the air hose (Whisper Swivel II, Respironics Inc., Murrysville, PA, USA), or a specially designed valve with a variable resistor

that minimizes rebreathing (Plateau Valve, Respironics Inc., Murrysville, PA, USA) (Fig. 16.2a upper panel).

The plateau exhalation valve consists of a diaphragm that limits air-leaks at high pressures (during inspiration) and works as a larger leak port at low pressures (during expiration). Conversely, the Whisper Swivel has a "fixed" resistance, which results in varying leak rates depending on the pressures across the leak port. The non-rebreathing valves may have the form of mushroom, diaphragm, or balloon (Fig. 16.2b upper panel).

It has been shown that there are important differences in expiratory resistance among commercially available expiratory valves [6]. These differences may influence the inspiratory and expiratory efforts in patients with high ventilatory demands and/or short expiratory time causing auto-PEEP. It should also be pointed out that the non-rebreathing valve can potentially malfunction when the valve material becomes stiff and soiled by secretions. Very recently, in a bench study [7] it was demonstrated that different circuit setups (dual-limb circuit with an oro-nasal mask, dual-limb circuit with a helmet interface, single-limb circuit with a passive exhalation valve, single-limb circuits with custom made additional leaks, single-limb circuits with an active exhalation valve), with or without adding heat moisture exchanger (HME) and low pressure filters, may significantly impact ventilator performance during CPAP/NIV. More specifically, the setup with dual-limb circuit with an oro-nasal mask achieved the best performance (lowest inspiratory effort to

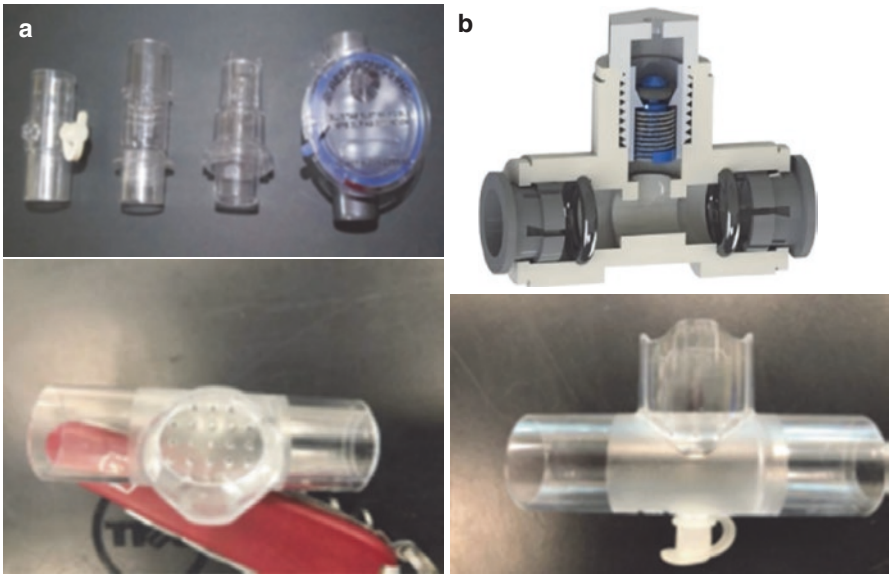

Fig. 16.2 Different types of detachable expiratory ports. Upper panel: (**a**) Disposable Expiratory Ports: Whisper Swivel, Whisper Swivel II, and Plateau Valve (Respironics Inc., Murrysville, PA, USA), (**b**) Non-rebreathing valve (Sanders NRV-2). Lower panel: (**a**, **b**) Different views of an expiratory port with a low restrictor

trigger the ventilator), while the addition of intentional leaks (Whisper-Swivel and the custom-made EPs) decreased the pressurization without a significant impact on the WOB and the patient–ventilator asynchronies. Finally, the addition of HME and low pressure filters increased the inspiratory effort to trigger the ventilator, increased the WOB, and decreased both the pressurization and the V_T.

The type of EP substantially influences the ability in reducing CO_2 rebreathing. Ferguson and Gillmartin [4], in their pioneering clinical study, concluded that the plateau valve and the non-rebreathing valve (Sanders NRV-2), as opposed to the standard fixed-resistance exhalation device (Whisper Swivel), almost eliminate CO_2 rebreathing by reducing dead space during bilevel positive airway pressure (BiPAP) ventilatory assistance, even with lower EPAP settings. Unlike at rest, the plateau exhalation valve seems to perform poorly during exercise in severe COPD patients. In a recent study, Ou et al. [8] evaluated CO_2 rebreathing in 18 patients with stable severe COPD, at rest and exercise, assisted by NIV (IPAP/EPAP 14/4 cmH_2O) with a single-limb circuit and plateau exhalation valve. The authors concluded that the plateau exhalation valve caused CO_2 rebreathing. They also reported that the patients who produced mean expiratory flows >0.6–0.73 L/s during exercise may be predisposed to a higher risk of CO_2 rebreathing.

Additionally, in a lung model and clinical study using a BiPAP device, Lofaso et al. [3], found that the non-rebreathing valve, as opposed to the standard exhalation device (Whisper Swivel), prevented CO_2 rebreathing, but at the expense of greater expiratory resistance. Therefore, expiratory resistance is another important aspect to take into consideration when selecting EPs.

The use of PEEP could also help with the "wash out of CO_2." Ferguson et al. [4], using a specific non-rebreathing valve (Sanders NRV-2), found that a PEEP level of 6–8 cmH_2O was necessary to prevent rebreathing. Furthermore, Samolski et al. [9], using a mask with exhaust vents (vented masks), managed to reduce the PEEP to 4 cmH_2O without rebreathing. These results are in agreement with those described by Schettino et al. [10] who suggested that the vented masks offer better CO_2 kinetics which lead to reduction of CO_2 rebreathing.

Only a few studies have addressed the influence of mask volume on the wash out of CO_2. In normal individuals it was demonstrated that CO_2 rebreathing is not common in newly designed masks (nasal or oro-nasal) with built-in EP even when EPAP was as low as 4 cmH_2O or when a spacer (with volume up to 175 mL) was added to the circuit close to the mask [9]. Nevertheless, in a lung model (hypercapnia due to COPD) during CPAP and BiPAP, Schettino et al. [10] reported that an oro-nasal mask (smallest volume) with built-in EP experienced less rebreathing than either the oro-nasal mask with EP on the circuit or the total face mask with built-in EP.

Furthermore, in a lung model study, Saatci et al. [2] attempted to determine the influence of different designs of all commercially available face masks and different NIV modes on the total dynamic dead space (physiological plus apparatus dead space). The authors concluded that the EPs over the nasal bridge of face masks exert beneficial flow patterns within the mask and significantly decrease the dynamic dead space provided that positive pressure is applied throughout the expiratory phase.

Addressing the possible impact that the position of EP would have on CO_2 rebreathing, Schettino et al. [10], in a lung COPD model, compared three different types of interface setting during CPAP and PSV provided by a single-limb circuit. They found that the full face mask (inner volume of 165 mL) with an EP within the mask experienced less CO_2 rebreathing and less inspiratory load compared with the same mask using the EP on the circuit, and the total face mask (inner volume 875 mL) with the EP within the mask. Thus, CO_2 elimination is most efficient when the smallest full face mask is used and when the EP is placed on the top of the mask near the nasal bridge.

16.4 Effects of Expiratory Ports on the Dispersion of Infected Aerosols/Droplets During NIV

Apart from avian influenza A (H_7N_9) and A (H_5N_1), severe acute respiratory syndrome coronavirus (SARS-COV) and Middle East respiratory syndrome COV (MERS-COV) may lead to respiratory failure with high mortality rates. It is well known that CPAP/NIV via mask or helmet may be required for the most severe cases. However, these modalities can generate respiratory droplets and can be associated with nosocomial transmission posing a significant risk to health care personnel. Notably, many scientific societies have issued precautionary statements and guidelines for the use of CPAP/NIV during pandemics.

Up until now, several bench studies have shown that the dispersion of exhaled air differs depending on the respiratory therapies (standard O_2 therapy, CPAP, NIV) and interfaces (nasal cannula, oro-nasal mask, or helmet) used [11–13]. On a human patient simulator, Hui et al. evaluated exhaled air dispersion using the laser smoke visualization method. Oxygen delivered via a simple face mask had lateral dispersion through vent holes of the mask at a distance ranged from of 0.2 m at oxygen flow of 4 L/min to a maximum of 0.4 m at oxygen flow of 8 L/min [11]. In another study, the same group of investigators using an identical laboratory set-up, concluded that there was significant exposure to exhaled air within a 1 m region from patients receiving BiPAP via vented and non-vented (with attached expiratory valve) oro-nasal masks. Notably, the dispersion was greater with the latter masks, especially at higher inspiratory positive airway pressures (IPAP) [12]. Interestingly, an oro-nasal mask with intergraded EP built-in on the upper part of the mask (Ultra Mirage Medium; Resmed®) was found to disperse exhaled air within a 0.5 m radius of patients receiving NIV [12]. Using another Philips-Respironics total face early model with NIV (single-limb circuit), exhaled air through the integrated EP reached a maximum radial distance of 0.92 m [12].

When the performance of CPAP with the Quattro Air mask (ResMed®) was examined, there was no significant leakage when pressures up to 20 cmH_2O were applied. Interestingly, exhaled air dispersed evenly via the vent holes located circularly around the elbow connection point in all directions at very low normalized smoke concentration [13] (Table 16.1).

Table 16.1 Exhaled air dispersion according to interfaces, ventilatory modes, and parameters

Interfaces and pressures (in cm H_2O)	Maximum exhaled air distance (in meters)
Resmed® Ultra MIrage mask (IPAP/EPAP)	
10/4	0.40
14/4	0.42
18/4	0.45
Resmed® Quatro Air mask	
CPAP 10–20 cmH_2O	Negligible
Respironics® Total Face (IPAP/EPAP)	
10/5	0.61
18/5	0.81

CPAP continuous positive airway pressure, *EPAP* expiratory positive airway pressure, *IPAP* inspiratory positive airway pressure

In the only study using a real human model, Simmonds et al. [14] evaluated the characteristics of aerosol/droplet dispersion in normal individuals, individuals with coryzal symptoms, and patients with chronic lung disease admitted to hospital with infective exacerbation. Each group received O_2 therapy, NIV via a vented mask, and NIV via a non-vented mask with an exhalation filter placed between the EP and the mask. The investigators found that NIV via a vented mask generates large-sized droplets (>10 μm) in patients and coryzal individuals as opposed to the baseline droplet counts (without any intervention) with significant numbers found to be within a distance of 1 m. This augmentation in large droplets was not noticed using NIV with a non-vented mask and exhalation filter, whereas O_2 therapy did not produce droplet counts in any size range. These findings suggest that health care personnel providing NIV with vented masks and working within 1 m from infected patients should take special precautions.

During the SARS COVID-19 pandemic dispersion of air-born virus could be mitigated by the following practical strategies [15, 16].

1. Use CPAP (up to 10 cmH_2O) and BiPAP (with IPAP up to 25 cmH_2O).
2. Avoid nasal masks.
3. Use full face non-vented masks with EP attached to a single-limb circuit. As an alternative, use full face vented mask with negligible exhale air dispersion during CPAP (i.e., Quattro Air mask (ResMed®) (Table 16.1).
4. Install a bacteriological/viral filter between the patient interface and the exhalation port.
5. Try to reduce mask/face leaks to zero.
6. It is preferable to use the standard expiratory port circuit available on the market. If this is not possible, use EP with flow restrictor and a bacteriological filter (HEPA type) adapted to the EP (Fig. 16.3).
7. The addition of “T” or “Y” tube with an over-flow, as close to the mask as possible, allows filtering of all intentional leaks. In this case, the bacteriological filter is connected before or after the EP (with a restrictor). The combined resis-

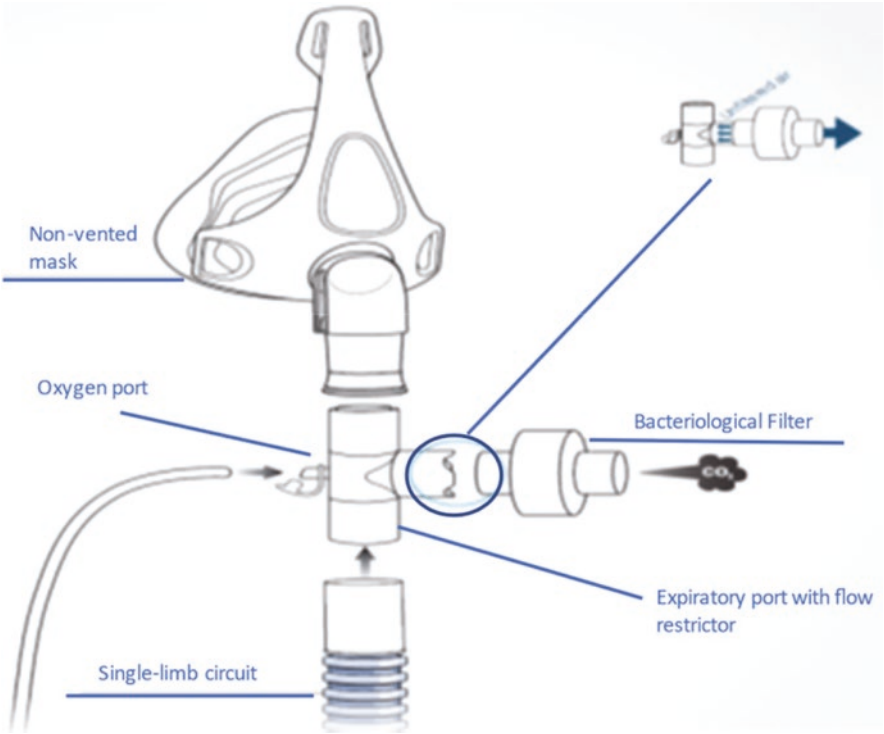

Fig. 16.3 Non-vented mask connected to a single-limb circuit through an expiratory port with a flow restrictor attached to a bacteriological filter. Ideally this setting should be used to limit aerosol dispersion. The exhalation port with reduced jetting has a shroud around the exhalation holes to reduce air entrainment and an array of small holes creating a diffuse flow. A low resistance bacteriological filter is recommended to mitigate CO_2 rebreathing and maximize the amount of gases filtered.

tance coming from filter and EP can dissipate almost all the pressure from the ventilator. This arrangement can produce a leak flow of 12 L/min at 3 cmH_2O and 35 L/min at 25 cmH_2O providing adequate ventilation at most bilevel settings without significant CO_2 rebreathing.

16.5 Conclusion

CO_2 rebreathing is a potential cause of treatment failure during mask NIV. In a single-limb setting, EPs play a significant role in reducing CO_2 rebreathing. Thus, an in-depth understanding of the mechanisms governing CO_2 rebreathing and a thorough knowledge of EPs are essential for selecting the proper setting on an individualized basis to avert NIV failure. Additionally, in the current COVID-19 crisis, it is of great importance to reduce and even eliminate the exposure of health-care personnel to potentially dangerous aerosols by using the appropriate NIV setup.

Key Major Recommendations

- CO_2 rebreathing is a potential cause of treatment failure during mask NIV
- The least CO_2 rebreathing occurs using double-limb circuits
- The best ventilator performance is achieved by a double-limb circuit attached to an oro-nasal mask
- To reduce CO_2 rebreathing during mask NIV with a single-limb circuit, it is recommended to:
  - Optimize ventilatory support (i.e., reduce respiratory rate, increase the T_e, ensure an adequate inspiratory V_T, add PEEP ≥4 cm H_2O),
  - Select a mask with the smallest inner volume equipped with a built-in EP, the plateau and the non-rebreathing valve (it has the highest resistance) are preferred over the Whisper-Swivel
- To minimize aerosol dispersion during mask NIV with a single-limb circuit, select a non-vented mask connected to a bacteriological/viral filter between the patient interface and the standard exhalation port.

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17 Patterns of Noninvasive Ventilation Response (Success and Failure) during Noninvasive Mechanical Ventilation

Mariano Alberto Pennisi and Edoardo Piervincenzi

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The success or failure of noninvasive ventilation (NIV) as a treatment in the various scenarios of respi ratory failure is a complex process with numerous critical issues. The success of NIV depends substantially not only on the careful selection of patients and available equipment but also on finely coordinated teamwork.

NIV failure has been defined as the need for endotracheal intubation (ETI) or death. Its rate greatly varies in literature between 5 and 60%, depending on numerous factors, first of all from the cause of respiratory failure [1].

To date, no single parameter is capable of providing us with predictive information on the success or failure of NIV treatment.

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_17

In clinical practice there is still no univocal method of evaluating treatment with NIV to predict the response, but as it is widely emphasized in the literature how the failure of noninvasive treatment often leads to a delay in ETI, it is always associated with worse outcomes [2, 3].

A brief digression is necessary to point out that the terms CPAP and NIV are sometimes mistakenly considered as the same therapy. This, from a pathophysiological point of view is incorrect for a series of reasons analyzed below: CPAP, through the delivery of a single constant higher pressure than the atmospheric one, allows the recruitment of collapsed alveolar areas and favors the opening of the upper airways.

Noninvasive positive pressure ventilation has been developed over time with multiple technical variants, whose analysis is beyond the scope of this chapter, and to simplify, we will assimilate it to a constant end-expiratory pressure (PEEP) plus a higher pressure which will be added. This "higher" pressure can be considered on the mechanical ventilator setting as an absolute value or sum of the two depending on the type of the machine used (IPAP-Psupp-Pinsp, etc.).

Due to the presence of an inspiratory pressure, NIV will be able to unload the patient's muscular respiratory work and provide an additional PEEP to the respiratory efforts.

This chapter will discuss the aspects of the response to NIV without considering the multiple applications of CPAP.

Below we will analyze the main clinical conditions extrapolated from the literature to evaluate the response to the NIV in each of them.

- NIV response in acute respiratory failure: ARDS and pneumonia
- NIV response in COPD exacerbation
- NIV response in postoperative period
- NIV response in hematologic malignancy with ARF/ARDS
- NIV response in acute cardiogenic pulmonary edema
- Timing of NIV failure

17.1 NIV Response in Acute Respiratory Failure: ARDS and Pneumonia

As described by Antonelli et al., plenty of RCTs show how NIV can be used safely and effective in an acute respiratory failure from various etiology: COPD, acute pulmonary edema, CAP (community acquired pneumonia), and also in acute respiratory failure in immunocompromised patients (solid organ transplantation, hematological diseases, etc.) [4].

An early and cautious use of NIV can prevent the use of invasive mechanical ventilation (IMV) reducing complications related to tracheal intubation.

In the paper written by Duan et al. in 2017, the authors have combined some variables, obtaining a score with good specificity and sensitivity in the prediction of NIV failure in hypoxemic patients 1 h after the start of treatment. In this study, after the first hour from the start of NIV, a multivariable logistic regression analysis

showed that heart rate, acidosis (assessed by pH), consciousness (assessed by GCS), oxygenation, and respiratory rate were independent risk factors for NIV failure in the analyzed cohort. The authors elaborate on a risk scale, named HACOR, to predict NIV failure. They tested this score at 1, 24, and 48 h from the start of NIV and immediately before intubation when NIV failed. At 1 h of NIV treatment, 87.1% of patients with a HACOR score of >5 required intubation and 81.6% of patients with HACOR score ≤5 did not require intubation. These results highlight the increased risk of noninvasive treatment failure for those patients with a HACOR SCORE greater than five points [5].

A fundamental role in the therapeutic success of NIV is played by a number of factors: first, a careful choice of patients; second, the use of comfortable and performing interfaces and the team's experience in managing NIV.

A close monitoring of the patient is mandatory during the use of NIV, especially in hypoxemic respiratory failure, where the absence of a rapid improvement in gas exchange parameters after a short cycle of NIV (1 h) requires invasive airway management and IMV to avoid potentially fatal consequences.

As reported in the paper written by Antonelli et al. in 2001, age > 40 years, SAPSII score, the presence of ARDS/CAP, and the failure to improve in the P/F ratio after 1 h of application of the NIV are independent parameters associated with the failure of the noninvasive respiratory support [4].

NPPV failed in 30% (108/354) of patients. The highest intubation rate was observed in patients with ARDS (51%) or community-acquired pneumonia (50%). The lowest intubation rate was observed in patients with cardiogenic pulmonary edema (10%) and pulmonary contusion (18%).

One aspect that should not be underestimated in hypoxemic respiratory insufficiency as a possible cause of noninvasive ventilation failure is self-inflicted lung injury. This damage, which is added to the primary damage of the cause of respiratory failure, is caused by the powerful inspiratory efforts that cause pleuropulmonary physio-pathological alterations.

In a prospective observational study on patients receiving noninvasive ventilation for acute hypoxemic respiratory failure Carteux et al. demonstrated that a high expired tidal volume is independently associated with noninvasive ventilation failure. In patients with moderate to severe hypoxemia, an expired tidal volume above 9.5 mL/kg predicted body weight predicts NIV failure [6].

However, a low expired tidal volume is almost impossible to obtain in the majority of hypoxemic patients receiving noninvasive ventilation.

In this regard, the use of high PEEPs with modest support pressures and the monitoring of the tidal volumes generated would seem to have a protective role in the prevention of this additional damage [7].

A percentage ranging from 60 to 90% of patients with community-acquired pneumonia develop acute respiratory failure and require intubation and mechanical ventilation (MV) as life-support treatment.

NIV has been shown to decrease, to various degrees, morbidity and mortality associated with invasive MV in ARF of different etiologies; the key point is always a careful patient selection.

17.2 NIV Response in COPD Exacerbations

NIV is nowadays one of the first line treatments in COPD exacerbation with hypercapnic respiratory failure in ER/ICU.

In the literature, the failure rate of NIV fluctuates around 20–25%, although there are studies carried out by experienced specialists with much lower failure rates, e.g., Nicolini et al. enrolled 1089 patients with COPD to be submitted to NIV; 1017 (93.4%) were successfully treated with NIV and only 72 (6.6%) were intubated [8].

The few patients who were intubated in this study had a very high mortality rate of more than 80%. These authors also emphasize the importance in early recognition of NIV failure and show how ventilator interface and tolerability with an early improvement in arterial pH, respiratory rate, and hemodynamic stability indicate a short-term favorable outcome.

The authors also point out that staff experience and interface knowledge play a crucial role, as mask intolerance remains the major cause of NIV failure and, in case of poor tolerance, it is reasonable to apply the so-called rotating strategy.

Miller et al. analyzed a 6-year case series of 240 patients with COPD hypercapnic exacerbation and showed how younger patients with a lower urea, higher pH, and lower pCO_2 at baseline, and who demonstrate an improvement in pH within 1 h, are more likely to have a successful outcome when given NIV for a hypercapnic exacerbation of COPD [9].

Duan et al. in 2019 also validated the risk score HACOR in COPD patients; with hypercapnic respiratory insufficiencies, undergoing noninvasive ventilation with good results, the predictivity of this score is maximum for NIV failures within the first 48 h [10].

Home treatment of COPD patients with home-care ventilators is beyond the scope of this chapter.

17.3 NIV Response in Postoperative Period

Postoperative respiratory failure was defined by Arozullah et al. as the need of mechanical ventilation for more than 48 h after surgery or the need for reintubation and mechanical ventilation after postoperative extubation [11].

In recent years, NIV has also been used to prevent the occurrence of acute respiratory failure after surgery (prophylactic use) or to treat acute respiratory failure (therapeutic use).

Chiumello et al. performed a review including 29 studies analyzing NIV use in the postoperative setting and identified an incidence of respiratory complications reported between 5 to 10% of all surgical patients and an incidence between 9 and 40% in patients undergoing abdominal surgery, with a development of at least one postoperative pulmonary complication.

Postoperative complications in the aforementioned review include atelectasis, postoperative pneumonia, pulmonary edema, and acute respiratory failure, although incidence and clinical significance may vary among them [12].

Many clinical trials have been performed in the postoperative setting using NIPPV, CPAP, or both in various clinical settings with different types of patients undergoing different surgeries.

From a practical point of view, these trials can first be divided between those that use CPAP or positive pressure ventilation for prophylactic purposes and those that use it for therapeutic purposes to correct a pathophysiological alteration [13, 14].

To date, there are still no data that unambiguously indicate the usefulness or otherwise of NIV/CPAP for prophylactic purposes in the postoperative period. Certainly, positive pressure ventilation or CPAP remain useful therapeutic tools in those cases in which respiratory distress develops in the postoperative period.

The selection of patients, the choice of the best interface, and the appropriate settings for each clinical situation remain absolutely fundamental for the success of the treatment.

Wallet et al. in 2010, in another RCT, reported that a lack of improvement or a worsening in P/F ratio after 1 h is a strong predictor of NIV failure in postoperative patients with ARF, as is the presence of nosocomial pneumonia [15].

17.4 NIV Response in Hematologic Malignancy with ARF/ARDS

Patients with hematological malignancy are a particular sub-category of patients, extremely fragile who have a very high mortality when admitted to intensive care and subjected to invasive mechanical ventilation. For this reason, over the years, they have increasingly been treated with CPAP or NIPPV when they develop respiratory failure.

In a reported retrospective series of 99 pts. with hematologic malignancy and ARF, "hospital mortality" was 79% in those who failed noninvasive ventilation, and 41% in those who succeeded. Patients who failed noninvasive ventilation had a significantly longer *ICU length of stay.*

Factors independently associated with noninvasive ventilation failure by multivariate analysis were respiratory rate under noninvasive ventilation, longer delay between admission and noninvasive ventilation first use, need for vasopressors or renal replacement therapy, and acute respiratory distress syndrome [16].

Gristina et al., in 2011, analyzed more than 1300 pts. in a retrospective multicenter study that showed better outcomes were associated with successful noninvasive mechanical ventilation (vs. invasive mechanical ventilation ab initio and vs. invasive mechanical ventilation after noninvasive mechanical ventilation failure), particularly in patients with acute lung injury/adult respiratory distress syndrome (mortality: 42% vs. 69% and 77%, respectively). Delayed vs. immediate invasive mechanical ventilation was associated with slightly but not significantly higher hospital mortality (65% vs. 58%, $p = 0.12$) [17].

In patients with hematologic malignancies, acute respiratory failure should probably be managed initially with noninvasive mechanical ventilation but further study is needed.

17.5 NIV Response in Cardiogenic Pulmonary EDEMA

In the literature, numerous studies establish NIV as a key treatment of acute cardiogenic pulmonary edema in association with usual pharmacological therapies.

A Cochrane review from Vital et al. that included 21 studies and over 1000 patients with acute pulmonary cardiogenic edema highlights a significant reduction in number of IOT and in-hospital mortality in patients treated with NIV versus patients treated with standard medical therapy [18].

It should be emphasized that in the pre-hospital setting, treatment with CPAP is achievable with many systems: Boussignac masks, helmet or masks with Venturi systems, and PEEP valves play an increasingly important role in the temporary treatment of acute respiratory failure due to pulmonary edema.

In an observational study on 100 patients treated with NIV for pulmonary edema Ferreira et al. demonstrated that initial PaO_2/FiO_2 ratio was significantly lower in the failure group and inadequate pH correction after 2 h of NIV is associated with NIV failure [19].

17.6 Timing of NIV Failure

Failure of NIV can be summarised in immediate failure, early failure and late failure; each of these moments has well-defined risk factors identified by numerous works in the literature.

Failure of NIV results in either orotracheal intubation or death of the patient from cardio-respiratory arrest.

Based on the work of Ozyilmaz et al., three moments in which NIV is at risk of failure are identified, and the main factors responsible for the failure are summarized below, divided by timing of onset. Factors for which NIV is contraindicated or independent factors associated with failure of noninvasive ventilation were excluded [20].

Immediate (few minutes): caused by the inability to mobilize respiratory secretions or excessive secretions, psychomotor agitation or coma and excessive asynchrony with the patient who "fights against the machine"

Early 1–48 h: failure to improve gas exchange or pH, increase in respiratory rate >25 breaths/min (in the hypoxemic ARF) or >35 breaths/min (in the hypercapnic ARF)

Late > 48 h: the late failure of NIV has been analyzed much less by the various trials available and data are mainly available from patients with hypercapnic respiratory failure. Sleep disturbances, delirium, and infectious complications are recognized as some of the predisposing factors.

It is important to underline that late failure is associated with an extremely high mortality of approximately 70% [1].

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Predictive Factors of Noninvasive Mechanical Ventilation Failure

18

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_18

18.1 Introduction

Acute respiratory failure (ARF) is defined as the inability of the respiratory system to meet the oxygenation, ventilation, or metabolic requirements of the patient. ARF accounted for a continuing increase in the number of hospitalizations at an average annual rate of 11.3% in 2001–2009, but with a decline in inpatient mortality in the United States [1]. ARF is characterized by impairment of the respiratory system to exchange gases and to oxygenate the blood, resulting in hypoxia with or without hypercapnia [2]. Two main mechanisms of ARF include:

1. A failure in pulmonary ventilation. It may be due to neuromuscular diseases, chest wall deformities, and obstructive pulmonary diseases.
2. A failure in gas exchange caused by pneumonia, airspace collapse (atelectasis), adult acute respiratory distress syndrome acute cardiogenic pulmonary edema, severe status asthmaticus, and pulmonary embolism [3].

The symptoms and signs of these patients with ARF are related to arterial hypercapnia and hypoxemia.

Noninvasive ventilation (NIV) refers to the delivery of mechanical ventilation without using an endotracheal tube or tracheostomy tube. Its use has been increasing in the past two decades [4]. NIV can decrease the length of stay in the ICU, reduce the number of possible complications, increase quality of life, reduce risk of infection, and improve survival, compared to conventional invasive ventilation [5–7].

The effectiveness of NIV depends on the etiology of respiratory failure; therefore, not all diseases will benefit from NIV in the same way [8]. The prediction of NIV failure is very important to prevent a delayed intubation and an increased risk of morbidity and mortality [9]. The risk of NIV failure determines the intensity of monitoring needed [10–12]. One approach to determine the need for monitoring is to assess the patient's risk of NIV failure [12] . Some of these are simple bedside assessments, such as ability to cough, respiratory rate, etc. Other methods require analysis as a determination of arterial blood gases (ABG). Other methods require proven evaluation protocols: Acute Physiology and Chronic Health Evaluation (APACHE) II or Simplified Acute Physiology Score (SAPS) II. Some novel clinical scoring of the NIV failure among patients with ARF have proven their usefulness. Liengswangwong et al. [11] demonstrated that NIV failure was associated with heart rate >110 bpm, systolic BP <110 mmHg, SpO_2 < 90%, arterial pH < 7.30, and serum lactatthe. In addition to all these factors that we can evaluate, the experience of the team in charge of these patients is not less important due to the speed that the changes occur. A patient with multiple risk factors for NIV failure should be placed in a closely monitored setting such as an ICU or a step-down respiratory unit.

Three critical periods for detecting NIV failure have been defined [13] (Fig. 18.1):

1. Immediate failure (within minutes to <1 h),
2. Early failure (1–48 h), and
3. Late failure (after 48 h).

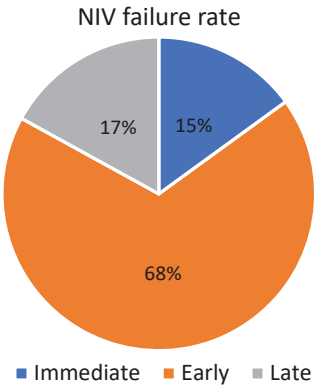

Fig. 18.1 Mean NIV failure rates based on timing according to the data of randomized controlled trials [13]

18.2 Immediate NIV Failure

Immediate NIV failure refers to failure within 60 min after the start of NIV. Predictors of failure in this period have never been systematically analyzed. A weak cough reflex leading to inefficient clearance of excessive secretions from airways is a common cause of immediate NIV failure. The inability to spontaneously remove secretions is considered a contraindication to NIV, e.g., patients with impaired consciousness and depressed cough reflex. Hypercapnic encephalopathy (HES) has often been considered a cause of immediate NIV failure because of poor compliance due to confusion and/or agitation. It is a relative contraindication because of the increased risk of aspiration, which is minimized by the rapid improvement of neurological status. Patient tolerance has been shown to be critical for NIV success, especially in the first few minutes while the patient adapts to this "new mode" of breathing [14].

18.3 Early NIV Failure

Nearly 65% of NIV failures occur within the first 48 h of NIV use [13]. This time interval has received more attention in assessments of NIV failure than any other. Several investigators have tried to assess the best predictors of NIV failure. Confalonieri et al. [14] found that individuals likely to experience NIV failure had more severe respiratory acidosis, a lower level of consciousness, were older, more hypoxemic, and/or had a higher respiratory rate on presentation. Clinical signs that are only equivocal on presentation become more definitively predictive of failure if they persist after 2 h of NIV. It is important to assess clinical trajectory during the first 2 h of NIV. Individuals who have a pH < 7.25, an APACHE II score >29, and a Glasgow coma score < 11 on presentation to the hospital have failure rates ranging from 64 to 82% and are at risk for early failure. Moreover, patients with excessive respiratory secretions or without improvement of clinical and/or after 60 min of NIV have high risk of failure.

18.4 Late NIV Failure

Late NIV failure (after 48 h) is an event occurring after an initial good response to NIV. It is more likely in individuals who, at the time of admission, showed functional limitations evaluated using a score correlated to activities of daily living (ADL), a higher number of comorbidities (such as renal failure, chronic heart failure, diabetes), a lower pH at baseline, and the underlying cause of acute respiratory failure (ARF), e.g., pneumonia. NIV is being increasingly used for the management of acute and chronic respiratory failure. Over the past two decades, increasing evidence has established its place as the first line therapy for certain forms of ARF [15], particularly those resulting from acute exacerbations of chronic obstructive pulmonary disease (COPD) and cardiogenic pulmonary. Over time, NIV was used in more severe patients and several clinical situations with proven efficacy (e.g., restrictive lung diseases, obesity hypoventilation syndrome (OHS), and weaning from invasive mechanical ventilation) [14]. Since NIV can have failure rates ranging from 5 to 50%, NIV failure may cause intubation delay, increasing morbidity and mortality [13]. The risk factors of NIV failure based on timing are summarized in Table 18.1.

Table 18.1 The risk factors of NIV failure based on timing

Time	Risk factors
Immediate	1. Weak cough reflex and/or excessive secretions
	2. Hypercapnic encephalopathy and coma
	3. Psychomotor agitation
	4. Patient–ventilator asynchrony
Early Hypoxemic ARF	1. Baseline ABG and inability to correct gas exchange (P/F < 150)
	2. Baseline severity scores (SAPS II >35)
	3. The presence of ARDS/pneumonia/sepsis/multiorgan failure (OR: 4–28)
	4. Increased respiratory rate (>25 breaths/min)
	5. Miscellaneous: Delay between admission and NIV use, number of fiber optic bronchoscopes performed, duration of NIV use, increase in radiographic infiltrates within the first 24 h, causal diagnosis (as "de novo")
Early Hypercapnic ARF	1. Baseline ABG and inability to correct gas exchange (pH < 7.25)
	2. Increased severity of disease
	3. Increased respiratory rate (>35 breaths/min, OR for baseline and after 2 h of NIV: 2.66 and 4.95)*
	4. Mixed indices:
	GCS, APACHE II score, respiratory rate and pH
	Respiratory rate, random glucose level and APACHE II
	Anemia and WHO-PS
	5. Miscellaneous: Poor nutritional status, Increased heart rate, Higher baseline C-reactive protein/white blood cell count, Lower serum potassium, Airway colonization by non-fermenting gram-negative bacilli
Late	1. Sleep disturbance
	2. Functional limitation
	3. Possible initial improvement in pH
	4. Hyperglycemia

Adapted by Ozyilmaz et al. [13]
ABG arterial blood gas, *APACHE II* acute physiology and chronic health evaluation, *GCS* Glasgow coma scale, *OR* odd ratio, *P/F* Ratio of PaO_2 to FiO_2, *WHO-PS* World Health Organization performance status

NIV failure depends on the type of respiratory failure and on the type of pulmonary or extra-pulmonary disorders. Martín-González et al. [16] recruited 410 consecutive patients with NIV treated in an Intensive Care Unit with different etiologies of ARF. NIV was seen to have a high probability of success in three types of patients (chronic obstructive respiratory disease (COPD) exacerbation, acute cardiogenic pulmonary edema, and hypercapnic RF without COPD), while failure in hypoxemic ARF was very high (73.7%). Overall, their data suggested that more severe patients, with poorer initial response to NIV, were more likely to fail. Equally interesting was that serum bilirubin prior to initiation of NIV was a predictor of failure.

Therefore, for a practical approach, we have divided predictive factors according to the type and disorder involved in the cause of ARF.

1. Hypercapnic ARF due to chronic obstructive respiratory disease (COPD)
2. Hypercapnic ARF due to obesity-hypoventilation (OHS)
3. Hypercapnic ARF due to neurological and neuromuscular disorders (NMD)
4. Hypoxemic ARF due to pneumonia
5. Hypoxemic ARF due to SARS CoV2 infection (COVID 19)

18.4.1 Hypercapnic ARF Due to Chronic Obstructive Respiratory Disease (COPD)

Patients with hypercapnic respiratory failure, particularly with COPD exacerbations, have a better response while people with hypoxemic respiratory failure have poorer response to NIV. Randomized controlled trials have shown successful use of NIV in the management of acute hypercapnic respiratory failure (AHRF) to reduce the likelihood of mortality and endotracheal intubation in patients admitted with AHRF secondary to an acute exacerbation of COPD [17]. Patient selection is one of the most important factors in determining the NIV success because not all hypercapnic COPD patients are responsive to NIV [18]. A higher APACHE II score (>29), lower Glasgow Coma Score (<11), pH < 7.25, respiratory rate > 35/min, air leakage, copious secretions, asynchrony, and lack of compliance or tolerance are found to be predictors for failure of NIV in these patients. Technical aspects such as choice of interface and ventilator settings are clearly important for NIV success. The optimal location for NIV application remains a matter of debate. There are many reports supporting the use of NIV in intensive care units (ICUs) [19]. However, in recent years, there are also some studies recommending the initiation of NIV in emergency departments and in general wards [20, 21]. On the other hand, the number of patients with chronic respiratory failure and using home mechanical ventilation are increasing. According to the Eurovent survey, the estimated prevalence of home mechanical ventilation in Europe is 6.6 per 100,000 people [22]. There are no clear data on how these patients respond to NIV therapy during their AHRF attack. In terms of factors influencing the NIV response in the early period, nocturnal application was significantly associated with better response, prior home ventilation, and requirement of higher pressure support (PS) levels significantly and independently associated with poorer response to NIV therapy [23].

18.4.2 Hypercapnic ARF Due to Obesity-Hypoventilation Syndrome (OHS)

More than 30% of patients with OHS are diagnosed initially when hospitalized for acute on chronic respiratory failure. Patients with OHS often respond well to NIV. The pathophysiology of OHS results from complex interactions between various sleep breathing disorders (obstructive sleep apnea, reduced REM, sleep hypoventilation), increased work of breathing due to decreased thoraco-abdominal compliance, and altered ventilatory drive. Respiratory system compliance in obese individuals can be reduced by the restrictive effect of fat on the chest wall, a tendency to breathe at low lung volumes, and/or fat distribution that contributes to high pleural pressures. This last factor leads to low end-expiratory volume with flow limitation in the supine patient. Obesity increases the stiffness of the total respiratory system with consequent development of low lung volume. Breathing at low volumes increases airway resistance with expiratory flow limitation and gas trapping due to early airway closure and subsequent generation of intrinsic positive end-expiratory pressure and ventilation mismatching, especially in supine position and during sleep [24]. These mechanisms can be successfully corrected by NIV. Patients with OHS can be treated in an acute care setting with better results than other diseases such as COPD. NIV reduces the respiratory load, increases minute volume for a given breathing effort, and provides ventilation during central apnea episodes. In obese patients with ARF, neither pH nor $paCO_2$ accurately predicted patient response to NIV in the first hours of NIV treatment.

The decreased responsiveness in hypoxic and hypercapnic ventilatory drive that characterizes this last category may explain why they need more time than expected to correct respiratory acidosis compared to other patients. Delay in the reduction of $PaCO_2$ may be due to:

1. Inadequate level of IPAP or EPAP: in obese patients IPAP should range from 12 to 30 cm H_2O and EPAP from 6 to 8 cm H_2O or greater [25].
2. Inadequate duration of NIV: the obese patients require longer NIV therapy than non-obese ones, especially during the night; their apnea or hypoventilation worsen during hours of sleep [26].

These findings suggest that NIV settings need to be monitored more aggressively in OHS (when acute illness precipitates respiratory decompensation) than in other syndromes. During NIV therapy, observation and monitoring of the level of consciousness, vital signs, respiratory pattern, oxygen saturation, and ABG are crucial.

18.4.3 Hypercapnic ARF Due to Neurological and Neuromuscular Disorders

Many neurological diseases may cause ARF due to involvement of bulbar respiratory center, spinal cord, motoneurons, peripheral nerves, neuromuscular junction, or

skeletal muscles. Commonly, patients develop primarily ventilatory impairment causing hypercapnia. Moreover, inadequate bulbar and expiratory muscle function may cause retained secretions, complicated by pneumonia, atelectasis, and finally, hypoxemic ARF.

The adult neuromuscular disorders that may present with ARF at onset are the following:

- Amyotrophic lateral sclerosis (ALS)
- Pompe disease
- Myotonic dystrophy type 1 (DM1)
- Myofibrillar myopathies
- Some Limb-girdle muscular dystrophies (LGMD)

Two main categories of ARF can be identified:

- Acute exacerbation of chronic respiratory failure, which is common in slowly progressive neurological diseases, such as movement disorders and most neuromuscular diseases.
- Sudden-onset respiratory failure which may develop in rapidly progressive neurological disorders including stroke, convulsive status epilepticus, traumatic brain injury, spinal cord injury, myasthenia gravis, and Guillain–Barré syndrome.

The use combined NIV and mechanical insufflator-exsufflator (MI-E) for ARF in patients with neuromuscular disease (NMD) is an efficient means of averting intubation in NMD patients with ARF. Clinical features within 8 h of the institution may predict treatment outcome. A prospectively observational study of 62 patients (with a median age 13 years) with ARF was conducted in a pediatric intensive care unit. ARF was primarily due to pneumonia (65%). The treatment success rate was 86%. Heart rate, respiratory rate (RR), pH, and $PaCO_2$ showed a progressive improvement, particularly after 4 h following successful NIV/MI-E treatment. RR decrease at 4 h, and pH increase and PaCO2 decrease at 4–8 h might predict success of NIV/MI-E treatment. The multivariate analysis identified PaCO2 at 4–8 h of 58.0 mmHg as an outcome predictor of NIV/MI-E treatment [27].

Amyotrophic lateral sclerosis (ALS), is a progressive neurodegenerative disease characterized by a progressive degeneration of motor nerve cells in the brain (upper motor neurons) and spinal cord (lower motor neurons). NIV has been shown to improve survival and quality of life in ALS patients with respiratory failure, but scant literature has investigated the predictors of NIV tolerance. Compliance with and tolerability of NIV are the key factors in determining the success of treatment. Overall, it is felt that people who are more compliant and can better tolerate NIV gain the most significant overall benefit, and this has been shown in a number of studies. Bourke et al. found that the survival benefit they observed in their small (n = 22) prospective study correlated with NIV compliance [28]. Furthermore, in the same study, in multivariate analysis, compliance with NIV was the only factor that correlated with quality of life. Kleopa et al. also found a significant survival

benefit for those who had good NIV tolerance greater than 4 h per night versus those who did not tolerate and therefore did not use NIV [29]. It has been found that the area of onset of MND, i.e., limb or bulbar, did not affect tolerance, while other studies have found that bulbar symptoms have been associated with poor NIV tolerance and therefore reduced benefit [30]. Russo et al. [31] demonstrated in patients with ALS the average time of adaptation was 7.82 days. The presence of sialorrhea and neurobehavioral impairment, and absence of respiratory symptoms were negative predictors of NIV adaptation.

Myasthenia gravis (MG) is clinically characterized by weakness that can be severe enough to cause respiratory failure [32]. In the first 2 years after diagnosis of MG, approximately 15–20% of patients develop myasthenic crisis (MC), a potentially life-threatening condition, that may require ventilation, either NIV or mechanical (MV). Lori et al. [33] found that early use of NIV outside an ICU setting is feasible, and NIV failure may occur only in a third of cases. The clinical parameters significantly associated with NIV failure and need of tracheal intubation were male gender, infections (especially of upper respiratory tract), older age at onset and concurrent morbidities.

18.4.4 Hypoxemic ARF Due to Pneumonia

Severe community-acquired pneumonia (sCAP) is defined as pneumonia requiring admission to the intensive care unit or carrying a high risk of death. The treatment of sCAP consists in antibiotic therapy and ventilator support. There is a greater variability in NIV failure rates. Carrillo et al. [34] noted the following risk factors: worsening radiological infiltrate 24 h after admission, maximum sepsis-related organ failure assessment (SOFA) score at admission and SOFA after 1 h of NIV, higher heart rate, lower oxygen arterial pressure/oxygen inspiratory fraction ratio (PaO_2/FiO_2), and bicarbonate. The debate concerning the use of NIV for the treatment of sCAP increased during the H1N1 pandemic. Initially, it was not recommended; nevertheless, the number of NIV successes progressively increased. This initial, unwarranted pessimism was dispelled by successful employment of NIV in diverse geographical settings. More evidence concerning the efficacy of NIV is now available. Nicolini et al. prospectively assessed 127 patients with sCAP and severe acute respiratory failure [oxygen arterial pressure/oxygen inspiratory fraction ratio (PaO_2/FiO_2)] <250. They found that NIV failed in 32 patients (25.1%). Higher chest X-ray score at admission, chest X-ray worsening, and a lower PaO_2/FiO_2 and higher alveolar-arteriolar gradient (A-aDO2) after 1 h of NIV all independently predicted NIV failure. Higher lactate dehydrogenase and confusion, elevated blood urea, respiratory rate, blood pressure plus age ≥ 65 years at admission, higher A-aDO_2, respiratory rate and lower PaO_2/FiO_2 after 1 h of NIV, and intubation rate were directly related to hospital mortality [35].

In patients with hypoxemic ARF and pneumonia, we can use other noninvasive respiratory strategies (NIRS) such as high-flow nasal cannula (HFNC). The respiratory rate–oxygenation (ROX) index, based on oxygen saturation

measured by pulse oximetry (SpO_2), fraction of inspired oxygen (FiO_2), and respiratory rate, can help to identify the risk of HFNC failure and intubation [36].

18.4.5 Hypoxemic ARF Due to SARS CoV2 Infection (COVID-19)

The efficacy of NIV, including both bilevel positive airway pressure (BiPAP) and continuous positive airway pressure (CPAP), in patients with ARF secondary to coronavirus disease 2019 (COVID-19) is still debated [37]. Some authors believe that NIV represents a questionable option and controlled mechanical ventilation should be established as soon as possible because of the risks of patient self-inflicted lung injury and delayed intubation [38], but there is evidence in favor of early intubation in COVID-19 ARF. Recent studies showed that a short NIV trial could be beneficial to treat COVID-19 mild-to-moderate hypoxemic ARF [39]. Boscolo et al. performed an observational multicenter study including COVID-19 adult patients who underwent endotracheal intubation after NIV failure. A total of 280 patients were enrolled. Only the length of NIV application before ICU admission (OR 2.03, $p = 0.03$) and age (OR 1.18, $p < 0.01$) were identified as independent risk factors of in-hospital mortality; while the length of NIV after ICU admission did not affect patient outcome [40].

Recently, a simple nomogram and online calculator has been developed to identify patients with COVID-19 who are at risk of NIRS failure (including both HFNC and NIV). The patients might benefit from early triage and more intensive monitoring. The nomogram was based on age, number of comorbidities, ROX index, Glasgow coma scale score, and use of vasopressors on day 1 of NIRS [41].

18.5 Conclusions

The prediction of NIV failure in patients with ARF is very important to prevent a delayed intubation and an increased risk of morbidity and mortality. The factors involved will depend on the characteristics of respiratory failure and their etiology [42]. An adequate follow-up will be necessary at each NIV treatment.

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19 Noninvasive Ventilation Failure: How to Foresee, Prevent, Diagnose It, and When to Switch to Invasive Mechanical Ventilation

Nicola Launaro and Monica Giordanengo

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_19

In recent years, noninvasive ventilation (NIV) has become an increasingly popular procedure for the treatment of various conditions that cause acute respiratory failure (cardiogenic pulmonary edema or acute exacerbations of chronic obstructive pulmonary disease (COPD), community-acquired pneumonia or acute respiratory distress syndrome (ARDS), or interstitial pneumonia during the recent COVID 19 pandemic).

Numerous studies have shown that the early application of NIV in diseases such as COPD exacerbation, acute pulmonary edema, and pneumonia significantly reduces in-hospital mortality and the length of hospitalization as well as the need for intubation [1, 2, 3, 4, 5, 6].

It is also necessary to bear in mind that patients who have experienced NIV failure have a higher mortality than those who have been subjected to intubation and invasive ventilation since the start of the acute event [7, 8].

It is therefore of fundamental importance to carry out an adequate and careful evaluation of the patients to be treated with NIV by implementing all the necessary procedures to avoid the failure of this treatment [9, 10, 11, 12, 13, 14, 15, 16].

Studies in the literature have analyzed the possible factors responsible for the failure of NIV. In most of them, the main parameters were acidosis, hypoxemia, severity (SAPS; APACHE), respiratory pattern (respiratory rate), and level of consciousness. The search for a predictive score such as the HACOR score [Heart rate, acidosis (assessed by pH), consciousness (Glasgow coma score), oxygenation, and respiratory rate] is interesting [17] (Table 19.1). This score shows

Table 19.1 Hacor score

Variables	Measure	Score
Heart rate (beats/min)	≤120	0
	≥121	1
pH	≥7.35	0
	7.30–7.34	2
	7.25–7.29	3
	<7.25	4
GCS	15	0
	13–14	2
	11–12	5
	≤10	10
PaO_2/FiO_2	≥201	0
	176–200	2
	151–175	3
	126–150	4
	101–125	5
	≤100	6
Respiratory rate (breaths/min)	≤30	0
	31–35	1
	36–40	2
	41–45	3
	≥46	4

Table 19.2 Criteria for the success of NIV

1.	Proper patient selection
	a. Basic pathology and severity
	b. Comorbidity
	c. Collaboration of the patient
2.	Experience of the team and level of organization of the department
3.	Definition of the procedure: protocols

good reliability in predicting NIV failure in patients with exacerbated COPD in the first 48 h of treatment. Subsequent works have demonstrated its validity also in patients with pneumonia and ARDS, especially as an indicator in the first hour of treatment.

In this chapter, we will evaluate:

1. The parameters to be used in the decision-making process that will define whether to undertake noninvasive ventilation or to subject the [18] patient to orotracheal intubation and then invasive ventilation (Table 19.2).
2. How to recognize the ineffectiveness of NIV in every single situation
3. When to perform tracheal intubation

19.1 Patient Selection

19.1.1 Condition that Led to Acute Respiratory Failure and Co-Morbidities

The most important criterion is the pathology responsible for acute respiratory failure. NIV is more effective in hypoxic–hypercapnic respiratory failure conditions, especially in patients whose pre-existing condition caused respiratory failure resulting from pathologies not only respiratory (Table 19.3) [19, 20, 21].

19.1.1.1 COPD Exacerbation

The role of NIV is now consolidated in the exacerbation of COPD. In fact, in this condition, the validity of an adequate medical therapy associated with an administration of oxygen with SaO_2 target 88–92% (evidence grade A) is demonstrated. Subsequent intervention with NIV when pH < 7.35 and $PaCO_2$ > 50 mmHg demonstrated a significant reduction in mortality both in relation to medical therapy and oxygen and to treatment with invasive ventilation (evidence grade A). The success of the treatment is related to the early intervention [22, 23, 24, 25, 26, 27, 28, 29].

The patient must be carefully monitored especially in the first 2 h of treatment to identify any worsening of physiological parameters (pH, respiratory rate, state of consciousness). Any worsening does not require immediate conversion to invasive ventilation and admission to the Intensive Care Unit, but it is advisable to review and correct the interface and setting of the ventilator.

Table 19.3 Main causes of hypoxic–hypercapnic respiratory failure

1. Obstructive bronchial diseases
a. Chronic obstructive pulmonary disease (COPD)
i. Emphysema
ii. Chronic bronchitis
b. Asthma
2. Bronchiectasis
3. Neuromuscular diseases
a. Dystrophies
b. Myasthenia
c. Motor neuron diseases
d. Polyneuropathies
4. Hypoventilation obesity syndrome
5. Chest wall anomalies
a. Kyphoscoliosis
b. Thoracoplasty

Severe acidosis (pH < 7.25) before starting treatment correlates with a high number of failures but this should not preclude, in expert centers, carrying out a trial in a protected environment (sub-intensive/intensive areas) under careful monitoring.

19.1.1.2 Asthma Attack

In patients with acute respiratory failure for an asthma attack, NIV is not the first choice of treatment. It is indicated in the presence of a deterioration in the respiratory pattern and hypercapnia only in expert centers, given the lack of scientific evidence.

The main causes of failure are attributable to the patient's poor tolerance and the risk of increasing lung hyperinflation (PEEPe > PEEPi).

19.1.1.3 Chest Wall Disorder

In rib cage deformities presenting with acute respiratory failure, it is indicated to initiate NIV treatment even without the development of respiratory acidosis to prevent and/or treat respiratory muscle fatigue. The main indicator of failure is the persistence of tachypnea.

19.1.1.4 Neuromuscular Diseases

Numerous neuromuscular diseases progress toward chronic respiratory failure. Acute respiratory failure can develop, even without previous chronic respiratory failure, often due to even mild airway infections. In these cases, NIV is first-line treatment.

19.1.1.5 Cardiogenic Pulmonary Edema

In the treatment of respiratory failure caused by acute pulmonary edema, NIV use is supported by a multitude of evidence in the guidelines of scientific societies (ESC, ATS, NICE).

A reduction in mortality and a faster resolution of acute respiratory failure with a reduced incidence of need for tracheal intubation are evident in patients treated early. The ATS guidelines recommend its use in the pre-hospital phase with CPAP.

A recent Cochrane review showed that the incidence of adverse events was comparable to patients treated with standard medical therapy.

19.1.1.6 Obesity-Hypoventilation Syndrome

In these patients, NIV should be initiated following the same criteria as COPD exacerbation. Various authors recommend NIV in some hospitalized obese hypercapnic patients with daytime sleepiness, sleep-disordered breathing, and/or right-sided heart failure in the absence of acidosis.

19.1.1.7 Community-Acquired Pneumonia (CAP) – ARDS

Lower respiratory tract infections represent a major global infectious cause of mortality in all age groups. Six percent of all ICU admissions are respiratory failure in CAP. Intensive care mortality is over 30% in most case series, and overall hospital mortality is around 50%. ARF can occur in 58–87% of patients with severe CAP.

From the first studies, it was evident that in the presence of a more severe clinical picture (SAPS II > 34) and more compromised respiratory parameters ($PaO_2/FiO_2 < 200$) failure of NIV was more frequent. Another important criterion, also present in other conditions, is the presence or absence of respiratory failure prior to the acute event with an increase in failures in patients who presented with acute de novo respiratory failure.

Finally, a worsening of gas exchange after 1 h of treatment is a clear indication of NIV failure and requires conversion to invasive ventilation.

In conclusion: in patients with ALI/ARDS as a consequence of a pulmonary infectious episode, it is indicated to carry out a trial of NIV with an experienced team and ready availability to carry out invasive maneuvers in all those patients presenting a mild ARDS, in accordance with the Berlin definition (2012). Patients must be closely monitored and a re-evaluation of the blood gas analysis is mandatory after 60 minutes of treatment even in the presence of stable hemodynamic parameters.

19.1.1.8 Immunocompromised

In patients with hypoxemic respiratory failure, NIV reduces mortality and the need for intubation compared to oxygen therapy alone. In immunocompromised patients treated with intubation and invasive ventilation, mortality ranges from 50 to 70%. Better results are obtained in patients who develop acute respiratory failure following pulmonary edema, while there is a higher rate of NIV failures in patients with pneumonia or who have a more critical clinical picture.

Based on these considerations, the ERS/ATS guidelines provide the following indication: *"The currently available literature supports the use of NIV as a first-line approach for the management of mild to moderate ARF in selected patients with immunosuppression of various etiologies."*

19.1.1.9 COVID-19 Infection

Currently available data are not sufficient to define a superiority of NIV in terms of mortality over early intubation. It is not possible to conclusively deduce whether bankruptcies are responsible for an increase in mortality. The treatment with helmet CPAP has certainly proved effective in treating patients with moderate hypoxemic respiratory insufficiency ($PaO_2/FiO_2 > 150$) and the use of the prone position during treatment with CPAP and helmet is equally effective. In the absence of clear references, it is believed that possible complications include an increase in tachypnea (>35 beats/min), worsening of hypoxemia ($PaO_2/FiO_2 < 150$), deterioration of hemodynamic parameters, development of sepsis and septic shock.

19.1.1.10 Contraindications for Noninvasive Positive Pressure Support Ventilation

The following contraindications must be evaluated according to the patient's general clinical picture, the expected outcome of the NIV and above all the level of preparation of the team dedicated to the patient. For example, treatment with NIV is possible for a patient undergoing vasopressor therapy in an intensive setting, with invasive blood pressure monitoring or with difficulty in managing secretions independently, if you have physiotherapists dedicated to this treatment.

1. Absolute
   a. Respiratory arrest
   b. Unstable cardiac arrhythmia
   c. Uncooperative patient/coma
   d. Facial trauma, burns to the face
   e. Inability to place the mask
   f. Recent facial or upper airway surgery
2. Relative
   a. Severe hypoxemia ($PaO_2/FiO_2 < 100$)
   b. High severity score [Simplified Acute Physiology Score (SAPS) II ≥35]
   c. Need for vasopressors
   d. Need for renal replacement therapy
   e. Untreated pneumothorax
   f. Inability to protect own airway
   g. Difficulty managing copious secretions

19.2 Experience of the Team and Level of Specialization of the Department

NIV treatment is a demanding procedure that requires a high workload even in a trained team.

The main causes of successful NIV treatment, in addition to the correct selection of patients, include correct and timely treatment of any problems that may arise (air leaks, discomfort, agitation, and a feeling of lack of improvement on the part of the patient).

An important aspect is represented by a clear and defined treatment plan (timing, variations, personalization).

Finally, the availability of equipment for the treatment and monitoring of patients (masks, ventilators, monitors).

19.2.1 Definition of Expert Team

It must be understood as a multidisciplinary team that involves various medical specialists (pulmonologists, emergency doctors, intensive care physicians), nurses, respiratory therapists. The team will need to have skills regarding the

a. Pathophysiology of respiratory insufficiency, diagnosis, and its treatment in the specific causes
b. The ventilation methods and their application in the specific conditions
    i. CPAP (continuous positive airway pressure) remembering that a ventilation mode cannot be defined
    ii. BiPAP (bilevel positive airway pressure)
    iii. Pressure support ventilation (PSV)
    iv. Synchronized intermittent mandatory ventilation (SIMV) in pressure (PC-SIMV) or volume (VC-SIMV) mode
    v. AVAPS (average volume assured pressure support)
    vi. Assist-control mode (A/C)
    vii. Pressure control ventilation (PC)
    viii. Volume control ventilation (VC)
    ix. Pressure regulated volume control (PRVC)
    x. PAV (proportional assist ventilation)
    xi. Adaptive servo ventilation (ASV)
    xii. NAVA (neurally adjusted ventilator assist)
    xiii. HFNC (high flow nasal cannula): oxygen therapy modality that provides a low level of PEEP
c. The Ventilators
    i. Set the ventilation according to the clinical conditions of the patient with possible back-up ventilation whenever using an assisted mode without controlled acts
    ii. Alarms
    iii. Evaluate both graphical and numerical monitoring provided by the ventilator
    iv. Implement the necessary interventions to improve patient–ventilator interaction and gas exchanges
d. The interfaces
    i. Use different models to adapt the prosthesis to conform to the patient's face and the patient's requests. The goal is to provide the greatest possible comfort to the patient to obtain their maximum collaboration
        Nasal mask
        Facial mask

Total face mask
Helmet

ii. Decide according to the respiratory disorder and modify according to the tightness (no leakage) and the ventilatory response

e. The techniques of humidification and management of tracheobronchial secretions
   i. Active and passive humidification
   ii. Use of aids for cough assistance
   iii. Aspiration of secretions
   iv. Bronchoscopy to remove secretions occluding the airways
f. Oxygen therapy
g. Adjustment according to the degree and type of respiratory insufficiency
h. The management of pain, agitation, and delirium
i. Invasive and noninvasive hemodynamic and respiratory monitoring
j. Nutrition

The role of nurses in the management of interfaces and in the development of an active collaboration of the patient in treatment is fundamental. This requires a numerically adequate staff who can dedicate time to the patient to generate the sensation of attentive care and sharing in the patient's needs.

Various studies have shown that the application of NIV by inadequately trained personnel increases the risk of intubation and death even in an intensive environment.

19.2.2 Treatment Plan

The team will have to define an adequate treatment plan. The plan should provide general and at the same time specific information for each patient. The main reason for success is the personalization of ventilatory treatment.

The plan must include:

a. Treatment indication: severity of respiratory insufficiency. Responsible pathology and comorbidities
b. Timing of start and end of treatment: the earlier the treatment is started, the lower the failure rate
c. Ventilation management protocol based on patient responses and changes in blood gases
   i. Start NIV and evaluate after 60 min
   ii. Correct the ventilation parameters and continue if the gas exchange response is adequate
   iii. Evaluate tracheal intubation when protocol-predicted improvement does not occur
d. Monitoring level and timing: to be defined according to the severity of the clinical picture
   i. During noninvasive ventilation, evaluations will be more frequent in the first hours of treatment.

   ii. Keep monitoring continuously for at least the first 24 h of treatment
   iii. A delay in converting from invasive ventilation significantly increases mortality
e. Management and prevention of complications: air leaks, mask decubitus, agitation, inhalation
f. Protocol for the treatment of delirium and for sedation
g. Protocol for the treatment of any arrhythmias
h. Protocol for the use of inotropes and vasoconstrictors

19.2.3 Organization of the Structure

a. The hospital must be able to provide treatment with NIV to all patients who have the indications
   i. Depending on the level of severity, rooms with an adequate number of beds must be defined
   ii. The beds defined must have the staff with the skills described above
   iii. It is necessary to provide for different locations of the beds according to the severity of the clinical picture
b. Intensive care units
   i. Patients with severe respiratory insufficiency with risk of intubation
   ii. Patients with comorbidities or other organ failure
   iii. NIV continues
   iv. Need for a more accurate monitoring level and high level of care
c. Subintensive care units or level 2 ICU
   i. Moderately severe (pH > 7.30)
   v. Low risk of intubation
   vi. NIV continues for 24 h then intermittent or nocturnal
   vii. Continuous monitoring
d. Ordinary ward
   i. Exclusively in specialized departments with a specific team
   ii. Moderately severe (pH > 7.30)
   iii. Low risk of intubation
   iv. NIV intermittent or nocturnal
   v. Low level of monitoring
e. Emergency department
   i. Depending on the level of equipment, the degree of experience of the team dedicated to ventilation and the number of staff, patients with a higher severity (such as intensive care) or lower (such as subintensive therapy) can be expected
f. The number of staff members will be defined according to the hospital beds and the severity level of the patients who are hospitalized
g. Each bed must be equipped with a ventilator, monitor, drug infusion pumps, aspirator

h. Ventilators will have to
   i. Offer different ventilation modes
   ii. Have a display where they can be viewed
      - Information on patient ventilation
         - tidal volume
         - respiratory rate
         - minute volume
         - losses
      - Ventilation settings

i. They must always be subject to continuous monitoring
   i. SaO_2
   iii. ECG
   iv. Blood pressure
   v. Optional
      - Ptc CO_2 and Ptc O_2
      - Invasive blood pressure
      - Hourly diuresis
      - Temperature

19.3 How to Recognize the Failure of NIV

The persistence or worsening of respiratory acidosis, after corrective surgery, is an indication of the failure of NIV and requires conversion to invasive ventilation.

In COPD, a respiratory rate greater than 35 acts/min, during NIV with optimization of the abnormalities, expresses a failure of the procedure and is an indication for invasive treatment. Likewise, a patient–ventilator dys-synchrony with a worsening of gas exchange is an indication of failure (Fig. 19.1).

Severe hypoxemia ($PaO_2/FiO_2 < 200$) after 1 h of treatment requires a reassessment of the clinical picture and diagnosis. In these cases, it is mandatory to transfer to the intensive care unit and invasive treatment that will allow to determine and manage the adequate values of PEEP and FiO_2.

Fig. 19.1 Patient dys-synchrony ventilator in PSV

Even in patients with acute pulmonary edema: the presence of tachypnea, respiratory acidosis, and failure to correct hypoxemia after 2 h of treatment are indicators of NIV failure.

In obesity hypoventilation syndrome, the indicators of failure are comparable to those of COPD patients. The constant presence of an obstruction in the upper airways requires a high EPAP setting which can reduce the tidal volume and cause increased mask leakage. These patients often have a high degree of difficulty in orotracheal intubation and the detachment from invasive ventilation and the possible execution of a tracheotomy are also complex. Because of these conditions, it is advisable to implement all procedures to ensure effective NIV.

During the asthma attack, given the drama of the clinical picture, the patient will have to be monitored and treated in the intensive area. Increased agitation and tachypnea even after a few minutes of treatment are indicative of failure and require tracheal intubation and invasive ventilation.

In patients suffering from neuromuscular diseases, the main cause of failure is represented by the difficulty in eliminating tracheobronchial secretions. In these patients, worsening is often rapid precisely due to the occlusion caused by secretions. It is therefore advisable to combine the ventilatory treatment with an adequate cough assistance program with physiotherapy sessions and cycles with cough assistance devices. It is also recommended to have specialists able to carry out an emergency bronchoscopy for unblocking the airways (Fig. 19.2).

Given the difficulty of extubation in these patients, it is necessary to clearly define a personalized treatment plan before undertaking any treatment.

A frequent indication of failure is the appearance of decubitus at the contact points of the mask on the face (Fig. 19.3). The use of different masks is therefore of fundamental importance, which must be alternated with a defined periodicity.

Sedation should not be a treatment to be applied indiscriminately to all patients but may be required during treatment with NIV. An agitated and uncooperative patient will surely fail. It is advisable to undertake a sedation treatment using specific protocols both pharmacological and to evaluate the depth of the sedation level

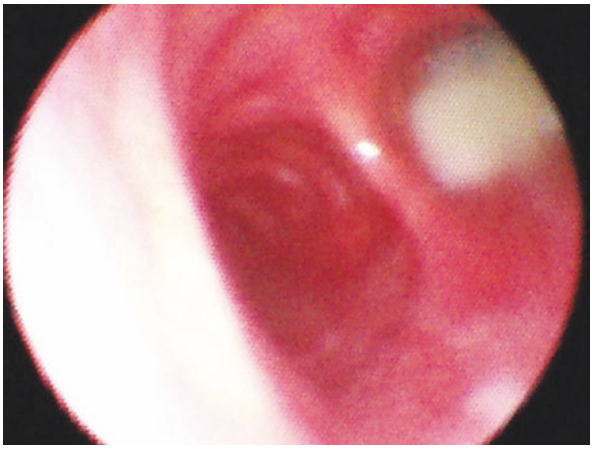

Fig. 19.2 Bronchus occluded by secretions in a patient with amyotrophic lateral sclerosis

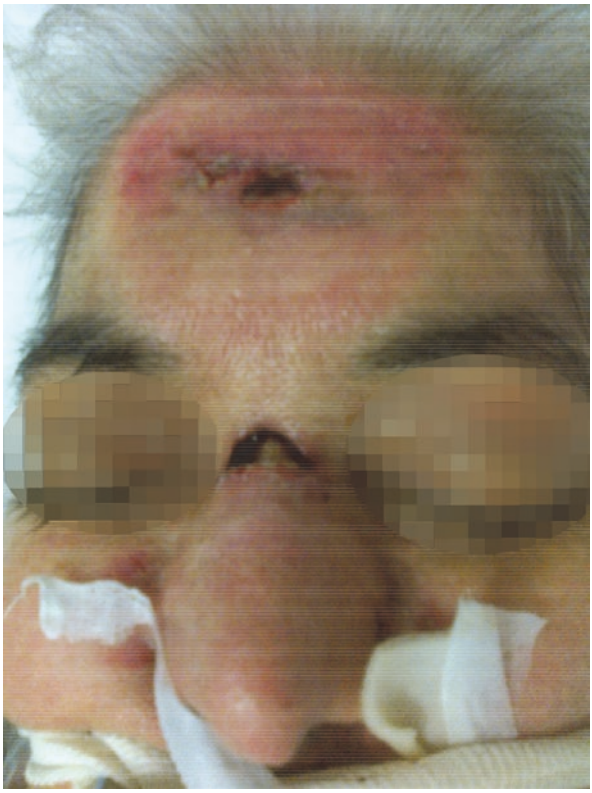

Fig. 19.3 Decubitus caused by the mask

to avoid an impairment of consciousness that makes the patient's collaboration vain. It is known that in patients admitted to intensive care units, the onset of delirium is a frequent occurrence (in some cases up to 80% of patients treated). Hypoxemia, fever, mechanical ventilation itself, the administration of benzodiazepines, as well as the loss of the sleep–wake rhythm are the main causes. All patients undergoing long-lasting NIV (>24 h) should be assessed with the appropriate scale (CAM ICU). The appearance of delirium should be treated immediately.

Patient–ventilator dys-synchrony must be carefully evaluated and treated by correcting the ventilator parameters.

The factors that we have previously described may be responsible for a failure of treatment with noninvasive ventilation in different periods of the evolution of the disease.

Early failures (1–2 h) may occur mainly due to patient agitation and intolerance of the interface, patient dys-synchrony non-correctable ventilator, hypercapnia-induced encephalopathy, airway occlusion due to abundant secretions and/or deficiency of cough, regurgitation, and inhalation. Subsequently, the causes can be the lack of improvement of the blood gases, a worsening of the disease (hemodynamic instability, sepsis, multiorgan insufficiency), or the appearance of facial decubitus that make it impossible to position the mask. A very important late phenomenon is due to the appearance of delirium, which often makes the patient intolerant to ventilation.

Table 19.4 describes the interventions to be implemented to prevent NIV failure.

Table 19.4 Failure indicators and possible corrections

Interface	1. Losses 2. Comfort 3. Decubitus	1. Alternate at least two different masks 2. Replace the mask 3. Position avoiding excessive compression
Patient - ventilator asynchrony	1. Mode of ventilation 2. Trigger a. Ineffective efforts b. Auto-triggering c. Double-triggering d. Short/long cycle 3. Losses 4. Airway obstruction 5. Muscles fatigue a. Abdominal paradoxical breathing	1. Correct the parameters a. IPAP; PS; PC b. PEEP, EPAP c. RR d. Ti/I: E e. Trigger 2. Change the ventilation mode 3. Re-evaluate the interface 4. Treats any agitation
Tachypnea	1. Low tidal volume 2. Losses	1. Treats any agitation 2. Increase IPAP or PS 3. Re-evaluate the mask
Agitation/delirium	1. Patient–ventilator asynchrony	1. Treats any agitation

19.4 Indications for Tracheal Intubation and Invasive Ventilation

1. Worsening of gas exchanges
   a. Worsening of respiratory acidosis (pH < 7.25)
   b. Severe hypoxemia (PaO_2/FiO_2 < 150)
2. Aggravation of clinical conditions
   a. Shock requiring support with inotropes and/or vasopressors
   b. Appearance of arrhythmias with hemodynamic compromise
   c. Coma
3. Agitation
   a. Psychomotor agitation with frequent mask removal
   b. Need for deep sedation with reduced respiratory drive
   c. Delirium
4. Lack of protection of the airways from aspiration
   a. Absence of reflexes of the upper airways
   b. Abundant secretions in the presence of cough deficiency
   c. Gastroesophageal reflux
5. Worsening of respiratory mechanics and the need to increase pressures. In these patients, it is necessary to increase the pressure of the mask on the face to avoid air leaks. Excessive compression promotes the formation of decubitus
   a. PEEP >10 cmH_2O
   b. Pressure control/Pressure support >30 cmH_2O

19.5 Conclusions

NIV is now an effective and ubiquitous method for the treatment of acute respiratory failure. The main objectives, whenever it is decided to undertake this therapy, are the prevention of tracheal intubation, the reduction of ventilation-related morbidity, and the reduction of mortality in its entirety.

NIV is effective in pursuing these objectives as long as it is undertaken according to precise lines of treatment and with an adequate organization of the department.

It is not acceptable to start this therapy considering it as a first-line attempt before moving on to intubation because, as we have seen, a delay in intubation, in patients who needed it from the beginning, is burdened by high mortality. At the same time, the failure of NIV due to clinical or organizational errors in patients who have been adequately selected leads to an increase in mortality.

It is therefore advisable to establish a specialized multidisciplinary team at each hospital that operates in areas with dedicated beds and specific protocols (Fig. 19.4).

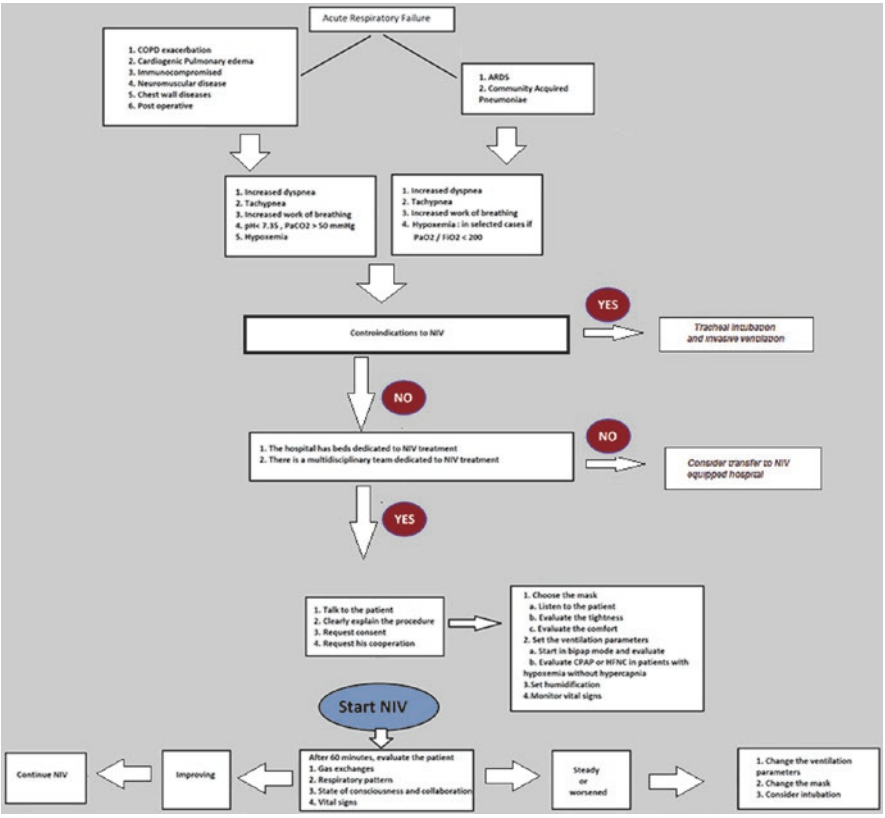

Fig. 19.4 Algorithm for NIV treatment in patients with acute respiratory failure

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Withdrawal of Noninvasive Mechanical Ventilation

20

Gaurav Jain and Udhay Chander

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20.1 Introduction

Noninvasive ventilation (NIV) is increasingly being used as a vital option for providing ventilatory support in acute respiratory failure (ARF) and during recovery from invasive ventilation under varied clinical pathologies, including acute exacerbation of chronic obstructive pulmonary disease (AECOPD), acute cardiogenic pulmonary oedema (ACPE) pneumonia, immunocompromised state, neuromuscular diseases, and trauma [1–3]. However, there is a paucity of available evidence and

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_20

even coherence among the methods described in the literature for weaning from NIV in hospitalized patients recovering from respiratory failure. An early withdrawal from NIV may lead to respiratory deterioration with a consequent need for intubation and invasive ventilatory support. In contrast, delayed NIV withdrawal may lead to prolonged ICU/hospital stay, increased incidence of related complications, and unbearable cost of care [4, 5]. Thus, in absence of clear validated protocols for NIV discontinuation, further research is imperative to determine the best time-point and schedule to withdraw NIV after recovery from respiratory failure. This chapter reviews the current literature and the supporting evidence on the protocol for NIV withdrawal and the determinants of weaning failure.

20.2 Determinants of Weaning Failure

The respiratory system's ventilatory efficiency depends upon a delicate balance between the respiratory load by the underlying metabolism, the adeptness of respiratory muscles or the neuromotor drive and the cardiovascular response to spontaneous breathing trial (SBT). The factors indicating an increased respiratory load include poor respiratory drive, increased respiratory rate (RR), lower tidal volume (TV), increased airway resistance and lung elastance, lower lung compliance, shortened respiratory time, and lower inspiratory flow. A low respiratory drive is indicated by a corresponding lower $P_{0.1}$ value, the airway occlusion pressure at the first 100 milliseconds of inspiration. Though its normal value excludes respiratory drive as a cause of difficult weaning, $P_{0.1}$ may also be a variable in ventilator-dependent patients [6, 7]. An associated lower TV indicates a poor inherent respiratory output, and thus, a higher rapid shallow breathing index (RSBI = RR/TV) predicts a weaning failure in such patients [6, 8]. A higher RSBI also has its limitations, especially in AECOPD patients having weaning failure in the setting of a low RSBI ratio [6]. The underlying mechanics include an increased intrinsic positive end-expiratory pressure, higher airway resistance, expiratory flow limitation, and reduced pressure-generating capacity of inspiratory muscles. It results in progressive air-trapping, dynamic lung hyperinflation, and increased work of breathing. As the required trigger to initiate inspiratory flow increases, the patient's inspiratory efforts become ineffective. The pulmonary elastance has also been shown to increase substantially during a SBT in failure to wean patients [9]. Increased intra-abdominal pressure and thoracic cage abnormalities such as rib-spine deformities, morbid obesity, and pleural effusion also makes weaning difficult by decreasing thoracic compliance. A decreased lung compliance, ventilation perfusion mismatch, and inadequate gaseous exchange due to any pulmonary pathology also exerts an additional work load on the respiratory muscles, resulting in muscle fatigue and difficult weaning [10].

Further, factors determining the efficacy of respiratory muscles and neuromotor drive may include any defect right away from the medullary respiratory center to the respiratory muscles' myocytes. It may consist of abnormalities involving neural (amyotrophic lateral sclerosis, phrenic nerve dysfunction, critical illness polyneuropathy) or neuromuscular junctions (Guillain–Barre syndrome, myasthenia gravis,

drugs) or because of poor muscle strength in conditions such as malnutrition, critical illness myopathy, acid–base–electrolyte disturbances, or decreased cardiac output. The determinants of respiratory muscle dysfunction include maximal inspiratory pressure (MIP) generated by inspiratory muscles and assessment of the diaphragmatic strength [10]. Although the MIP values have an excellent negative predictive value, the measurements more positive than the normal range do not prove muscle weakness due to dependency on patient cooperation. The other option is measuring diaphragmatic strength through transdiaphragmatic pressure (Pdi), twitch transdiaphragmatic pressure, and twitch airway pressure, or estimating the fatigue threshold of the diaphragm by calculating its tension-time index [11–14]. Although reliable in determining the potential respiratory reserve, these parameters are either invasive or require spontaneous unassisted ventilation, and thus are too complicated for use in routine practice. Hypercapnia, change in breathing pattern, and RSBI are also considered indirect markers of measuring the capability to sustain unassisted breathing and muscle strength. The neuromotor drive, estimated through electromyography of the diaphragm (EAdi), is considered a gold standard test to detect patient–ventilator asynchronies [13]. An improved VT/EAdi or Pdi/EAdi ratio predicts good neuroventilatory efficiency and thus successful weaning from NIV [13]. Ultrasonography has also been investigated to measure inspiratory/expiratory muscle thickness and diaphragmatic dysfunction in ready to wean patients. The limitations include a patient subset with an acutely paralyzed diaphragm having normal thickness or distinction between diaphragmatic atrophy and a thin diaphragm in a low body weight individual. Among the different parameters, the change in diaphragmatic thickness (ΔTDI) is the most sensitive parameter in assessing the diaphragmatic functions [15–17]. The literature on ultrasound measured abdominal muscles is still too sparse to have any recommendation.

The ventilatory transition from positive pressure breathing to a spontaneous breathing effort significantly impacts cardiac physiology in terms of increased venous return (preload), augmented afterload (adrenergic stress), higher oxygen consumption, and increased workload on both the left and right ventricle. It could lead to myocardial ischemia in patients with coronary artery disease. An underlying cardiac dysfunction thus causes failed weaning. The decompensation can be systolic or diastolic in origin. A negative passive leg-raising test undertaken in ready to wean patients indicates that preload independence is associated with SBT-induced cardiac dysfunction [18]. In failure to wean patients, a response to decreased oxygen delivery due to cardiorespiratory decompensation is also manifested as increased oxygen extraction and thus lower venous oxygen saturation [19]. Mixed venous/superior vena cava oxygen saturation has been used as a surrogate marker of cardiac performance in patients on weaning trial [19]. However, lower venous oxygen saturation should be interpreted with caution, as it only indicates increased metabolic load, which could be a normal response in patients on SBT. However, cardiac dysfunction is unlikely in the presence of normal venous saturation [20]. Through transthoracic Doppler echocardiography, measurement of ejection fraction and the ratio of mitral inflow velocity to annular tissue wave velocity can provide a reliable estimate of systolic and diastolic dysfunction, respectively. The failure of diastolic

relaxation during an SBT also indicates impending weaning failure [21, 22]. Pro-brain natriuretic peptide, a neurohormone produced by cardiac myocyte, is released into the circulation upon the ventricular stretch [23]. Its serum concentration is directly proportional to ventricular overload and thus signifies ventricular dysfunction. However, the levels are significantly raised only in patients with acute cardiac dysfunction at the end of SBT.

20.3 Sedation and Analgesia During Weaning

For patients undergoing SBT, provision of sedation and analgesia is aimed at maintaining adequate patient arousability, respiratory drive, cough reflex, and airway protection while avoiding any psychomotor agitation, hypoxemic stress, increased RR and RSBI, hypercapnia, sleep disturbance, and delirium [24]. It requires integrated protocols to guide sedation and analgesia administration, precise drug selection based on patient requirements, and meticulous monitoring to titrate the needs. There is, however, a lack of consistency in the current literature on an ideal sedo-analgesia protocol or choice of medication among numerous sedo-analgesics with variable clinical effects. Several available scores for monitoring sedation depth include Ramsay sedation scale, sedation agitation scale, Richmond agitation-sedation scale, and the bispectral index [25]. Similarly, commonly applied pain scales include the numeric rating scale, behavioral pain scale, critical care pain observation tool, and the nonverbal pain scale [26]. The standard choice of sedo-analgesics includes dexmedetomidine, midazolam, remifentanil, and propofol. Dexmedetomidine, an α2-receptor agonist, provides adequate sedation, analgesia, and anxiolysis with preservation of respiratory drive, cough reflex, and low risk of delirium. The limitations include the possibility of hypotension and bradycardia [27]. Midazolam, a GABA receptor agonist, though an effective sedative, is associated with ICU delirium, cognitive impairment, and can accumulate during prolonged infusion [28]. Remifentanil, a μ-opioid receptor agonist, exerts a predictive, dose-dependent, ultra-short sedo-analgesia, which wears off quickly on stopping the drug even after prolonged infusion. The other advantages include extrahepatic elimination, which is not affected by organ dysfunction [29]. The limitations include respiratory depression at higher infusion doses. Propofol, an anesthetic agent, induces sedation, anxiolysis, and amnesia without any analgesia. It can, however, cause cardio-respiratory depression, hypotension, and rarely propofol infusion syndrome, primarily when used in high doses for prolonged infusion [25].

20.4 When to Consider NIV Withdrawal

The weaning process from NIV can be differentiated into two distinct stages: determination of readiness for NIV withdrawal and methodology to follow for its withdrawal. The NIV support in respiratory failure is targeted to unburden the respiratory muscles' workload for better oxygen delivery and efficient removal of carbon

Table 20.1 Weaning criteria and failed weaning from noninvasive ventilation

Weaning criteria for NIV withdrawal
1. The underlying reason for NIV has been stabilized and the patient is improving.
2. Adequate oxygenation defined as oxygen saturation (SpO_2) > 90% on $FiO_2 \leq 50\%$, $PaO_2/FiO_2 > 200$ mmHg during NIV with $FiO_2 < 0.5$.
3. Arterial pH ≥ 7.35, respiratory rate ≤ 24/min, without use of accessory respiratory muscles.
4. Heart rate < 110/min, systolic blood pressure ≥ 90 mm Hg.
5. No signs of respiratory distress such as agitation, diaphoresis, or anxiety.
Criteria for weaning failure
1. Respiratory rate > 25/min or increase of > 50%.
2. Heart rate > 140/min or increase > 20%.
3. $SpO_2 < 90\%$ on FiO_2 of 50%.
4. Arterial blood pH < 7.35, or respiratory distress.
5. Respiratory rate > 25/min or increase of > 50%.

dioxide from circulation. The applied PEEP counteracts the intrinsic-PEEP, alleviating the raised inspiratory threshold often present in patients with AECOPD and those with dynamic hyperinflation. The British thoracic society (BTS) has recommended considering NIV withdrawal 24 h after its initiation if pH and RR have normalized and the underlying pathology has resolved [30]. Thus, NIV withdrawal should be considered once the patient has recovered from primary pathology, the respiratory physiology has normalized, and blood gas parameters have improved as determined by various clinical and ventilatory parameters (Table 20.1) [30–32]. The appearance of any sign of clinical or arterial blood gas deterioration within 48 h of NIV withdrawal may indicate failed weaning, requiring reinstitution of NIV or even intubation [31]. After successful weaning in some patients with AECOPD, the partial pressure of carbon dioxide ($PaCO_2$) may remain on the higher side while PaO_2 is subnormal, though still, patients may not require NIV. Therefore, the criteria for NIV withdrawal should also be based upon primary pathology, which requires NIV. However, the current literature is still limited on this issue, with inconclusive recommendations. Moreover, the described parameters are variable among the published literature. In the presence of different advocated functioned parameters to decide from, it becomes challenging to idealize a general protocol for NIV discontinuation.

20.5 Method for NIV Withdrawal

Various strategies have been described in the literature for initiating NIV discontinuation. They include the immediate withdrawal of NIV, direct discontinuation of NIV with nocturnal support, or stepwise discontinuation of NIV either by a progressive reduction of duration applying NIV or stepwise reduction of inspiratory and expiratory pressure support.

20.5.1 Immediate Withdrawal of NIV

In this technique, NIV is abruptly discontinued once the patient fulfills the weaning criteria for NIV withdrawal. The free flow oxygen is, however, provided via nasal cannula or face mask as desired. Subsequently, the patient is monitored for any signs of clinical or arterial blood gas deterioration over the next 2–3 days. Its potential advantage includes considerable shortening of the weaning duration; however, the risk of clinical deterioration in hypercapnic respiratory failure from sudden NIV discontinuation with a consequent need for NIV or even IPPV is a significant concern. Thus, it may inadvertently prolong the weaning duration. To offset this possibility, after NIV withdrawal, nocturnal NIV support is provided for a few days. The proposed basis is that, in AECOPD patients, transient hypoventilation episodes are bound to occur during rapid-eye-movement (REM) sleep stages. Therefore, nocturnal NIV application in such patients may avoid any episode of hypoxemia and the possible subsequent weaning failure. Lun et al. compared stepwise versus immediate NIV withdrawal in AECOPD patients presenting with acute hypercapnic respiratory failure (AHRF) [33]. In the stepwise approach, the duration of NIV use was reduced from 16 hours/day (day 0) to 12, 8, and 0 h/day on days 1–3, respectively. The success rate with this approach for the stepwise and immediate withdrawal group was 74% and 56%, though statistically insignificant. Sellares et al. compared direct discontinuation of NIV with or without additional nocturnal support after recovery of AECOPD patients from AHRF [34]. The nocturnal support included NIV support for three additional nights, while the no support group received only conventional oxygen therapy. They observed that the nocturnal NIV support did not prevent subsequent ARF occurrence and concluded that NIV could be directly discontinued once the patient has stabilized and tolerated SBT. Venkatnarayan et al. compared three different strategies for the withdrawal of NIV among patients with AECOPD recovered from AHRF [35]. They included immediate withdrawal, stepwise reduction of pressure support, or stepwise reduction in the duration of NIV. Among all, the immediate NIV withdrawal was comparable to other approaches in terms of successful weaning but led to a shorter hospital stay. Thus, it proved to be a feasible option, which did not increase the risk of weaning failure from NIV.

20.5.2 Stepwise Reduction of Duration

In this stepwise approach, the duration of NIV support is gradually reduced until the patient can tolerate spontaneous breathing. Kramer et al. attempted a gradual reduction in the duration of NIV support in patients presenting with ARF once patients become clinically stable for at least 6 h after its initiation [31]. Eleven out of 16 patients were weaning successfully via this approach within 3–4 days, while the remaining required night support for another 3–4 days. Damas et al. evaluated this approach by progressively increasing the duration of NIV breaks over a period of 3 days [36]. They observed that all 65 patients admitted for acute exacerbation of chronic respiratory failure could be successfully weaned without any need for subsequent ventilatory support. However, this study did not compare its efficacy with

any other approach. Faverio et al. described another method in which ready to wean patients were subjected to interruption of one of the three daily NIV sessions (at least 3-h duration) at the time, starting in sequence from first in the morning to last at night [37]. They observed that 39% of patients could successfully complete the protocol without any further need of NIV. They advocated that this approach may prevent AHRF relapse in the early stages of NIV withdrawal in elderly patients. Plant et al. also proposed a protocol using stepwise reduction in duration of NIV support [38]. The patients were encouraged to use NIV for a maximal possible duration on day-1, for 16 h on day-2, for 12 h on day-3, and NIV was completely withdrawn on day-4. The BTS also recommended this stepwise protocol of gradual NIV withdrawal and allowed patient-determined earlier NIV withdrawal if clinical improvement occurs rapidly [30].

20.5.3 Stepwise Reduction of Pressure Support

The stepwise reduction in inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) has also been suggested for NIV withdrawal in ready to wean patients. It involves careful assessment of patient tolerance for each individual pressure level with titration according to patient need. The IPAP/EPAP is usually reduced by 2–4 cm H_2O every 4–6 h until a target IPAP<8 cm of H_2O and EPAP<4 cm of H_2O is achieved, after which NIV is completely withdrawn. Though it could be the safest way to discontinue NIV, the associated risk includes unnecessary prolonged NIV withdrawal time and increased complications related to NIV use. To date, not much work has been done using this approach for NIV withdrawal. Venkatnarayan et al. observed a similar NIV withdrawal time, hospital stay duration, and weaning success rate when comparing this approach with immediate NIV withdrawal [35]. Momii et al. described a similar stepwise reduction of FiO_2, IPAP, and EPAP-based protocol for NIV weaning of patients with ACPE; once respiratory distress settled, oxygenation improved and remained stable for 30 min [39]. They observed that this protocol facilitated a quick and safe initiation and termination of the NIV support in ACPE. They recommended that though NIV induces a dramatic rapid improvement in clinical and laboratory parameters in ACPE, the physician should avoid immediate NIV withdrawal in such patients. Further studies are desired to clarify the unique advantage of either strategy or the best-suited approach for NIV withdrawal.

20.6 Need of Long-Term NIV Support

Although NIV could be successfully withdrawn in most patients, a few could not be weaned from ARF and thus discharged on home NIV support for long-term domiciliary treatment. Long-term NIV not only provides intermittent respiratory support but is also aimed to reduce recurrent deterioration of the respiratory system [40]. The reported incidence for need of long-term NIV varies widely in the literature depending upon the severity and type of primary pathology [41, 42]. Therefore, the

Table 20.2 Criteria for initiating long-term noninvasive ventilation (all three required)

1. The underlying reason for NIV has been resolved and the patient has improved clinically.
2. Inability to discontinue NIV in at least eight consecutive days after two failed weaning attempts, due to worsening of clinical (respiratory exhaustion) or arterial blood gas parameters (hypercarbia) without any identifiable cause.
3. Discharged home on domiciliary NIV therapy.

decision to completely withdraw NIV needs to be individualized. For AECOPD patients, long-term NIV is considered if the patient has either recurrent episodes (>3 episodes) of AHRF requiring hospitalization and treatment, carbon dioxide retention in spite of initiating supplemental oxygen after NIV withdrawal, or symptomatic sleep disturbance. AHRF secondary to clinical situations such as spinal cord injury, neuromuscular injury, and chest wall deformity may also require long-term NIV therapy. Though a broad criterion for initiating long-term NIV exists (Table 20.2), a standardized, evidence-based protocol for NIV withdrawal is still desired to identify patients requiring long-term NIV to avoid failed weaning attempts and the associated morbidity [30, 43].

20.7 Conclusion

1. There is a paucity of literature to define a validated protocol for withdrawal of NIV after ARF.
2. Different clinical and laboratory parameters such as RSBI, MIP, and ΔTDI have a potential role in identifying readiness for NIV withdrawal, but an ideal model is still desired to identify an appropriate threshold for NIV withdrawal.
3. Any sedo-analgesic used during NIV withdrawal should maintain adequate patient arousability, respiratory drive, and airway protection while avoiding any patient agitation, hypotension, and delirium.
4. Different strategies described for discontinuing NIV include immediate withdrawal, stepwise reduction of NIV duration, or gradual reduction of pressure support. Further studies are desired to clarify the unique advantage of either approach for NIV withdrawal.
5. Long-term NIV not only provides respiratory support to failure to wean patients but may also reduce recurrent deterioration of the primary pathology.

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Psychological Factors during Noninvasive Mechanical Ventilation

21

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21.1 Introduction

Psychological factors have a significant influence on patient compliance with NIV. Fear of death has been reported to be a facilitator for the initiation of and the adherence to NIV. Other psychological factors associated with NIV acceptance focus on patients who perceive benefits from NIV and a positive lifestyle. NIV can also be utilised in patients who have declined tracheostomy. Most research into the psychological determinants of NIV outcomes has been conducted in patients with amyotrophic lateral sclerosis (ALS) or other neuromuscular diseases. Significantly less inquiry has been undertaken in children and older patients and in patients of all ages with acute respiratory failure (ARF). Clinicians are sometimes unaware of the extent to which patients with emotional and/or behavioural difficulties need close

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_21

support and guidance, regardless of whether these difficulties arise from or are unassociated with the use of NIV. Patients with chronic disease can experience psychological impairment which, depending on the individual and the disease, can aggravate the symptoms [1]. During NIV, psychological alterations may be a result of somatic symptoms, but they may likewise impact the course of the illness, as in other chronic conditions. Patterns of acceptance of NIV are examples of the communication between psychological and physical aspects. Even though the NIV can confer significant clinical improvement of their illness, patients often reject NIV or neglect to use it correctly. NIV refusal or its inappropriate use result in worse clinical outcomes and increased health care expenses [2, 3]. Patients whose ARF is treated with NIV are often anxious. This response may be triggered and sustained, however, by underlying psychiatric disorders. In some cases, the need to titrate sedating medications and/or offer close emotional support can be evaluated in improving NIV tolerance.

21.2 Discussion

Unfortunately, there are many gaps in the literature on this issue; psychological aspects are relevant but may be different in disparate pathologies. If we think of a patient suffering from congenital muscular dystrophy, the psychological profile and disability are perceived differently in a patient with ALS, or in a patient with chronic obstructive bronchopathy. Different pathologies have different times of onset of the disability and very different life expectancies, and this certainly interferes decisively with the treatment path but also depends on the presence or absence of a caregiver. Noninvasive mechanical ventilation is used in various pathologies with a common purpose but the presence of greater or lesser dependence on NIV could play a key role. Patients dependent on NIV, regardless of the underlying disease, are the most disadvantaged, since their autonomy is severely limited compared to a patient who uses intermittent NIV.

21.3 Anxiety and Depression

Although physical symptoms impact the psychological spheres, the converse is also true: in fact, depression and anxiety appear to increase the risk of death [4], to raise the number of hospitalisations due to exacerbations, to increase dyspnoea episodes [5], and to worsen patients' health-related quality of life. This is true in the COPD patient but also in patients with neuromuscular disease. Patients with chronic respiratory disease must face a progressive change in their lifestyle. The need to adapt quickly to sudden changes causes a continuous imbalance of the patient's fragile psychological structure. Very frequently they have to give up their habits and give up hobbies and passions that would contribute to psychological harmony. The clinician's aim should be whenever possible to preserve small positive habits or the possibility of pursuing a hobby that brings satisfaction.

A significant reason for withdrawal is inherent to the treatment itself (i.e., the mask and the forced air pressure), and this is not simply related to comfort issues [6]. Rather, the patients' negative responses to NIV are generated as a result of fear and reflection on their threatened autonomy. The mask is perceived as limiting one's autonomy; in fact, it interferes with social life and is seen as a source of vulnerability. In line with this, high adherence to ventilation is found to be related to individuals with higher self-efficacy [6, 7].

21.4 Acceptance of NIV

Martin et al. described the analysis of the physical, cognitive and psychological characteristics of 32 ALS patients who had been diagnosed at least 6 months previously and who made one or more decisions regarding NIV and/or gastrostomy tube placement during the 3-month follow-up interval. The interesting aspect was that a greater burden of physical ailments was associated with decisions made within the observation period. Patients who felt that they understood their illness less well, those with a proactive attitude to decision-making, and those with fewer depressive symptoms, were more likely to refuse either intervention [8]. The authors concluded that ALS patients who had a more passive approach to interventions and fewer years of education, in contrast to those who were better informed about the disease and had clear opinions about interventions, may benefit from assistance to make informed decisions. Patients who refused NIV have expressed that it undermines their sense of identity, dignity and/or autonomy. All these aspects are probably also closely correlated with the age of the patient, with the presence of a caregiver in the family unit or to the education and religion of the individual. On the other hand, the utilisation of NIV and its outcome are strongly linked to demographic and personal aspects. In various countries, young male patients frequently prefer the use of NIV [9]. Chiò et al. described differences between the Italian National Health System ALS patient treatment and that in the United States [9]. In Italy ventilation support and home assistance are provided free of charge and are not contingent on the patient's social status or educational level. It was also observed that married patients commonly accepted and used NIV. Married patients who accepted and used NIV lived longer than unmarried patients. The help of a family member encourages the patient's noninvasive support and specialised clinical interventions, producing positive effects on patient care and survival. Although NIV increases the caregivers' burden and may negatively affect their physical function (which manifest in signs of exhaustion, such as insomnia, anxiety disorders, or loss of attention) it does not significantly increase caregiver stress [10].

21.5 Doctor–Patient Interaction

The extent to which clinicians are compassionate, receptive and circumspect in their counselling about NIV can significantly influence a patient's perspective about therapy. This perception is associated with a generalised disdain for hospitals

and a sense of threatened autonomy. Patients have sometimes reported perceiving doctors to enforce NIV. Tolerance of NIV can be improved when patients trust that their clinicians will be attentive to their emotional and physical needs and when continuity of care by the same clinicians is maintained [8]. It is very important that the patient has confidence in the doctor to suggest the best path to follow and respects life, the quality of life and, above all, the dignity of life. More research is needed to elucidate the attitudes and practices that clinicians should foster to best help patients and their families cope with NIV. The doctor–patient relationship is decisive in choosing one therapeutic option over the other. The patient who understands the perspective offered by the doctor and believes and trusts it makes possible a better and faster acceptance of change. Trust in the referring clinician is necessary to continue a journey often undermined by many difficulties. Although the presence of a caregiver can, in most cases, represent an element of positive support, in some cases we have recorded an attitude of acceptance on the part of the patient and high resistance on the part of the caregiver, which negatively influenced the patient's choices.

21.6 Sexuality

The sexual sphere has significant repercussions on the patient's psychology. When compared with normal individuals, the sexual activity and masturbation rate of patients with NIV are significantly reduced in the total population and are reduced further with increasing age. Hence, in the opinion of patients, 80% attribute their reduction of sexual activity to somatic effects of a chronic disease [11]. Sexual activity produces an increase in tidal volume and breathing frequency [11] that is correlated with an increased cardiopulmonary load. Consequently, in individuals with chronic lung diseases, sexual activity may often be decreased because of exertional dyspnoea. Accordingly, sexuality in patients receiving NIV for chronic respiratory failure is significantly reduced compared to that of normal individuals. In fact, in a high percentage of patients who used NIV, sexual activity was influenced by the initiation of NIV. Most of the respiratory diseases requiring NIV are chronic and progressive, and therefore the decrease in sexual activity could be due to progression of the disease rather than the NIV itself. Compared to the sexually inactive group, the active population was characterised by better lung function, younger age and living with a spouse or partner [12]. It is difficult to establish whether the reduction in sexual activity is linked in some cases to the depressive component that occurs with the progression of the disease. The evolution of the disease can cause increased fatigue and dyspnoea, which also limit the sexual sphere. They are multifactorial aspects that influence each other and have negative repercussions on the psyche of the individual.

21.7 Conclusions

Disease experience appears to assume different characteristics from patient to patient, as happens for the body–mind connection image. There is a strong link between physical and mental conditions. In pathological conditions, but also in healthy individuals, this connection can turn out to be a vicious circle: if an individual formulates bad thoughts and feelings it determines a worse symptomatology, while a negative physical state generates terrible quality of cognitions and emotions of life. The character of the individual can exacerbate this condition. Caregivers should also be involved in the planning of care and should receive therapeutic education training.

Psychological interventions for caregivers are necessary to help them to cope with this challenge. It is important to control the psychological factors of NIV acceptance because better compliance with NIV is related to better survival. The age of the individual might change the acceptance of NIV; children, due to the precocity of the disability or the presence of the caregiver, are probably more willing to change their lifestyle with the onset of NIV. Some authors examined a heterogenous group of paediatric patients with neuromuscular disorders. Discussion on the practice of long-term ventilation in children severely affected with neuromuscular diseases is also still divergent and indeed determined by individual experience. In the paediatric patient, some studies point out that the use of the ventilator per se is not the limiting factor for the quality of life and mental health of children suffering from degenerative disease and their families [13].

In both children and adults, all our efforts must converge towards the best possible quality of life (QOL). A good QOL is associated with the desire to live longer, with the presence of a caregiver and consequently with NIV compliance. QOL cognition and emotions derive in the individual from a complexity of factors that depend on character, age, family and educational and religious aspects. The dignity of life remains an objective to be preserved and its achievement depends on various factors, including the presence and support of caregivers and psychologists, as well as professional help in dealing with the idea of progression of the disease, which is often inevitable.

Key Major Recommendations

- Anxiety and depression can result from the progression of the disease
- Psychological factors can influence NIV acceptance
- The doctor–patient relationship can play a key role
- The sexuality of the patient in NIV can be compromised
- Psychological impairment can be different in individual pathologies with different degrees of disability

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Part VI

Monitoring, Complications and Hospital Transport

Nocturnal Monitoring in the Evaluation of Continuous Positive Airway Pressure

22

Nicola Vitulano

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22.1 Introduction

Sleep is the natural state of rest, and about one third of human life is spent sleeping; thus, the importance of self-regulation is well-established [1]. Therefore, every physical and/or medical condition that provokes sleep interruption could cause detrimental effects for human health. It is estimated that OSAS affects 4% of men and 2% of women [2], with an increased prevalence and incidence overall in the past few decades, above all when sleep respiratory diseases are detected in patients with cardiovascular disease. Despite efforts for behavioral interventions such as sleep positioning and weight loss, the first-line intervention for OSAS is continuous positive airway pressure (CPAP). Nightly apnoic events are due to repeated episodes of airway obstruction during sleep. An important contribution is given by anatomo-functional abnormalities in the upper airway. The benefits of CPAP to correct these aspects have been shown extensively. By normalizing sleep breathing, CPAP

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_22

improves clinical endpoints such as sleep quality, daytime sleepiness, symptoms reduction, cognitive performance, and overall quality of life. However, CPAP requires a persistent and consistent use, and is afflicted with poor compliance in many patients. Reported rates of compliance show that it achieves approximate 50%, meaning that many patients who would benefit from CPAP are unable to tolerate this treatment [3, 4]. Patients diagnosed with OSAS, after starting CPAP treatment, undergo a second overnight sleep study for titration to an effective level of CPAP. Polysomnography (PSG) would be the gold standard for diagnostic control and to improve the parameters of treatment, but PSG requires many skin-contacted sensors to monitor patient's parameters and vital signs, which may also hinder patients' sleep and do not correctly validate the control. Moreover, PSG may be an expensive and labor-intensive diagnostic modality that may not always be feasible in all countries or in non-tertiary hospitals. Thus, using another tool to nightly monitor the treatment or screening or prediction of OSAS could be feasible and efficient at the same time.

22.2 Nocturnal Monitoring Tools

22.2.1 Overnight Oximetry

An approach less suited for long-term monitoring over several nights, but of prompt availability and easy use, is pulse oximetry at the fingertip. Pulse oximetry is a part of standard PSG; it is a simple and noninvasive method of measuring blood oxygen saturation (SpO_2) using a finger probe that measures the oxygen saturation in the blood by shining light at specific wavelengths through tissue. Deoxygenated and oxygenated hemoglobin absorb light at different wavelengths (660 nm and 940 nm, respectively), and the absorbed light is processed by a proprietary algorithm in the pulse oximeter to indicate a saturation value. During the night, apnoic and hypopnoic events cause drops in SpO_2 (i.e., desaturations); pulse oximetry recordings allow tracking the changes in oxygen saturation. This simple alternative could provide home screening not only to investigate the OSA severity in the comfort of the patients' home but also to monitor therapy effectiveness. The McGill oximetry score (MOS) is an example tool that is a validated severity scoring system; it might be used when despite therapy, the overnight oximetry reveals parameters significant enough to prioritize to the adenotonsillectomy surgical list [5]. In addition to at-home continuous overnight use, pulse oximetry can be used to screen OSA in patients scheduled for bariatric surgery [6], it is even feasible for home monitoring CPAP treatment efficacy. Long-term oxygen therapy and CPAP are prescribed to maintain SpO_2 at a safe level for the human body, adjustable flow rates of the device are set to warrant oxygen availability regarding organism requests. SpO_2 sensors are utilized to understand if oxygen flow rates are adequate for the underlying pathological condition. The main limitation of these devices is sensor location. The most common locations for SpO_2 sensors are at the fingers and wrist; but both sites are subject to considerable movement during everyday activities; therefore, they may

lose the accuracy of recorded data because of considerable noise and error [7]. Thus, alternative locations or different monitoring devices could be useful. In fact, a recent study found that the performance of reflectance pulse oximetry measured at the upper arm during sleep is superior to measurements at the wrist; probably in the last one the parameters are perturbed by undesired large fluctuations suspected to be caused by venous blood [8]. Another innovative study considers a peculiar alternative location for a novel SpO_2 sensor through its placement in the nasal septum to continuously monitor blood oxygen levels in patients. This region does not suffer from daily disturbances; therefore, the sensor will monitor SpO_2 levels constantly and the nose-based sensing location allows for easy integration into existing equipment such as nasal cannulas [9].

22.2.2 Rhinomanometry

Nasal resistance contributes as a risk factor for SDB [10]; in fact, it is a predisponent factor, following increasing negative inspiratory pressure, for the tendency for the upper airway to collapse. In this setting, rhinomanometry is useful to predict the impact of structural nasal modifications on the positive pressure to support decision-making in relation to change in therapy or to refer to surgery. In patients using CPAP during sleep, the recorded noninvasive measurements of nasal resistance during wakefulness were tested to verify their usefulness as a predictor of directly assessed upper airway resistance; in this study, acoustic rhinometry (AR) and active anterior rhinomanometry (RM) were used, but it was found that upper airway resistance measured during nightly CPAP treatment did not show significant relationships with any of the awake measurements of nasal resistance (in the sitting and supine positions, only but weak correlation in the supine position [11]. Hueto et al. tried to link CPAP parameters and data collected by rhinomanometry; in this study, patients underwent computerized anterior active rhinomanometry (ATMOS Rhinomanometer 300), whether sitting or supine, and after vasoconstriction; in patients with OSA, rhinomanometric measurements should preferably be performed with the patient in a supine position and after vasoconstriction [12]. Nasal airway function is a significant component in the multifactorial process leading to sleep apnea syndrome, perhaps it plays a key role in patients affected by this condition but who are not overweight. AR, having advantages over traditional rhinomanometry, could provide a better evaluation of the patient suffering from and treated for OSA. Forty-four patients were valued for nasal airway anatomy measured by AR, and this assessment was related to the patients' subjective perception of obstruction and to nCPAP titration levels and respiratory disturbance index, suggesting that the nasal airway partially contributes to the overall process of SDB, and that nonoverweight patients may be the best responders to nasal surgery for SDB [13]. The aim of nocturnal monitoring is also to supply all data useful to guarantee the best treatment for OSA patients. The data from a pilot study show that objective evaluation of the nasal airway is helpful in predicting patients who will not tolerate nCPAP: inferior turbinate hypertrophy – a cross-sectional area of 0.6 cm^2 or a cross sectional

area for the head of the inferior turbinate minor of cross sectional area for internal nasal valve at the junction of the upper lateral cartilage and septum – may be a cross sectional area for a sensitive and specific predictor of CPAP intolerance [14]. Tests easily performed by sleep specialists are AR and four-phase high-resolution rhinomanometry; they characterize nasal resistance in sleep apnea patients. Toh et al. found that patients who did not demonstrate a decrease in nasal resistance measure by four-phase high-resolution rhinomanometry and acoustic rhinometry with inclined position were more likely to be noncompliant with nasal CPAP [10].

22.2.3 "Smart" Technologies

Home self-monitoring of snoring, sleep apnea, or their treatment is the actual frontier for the new generation of tools for maintaining good health among the general population. Smartphones with various sensors and signal processing capabilities have been used as devices for home healthcare. The phone oximeter (PO) is another example of an OSA screening tool that provides a platform for overnight oximetry recordings. The PO consists of a pulse oximeter combined with a mobile phone, providing both SpO_2 and photoplethysmography (PPG) signals (a signal that provides an indication of blood volume changes in tissues) [15, 16]. The data acquired by using a smartphone (mid-range phone with a high-quality microphone) system through acoustic, accelerometric, and pulse oximetry signals were analyzed to detect apneic events and monitor sleep position. Nineteen patients with spinal cord injury were compared to 19 control individuals; overnight recordings were obtained using a smartphone Samsung Galaxy S5 SM-G900F with Android 6.0.1, and it was placed and fixed with an elastic band over the sternum. During the acquisition, the smartphone was in flight mode and the screen switched off. The proposed mHealth system recorded three signals simultaneously: audio, using the smartphone built-in microphone; tri-axial accelerometry, (MPU-6500 sensor); oxygen saturation (SpO_2), using an EMO-80 wireless fingertip pulse oximeter (EMAY Ltd., Hong Kong, China). The Android app used was "Automate" and data were automatically stored in the internal memory of the smartphone. This study demonstrated the feasibility of the application of new technology in the setting of home monitor therapy. A smartphone system is a simple noninvasive tool that would reduce the costs and complexity of medical sleep monitoring [17, 18].

22.2.4 Novel Technologies

New approaches to the nocturnal monitor of OSA therapy could come from the experience of other medical settings, such as in the population with a history of stroke. Ultrasound-tagged near-infrared spectroscopy (UT-NIRS) is a novel technology able to detect cerebral blood flow noninvasively and in real-time, displaying cerebral flow as cerebral flow index (CFI). This parameter may not be as useful in the monitoring of CPAP impact because in a short group of patients single-night

PAP therapy does not improve overall cerebral blood flow, as defined by CFI [19]. Moreover, impulse-radio ultra-wideband (IR-UWB) radar can detect the movements of heart and lungs without contact, and it may be utilized for vital sign monitoring during sleep. A single sensor of IR-UWB radar (XK300-VSA; Xandar Kardian, Delaware, USA) can be placed in the sleep room 0.5 m above the head side of the bed. Data collected from the radar were linked simultaneously with PSG in an experimental study. The IR-UWB radar could accurately measure BRs and HRs in sleeping patients with OSA. Therefore, IR-UWB radar may be utilized as a cardiopulmonary monitor during sleep [20].

22.3 Conclusions

Every new technological device can show several limitations at the beginning of its use. However, in addition to validated tools such as nightly oximetry, it is important to develop other monitor instruments to improve the surveillance of patients with sleep apnea before, during, and after treatment. The accuracy of cardiorespiratory monitoring is a crucial to optimize the therapy and guarantee the best respiratory support to the patient.

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Complications During Noninvasive Pressure Support Ventilation

23

Meltem Çimen and Müge Aydoğdu

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_23

23.1 Introduction

Noninvasive ventilation (NIV) has been used more frequently in the past two decades for acute and chronic respiratory failure. It is preferred especially as a first-line treatment modality for patients with acute respiratory failure due to chronic obstructive pulmonary disease (COPD) exacerbations and acute cardiogenic pulmonary edema and chronic respiratory failure due to chest wall disorders or neuromuscular diseases [1]. Its effectiveness has been shown in many studies with the advantage of lower risk of nosocomial infection compared to invasive mechanical ventilation and with a successful role as a weaning step [2, 3].

However, many mild or serious complications may occur during NIV applications due to mechanical factors or usage errors [4–6]. It is important to recognize and treat these complications as soon as possible. Therefore, this chapter discusses the possible NIV complications and their treatment and/or prevention modalities.

23.2 Complications During Noninvasive Pressure Support Ventilation

Noninvasive ventilation complications can be discussed in two categories as minor and major complications [4–7].

23.2.1 Minor Complications of Noninvasive Ventilation (Table 23.1) [4–7]

23.2.2 Problems Related to The Mask

23.2.2.1 Mask Discomfort and Intolerance

The most common problem encountered during use of NIV is mask discomfort and intolerance. To increase the NIV compliance and success, mask selection and adjustment should be given utmost attention. The different types of interfaces share some similar problems, but others depend on mask type (Table 23.1). The most common problem is discomfort at points of skin contact, related to the tension necessary to control air leaks. The mask should fit the face properly and its ties should be adjusted properly to prevent air leakage, but should not be too tight. A non-fitting interface cannot provide adequate gas exchange; additionally, dry eyes may develop as a result of air leaks.

23.2.2.2 Claustrophobia

Claustrophobia is another mask-related NIV complication. The lowest incidence is reported with nasal masks [8]. The most commonly used oronasal mask may cause more claustrophobia but leads to better dead space ratios. Helmets or full face masks cause less nasal ulcers and less claustrophobia, but they create more dead space areas.

Table 23.1 Minor complications [4–7]

Complication	Mask type	Recommended
Mask Discomfort and Intolerance	Nasal, Full-Face, Helmet, Oronasal (Most common in the oronasal mask, less common in the nasal mask)	– Select the appropriate patient – Select the mask and size suitable for the patient – Make sure that the mask fits well and that the straps are not too tight – Make appropriate ventilator settings. Try to set the lowest pressure ventilator with the least air leakage – Inculcate the patient – Think mild sedation. Avoid deep sedation – Check the patient, circuit, air leak frequently, and do intermittent NIV
Dryness in the Airways and Nasal	Nasal, Oronasal, Full-Face, Helmet	– Select the appropriate patient – Select the mask and size suitable for the patient – Use nasal saline, topical decongestant, steroid, antihistamine/decongestant combination – Set the appropriate ventilator setting to keep air leakage and breathing pressure to a minimum – Use a heating humidifier – Keep the patient's fluid balance optimal
Eye Irritation	Nasal, Oronasal, Full-Face, Helmet	– Select the mask and size suitable for the patient – Set the appropriate ventilator setting to keep air leakage and breathing pressure to a minimum – Use artificial tear solution – Check the compression of the mask ties
Claustrophobia	Nasal, Oronasal, Full-Face, Helmet (Mostly Oronasal Mask)	– Select the appropriate patient – Select the mask and size suitable for the patient – Make appropriate ventilator settings. Try to set the lowest pressure support ventilation with the least air leakage – Adjust the ventilator setting best suited to patient comfort – Consider using a helmet or a full-face mask – Inculcate the patient – Think mild sedation. Avoid deep sedation

(continued)

Table 23.1 (continued)

Complication	Mask type	Recommended
Nasal Ulceration	Nasal, Oronasal	– Select the appropriate patient – Select the mask and size suitable for the patient – Make sure that the mask fits well and that the straps are not too tight – Make appropriate ventilator settings. Try to set the lowest pressure – Consider using a helmet or a full-face mask – Application of barrier enhancers and do intermittent NIV sessions – Consider dermatology consultation
Arm Edema and Venous Thrombosis	Helmet	– Select the appropriate patient – Check regular helmet straps and use elastic bandages if needed – Make appropriate ventilator settings. Try to set the lowest pressure
Gastric Insufflation/ Aerophagia	Nasal, Oronasal, Full-Face, Helmet	– Select the mask and size suitable for the patient – Make appropriate ventilator settings. Try to set the lowest pressure – Application with nasogastric drainage tube – Simethicone can be applied – Inculcate the patient – Avoid deep sedation – Keep the patient's head up to avoid aspiration
Vomiting	Nasal, Oronasal, Full-Face, Helmet	– Select the mask and size suitable for the patient – Make appropriate ventilator settings. Try to set the lowest pressure – Application with nasogastric drainage tube – Antiemetic can be applied – Check patient regularly
Air Leaks	Nasal, Oronasal, Full-Face (Most common in the Oronasal Mask, Less common in the Full-Face Mask)	– Select the appropriate patient – Select the mask and size suitable for the patient – Choose ventilators with air leakage compensation – Make sure that the mask fits well – If the patient has a denture, apply NIV with the denture. – Make appropriate ventilator settings. Try to set the lowest pressure – Consider using a helmet mask

23.2.2.3 Compression and Ulceration

Tissue loss and ulceration of the skin can occur due to pressure applied by the mask, which is frequently seen with oronasal and nasal masks. The ill-fitting masks and overtightening of these masks to prevent air leaks may lead to this tissue loss and ulceration. Nasal bridge ulcer is among the serious mask-related complications. In advanced cases, skin grafts may be required. Ulcerations may also develop on the auricles. The use of appropriate masks, application of barrier enhancers and intermittent NIV sessions can reduce the risk of ulceration. When ulceration develops, a helmet or a full-face mask can be applied, but it should be kept in mind that ulcerations may develop under the armpit and around the neck with a helmet mask. When the oronasal mask is compared with the full-face masks, it has been reported that pressure ulcers are less common with a full-face mask and occur after a longer period of time and patient comfort is higher [9].

23.2.2.4 Arm Edema and Venous Thrombosis

These complications are mostly seen with the use of helmet masks. The helmet is fixed to the soft collar of the mask with straps passing under both armpits. If it is used for a long time, the armpit slings may exert pressure and thus venous and lymphatic drainage may be impaired. As a result, edema and thrombosis may develop. This complication can be prevented by replacing underarm straps with elastic bandages fixed to the bed.

23.2.3 Problems Related to Air Pressure and Flow

23.2.3.1 Nasal Congestion and Dryness

During NIV, with the administration of dry air and oxygen, dryness and irritation of the upper airways and nasal mucosa can occur. As a result of this irritation, the inflammatory mediators can be released and nasal congestion can develop. Mucus plugs and atelectasis may develop. When nasal dryness becomes severe, epistaxis may occur during use of nasal ventilation. Humidifiers, which are used for heating and moisturizing, topical nasal decongestants, nasal saline or lubricating jelly gently applied to the internal surface of the affected areas can be used to relieve dryness related complications (Table 23.1).

23.2.3.2 Eye Irritation

Eye irritation is another adverse effect of airflow caused by air leakage under the mask on the sides of the nose lateral to the nasal bridge. This is occasionally caused by excessive tightening of mask straps and may respond to loosening or use of soothing eye drops. More often, however, the problem is related to an ill-fitting mask and an alternative mask must be used to correct the problem.

23.2.3.3 Gastric Insufflation

Gastric insufflation is a pressure and flow related NIV complication. Aerophagia is air swallowing of patients during NIV administration. During the application of

NIV, not all of the ventilation volume reaches the lungs, but a part of it goes to the stomach. Lung airway resistance and lower esophageal sphincter pressure are important in gastric insufflation. High tidal volume, high airway pressure, and low respiratory system compliance increase the airway pressure and increase the passage of air to the stomach. Gastric distension occurs at airway pressures above 20–25 cmH_2O. Therefore, care should be taken not to have airway pressures above 20 cmH_2O to prevent gastric distension and vomiting [10]. It should not be forgotten that gastric distension will compress the diaphragm and reduce the lung volumes.

23.2.3.4 Ear, Nose, and Sinus Pain

Air pressure in the nose and sinuses may cause sinus or ear pain, burning, or coldness. To prevent this problem, NIV should be initiated with relatively low peak inspiratory pressures (8–12 cmH_2O) [6]. Pressures than can be gradually titrated upward if needed with close attention to patient response [6].

23.3 Major Complications of Noninvasive Mechanical Ventilation [4–7] (Table 23.2)

23.3.1 Aspiration and Pneumonia

Aspiration is one of the most serious complications of NIV. Gastric distension during NIV may cause vomiting and aspiration. Using a nasogastric tube will be beneficial, but the nasogastric tube may cause an increase in air leakage and ineffective NIV administration.

Pneumonia, one of the other important complications of NIV, can occur not only with the aspiration of vomiting but also with the aspiration of water within the ventilator circuits and aspiration of the patients' secretions. Patients who cannot protect their respiratory tract and who cannot discharge their secretions have an important risk. To prevent pneumonia, patients' heads should be kept up, and patients should be followed carefully to avoid the development of gastric distension.

23.3.2 Pneumothorax

Barotrauma may develop with positive pressure ventilation. Pneumothorax is more common after the application of invasive mechanical ventilation. It is more common in patients with chronic obstructive pulmonary disease (COPD), acute lung injury secondary to pneumonia, interstitial lung disease, cystic fibrosis, and neuromuscular disease. Pulmonary barotrauma fortunately occurs rarely during NIV because inflation pressures are usually much lower than those used during invasive ventilation. If the patient has low lung compliance, has emphysema and blebs, their peak inspiratory pressures should be below 30 cmH_20 and auto-PEEP (positive end expiratory pressure) formation should be prevented by setting appropriate inspiration and expiration times [11].

Table 23.2 Major complications [4–7]

Complication	Mask type	Recommended
Aspiration	All mask types	– Select the appropriate patient – Application with nasogastric drainage tube – Make appropriate ventilator settings. Try to set the lowest pressure. – Avoid deep sedation – Keep the patient's head up to avoid aspiration, avoid the development of gastric distension
Pneumonia	All mask types	– Select the appropriate patient – Avoid the patient who is unable to protect the airway and cannot remove their secretion – Avoid deep sedation – Keep the patient's head up to avoid aspiration, avoid the development of gastric distension
Pneumothorax	All mask types	– Select the appropriate patient – Make appropriate ventilator settings. Try to set the lowest pressure – Check patient ventilator pressure regularly – Always be ready for tube thoracostomy
Hemodynamic Instability	All mask types	– Select the appropriate patient – Make appropriate ventilator settings. Try to set the lowest pressure – Keep the patient in adequate fluid balance – If necessary, evaluate the cardiac status of the patients with echocardiography and initiate appropriate medical therapy
CO_2 Rebreathing	Oronasal, Full-Face, Helmet (Most common in Helmet and Full-Face masks than Oronasal mask)	– Select the appropriate patient – Select the mask and size suitable for the patient – Adjust the appropriate ventilator setting to ensure the patient's adequate tidal volume and expiration time – Prefer a double ventilator circuit and a mask with exhalation ports – Reduce dead space area

23.3.3 Hemodynamic Instability

Positive pressure ventilation increases intrathoracic pressure and thus increases right ventricular afterload, resulting in the reduction of venous return and preload. Consequently, hypotension may develop. Continuous positive airway pressure (CPAP) has been shown to favorably affect hemodynamics in patients with cardiac failure [12]. By increasing intrathoracic pressure in patients with high preload and

afterload, CPAP can lower preload by decreasing venous return and afterload by reducing pressure gradient between the thorax and peripheral vasculature. Patients especially having low intravascular volume, severe left ventricular failure, and unregulated heart disease are at higher risk of these hemodynamic problems. PEEP and tidal volume titration should be done carefully in patients with left ventricular failure with low lung compliance, regardless of the presence of lung hyperinflation. If hypotension occurs in a patient with COPD exacerbation, the possibility of auto PEEP should also be considered. A conservative treatment approach will be appropriate in these patients. When applying NIV, the fluid balance of patients should be corrected and high inspiratory pressures should be avoided. If hypotension and evidence of organ hypoperfusion persists despite these measures, intravenous vasopressors can be initiated. Besides, in patients with evidence of organ hypoperfusion, intubation and controlled breathing are usually recommended to minimize oxygen consumption by respiratory muscles.

23.3.4 Inadequate Gas Exchange

(i) **Patient–ventilator asynchrony** is the most common cause of inadequate gas exchange. It results frequently from air leaks occurring due to inappropriate mask selection and use. These problems can be considered in two categories: failure of triggering and cycling [13]. "Failure of cycling" points out that at the end of the patients' inspiration, they have to use their expiratory muscles to overcome the high inspiratory flow still generated by the ventilator. "Failure of triggering" occurs with air leaks. With excessive air leaks, the pressure inside the mask decreases and the ventilator responds as if the patient has triggered breath or the patient cannot trigger the device due to the leak.

The mask type and the ventilator mode are factors affecting the patient–ventilator relationship during NIV. The level of pressure support and tidal volume generated are important. With the application of high-pressure support levels, there is a delay in completing the expiratory cycle. With low-pressure support levels, expiration begins while the contraction of inspiratory muscles still continues.

Water in the ventilator circuits can trigger the ventilator. Therefore, when adjusting the trigger, it must be high enough to prevent excessive triggering, but it should be as low as the patient can trigger the ventilator.

(ii) **Carbon dioxide (CO_2) re-breathing** may occur during NIV. It may be related with the mask, interconnection, ventilator circuit, and ventilator settings. Excessive devices and connectors should be removed as much as possible to prevent dead space ventilation. Carbon dioxide re-breathing is lower with nasal masks due to small dead space areas. If there is a need to use larger masks such as helmet masks, the fresh gas flow should be kept high. If the exhalation valve

is not used with a single circuit ventilator device, rebreathing will occur. Double circuit devices with non-breather valves and masks with exhalation ports should be preferred to prevent carbon dioxide rebreathing during NIV.

(iii) **Hypoxemia** Oxygen, if needed, should be delivered to the patient during NIV. However, since most portable NIV devices do not have an oxygen–air mixing system, the oxygen tubing is connected directly to the mask or to the ventilator circuit and flow rate is titrated until an adequate oxygen saturation has been achieved. Due to problems with this supply, hypoxemia can sometimes develop. In hypoxemic acute respiratory failure patients (ARDS or pneumonia), the use of NIV can be challenging [14, 15]. In such patients, NIV can be used initially with close follow up without delaying intubation. In these patients, the use of ventilators with oxygen blenders that provide FiO_2s (fraction of inspired oxygen) up to 100% is recommended. In addition, increases in expiratory pressure may be helpful to reduce the FiO_2 requirement. However, when expiratory pressure is increased, the inspiratory pressure should also be increased in proportion to maintain pressure support. This may lead to intolerance if pressures are excessive [14, 15]. Therefore, in these patients invasive mechanical ventilation should be preferred.

23.4 Conclusion

Noninvasive mechanical ventilation, which is used as a step therapy in respiratory failure, reduces mortality and morbidity. It is generally safe and has few major complications when used in appropriately selected patients. The most frequently encountered adverse effects are minor ones, related to the mask and air pressure and flow. By knowing these possible complications and taking precautions, the rate of complications will decrease.

Key Major Recommendations

- Noninvasive mechanical ventilation is generally safe and has few major complications when used in appropriately selected patients
- The most common complication of NIV is mask discomfort and intolerance. The mask should fit the face properly and its ties should be adjusted well to prevent air leakage, but should not be too tight
- Some complications of NIV are related to air pressure and flow adjustments (eye irritation, nasal congestion and dryness, gastric insufflation, etc.)
- Patients and ventilator adjustments should be monitored closely to prevent minor and major NIV complications such as pneumothorax, hemodynamic disturbances, hypoxemia, gastric distension, etc.

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Intra-Hospital Transport During Noninvasive Mechanical Ventilation

24

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_24

24.1 Introduction

Intra-hospital transport (IHT) of critically ill patients is a hot topic due to the frequency with which this procedure is carried out, and the clinical risks that it has for patients. IHT is performed when a patient needs diagnostic or therapeutic procedures that cannot be performed at his/her bedside (e.g., computed tomography scan, surgical intervention), or the transfer to another clinical care setting (intensive care unit, high dependency care unit).

Continuous positive airways pressure (CPAP) or noninvasive respiratory support through bilevel ventilation (BiPAP) are a widely used strategy of treatment in critically ill patients with the aim to prevent endotracheal intubation and invasive ventilation and their complications, especially ventilator associated pneumoniae (VAP). Therefore, IHT of noninvasive ventilation (NIV) patients can usually involve emergency department, high dependency units (HDU), intensive care units (ICU), radiological department (to perform X-rays, computed tomography, or magnetic resonance imaging), and special invasive diagnostic/therapeutic units (e.g., endoscopic or hemodynamic operating unit) [1].

Medical and nursing literature highlights the complications related to intra-hospital transport: adverse events are reported in 22.2–75.7% of the transports, and life-menacing events occur in 4.2–31% of total IHT, with 2% of deaths related to this procedure [1, 2].

Nevertheless, in the current literature covering the issue of critically ill patients transport, it is difficult to discriminate between the concept of complication (an unanticipated problem coming from a procedure, treatment, or illness exerting influence on the prognosis or outcome of an illness) and a preventable adverse event (a harm caused by medical treatment that could be preventable, for example, the accidental removal of an intravascular catheter).

A complete list of complications and preventable adverse events related to IHT from the current published literature is reported in Table 24.1. As a result, many scientific societies produced guidelines including organizational, technical, and clinical interventions to prevent patients' adverse events.

There is no published literature specifically focusing on complications and preventable adverse events occurring during IHT of NIV patients, and current guidelines are still lacking in specific recommendations addressing this patient population. Only recently, some authors described key recommendations to accomplish a safety transport procedure, but studies aimed to evaluate the outcomes of these interventions on NIV patients are needed [1].

IHT requires accurate and standardized planning addressing the optimization of personnel, equipment, and timing resources.

This chapter aims to identify the risks of complications and adverse events for IHT of NIV patients and the planning of interventions to perform this procedure according to high standards of safety. Moreover, special considerations about the IHT of NIV patients under airborne precautions are added considering the recent SARS-CoV2 pandemic.

Table 24.1 Risk of complications and preventable adverse events for NIV/CPAP patients during intra-hospital transport [3, 4]

Area	Mishap/adverse event
Respiratory	Hypoxemia Pneumothorax Bronchospasm Patient–ventilator dissynchrony Aspiration Derecruitment Chest tube loss Underventilation
Cardiocirculatory	Hypotension Hypertension Tachycardia Bradycardia Dysrhythmia Cardiac Arrest Bleeding Air embolus Hypothermia
Neurological	Agitation Pain
Equipment	Ventilator disconnection Ventilator failure Lack of oxygen supply SpO_2 probe disconnection/loss Exhausted monitor power supply Vascular catheters disconnection/loss EKG leads disconnection Tubes and wires entanglement
Surveillance	Gaps in monitoring
Treatment	Missed drugs administration

EKG electrocardiogram, *SpO_2* peripheral capillary oxygen saturation

24.2 Intra-Hospital Transport Planning

The decision to perform an intra-hospital transport of a patient on NIV support should be taken after balancing the risks and benefits of the procedure. NIV patients should undergo IHT only if they show an adequate level of consciousness, preserved airways protective reflexes, and hemodynamic stability. Otherwise, conditions as patient–ventilator dyssinchronies, agitative/uncooperative status, and excessive secretions require accurate assessment and management to gain the necessary safe conditions to carry out IHT [1].

Once the need to perform IHT and the criteria to carry it out are identified, intra-hospital transportation requires systematic proactive planning to prevent complications and preventable adverse events. The planning should cover logistical, organizational, and clinical variables that must be accurately assessed and managed.

24.2.1 Logistical Planning

Logistical planning of IHT for NIV patients includes the retrieval of important information about some variables to control them and prevent adverse events: the viability of intra-hospital paths (e.g., the measurements and capacity of elevators and corridors), the characteristic of the destination areas (e.g., availability of wall suction systems, airways management equipment, ventilator, oxygen supply, multiparametric monitor, infusion pumps, electric sockets, other equipment, etc.), and the approximate expected time to accomplish the transport procedure and return to the ward/department of provenance. Authors recommend that IHT transport timing should not exceed 15 min for patients on NIV support; nevertheless, this timeframe can be quite variable due to the presence of many clinical, logistical, and organizational factors that must be meticulously controlled. In the case of a diagnostic or therapeutic procedure, the timing of the round trip can vary from 30 to 90 min [1].

The control of these variables, associated with the evaluation of the patient's clinical characteristics, allows the healthcare staff to choose the mean of transportation between the gurney (narrow and essential) and the bed (more comfortable than the gurney, but also less easy to handle). Lastly, the transport equipment, composed of monitor/defibrillator, mechanical ventilator (or high-flow devices delivering CPAP), infusion syringe pumps, and an emergency crash backpack (including advance life support equipment and drugs) should always be available and checked daily.

24.2.2 Organizational Planning

Planning should take into account the transport team skills and expertise, communication issues and adequate transport and clinical documentation.

Regardless of the number and the composition of the IHT team, good clinical sense indicates that the presence of a physician and a nurse with high expertise and skills in NIV equipment, advanced life support (ALS), and difficult airways management should be provided [1]. It is essential that the IHT team should be adequately skilled and experienced to provide an efficient anticipatory and prompt answer to the acute patients' needs during every phase of the transport [5]. In fact, authors identified the lack of transport training and experience as two main risk factors for the occurrence of adverse events during IHT [3].

Communication and pre-transport coordination are two factors that should be optimized to guarantee adequate standards of safety for IHT [1]. Good communication and coordination levels inside the IHT team, as well as between the IHT team and the healthcare staff of the destination unit, can avoid wasting time, delays, and improve the prevention and management of adverse events, complications, and life-threatening emergencies.

The patient's clinical documentation that is not sharable by local hospital's intranet should be timely collected and prepared to accompany the patient during IHT.

Lastly, a reserved IHT clinical chart should be designed to record vital signs, complications, adverse events, scheduled and urgent drugs administrations, and other interventions performed on the patient outside the protected environment. This documentation, beyond the strict legal value, could be essential for research and the drawing up of an incident reporting system. This kind of registry is useful to the planning of improvement interventions for patients' safety during IHT [6].

24.2.3 Clinical Planning

The clinical planning of IHT of NIV patients should take into account three pivotal issues: risk of patient's complication and preventable adverse events, monitoring level adequate to the patient's clinical conditions, and patient setup for the transport.

The clinical planning is focused on the concept of anticipation. In fact, during IHT, the neurological, respiratory, hemodynamic changes, as well as discomfort, are due to changing in position, movement from one surface to another, and pain caused by the stiffness of radiological stretchers or by the diagnostic/therapeutic procedures performed on the patients. All these variables, as well as the risk of accidental removal of medical devices or equipment falls, can be prevented by an attentive anticipation [3].

Therefore, an adequate level of monitoring and patient's setup are the two key interventions to prevent complications and adverse events during IHT.

24.2.3.1 Monitoring level

Ideally, during IHT critically ill patients should be provided with the same level of monitoring as during their stay in the Intensive Care Unit (ICU). Patients undergoing NIV support or CPAP should be at least monitored for level of consciousness, respiratory rate, SpO_2, ventilatory parameters and waveforms, continuous electrocardiogram (EKG) tracing, intermittent blood pressure measurement, urine output, and body temperature. If available, an indwelled arterial catheter and continuous invasive blood pressure monitoring should be maintained during the IHT. Other levels of monitoring (e.g., central venous pressure) are rarely useful during IHT, and their need should be carefully evaluated before the setup. In fact, the risk of adverse events related to the equipment could also be increased by the number of medical devices in place. The only exception is by the pulmonary artery catheter that should also be connected to the multiparametric monitor during the transport, to identify early the occurrence of accidental wedging in a pulmonary capillary by the pressure waveform [6].

24.2.3.2 Patient Setup for the Intrahospital Transport

The principles that guide the transport team interventions in this critical phase of the process are to preserve the patient's stability, safety, and comfort.

The planning of the intervention should preferably follow a clinical checklist according to a systematic ABCDE (airways, breathing, circulation, disability, exposure) assessment–intervention–re-evaluation circle [7].

One of the commonly supported recommendations on the transport of critically ill patients is to achieve the stabilization of physiological parameters before the departure, excepting for some major surgical emergencies, for which a delayed arrival in the operating room can be fatal [6].

A—Airways

Preparing NIV patients for intrahospital transportation requires an accurate assessment of the level of consciousness and the ability of patients to collaborate. A Kelly-Matthay score ≥ 3 and the lack of good levels of protective reflexes should direct clinicians toward the decision to secure the airways through endotracheal intubation before transporting the patient. Also, severe agitation represents another major contraindication to NIV as well as the occurrence of vomiting. These two events require adequate management before going ahead with the transport procedure (e.g., light sedation management, nasogastric tube insertion).

The choice of the NIV interface should be made taking into account the patient's destination. For example, if the patient is undergoing a scheduled radiological procedure, the use of a helmet could be challenging due to the limited space on the radiological stretcher and for the position to be maintained; therefore, an oronasal or a full-face mask could be the better choice.

Furthermore, as a general good sense-based recommendation, if the patient is ventilated through a nasal mask or mouthpiece, it is preferable to shift to interfaces that could be more suitable for the management of acute patients (oronasal mask, full-face mask, helmet) to prevent adverse events.

All masks should be provided with different typologies of elbows (e.g., standard or entrainment) according to the ventilator selected for the transport; in fact, standard (closed) elbows should match ICU or transport ventilator circuits, while entrainment elbows should match BiPAP ventilators circuits with intentional leaks. This precaution should prevent adverse events due to the improper management of the unintentional and intentional leaks, as uncompensated air-leak levels, or lack of wash-out for the mask dead space. The first occurrence can produce a reduction of delivered tidal volume and patient–ventilator dyssinchronies, while the second event can generate an increase of CO_2 rebreathing.

Patients with oronasal or full-face mask should be checked for the presence of denture, their stability inside the mouth, and the influence exerted on the leaks and the performance of NIV.

Lastly, the position of patients during IHT should be maintained strictly with a head of the bed elevation of 30°–45° to prevent oral ingestion of gas and abdominal distension, increasing the risk of ventilation worsening and vomiting.

B—Breathing

The bed or the transport stretcher should be provided with an adequate oxygen supply in a cylinder well fastened to a side of the transport. The transport team should calculate the oxygen supply needed, taking a large amount of reserve over the oxygen liters obtained by the inspiratory minute volume (displayed on the ventilator) multiplied by the minutes estimated for the round trip. If the patient is on CPAP, the

problem related to high-flow gas supply could be dealt with using venturimeters. However, the transport team must take into account that if high levels of FiO_2 are required, low total flows are delivered to the patient, and a reduced time of oxygen supply will be available.

The ventilators used for the transport must be regularly checked for operationality, circuits and valves integrity, and the charge of battery supply. The mechanical ventilator should be secured to the bed or transport stretcher taking into account also the encumbrance provided when the transport stretcher enters the elevators or goes through hospital doors.

Ideally, patients should be transported with the same mechanical ventilator and ventilation parameters settings used in the ICU or HDU. If the ventilator have to be changed with a transport ventilator because of problems related to its dimensions or the battery life, the respiratory stability of the patient supported by NIV through the new ventilator should be adequately assessed before the departure.

Regardless, the use of BiPAP ventilators (single limb circuit with intentional leaks), ICU ventilators (double limb circuit with expiratory valve) or transport ventilators (single or double limb circuits with expiratory valve), the transport team must settle the ventilation parameters, check the alarm levels (that should be fitted on the single patient's characteristics), adjust the interface fitting, set the expiratory trigger levels and the maximum inspiratory time to prevent inspiratory hang-up due to excessive unintentional leaks (often when ICU or transport ventilators are employed).

The implementation of an arterial blood gas analysis is recommended soon before the departure and after the return.

During transport, the respiratory rate, expiratory tidal volume, the amount of unintentional leaks, patient–ventilator synchrony, as well as the patient's respiratory pattern must be monitored. Breathing circuit should be arranged to prevent the occurrence of kinking and breaking.

Owing to the limited timeframe usually required by the intra-hospital transport procedure, the issues related to the humidification of the inhaled gas are not relevant, and the IHT should be performed without humidification systems. Since the American Association of Respiratory Care Guidelines do not recommend the use of heat and moisture exchanger filters during NIV, their application should also be considered ineffective to achieve sufficient levels of airways humidification during IHT [8].

C—Circulation

The monitoring equipment must be secured to the means of transport to prevent falls.

The heart rate and all hemodynamic parameters should be alarmed, based on the individual patient's conditions.

All invasive pressures should undergo zeroing before the departure; the saline solution bag in pressure-bags should be maintained at 300 mmHg, and the drip chambers completely filled with solution to prevent accidental air embolism if the pressure bags should be placed laying on the bed or the transport stretcher.

Fluid status and electrolytic balance must be adequately fixed before the departure to prevent arrhythmias and hemodynamic instability of the patient.

All venous and arterial lines should be checked to prevent kinking and occlusion; all line connections and stopcocks should be checked and tightened. Unused lumen of intravascular catheters should be flushed with saline solution to prevent occlusion. The syringe pumps should be checked for their battery power supplies and secured on the transport mean to prevent falls, and placed over the patient level to prevent infusions backflow. Moreover, at least one electrical cable should be promptly available [9].

Scheduled drugs should be administered during transport only if undelayable, such as antibiotic medications. Urine output using an urometer should be monitored in patients transported and staying outside the intensive care unit for long-term procedures.

D—Disability

The transport team should monitor the patient's level of consciousness during the transport procedure, and detect early every sign of agitation, discomfort and pain, treating these problems adequately with pharmacological and non-pharmacological interventions to increase his/her compliance and prevent NIV failure during IHT.

D—Drainages

Drainages should be secured before the departure to prevent the occurrence of accidental removal. Chest drainages deserve particular attention because they must be maintained open and below the level of the patient's chest. If the drainages should be kept under continuous suction during the transport, a portable suction unit should be available. Otherwise, the suction of chest drainage can be repristinated once the patient has arrived at the destination, with a wall suction unit [9].

If needed, a Heimlich valve can be applied to thoracic pigtails, to prevent air suction in the chest wall in case of accidental disconnection of the drainage bag.

If enteral feeding is administered in the ICU or HDU, it should be stopped, the stomach should be voided with a syringe, and the nasogastric tube with a drainage bag should be left, under the patient's level.

Exposure

Intermittent monitoring of body temperature is important, especially if hyperthermia occurs. Hyperthermia determines an increase of the respiratory and heart rates due to a higher oxygen demand. Furthermore, this physiologic response can also add some difficulties in NIV management. Therefore, the transport team should manage hyperthermia pharmacologically to reduce tachypnea and tachycardia and improve the patient's comfort [7].

On the contrary, hypothermia and shivering should be prevented through passive rewarming means, and overall, avoid letting the patient be exposed during the transport.

Finally, the transport team should perform a fast head to toe exposure, re-checking the patient to determine and solve unseen critical problems before the departure.

24.3 Intrahospital Transport of Patients under Airborne Isolation Precautions

The recent outbreak of Coronavirus Disease 2019 (COVID-19) due to SARS-CoV2 has dramatically changed the approach of the healthcare systems toward the care of infected patients, due to the high risk of transmission of the virus.

Patients affected by COVID-19 often need respiratory support to counteract the severe hypoxemia related to the pneumonia and the microcirculation impairment that is one of the most dangerous features of this new illness. Therefore, NIV supports (both CPAP and BiPAP) are largely employed in COVID-19 patients [10].

Moreover, the lack of ICU and HDU beds has caused another push toward the diffusion of NIV utilization in all the hospital settings, especially the general wards. Therefore, an increasing number of patients in severe clinical conditions have been managed in low levels of care settings with the rising need to frequently perform IHT for diagnostic purposes or to transfer them in HDU or ICU, when beds became available.

IHT of NIV patients with airborne and contact precaution shows two main clinical difficulties. The first one is to perform the transport with the physical and sensorial hindrances that accompany wearing maximized personal protective equipment (PPE) (goggles, shield-visors, KN95 masks, suits, and several pair of gloves). The second one is to limit the potential spreading of aerosol with microorganism content in the environment during the transport, when patients should be maintained on NIV support for their critical conditions.

Hospitals organizations should identify special "isolation" pathways for these patients, separating the dirty paths from the clean ones. The planning and communication phase of the IHT should be accurate to avoid any possible waste of time outside the wards, especially the waiting of isolated patients in open areas outside radiological rooms while others are completing diagnostic procedures. If the radiology department is not provided with dedicated diagnostic rooms for infected patients, the procedures should be scheduled after all the other radiological examinations planned for "clean" patients (unless the occurrence of emergency conditions).

Healthcare providers performing the IHT should be focused only on the management of patient's monitoring and supports and their own safety. In fact, moving and interacting with the environment and other persons while wearing maximized PPE can be challenging and generate discomfort and risks of adverse events [11], for example, the goggles can have the fog effect and postural stability impairment [12, 13].

Concerning the spread of microorganisms during transport of NIV patients, there are not many preventive interventions that can be added to those adopted during their stay in the clinical settings, except for the choice of the transport ventilator. Healthcare professionals should use a transport ventilator equipped with double-limb or single-limb circuits with a unidirectional expiratory valve. These kinds of ventilator circuits require the use of a standard (closed) elbow for the connection to the masks and the application of a HEPA filter proximal to the interface, providing the highest possible level of prevention for microorganism diffusion due to

maintaining a "closed system." However, the use of an NIV mask does not allow the complete prevention of aerosol spreading due to the unavoidable presence of non-intentional leaks around the interface.

Therefore, a NIV mask should be switched to a CPAP-helmet if compatible with the clinical conditions and the typology of diagnostic or therapeutic procedure that patient is undergoing at destination. In fact, a CPAP-helmet can offer a higher isolation precaution provided by the application of a HEPA filter on the outlet of the helmet, just before the PEEP valve, taking in account that outlets filters affect the level of CPAP actually delivered [14]. The CPAP-helmet can work with Venturi systems requiring only an oxygen cylinder, ideally avoiding the need of a ventilator, and therefore reducing the load on the bed or the transport gurney (Figs. 24.1 and 24.2). However, the risk of emergency intubation in these patients cannot be excluded. Therefore, it seems reasonable to carry around also the transport ventilator to avoid the risk of manual ventilation in case of intubation. This precaution can provide a higher standard of safety for patients and prevent the spread of microorganisms due to the closed system guaranteed by the cuffed endotracheal tube and the ventilator provided with the HEPA filter.

Fig. 24.1 IHT of COVID 19 CPAP patient delivered by helmet

Fig. 24.2 IHT with CPAP-helmet Venturi system

24.4 Conclusions

NIV patients are a special category of the critically ill patients undergoing IHT procedures. These patients require careful assessment and selection by the transport team before deciding to perform the transport because the risks related to the need of airways management can be present in any phase of the process. Moreover, the transport team should have high expertise and skills with NIV equipment, trouble-shooting, and ALS. Due to the high risk of complications and preventable adverse events, the planning and management of IHT for NIV patients should be conducted following a systematic approach provided by an ad-hoc step-by-step logistical, organizational, and clinical check list.

Being a high-risk procedure, IHT of NIV patients should be attentively monitored and documented, using clinical risk management and quality improvement tools as appropriate quality indicators, such as those reported in Table 24.2. Quality improvement programs integrated with the logics of the clinical risk management are the key factor to achieve patients' safety for this procedure. However, it should be kept in mind that "the other side" of the IHT procedure outcome is represented by the care provided to patients at the (diagnostic or interventional therapeutic) unit

Table 24.2 Examples of quality indicators in IHT of NIV patients

Typology	Indicator
Performance	N. failures of oxygen supply/N. performed IHT
	N. failures of monitor battery supply/N. performed IHT
	N. of equipment (monitor, ventilator, infusion pumps) accidental fall during transport/N. performed IHT
	N. of accidental removal of intravascular lines/N. performed IHT
	N. of accidental removal of drainages and tubes (including NG tubes and urinary catheters)/N. performed IHT
	N. of minutes of waiting before entering the examination room (x-ray; CT; MRI) of radiological department/N. performed IHT
	N. of patients-ventilator dyssynchronies (e.g., inspiratory hang-up) during the IHT/N. performed IHT
Outcome	N. of endotracheal intubations before the arrival at destination/N. performed IHT
	N. of deaths during IHT or within 1 h from the return in the ward

CT computerized tomography, *IHT* intra-hospital transport, *MRI* magnetic resonance imaging, *N* number, *Pts* patients

of destination. In fact, well-designed prospective observational studies are needed to provide data about the safety of performing IHT in NIV patients, but also about their management in the radiological department and in invasive diagnostic/therapeutic procedures units, when patients often must lie down on the stretcher, increasing their risk of complications.

Key Major Recommendations

- The planning of IHT should cover logistical, organizational, and clinical variables
- Patient setup for the IHT should preferably follow a clinical check list according to a systematic ABCDE (airways, breathing, circulation, disability, exposure) approach
- During IHT, patients undergoing NIV or CPAP should be at least monitored for: level of consciousness, respiratory rate, SpO2, ventilatory parameters and waveforms, continuous EKG monitoring, intermittent blood pressure measurement, urine output, and body temperature
- When feasible, the IHT of COVID-19 patients with noninvasive ventilation supports should be performed switching to CPAP-helmet if compatible with their clinical conditions

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Part VII

Chronic Applications Noninvasive Mechanical Ventilation

New Ventilatory Modes in Sleep-Disordered Breathing: Key Topics and Clinical Implications

25

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_25

25.1 Introduction

Clinical sleep medicine entered a new period, when Colin Sullivan, in the early 1980s, described the use of continuous positive airway pressure (CPAP) to treat obstructive sleep apnea (OSA) [1]. With this new clinical utility of home ventilation, scientific research and manufacturers increased interest in developing this new modality of home treatment and introducing new technological methods to enhance the effects of therapy and patients' comfort.

In essence, the concept of positive pressure therapy (PAP) depends on pumping air under positive airway pressure to splint the upper airway preventing its narrowing during sleep and increasing the functional residual capacity to improve oxygenation [2].

In patients with obstructive sleep apnea (OSA), the prescribed airway pressure has to be sufficient to ensure upper airway patency and normal comfortable breathing during sleep. On the other hand, in patients with central apnea or hypoventilation, the selected ventilatory mode and pressure setting have to ensure a normal breathing pattern during sleep. To determine this optimal airway pressure and ventilatory mode, patients usually undergo an in-lab sleep study to ensure normalization of breathing during sleep (Ahmed and Parthasarathy, 2010). Nevertheless, unattended titration of PAP therapy has become a well-established practice for patients with a high likelihood of moderate to severe OSA [3].

Newly developed intelligent PAP therapy devices use specialized built-in algorithms and equations to respond to abnormal respiratory events during sleep. This chapter discusses new modes in PAP therapy for sleep-related breathing disorders and their applications and limitations.

25.2 An Overview of PAP Devices Features

25.2.1 The Basic Concept of PAP Therapy

Basically, PAP devices comprise a flow-generating element (blower), a controller for the degree of positive pressure reaching the patient, measurements of the patient's airflow, ability to detect respiratory events during sleep, and the estimation of air leak. Smart new devices use the collected information to adjust delivered pressure or modify modes and provide useful tracking data for therapists. Nevertheless, maintaining synchronization between the patient's spontaneous breathing and PAP therapy remains the main challenge facing the success and hence adherence to this therapy.

The blower pulls ambient air through a filter and delivers it through the device outlet port to patients. A sensitive pressure sensor works to maintain a fast response and normal flow. The therapeutic airway pressure is delivered to the patient via an interface mask.

25.2.2 Essential Components of a PAP Therapy Device

In general, the essential components of a PAP device include a microprocessor, pressure sensor, integrated DC motor with blower, motor controller, flexible tube, and different interface masks [4]. Additionally, PAP devices contain transformers to control the speed of the engine, airflow, and pressure at a fixed point in the flow generator. Moreover, a sensor is built inside the PAP device to measure the mask's pressure. The reason for using multiple sensors is to help control airflow, pressure, humidity, and temperature and provide a smooth, tolerated output. In addition, recent algorithms monitor the exhalation phase to reduce the internal blower and hence pressure, making it easier and more comfortable for the patient to exhale.

25.2.3 Pressure Ramp-Up Feature

The pressure ramp-up feature in the PAP devices permits the device to provide pressure at a low point-set during a specific time period that builds up gradually to achieve the set pressure. For instance, if the optimal prescribed airway pressure is 12 cmH_2O, the ramp pressure may start at 5 cmH_2O and slowly increase over a preset time to reach the optimal target pressure. The start-up pressure and time slope can be adjusted according to the patient's comfort and clinical condition.

A new feature by some manufacturers is auto-ramp, which allows the system to start at low airway pressure while the patient is awake. Then, once it detects that the patient has fallen asleep, the ramping will automatically allow pressure to build up to the prescribed level. Additionally, auto-ramp low pressure will add comfort via providing a soft sound from the device while the patients and bed partner are still awake.

25.2.4 Expiratory Pressure Relief Algorithms

A major complaint of patients on PAP therapy is difficulty exhaling against high pressure. A new technological development to improve patients' comfort is pressure relief during the expiratory phase of the respiratory cycle. This technique reduces pressure during early exhalation to enhance the comfort of patients.

25.2.5 Leak Compensation

While using PAP devices, air leakage is one of the main problems that need to be monitored and fixed. Air leakage significantly affects the performance of the PAP device, the delivered pressure, the respiratory cycle, operating thresholds, and respiratory events identification, and hence patient comfort and adherence [5].

25.2.5.1 Leakage Compensation Mechanism

Leak compensation is achieved through continuous monitoring of deviations from the expected flow of breathing. Because there are common variations in the breathing cycles of patients, the average expected leakage is usually calculated over several breaths. If the leakage is higher than the accepted threshold, automatic devices compensate by lowering pressure, and this will seal the mask and decrease leakage. Leakage can be controlled from the flow rate at the end of exhalation [6].

Intentional leakage comprises the exhalation ports on the mask, which vary according to the type of mask and pressure level. On the other hand, unintentional leakage includes leakage from the mouth or around the mask [5]. Generally, the leakage should be less than 24 L/min in nasal masks and less than 36 L/min in full-face masks, but this may vary depending on the interface used [7].

25.2.6 Defining the Respiratory Cycle

It is essential to define inspiration and expiration to provide a two-level PAP, relieve expiratory pressure, and resolve automatic algorithms' inhalation flow limitations. The critical mark is the beginning of the breathing from the negative flow to the positive flow—the flow signal switches from positive to negative flow at the initiation of the expiration.

Servo-ventilators and some auto devices use a continuous definition of the breathing cycle, which differs according to the manufacturer. For example, the ResMed servo-ventilator microprocessor uses indefinable inference rules that look at the direction of flow rate and volume to determine the respiratory cycle stage. On the other hand, the Respironics ventilator servo device divides breaths into short periods (64 ms) to determine the average inspiration expected at other points of the cycle as defined by the length of exhalation to predict the duration of breathing [8].

25.2.7 Built-in Software and Display Screen

Several PAP devices demonstrate standard patient information statistics on the display screen, and others have optional advanced data tracking features via optional software programs.

Recent home PAP devices are supplied with built-in software that provides data, such as adherence, leaks data, tidal volumes, minute ventilation, respiratory rates, apnea-hypopnea index, average pressure, and the presence of periodic breathing or central apneas.

25.2.8 Data Collection, Display, and Analysis

New PAP devices have new technology to allow easy PAP therapy data downloads, transfer, and telemonitoring. This technology also encourages patients with sleep-disordered breathing to play an active role in monitoring their progress.

New software and apps offer unique insights into sleeping patterns, potential mask leaks, and any overnight pressure fluctuations, allowing tailoring therapy to individual needs. Many machines can view minute-by-minute reports; other machines can create day-by-day reports.

25.3 New Noninvasive Positive Airway Pressure (PAP) Ventilatory Modes

The initially developed PAP machines were simple continuous blowers. However, technology development added several new modes, from simple bilevel flow generator devices to the advanced adaptive servo-ventilator.

Technologies related to PAP systems have evolved from a simple pump that pushes air into the respiratory tract during inhalation and exhalation to developing technical additions that improve the performance of the PAP device to provide comfort to the patient and treat complex sleep-related breathing disorders.

The following sections discuss these new technologies.

25.3.1 Autotitrating Continuous Positive Airway Pressure (APAP)

Conventionally, PAP devices utilize a set fixed pressure that is determined during the titration study. The automatic positive airway pressure (APAP) machine has two separate pressure settings: low pressure and high pressure. A built-in algorithm allows the machine to automatically adjust the pressure between these two set points throughout the night to maintain airway patency as a patient change sleeping positions or shift sleep to various sleep stages. APAP therapy is a good option for patients with REM-predominant OSA, as it only increases pressure to compensate during this sleep stage [9].

Moreover, APAP may help reduce the average airway pressure needed to treat obstructive respiratory events, thus, theoretically reducing discomfort associated with the high airway pressure. Nevertheless, currently available evidence does not convincingly demonstrate an improvement in adherence with APAP [10].

The transformers check the motor speed, airflow, and pressure at a fixed point downstream of the flow generator. The sensor is placed in the device and not in the mask, so the device must calculate the mask's expected pressure according to flow measurements at different points in the system. Flow can be calculated based on the pressure changes at two points, and the length and diameter of the tube and the characteristics of the mask affect the continuous value [2]; therefore, the technical specialist must specify some measurements and enter them into the device settings such as the type of mask and tube for the microprocessor to perform the correct calculations.

The microprocessor adjusts the blower speed in response to pressure changes resulting from leaks or regular air pressure changes due to breathing. The flow signal is sent through low and high pass filters to separate respiratory flow signals

artifacts. Low-pass filters exclude the flow of large rapid deflections (e.g., coughing or sneezing), and high-pass filters exclude cardiac fluctuations. The feedback limits decide whether the flow or pressure exceeds the expected range of flow change at a specific motor speed (for example, tube fracture) and stop the device from providing too much or too little pressure [4].

Auto-CPAP algorithms differ from one company to another. Nevertheless, the concept of assessing the airflow passing through the upper respiratory tract remains the same. During auto-CPAP, the positive airway pressure is increased or decreased in relation to signs indicating upper airway resistance changes, such as airflow changes, circuit pressure changes, or vibratory snore.

Earlier versions of auto-CPAP algorithms detect snoring vibration changes, making them unresponsive to many critical events. However, most of the new auto-CPAP systems use snore detection in conjunction with airflow limitation detection. The flow is inspected multiple times per second, measured with a low pass filter to eliminate defects, and then the average flow can be determined for any length of time. For example, Respironics auto-CPAP uses the weighted peak flow (WPF) method to estimate ventilation. In contrast, ResMed auto-CPAP uses a low-pass filtered absolute value for respiratory flow and uses the square root method (RMS) to vary the medium's flow to match one moving period to another. On the other hand, DeVilbiss Intellipap Auto Adjust uses a graduated peak amplitude, while Auto Adjust 2 uses filtering techniques to fine-tune defects in peak flow.

It is recommended to change the CPAP minimum to the device's pressure at or below the pressure that was delivered to the patient 90–95% of the time; so that, fixed CPAP settings should be tried if patients do not do well with auto-CPAP.

If the selected pressure range in auto-CPAP devices is wide (e.g., 4–20 cmH_2O), the device may take too long to change to a therapeutic setting, which may result in the appearance of obstructive respiratory events, particularly in REM-predominant or position-related OSA.

Moreover, auto-CPAP devices are not recommended in patients with central sleep apnea or obesity hypoventilation syndrome.

Traditionally, PAP titration is done under attended-PSG monitoring to eliminate respiratory events during sleep. However, due to the long waiting lists and lack of sleep laboratories in some countries, auto-titrating PAP devices have been used to perform unattended titration for patients with a high likelihood of moderate to severe OSA.

Despite the advantages of APAP mode, it has shortcomings, including its higher cost, lack of solid evidence supporting improved adherence compared to conventional CPAP [11], and is not recommended in patients with chronic heart failure or obesity hypoventilation syndrome.

25.3.2 Autotitrating Bilevel Positive Airway Pressure (AUTO-BPAP)

Auto-BPAP delivers spontaneous bi-level therapy, automatically adjusting expiratory PAP (EPAP) and inspiratory PAP (IPAP) levels to meet the patient's

requirements [12]. Similar to auto-CPAP, different manufacturers use different algorithms in auto-BPAP. For example, some machines provide only stable pressure support (PS), whereas others specify maximum PS (PS_{max}), and some allow both minimum PS (PS_{min}) and PS_{max}. Thus, auto-BPAP devices may not provide adequate ventilatory support if some PS_{min} related upper respiratory tract obstructive events cannot be detected. In addition, simple auto-BPAP devices do not usually have spontaneous-timed (ST) mode backup breathing options; therefore, they are not recommended for use in people with central sleep apnea or obesity hypoventilation syndrome.

ResMed's VPAP-AutoBPAP and DeVilbiss AutoBPAP contain a constant set of PS. While Respironics Series 50 AutoBPAP fixes PS_{min} at two and permits setting for PS_{max}; on the other hand, Series 60 AutoBPAP has settings for both PS_{min} and PS_{max}. In addition, within PS_{min} and PS_{max} limits, Respironics AutoBPAP adjusts EPAP in response to occurrences of apneas (either two apneas or one apnea and one hypopnea) as well as snoring. Additionally, it modulates IPAP in response to instances of hypopneas (two hypopneas) and flow limitation. These adjustments are made using algorithms similar to those found in REMstar AutoCPAP [8].

25.3.3 Adaptive Servo-Ventilation (ASV)

Adaptive servo-ventilation (ASV) is a BPAP therapy mode frequently used to manage sleep-related breathing disorders, particularly different types of central sleep apnea (CSA). Similar to BPAP and CPAP, ASV provides a set to control obstructive related events by adjusting EPAP and tidal volume (V_T) augmentation via IPAP. Nevertheless, there are differences between ASV therapy and CPAP or BPAP, where ASV applies dynamic adjustments to support inspiratory pressure support (IPS) and uses an auto-backup rate to normalize breathing rate relevant to a predetermined target. In addition, ASV performs breath-to-breath analysis and delivers ventilatory needs accordingly to prevent the hyperventilation that drives Cheyne–Stokes breathing (CSB).

Manufacturers have introduced these progressive changes, for example, ResMed VPAP AdaptSV (equivalent to Teijin AutoSet CS) with ASV setting, AirCurve ASV, renamed AirCurve CS PaceWave with ASV, and ASVAuto settings, and Respironics BPAP AutoSV Advanced. Another device is SOMNOvent CR.

CSB is associated with increased mortality in heart failure patients (HF). CSB is seen mainly in patients with a low left ventricular ejection fraction, but it has also been seen in patients recovering from acute pulmonary edema, central nervous system lesions, chronic opioids use, and advanced renal failure [13]. The presence of CSB in patients with heart failure is associated with increased morbidity and mortality and impaired quality of life [14]. As ASV provides a breath-to-breath assessment of the breathing pattern, it has the advantage of preventing the hyperventilation that drives CSB.

ASV uses an algorithm that detects significant diminutions in airflow or V_T, or cessation in breathing, and reacts by delivering enough support to maintain the

patient's breathing at 90% of normal breathing (prior to decreased breathing). Figure 25.1 demonstrates a 2-min epoch of a patient with CSB on ASV. A recent randomized trial of patients with HF and an ejection fraction of ≤45% reported an increased risk of cardiac death with ASV therapy [15].

Therefore, the AASM published guidelines about ASV therapy in patients with CSB and HF. They endorsed that ASV being used to normalize the apnea-hypopnea index (AHI) should not be used to treat central sleep apneas related to HF in adults with an ejection fraction ≤45%, and moderate or severe CSA predominant sleep-disordered breathing (STANDARD) [16]. Moreover, they stated that ASV being used to normalize the AHI could be used to treat CSA related to congestive HF in adults with an ejection fraction >45% or mild CHF-related CSA (OPTION).

Older versions of ASV used a fixed EPAP; however, it samples airflow several times per second and changes IPAP throughout inspiration to reach target minute ventilation. However, recent algorithms use auto-EPAP.

For ResMed algorithms, the PS range can be 0–20 cmH_2O, a PS_{min} of 3, and a PS_{max} of 15 cmH_2O. The device determines a target minute ventilation based on the minute ventilation calculated for the last 3 min. ASV uses fuzzy logic to determine the respiratory cycle part and whether the present ventilation is lower than or above the required target and then modifies the PS throughout the cycle to reach that target; therefore, preventing sudden pressure changes. The auto-backup rate starts at the current auto rate based on a moving average calculated in several breaths. Then, it gradually adjusts during apnea to 15 beats per minute. ASVAuto (Respironics) also adjusts EPAP levels similar to AutoSet's algorithm in response to obstructive apnea, flow restriction, and snoring. When the breathing is normalized, the periodic breathing pattern will recede. However, if the device is cycling the pressures frequently, this implies an underlying periodic pattern, and frequently the patient will not tolerate the device, or there will be a suboptimal clinical response.

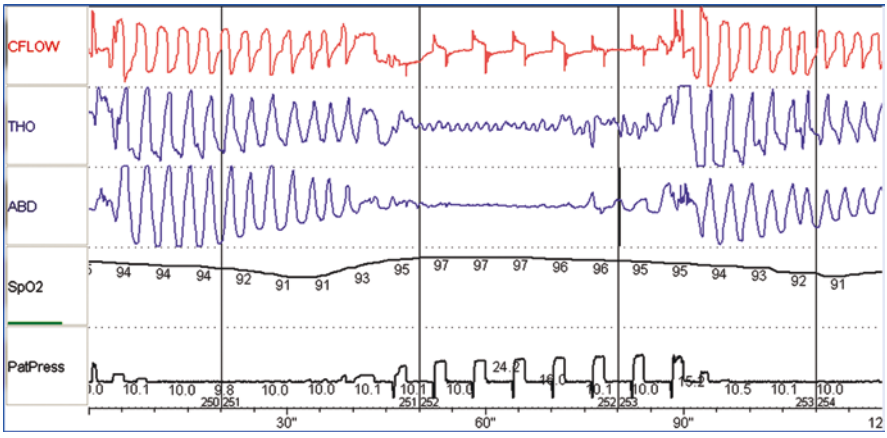

Fig. 25.1 A 2-min epoch from a patient with Cheyne–Stokes breathing (CSB) on adaptive servo-ventilation (ASV). ASV responds by delivering adequate support to maintain the patient's breathing to prevent the hyperventilation that drives CSB

On the other hand, advanced Respironics BPAP AutoSV is set with minimum and maximum EPAP, PS_{min} and PS_{max}, maximum pressure, and automatic or fixed rate. The inspiratory rise time (T_i) and Bi-Flex features can also be customized to achieve patients' comfort. The PS level is targeted, relying on mean inspiratory flow, which is the sum of inspiratory flows over a period divided by the number of samples to set limitation values. The target peak flow is usually tuned at 90–95% of the mean peak flow of the last 4 min. To normalize breathing in the setting of obstructive events (apnea [<20% flow], hypopnea [20–60% flow], and snoring), the target peak flow rises from 95% of the mean inspiratory peak flow across the last 4 min to the 60th centile of the inspiratory peak flow rates. Similarly, the target peak flow is increased to the 60th percentile if CSB features are noted based on a CSB index, which measures similarity to a CSB pattern or a flow index that measures fluctuations in breath size [8].

The EPAP adjustment algorithm of ASV uses a triggered breath or forced oscillation to differentiate obstructive from open airway events [8]. The automatic backup rate is determined based on a moving window of several spontaneous breaths. A compulsory breath is provided if the breath does not appear within specific set parameters.

25.3.4 Volume-Targeted Pressure Support (VtPS)

Deterioration of chronic hypoventilation in obesity hypoventilation syndrome, chronic obstructive pulmonary disease, and neuromuscular diseases may not respond well to the standard BPAP therapy [17].

Although patients are often treated with constant EPAP and PS settings, NIV modes are now available that automatically adjust pressure settings to provide adequate ventilation in response to various ventilation requirements. A theoretical drawback of fixed level BPAP is the variability of delivered tidal volume (V_T) due to respiratory effort variations, respiratory system elastance, and sleep position in OHS patients. Volume targeted pressure support (VtPS) combines the advantages of pressure-limited and volume-limited ventilation modes into one mode to attain sufficient V_T and minute ventilation throughout a sleep period and long term [18]. Built-in pneumotachograph examines delivered V_T, and when V_T falls below a preset level, the system automatically reacts by increasing IPAP to increase V_T to approach the target V_T (Fig. 25.2).

Volume-targeted (V_T) modes of positive airway pressure noninvasive ventilation (NIV) devices are hybrid modes to combine the advantages of assured minute ventilation produced by conventional volume-limited ventilator modes with the comfort and greater leakage compensation associated with pressure-limited ventilator modes. In addition, algorithms are also available with EPAP mechanisms to maintain upper airway patency and control obstructive respiratory events (auto-EPAP) in some VtPS devices. These devices react in real-time to changing pressure requirements during sleep and may have clinical benefits such as reduced air leakage and improved patient comfort.

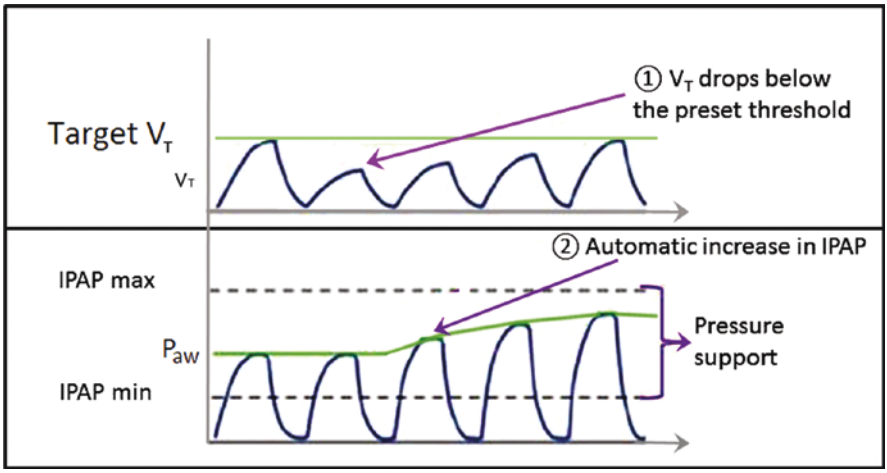

Fig. 25.2 An illustration of the operation of the VtPS ventilatory mode. When the tidal volume drops to less than the set tidal volume, the system discovers the reduction in tidal volume and automatically raises IPAP to rebuild tidal volume to the target tidal volume

A possible advantage of this mode over fixed BPAP is the capability to modify inspiratory support to maintain ventilation in spite of changes in lung or chest wall compliance that can arise from changes in sleep stage or body position.

In comparison to BPAP ST, clinical studies have demonstrated that VtPS resulted in higher IPAP levels with higher V_T or minute ventilation, yielding more significant reductions in overnight CO_2 [18]. Nevertheless, the improved nocturnal ventilation with VtPS did not offer any other health-related quality of life benefits [18].

In our opinion, this ventilation mode can be attempted in patients who continued to have hypoventilation despite adequate BPAP therapy. The suggested settings for VtPS include [19]:

1. Set the target V_T to approximately 7–8 mL/kg of ideal body weight or 110% of the demonstrated V_T when the patient is ventilated with ST mode and then modify settings according to the patient's response and tolerance.
2. Dial IPAP limits to a maximum of 30 cmH_2O and a minimum of EPAP + 4 cmH_2O (use auto-EPAP if available).
3. Set the respiratory rate to achieve adequate ventilation. It is advised to set a rate 2–3 breaths per minute below the resting respiratory rate.
4. Set the inspiratory time between 30–40% for control breaths if the patient has no COPD or asthma. A shortened inspiratory time of 25–30% is recommended if the patient has a small airway obstruction.
5. Adjust the above according to the response and tolerance of the patient.

25.4 Conclusion

A broader range of PAP device modes uses different algorithms, and ancillary features have been developed, allowing the treating therapist to choose suitable and more tolerable algorithms. The different algorithms and techniques allow therapists to choose the mode of therapy that best meets the patient's ventilatory requirements. Nevertheless, to achieve this goal, therapists need to understand the principles, mechanisms, indications, and contraindications of each ventilatory mode. In addition, automatically adjusting ventilatory modes may help optimize therapy in patients with complex sleep breathing abnormalities. Nonetheless, it must also be recognized that robust evidence displaying these newer modes of ventilation provide more significant clinical benefits than fixed pressure modes are lacking, and more research is needed to establish their roles and identify patients who may benefit from applying these new technologies.

New technologies also increase our chances for continuous long-term and remote monitoring of a patient's response to and acceptance of therapy [20]. It should always be remembered that new developments in technology and algorithms of ventilatory modes are an excellent addition to our arsenal of therapeutic options; nevertheless, they should not replace clinical assessment and judgment.

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Devices for CPAP in OSA

26

Ahmet Cemal Pazarli and Handan Inönü Köseoğlu

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26.1 Introduction

Positive airway pressure (PAP) therapy used in sleep apnea patients is called PAP therapy, and the machines used in this treatment are also called PAP devices. Treatment with PAP devices is the most commonly used and most effective treatment method in obstructive sleep apnea (OSA). Millions of sleep apnea patients worldwide have been using these devices during sleep for more than 40 years. PAP devices must be used every night while sleeping. It is very important for sleep apnea patients to understand this because some patients think that they will get rid of the disease after using it for 3–5 months. However, sleep apnea syndrome does not disappear with PAP treatment, only the day and night symptoms related to sleep apnea improve. Considering that these devices will be used for a lifetime, it is

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_26

extremely important to choose a PAP device suitable for the type and degree of sleep apnea disease. The CPAP device is the first of the PAP devices to be produced, and it is the most commonly used device in the treatment of sleep-disordered breathing (in patients with uncomplicated (without additional respiratory problems, etc.) sleep apnea). Later, the BPAP device was produced, which is often applied to people with additional respiratory diseases (asthma, COPD, restrictive lung diseases, etc.) or those who cannot tolerate CPAP. Auto-CPAP and other "auto" titled devices, as the name suggests, make pressure changes "according to the need/situation". It can be preferred especially in positional (supine) and REM-dependent sleep apnea patients. BPAP-ST – Servo ventilator and AVAPS devices basically work with BPAP logic. In patients with central apnea/Cheyne stokes breathing or obesity-hypoventilation, try other modes if one mode fails. Because the compliance of the device (the patient's compatibility with using the device) is the most important parameter, device companies add some features to their existing devices every year (Flex/EPR/SoftPAP/SensAwake/Check Mode) aimed to increase device compliance. These features are to ensure that the patient's breathing is as natural as possible and to increase the duration of use by not disturbing the patient. Sometimes a simple "ramp" feature or "heater humidifier" feature improves patient compliance with the PAP device. This chapter aims to discuss the features of PAP devices used in sleep apnea.

The purpose of all PAP techniques used in the treatment of sleep breathing disorders is to keep the upper respiratory tract (URI) open during sleep, to regulate respiration and sleep quality. PAP treatments do not have a completely curative effect on the disease, as the devices have no effect on the muscles of the URI and only act as a "healing device" as long as they are used [1, 2]. The generally accepted principle in this regard is that the patient uses their device >70% and that it is used for >4 h per night [3].

The main noninvasive mechanics used in the treatment of PAP ventilator types:

I. CPAP
II. Auto-CPAP (APAP)
III. BPAP
IV. BPAP-ST
V. AUTO-BPAP
VI. AVAPS
VII. ADAPTIVE SERVO VENTILATOR (ASV)

26.2 CPAP (Continuous positive airway pressure)

CPAP, the first of the positive airway pressure treatment techniques, is a standard, effective, and safe treatment for OSA [4]. The CPAP device, which was first described by Sullivan et al. in 1981, is widely used today [5]. It is a curative treatment device that transmits the room air to the patient at the desired pressure through a low-resistance hose and mask, can give continuous positive pressure thanks to its

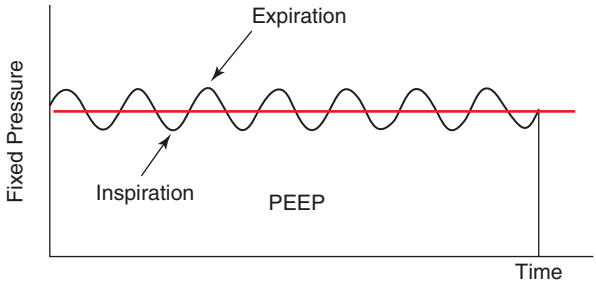

Fig. 26.1 Working principle CPAP

high-speed motor, and thus manages to keep the patient's upper respiratory tract open (pneumatic splint). The device adjusts the airflow pressure to keep the set pressure constant during inspiration and expiration (Fig. 26.1). It is generally produced as adjustable in the pressure range of 4–20 cmH_2O. Pressure titration can be started with 4 cmH_2O and increased to a maximum of 15 cmH_2O. The devices include the motherboard, pressure sensors, motor, pipes that provide air transmission, and filters that clean the air. In addition, there are sponge blocks that make it quieter while the device is operating. All electronics of the device are connected to the motherboard. Recommended usage parameters are saved in the memory on the motherboard. Thus, the device applies therapy pressure in accordance with the recorded respiratory parameters. This pressure is created by the engine with the air taken from the outside environment and transmitted to the patient. The air taken from the outside to the device and then delivered to the patient is filtered and purified from harmful particles. This is important both for the patient not to be exposed to polluted air and for the device to have a longer life. The pressure of the air created by the engine is measured by sensors before it is sent to the patient and the appropriate treatment pressure is applied. In addition, some devices can also measure the vibrations of the air transmitted to the patient through these sensors and thus analyze different respiratory-related parameters. Some features have been added to CPAP devices to increase patient compliance. These features, which aim to adapt to the patient's natural respiratory cycle, aim to make the patient's transition between inspiration and expiration softer, and to reduce the expiratory load [6]. Flex and EPR (expiratory pressure relief) features are some of them.

26.3 Auto-CPAP (APAP)

Usually, automatic positive airway pressure (APAP) devices work on the principle of increasing and decreasing pressure according to changes in airflow amplitude, airflow limitations, presence of snoring (vibration), and/or changes in airway impedance [7] (Fig. 26.2). APAP devices are frequently used in patients with positional or REM-related OSA and those who cannot tolerate a constant pressure CPAP device. The pressure application range of the device is between the preset initial lower limit and the maximum upper limit. Pressure is automatically increased when apnea and

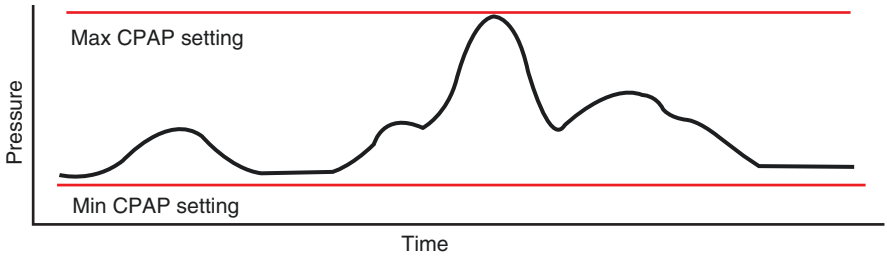

Fig. 26.2 Working principle auto-CPAP (APAP)

related findings occur in the upper airway and lowered when there is no apnea for a while. Pressure requirement may change in situations such as sleep stage, body position, use of alcohol and sedatives, and weight gain. In such cases, the patient's pressure requirement can be increased or decreased by APAP devices, but failure to distinguish between mask leaks or mouth air leakage and central/obstructive apnea may result in incorrect titration of these devices [8]. There is no clear data to suggest that APAPs are superior to conventional CPAP in terms of efficacy and compliance. In four meta-analyses on this subject, no difference was found between fixed-pressure CPAP and APAP in reducing AHI. Adjustment to the device and improvement in daytime sleepiness were found to be minimally more significant in APAP users compared to CPAP users [9–12]. APAP is not recommended in cases such as central apnea, obesity-hypoventilation syndrome, active cardiovascular disease, neuromuscular disease, chest deformity, and after uvulopalato pharyngoplasty operation.

26.4 BPAP (Bilevel Positive Airway Pressure)

It is not the first choice in the treatment of Obstructive Sleep Apnea Syndrome; however, it may be the first choice for those who cannot tolerate CPAP therapy, have difficulty in exhaling against high pressure, and have a disease that causes alveolar hypoventilation in addition. The most important difference of the BPAP device from the CPAP working principle is the delivery of air at different pressures during inspiration and expiration throughout the respiratory cycle (Fig. 26.3). The aim is to increase the patient's tolerance to positive pressure and to increase the compliance of using the device. Suggesting BPAP treatment in case the required CPAP pressure is 13 cmH_2O or higher facilitates the patient's compliance with the treatment. With BPAP treatment, the patient's upper respiratory tract remains open, and it also provides ventilatory support as well as the difference (delta pressure) between IPAP and EPAP pressures. BPAP devices reduce respiratory workload, allow respiratory muscles to rest, open microatelectasis, improve compliance, and solve the problem of central muscle weakness by lowering the hypercapnic threshold of the respiratory center. In most studies, in uncomplicated OSAS patients (additionally restrictive or obstructive pulmonary pathology, hypoxemia-hypoventilation syndromes, etc.) no

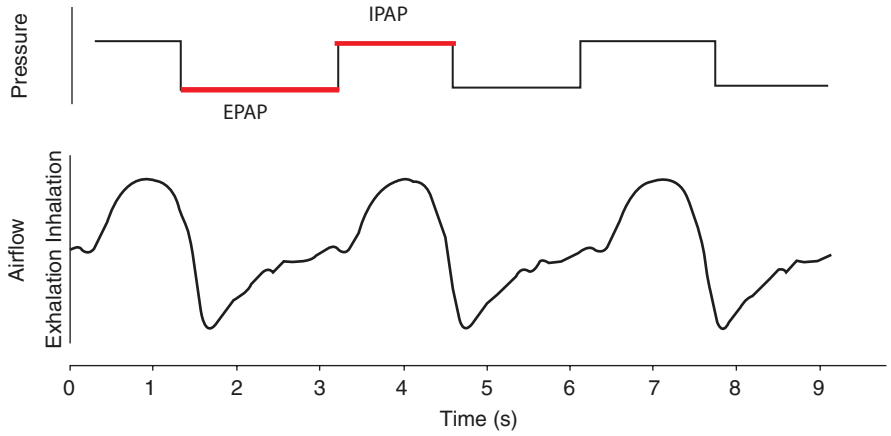

Fig. 26.3 Working principle BPAP (bilevel positive airway pressure). *EPAP* expiratory positive airway pressure, *IPAP* inspiratory positive airway pressure

different effects from the CPAP device were observed [13–15]. New versions have been added to the BPAP modalities. One of them is the "Biflex" feature. In Biflex mode, pressure transitions are softer at the end of inspiration and at the beginning of expiration, and the adjusted IPAP-EPAP pressures can change in accordance with the patient's respiratory effort. Newly developed BPAP devices also have the possibility to adjust the duration and rate of inspiration and expiration. In BPAP titration, it is recommended to set the initial pressure as IPAP: 8 cmH_2O and EPAP as 4 cmH_2O, and the IPAP-EPAP difference to be minimum 4 cmH_2O and maximum 10 cmH_2O [16]. The inspiration-EPAP differential works like a pressure support (PS) mode that supports the patient's tidal volume.

26.5 BPAP-ST

It includes the ST = spontaneous-timed feature. The patient should be breathing spontaneously, but the respiratory frequency number should be adjustable by the device. The BPAP-ST device should be tried in patients whose breathing is not regulated by BPAP, where higher pressure treatment is required, and especially in the presence of central apneas. In BPAP-ST mode, the device is adjusted according to the patient's respiratory frequency per minute, and if the patient cannot provide the trigger that will increase the EPAP value to the IPAP value due to central apneas or respiratory failure, the device triggers. It changes from EPAP pressure to IPAP pressure. With this pressure change, both respiratory support is provided and central apnea is terminated. In addition to the diagnosis of obstructive sleep apnea syndrome, it is indicated for use in patients with a pathology that causes alveolar hypoventilation such as restrictive lung disease, COPD, obesity-hypoventilation syndrome, sleep-related hypoventilation/hypoxemic syndrome [17, 18].

26.6 AUTO-BPAP

Its superiority over other PAP techniques has not been proven yet, but it is considered appropriate to use because there is an indication for BPAP and the applied BPAP pressure cannot be tolerated or the appropriate treatment pressure cannot be decided because the effective BPAP pressure is very variable [19] . A-BPAP devices are variable pressure devices. It is a mix of APAP and BPAP devices. It not only detects respiratory events such as apnea, hypopnea, flow restriction, and snoring but also makes pressure changes, and also detects inspiration and expiration periods.

26.7 AVAPS (Average Volume Assured Pressure Support)

Average volume assuring pressure support (Average Volume-Assured Pressure Support AVAPSTM, Philips Respironics) mode is a newly developed combined NIPPV mode that provides constant tidal volume in addition to the pressure support mode [20]. The results obtained from its use in the treatment of COPD, thoracic cage diseases, neuromuscular diseases and obesity-hypoventilation syndrome, especially with hypercapnia, are quite successful. It provides automatically varying pressure support (IPAP) to provide the patient with a constant tidal volume. That is, the actual IPAP fluctuates between IPAP max and IPAP min to provide the targeted adequate tidal volume (Fig. 26.4). It calculates the tidal volume with each breath of the patient and adjusts the pressure to maintain the balance between minute ventilation, mean tidal volume, and target tidal volume. Target tidal volume calculation is the ideal weight. Weight is calculated over 8 mL/kg or determined as 110% of

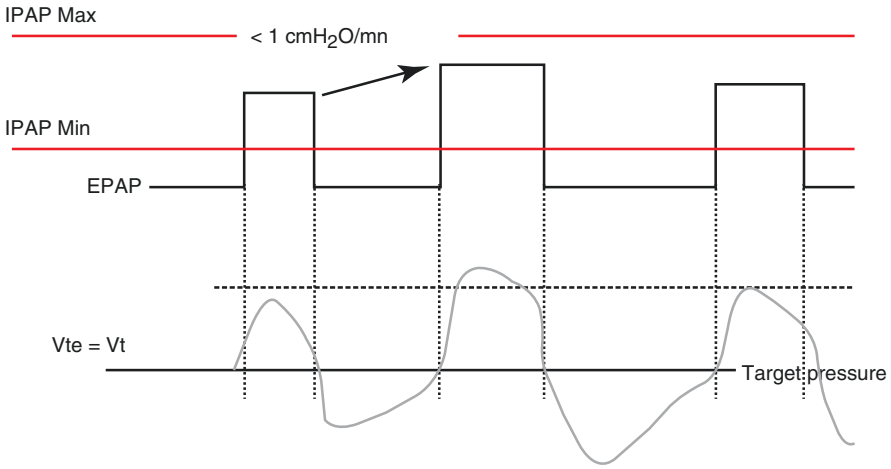

Fig. 26.4 AVAPS: Automatically adapts IPAP pressure to achieve guaranteed ventilation support. *EPAP* expiratory positive airway pressure, *IPAP* inspiratory positive airway pressure, *Vte* exhaled tidal volume, *Vt* tidal volume

awake tidal volume [18]. If the patient's tidal volume changes with position and sleep stages, it is necessary to use AVAPS-enabled BPAP devices to maintain a constant ideal tidal volume. In summary, it is a system that automatically adjusts the pressure to ensure that the patient has a good average ventilation.

26.8 ASV (Adaptive Servo Ventilator)

ASV is a noninvasive ventilatory treatment option created specifically for the treatment of adults who have obstructive sleep apnea and central and/or complex sleep apnea. It is one of the PAP units that continuously monitors and adjust to correct the patient's breathing problem. ASV is similar to the CPAP therapy used to treat obstructive sleep apnea, but there are important differences. The most important working principle of the ASV is to adjust the pressure according to the input from the patient. That is, the goal is not a fixed value, but rather the adaptation to the breathing pattern of the patient (Fig. 26.5). As the device constantly adjusts itself to meet the patient's needs, the pressure changes of the machine make the patient feel comfortable, completely avoiding the discomfort often reported by PAP patients. It prevents the formation of unnecessary idiopathic central apneas by keeping the variable pressure requirement of the patient at minimum pressures by making continuous adjustments. While necessary pressure support is increased in apneas and hypopneas, this support is decreased in case of hyperventilation. While the patient's breathing is stable, the ASV provides enough pressure support to reduce the patient's work of breathing by approximately 50%, making therapy much more comfortable for the patient. ASV-related findings, which are widely recommended as second-line PAP therapy in ejection fraction (EF) <45% heart failure (HF) central sleep

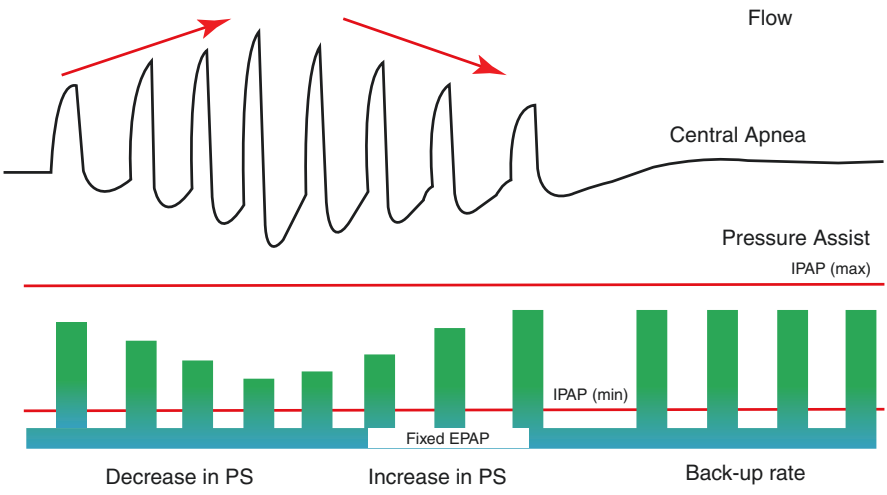

Fig. 26.5 Working principle ASV mode. *EPAP* expiratory positive airway pressure, *IPAP* inspiratory positive airway pressure, *PS* pressure support

apnea/Cheyne–Stokes respiration (CSA/CSR) patients who could not tolerate CPAP, especially until 2015, have completely changed with the results of the SERVE-HF [21] study and updated clinical practice, and entered the guidelines in American academy of sleep medicine (AASM) 2016 [22].

26.9 Conclusion

PAP therapy remains the most effective treatment for OSA patients. It is necessary to know that the selection of the device is important for the effective treatment of OSA. The CPAP device should be considered as the first option in treatment. In the case of pressure intolerance or comorbidities, BPAP may be preferred. APAP devices can be preferred when positional and REM-dependent OSAS is detected. The most critical device selection in CPAP treatment includes that APAP should not be used in patients with central sleep apnea syndrome, UPPP operation, and hypoventilation.

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Transnasal Insufflation: A New Approach to Treat Obstructive Sleep Apnea

27

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27.1 Introduction

Obstructive sleep apnea (OSA) is a common chronic disorder characterized by repetitive episodes of complete or partial collapse of the upper airway (mainly the oropharyngeal tract) during sleep. The consequent cessation/reduction of the airflow causes a progressive asphyxia that increasingly stimulates breathing efforts against the collapsed airway, typically until the person is awakened [1]. OSA is associated with a high incidence of cardiovascular and metabolic diseases and a high mortality rate. Continuous positive airway pressure (CPAP), available since the beginning of the 1980s, provides the most effective and commonly used treatment

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_27

for patients with OSA [2]. CPAP functions as a pneumatic support that allows maintaining upper airway patency by increasing the upper airway pressure above a "critical" value (pressure value below which the airways collapse). The device is applied to the patient, through a nasal or oronasal mask, overnight or during sleep hours at a set positive pressure. CPAP is extremely effective in controlling symptoms and preventing OSA-related morbidity and mortality [2]. However, it is important to note that the efficacy of CPAP strictly depends on its constant use and that a recurrence of symptoms occurs after 1–3 days from treatment interruption. Therefore, in the absence of any other intervention, CPAP will represent a lifetime treatment. In addition, not all patients with OSA tolerate CPAP due to some side effects. These include discomfort when breathing through a mask with a positive pressure applied, nasal congestion, dry mouth and eyes, skin irritation due to the mask contact, and claustrophobia. These side effects may significantly reduce adherence to the treatment, estimated around 50–60% [2]. Due to the problems with adherence, in the past few decades a number of alternative options to manage OSA have been under evaluation.

27.1.1 Transnasal Insufflation and High Flow Nasal Cannula

Transnasal insufflation (TNI), consists of an open nasal cannula system delivering warm and humidified air. The term high-flow nasal cannula (HFNC) refers to those devices first designed to provide oxygen at high flows, with an optimal degree of heat and humidification (Fig. 27.1). This device was first intended to treat acute

Fig. 27.1 Basic elements of nasal high flow therapy

hypoxemic respiratory failure in the acute setting [3]. In the past 10 years, HFNC devices have gained great attention and have been extensively used in all clinical settings, being well tolerated by the patients and easy to use for all physicians. Transnasal insufflation of high flows has important physiological effects in the airways and the lungs. These include (1) reduction of the anatomical dead space; (2) improvement in carbon dioxide (CO_2) wash-out; (3) reduction in the work of breathing; (4) generation of a positive end-expiratory pressure; (5) maintenance of a constant fraction of inspired oxygen. Through these mechanisms, HFNC effectively reduces dyspnea and improves oxygenation in respiratory failure from a variety of etiologies, thus avoiding escalation to more invasive supports.

In recent years, HFNC has been adopted to treat de novo hypoxemic respiratory failure, exacerbation of chronic obstructive pulmonary disease (COPD), post-intubation hypoxemia, and for palliative respiratory care [3]. In the past few years, the use of HFNC in acute respiratory failure has become routine not only as an alternative to conventional oxygen treatment but also to noninvasive mechanical ventilation (NIV).

The technique has the advantage of being more effective than low-flow oxygen and better tolerated than NIV. In addition, the results of recent clinical trials confirm the noninferiority of HFNC compared to NIV in selected patients. Outside the acute setting, new potential applications in patients with chronic respiratory diseases such as COPD or bronchiectasis are currently under evaluation [3].

27.1.2 Brief Description of the Device

The HFNC device is an open-circuit system consisting of a flow generator (air/oxygen blender, turbine, or Venturi mask), an active heated humidifier and a single heated noncondensing circuit. The circuit is connected to a silicone nasal cannula of different sizes to fit the patient's nostrils. The original device, intended to be used in environments of high-level healthcare, needed to be connected to a source of oxygen and a source of high-pressure air in order to generate flows. New devices have been produced that can be used at home, as high flows can be generated by turbines and can reach flows up to 60 L/min (Fig. 27.1). Parameters that can be set include the flow/minute, fraction of inspired oxygen (FiO_2), and temperature. In the currently available devices, the flow of gas can be regulated generally from 20 up to 60 L/min (depending on the device), whereas the FiO_2 can be regulated up to 60% or 100%, again depending on the device. The recommended temperature is 37 °C to warrant a content of 44 mg H_2O/L, which is 100% relative humidity [4]. Similar to CPAP, HFNC can generate pressure (although smaller) in the airways and, as mentioned before, the treatment exerts its benefits on the respiratory system by a number of different physiological mechanisms. Some of them have been extensively explored, but others still remain unclear. The most striking difference between CPAP and HFNC is the interface. CPAP is a closed circuit where the gas is delivered to the patients using a fitted nasal or facial mask. When using HFNC, air or air/oxygen is delivered through a nasal cannula, which provides an open system.

Indeed, the open interface of HFNC is better tolerated than a CPAP mask for overnight use [5].

27.1.3 Physiological Effect of Transnasal Insufflation in Upper Airway Patency

In patients with OSA the upper airway obstruction is due to increased pharyngeal collapsibility, which decreases inspiratory flow. Physiological studies have shown that an inflow stream may reopen the constricted and obstructed upper airway of these patients increasing nasopharyngeal pressure, thus alleviating obstructive events. Minimally invasive intrusive methods for delivering low levels of air pressure may be remarkably effective in treating hypopneas [6].

The generation of a positive end-expiratory pressure (PEEP) is an important effect of HFNC. Although this is an open system (while NIV is a closed system), the high flows produced are sufficient to prevail against the expiratory flow and generate a small positive pressure. If the patient is breathing with a closed mouth, so that there is little escape of gas, the pressure measured at the nasopharynx increases with increasing flows. Theoretically, an air flow of 10 L/min can generate approximately 1 cm H_2O of positive airway pressure. However, with a maximum flow of 60 L/min, the pharyngeal pressure usually ranges from 3 to 5 cm H_2O. It has also been reported that the pharyngeal pressure produced by high flows are affected by sex and body mass index. Also, age is important as differences have been shown between adults and children. A recent study has shown that in children airway replicas at a flow rate of 20 L/min generates a PEEP similar to CPAP set at 5 cm [5]. It has been hypothesized that the intraluminal pressure generated by high flows can overcome pharyngeal critical pressure, so that HFNC may be a possible candidate for treatment of OSA. In fact, there is evidence that the number of obstructive events is reduced by the application of transnasal high flows. Since the positive airway pressure generated by HFNC is small, some authors proposed additional mechanisms leading to a reduction in obstructive events. It has been suggested that the slight increase in pharyngeal pressure achieved with high flows increases lung volumes, leading to a stabilization of upper airways patency through genioglossus muscle activation [7]. Indeed, the physiological effects of HFNC are not fully understood.

27.2 Clinical Evidence on the Role of Transnasal Insufflation in the Management of Obstructive Sleep Apnea

27.2.1 Children

High flow nasal cannula was first designated as a respiratory support for neonates and infants with respiratory failure, particularly from respiratory distress syndrome and bronchiolitis. In neonates with respiratory distress syndrome, the system has

been shown to be at least as effective as nasal CPAP in decreasing the work of breathing and reducing respiratory rate [8].

In recent years, the technique has also been considered for the treatment of children with OSA. The standard treatment for OSA in children is adenoidectomy and/or tonsillectomy when indicated. In all other cases, CPAP is recommended by the guidelines. Unfortunately, many children, particularly those with developmental delay, cannot tolerate the mask required for delivering CPAP. Many attempts to improve tolerability and adherence to CPAP therapy have proven ineffective. A number of studies have shown that the application of nocturnal HFNC in children intolerant to CPAP improves symptoms and reduces apnea-hypopnea index (AHI), even in more severe cases (AHI > 15) [9]. In addition, in children, HFNC also reduces the number of arousals, improving the quality of sleep [10]. The compliance seems to be quite good compared to CPAP. In a small group of children with Down syndrome, HFNC produced a reduction in AHI and was well tolerated by 62% of the patients [7]. This data is particularly relevant as the management of these patients, who consistently develop OSA due to upper airway and tongue conformation, is particularly challenging for the clinician. One study reported that HFNC was also effective in infants with severe obstructive apnea, reducing the average AHI from 26 to 2. After the first application, the treatment was well tolerated at home, and the most common treatment complication was cannula dislodgement [11]. Less common side effects included skin irritation, dry mucus membranes, restlessness, oxygen desaturation, and increased central apneas. It is important to note that, differently from adults, children tend to manifest hypopnea-predominant OSA that is more easily corrected by HFNC. Interestingly, some laboratories have also proposed titration protocols for HFNC. In one study, high-flow humidified room air was delivered via device at an initial flow of 5 or 15 L/min for pediatric or adult-sized cannula, respectively, and was then titrated gradually in 5 or 15 L/min increments, respectively, based on symptoms of snoring, labored respirations, and oxygen desaturations [12].

HFNC is generally better tolerated than CPAP in children not only because it is an open system but also because the warm humidified air decreases the sensation of flow in the patients' nose. The possibility of avoiding a tight fitted mask in children is important. In fact, in developmental stages, the chronic use of CPAP has been associated with hindered development of the face due to constant mask use. Without a doubt, using a nasal cannula may avoid this issue [5]. Taken together, these data suggest that the use of HFNC deserves further exploration as a treatment alternative to CPAP in infants and school-age children. Reasons for putative HFNC recommendation include poor surgical candidacy, residual OSA following surgery, and CPAP intolerance.

27.2.2 Adults

Although to a lesser extent compared to children, treatment with CPAP in adults may be uncomfortable and although a variety of educational strategies have been

implemented to increase adherence to the treatment, compliance has remained stable over the past three decades. On average, a continuous and correct use of the device has been reported in around 50–60% of the patients.

The first studies adopting TNI to treat obstructive events in adults were performed using a flow of 20 L/min. The first study on adults with OSA was published in 2007 and included 11 patients with mild to severe OSA [13]. The device consisted of a modified air compressor coupled to a humidifier that was able to generate a maximum flow rate of 20 L/min with a temperature of 31–33 °C. They showed that an airflow of 20 L/min improved the AHI, which changed from average 28 to 10, and reduced the number of arousals/hour from 18 to 8, thus improving sleep quality. In the same study, to explore the mechanisms responsible for the effect of TNI on obstructive events, the inspiratory airflow, end-expiratory supraglottic pressure, and respiratory effort were assessed. Findings show that after the insufflation was initiated, an instantaneous increase in end-expiratory supraglottic pressure and inspiratory flow occurred [13]. As this was a pilot physiological study, none of the patients were subsequently treated with TNI, and therefore no data about adherence to treatment were available. In one larger study published successively, TNI (20 L/min) was applied during the night to 56 patients with a wide spectrum of OSA severity and standard sleep studies were performed. In the study, a therapeutic response was defined as a reduction of the respiratory disturbance index (RDI) below 10 events/h associated with a 50% reduction of the event rate from baseline and was used to identify subgroups of patients particularly responsive or resistant to TNI treatment [14]. The authors found that TNI decreased the RDI from 22 to 17 and a therapeutic response was observed in 27% of patients. Treatment responses were similar in patients with a low and a high RDI, but were greater in patients who predominantly had obstructive hypopneas or respiratory effort-related arousals and in patients who predominantly had rapid eye movement (REM) events. The presence of a high percentage of obstructive and central apneas seemed to preclude efficacious treatment responses. The authors therefore concluded that TNI can be used to treat subgroups of patients, particularly if their sleep-disordered breathing events predominantly consist of obstructive hypopneas or REM-related events [14]. Of note, in the study, the level of prescribed CPAP pressure did not predict the efficacy of TNI. Central apneas may develop during TNI, similarly to CPAP treatment. It has been proposed that the high flow exaggerates the ventilatory overshoot and insufflation of air into the nose, washing out the anatomic dead space and reducing CO_2 rebreathing, thereby contributing to the occurrence of central apneas. A higher ventilatory overshoot may be present more frequently in the supine position, which can also contribute to central apnea. Successively to these first reports, HFNC devices for transnasal insufflation have been commercialized with the advantage of delivering higher flows up to 60 L/min and the possibility to be used at home, as flows are generated by small turbines. Consequently, other studies have tried to evaluate the role of HFNC as an alternative to CPAP.

One recent prospective study compared the therapeutic effects of HFNC to CPAP in patients with OSA. Full polysomnography was performed so that respiratory parameters and sleep quality were evaluated. HFNC was titrated similarly to CPAP [15]. The initial flow rate was set at 20 L/min. After the patients fell asleep, the flow rate was increased by 10 L/min up to a maximum of 60 L/min to try to eliminate apneas, hypopneas, and desaturation in the supine position or REM sleep. HFNC therapy significantly reduced AHI from 34.9 to 14.8 events/h in the total recording period at median optimal flow rate of HFNC 60 (40–60) L/min. HFNC also significantly improved snoring indices and significantly increased the minimal SpO_2. HFNC could not improve sleep efficiency and total sleep time, but the respiratory arousal numbers showed a marked reduction. Again, HFNC increased central apneas, mainly in the supine position and NREM sleep. As expected, CPAP demonstrated a more favorable effect for respiratory events and sleep efficiency [15]. Moreover, the complaints from the patients regarding loud noise, nasal stuffiness, and discomfort due to airflow pressure and temperature were significantly higher for HFNC therapy and also influenced sleep quality.

Another study was designed to evaluate the effect and the short-term tolerability of HFNC to treat obstructive apnea in patients with post-acute ischemic stroke and nasogastric intubation. In fact, nasogastric tubes used for dysphagic patients with stroke may preclude the use of CPAP due to air leakage from the mask. It was found that HFNC at a flow rate up to 50–60 L/min significantly decreased the apnea-hypopnea index from 52 to 26 events/hour and the total arousal index from 34 to 15 and significantly improved SaO_2. The authors concluded that, as the treatment was also well tolerated, HFNC might be considered a temporary treatment option for OSA until dysphagia improves and the nasogastric tube is removed [16].

27.3 Summary

CPAP is the gold standard treatment for OSA; however, some patients scarcely tolerate the device and compliance with the treatment is often unsatisfactory; therefore, other treatment options have been explored in the past decades. Currently, a number of studies suggest that transnasal insufflations is an effective alternative to CPAP to manage OSA in infants and school-aged children, as this significantly decreases respiratory events and is better tolerated than CPAP in the majority of patients. Nasal insufflation of high-flow heated and humidified air might be an option in children with chronic disabilities (e.g., Down syndrome) those with poor surgical candidacy, residual OSA following surgery, and CPAP intolerance. The few studies available in adults have inconsistent results. These studies indicate that generally the application of HFNC at flow rates up to 50–60 L/min decreases the number of respiratory events, particularly hypopneas, and the number of respiratory-related arousals, remaining however inferior to CPAP. HFNC use has been suggested for subsets of patients, such as those symptomatic with mild OSA or with prevalent hypopneic events, who are intolerant to CPAP. It is important to note that the studies available have been designed to assess the physiological effect

of HFNC on respiratory events and sleep quality, while long-term studies on clinical outcomes are lacking. Currently, there is no evidence to recommend the use of transnasal insufflation as an alternative to CPAP to treat patients with OSA.

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Noninvasive Ventilation in Patients with Obesity Hypoventilation Syndrome

28

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28.1 Introduction

Hypoventilation is the abnormal gas exchange due to inadequate alveolar ventilation and is attributed to many pathological conditions. Obesity is related to many health problems such as obesity hypoventilation syndrome (OHS).

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_28

Worldwide the prevalence of obesity continues to increase. This phenomenon is more pronounced in the United States, where a quick, fourfold increase in the prevalence of BMI > 40 kg/m^2 was recorded from 1986 to 2000 [1]. As obesity becomes a rapidly expanding global epidemic, it is obvious that the prevalence of OHS is about to increase. In the general population the actual prevalence of OHS is unknown. Mokhlesi has stated that 0.15–0.3% of the adult population in the United States are likely to have OHS based on rates of obesity and obstructive sleep apnea (OSA) in the community (approximately 3% of the general population in the USA is morbidly obese with BMI >40 kg/m^2, half of these individuals may have OSA and 10–20% of the morbidly obese patients with OSA would have OHS [2].

In several retrospective studies, it has been observed that the prevalence of OHS in patients with OSA with a BMI of 30–35 kg/m^2 was 8–12%, and it was even higher in those with a BMI ≥40 kg/m^2 (18–31%) or those with a BMI ≥50 kg/m^2 (50%) [3, 4]. In East Asian populations, OHS is observed in patients with a lower BMI than in non-Asian populations [5].

The mortality rate in patients with OHS is very high due to many comorbidities such as left heart failure, cor pulmonale, and acute hypercapnic respiratory failure that leads to hospital admission. Therefore, clearly early diagnosis of the syndrome must be reached, before the patient needs hospitalization. Many times, these patients are misdiagnosed, even when they are hospitalized for acute respiratory failure [6].

28.2 Diagnosis and Clinical Presentation

The two most common clinical manifestations are acute-on-chronic hypercapnic respiratory failure and need for hospitalization or evaluation of symptoms such as breathlessness and somnolence by specialists (pulmonologists, sleep medicine doctors) in an out-patient form.

The diagnosis is based on the combination of a body mass index (BMI) ≥ 30 kg/m^2, daytime hypercapnia ($PaCO_2$ ≥ 45 mmHg), sleep-disordered breathing, and after excluding all the other reasons for daytime hypercapnia such as central, pulmonary, neuromuscular, metabolic, or chest wall disease [7]. Therefore, it is essential to perform further examinations such as chest X-ray, spirometry, electrocardiography, and assessment of MIP (maximum inspiratory pressure) and MEP (maximum expiratory pressure) to exclude other diseases related to nocturnal hypoventilation and daytime hypercapnia. Other complementary diagnostic criteria are serum bicarbonate level > 27 mEq/L and hypoxemia during wakefulness as it is measured by pulse oximetry (SpO_2 < 93%). According to ATS guidelines, in case of a low probability of OHS (<20%), the level of serum bicarbonate should be measured first, and if it is lower than 27 mmol/L, then it is not necessary to measure the $PaCO_2$ in arterial blood gases. Otherwise, $PaCO_2$ must be evaluated in order to confirm or exclude the diagnosis of OHS. In many cases of nocturnal hypoventilation, the level of serum bicarbonate increases before the patient presents daytime hypercapnia [8]. Approximately 90% of the patients with OHS also present OSA (obstructive sleep apnea) with AHI >5 events/h and 70% of them have severe OSA

(AHI ≥ 30). They often have symptoms such as fatigue, daytime sleepiness, snoring, and apneas. They also suffer from dyspnea due to hypoxemia and left heart failure [9]. The remaining 10% of patients with OHS have non-obstructive sleep hypoventilation (AHI <5). Continuous measurement of carbon dioxide levels during sleep by end tidal or transcutaneous monitoring is considered a reliable diagnostic method for sleep hypoventilation. The presence of OSA is not necessary to set the diagnosis of OHS [10].

Overnight polysomnography is required to determine the sleep disordered breathing pattern and individualize treatment.

The prevalence of OHS has been estimated to be approximately 0.4% in the adult population. Early diagnosis of OHS is essential because of the high morbidity and mortality that it presents in untreated patients [2].

28.3 Pathophysiology

Many parameters are related to the pathophysiology of OHS. The most significant seem to be the changes in pulmonary function and respiratory system due to obesity, impaired central respiratory drive, neurohormonal disorders, and sleep-disordered breathing.

28.3.1 Changes in Lung Function Secondary to Obesity

One parameter that affects the respiratory system in these patients are the changes that happen to the lung function due to obesity. The excessive fat that is deposited on the abdomen and the chest deteriorates the work of breathing and decreases the chest compliance. This leads to a significant reduction in lung volumes, such as functional residual capacity (FRC) and expiratory reserve volume (ERV) and a breathing pattern of lower tidal volume and higher frequency [11]. Moreover, the diaphragm's motion is cumbered because of the deposited fat, especially in the supine position. Respiratory muscles become weak because they are charged with greater load during breathing. In addition, gas trapping occurs since smaller airways close prematurely, which leads to an increase in intrinsic PEEP (auto- PEEP) and predisposes to ventilation/perfusion mismatch [12].

28.3.2 Sleep-Disordered Breathing and Impaired Central Respiratory Drive

The respiratory drive has to increase in obese patients so that the muscles can overcome the elevated respiratory work and patients remain eucapnic. In OHS, hypoventilation, initially during REM, occurs because the increased respiratory drive cannot be retained. Repetitive hypoventilation finally leads to impairment of respiratory drive and defective response to elevated levels of CO_2. Subsequently, CO_2 levels are increased during night and daytime hypercapnia [2].

28.3.3 Neurohormonal Disorders

Leptin is a hormone produced by adipose tissue and induces ventilation. In obese patients, the levels of leptin are elevated in order to stimulate the ventilation and eliminate the excessive CO_2. In OHS, there is a central resistance in leptin and thus a reduced respiratory drive that contributes to central hypoventilation [13].

28.4 Management of OHS

Since OHS is a severe, multisystemic syndrome, the approach to such patients should be conducted by many different specialists such as pulmonologists, cardiologists, sleep specialists, nutritionists, and bariatric surgeons. The main aim is to treat the SDB and the cardiovascular comorbidities.

The most common and widely accepted approach for the management of OHS is the appliance of PAP. There are many PAP treatments that can be applied. The most common is the Continuous Positive Airway Pressure (CPAP) and the Noninvasive Ventilation (NIV). The NIV models that are used are the pressure-support modes (BiPAP, Biphasic positive airway pressure with or without a backup respiratory rate) and the volume-controlled positive airway pressure (AVAPS, average volume-assured pressure support with backup respiratory rate). CPAP improves the upper-airway obstruction and the atelectasis that obese patients have, leading to improvement in lung volumes and reduction in $PaCO_2$. On the other hand, NIV increases the alveolar ventilation. According to the American Thoracic society, CPAP is the first step in the treatment of patients with OHS and concomitant severe OSA (AHI $\geq$ 30). When OSA does not coexist, the first treatment approach is NIV because, in this case, there are other underlying factors (nocturnal hypoventilation) that should be treated. PAP delivery in these patients is well proven to have a favorable effect in many ways [8].

1. It improves daytime and nocturnal hypercapnia and the gas exchange by relieving the respiratory muscles from the enhanced respiratory workload that they have to fulfill.
2. It modifies the sleep pattern, eliminates the nocturnal hypoventilation, treats the coexisting OSA, improves the percentage of TST with oxygen saturation <90%. Consequently, daytime sleepiness, fatigue, snoring, and dyspnea are eliminated to a great extent and the quality of life, as assessed by special questionnaires (FOSQ, SRI, SF36), is improved.
3. It prevents serious comorbidities such as cardiovascular diseases and left heart failure, when it is applied early. Moreover, mortality and morbidity are reduced.

28.4.1 CPAP (Continuous Positive Airway Pressure)

Considering the fact that the majority of patients suffer from severe obstructive sleep apnea [9, 14], CPAP seems to be a reasonable therapeutic choice in obesity hypoventilation syndrome. Because CPAP does not offer any direct ventilation benefits, NIV has regularly been the first choice and an ongoing debate has been taking place during the past years. One of the main reasons for this debate is the concern of cost, favoring CPAP, combined with the simpler implementation. The first reports of PAP treatment in OHS go back to 1983 in a small case series [15].

By resolving apneas, hypopneas and by stabilizing the upper airway, CPAP can reduce daytime $PaCO_2$ and improve respiratory failure. These benefits are well established in a number of observational and a few randomized clinical studies [9, 16, 17]. CPAP can also counterbalance iPEEP developed in obese patients and augmented in the supine position, as noted in one of the first studies conducted to identify neural respiratory drive in obesity. CPAP reduced inspiratory pressure swings by 25% and neural respiratory drive by 40% [18]. Apart from respiratory metrics, other favorable aspects of treatment with CPAP have been documented. After 3–6 months of CPAP use, there was an improvement in quality of life, assessed by the SF-36, and daytime sleepiness, objectively assessed by Epworth Sleepiness Scale [19]. In a large multicenter RCT, controlling the efficacy of CPAP, NIV and lifestyle modification as the control group, CPAP, apart from resolving daytime hypercapnia, improved sleep quality as well as quality of life. In this study, the difference in $PaCO_2$ in the CPAP group was more significant than in the control group, only after compliance adjustment [9]. This is also highlighted in other studies, where the magnitude of improvement of hypercapnia and PO_2 were directly related to adherence with PAP therapy [17, 20].

Switching from NIV (regularly introduced after a prior episode of hospitalization due to acute-on-chronic hypercapnic respiratory failure) to CPAP has been reported in 15 stable patients with OHS after 7 days of washout period. There were nonsignificant differences in mean AHI, gas exchange, and compliance [21].

Nevertheless, CPAP failure (severe persistent nocturnal desaturation during CPAP titration, decompensation of arterial blood gases exchange) is observed in a percentage of OHS patients. The risks of CPAP failure have not been yet elucidated. In an observational study with 29 newly diagnosed, clinically stable OHS patients, treatment failure at 3 months was correlated with the mean night-time SpO_2 during the first night of optimal CPAP titration and $PaCO_2$ at 1 month. CPAP failure was defined as daytime $PaCO_2 \geq 45$ mmHg, and/or oxygen saturation <90% over 30% of the night [22, 23]. Questions still remain concerning PAP titration strategies and parameters to be monitored. Ideally, titration should be guided by overnight respiratory monitoring and not empirically conducted.

28.4.2 Noninvasive Ventilation (NIV)

NIV is usually chosen when responding to previous CPAP treatment is inadequate or in cases where there is mainly nocturnal hypoventilation without severe OSA. It is often used in obese patients with acute decompensation of OHS who need admission to the hospital.

Many randomized control trials and observational studies have been published demonstrating the short- and long-term effects of NIV delivery in patients with OHS. In the Pickwick Randomized Controlled Trial, 96 patients with OHS without severe OSA were randomized in two groups and were observed regularly for 3 years. The first group received NIV, while the control group just modified their lifestyle.

Supplemental oxygen was added in both groups if needed. The primary outcome was the days of hospitalization and the secondary outcomes were mortality and utilization of other hospital resources. The long-term results between the two groups in hospitalization days, other hospital resource utilization, blood pressure, cardiovascular events, mortality, spirometry, and 6-min walk distance were the same. However, the patients that were allocated to the NIV group presented better results in arterial blood gas parameters ($PaCO_2$, HCO_3, and pH), quality of life (physical component of the SF36), and daytime sleepiness. $PaCO_2$ was reduced by 6 mmHg in the NIV group. In this study, the mortality rate was similar in the two groups but the cause of death was different in each group. In the NIV group the mortality was due to cardiovascular events while in the control group it was due to respiratory complications. NIV can reduce the acute respiratory failure in patients with OHS but without severe OSA [24].

In another randomized control trial, 86 participants without severe OSA (AHI <30) were allocated to an NIV intervention group and a life modification group, and they were observed for 2 months. The patients in the NIV group had larger improvement than the control group in $PaCO_2$ (−6 versus −2,8 mmHg, $p < 0.001$), serum bicarbonate (−3.4 versus −1 mmol/L, $p < 0.001$), AHI, nocturnal oxygenation, sleepiness, some health-related quality of life assessments. Moreover, the NIV group tended to use healthcare resources less after 2 months of follow up compared to the control group [25]. In the Pickwick study, in addition to the changes that were noted in the other studies, an improvement in forced vital capacity (FVC), forced expiratory volume in first second (FEV1), and in a 6-min walking distance was also observed in patients that were applied NIV treatment [9].

In a recent systematic review and meta-analysis, the efficacy of bi-level ventilatory support (BVS) in stable patients with OHS was appraised. Seven studies were included, t of which three compared bi-level support to lifestyle counseling (total $n = 264$, of which 130 patients received BVS), three compared BVS to CPAP (total $n = 247$, of which 118 with BVS), and two compared BVS delivery with AVAPS. One of the studies was included in two comparisons (BVS versus lifestyle counseling and BVS versus CPAP). The BVS delivery showed superiority in improving $PaCO_2$ (−2.90 mmHg; 95%CI 4.28–1.52), HCO_3 (−2.55 mmol/L; 95%CI 3.28–1.81), PaO_2 (2.89 mmHg; 95%CI 0.33–5.46), percentage of TST less than 90% (−30.55%;

95%CI 37.98–23.12), Epworth Sleepiness Scale (−2.52; 95%CI 4.16–0.88), and FOSQ (6.33; 95%CI 1.78–10.88) compared to lifestyle modification. However, there was no difference in any of the variables evaluated between BVS and CPAP or AVAPS. One important limitation of this study is the heterogeneity of the patients included, especially regarding the severity of OSA [26].

NIV also has a beneficial effect on the cardiovascular system of patients with OHS and seems to improve cardiac output, hemodynamics, left heart dysfunction, and pulmonary hypertension that often coexist in these patients [27, 28].

NIV can improve daytime hypercapnia, nocturnal desaturations and hypoxemia, serum bicarbonate, daytime somnolence, quality of life, symptoms such as breathlessness, and hemodynamic parameters when applied to patients with OHS.

28.4.3 AVAPS (Average Volume-Assured Pressure Support)

As previously stated, obese patients often present severe nocturnal hypoventilation, in the absence of obstructive respiratory events, attributed to the increased respiratory muscle workload and the impaired central respiratory drive. Bi-level pressure support ventilation mode may not be able to achieve the desirable ventilation and overcome the increased muscle load during sleep in such patients.

Thus, a ventilatory mode that provides a predefined volume and uses automated algorithms to adjust pressure support may be more suitable. Murphy et al. conducted a prospective, randomized controlled trial (50 patients, 4 drop-outs) to demonstrate advantages of an advanced PAP modality over conventional bi-level PAP. All patients underwent pulmonary functional tests, anthropometric and body composition measurements, arterial blood gases, assessment of health-related quality of life and daytime somnolence. They were randomly included in either a fixed bi-level PS group or AVAPS group with settings titrated to achieve adequate ventilation, and they were followed up for 3 months. The primary outcome was change in daytime hypercapnia and other outcomes appraised were body composition, physical activity, and health-related quality of life (SRI). There were significant within-group improvements in $PaCO_2$, HRQoL, daytime somnolence, oximetry, $tcCO_2$ and SRI between baseline and follow-up. However, there were no differences from baseline to follow-up in $PaCO_2$, gas exchange, anthropometric measures, spirometry, HRQoL or daytime sleepiness between the two groups. Improvement in daytime physical activity related to fat mass reduction was also observed in both groups [29].

In a recent study, average volume-assured pressure support-automated expiratory positive airway pressure (AVAPS-AE), a model that combines an automated positive expiratory pressure to a pressure support with a targeted tidal volume was compared to BiPAP S/T mode. After 2 months of use, sleep quality improved significantly without inter group difference (N3 and REM stage increased, arousal index decreased, signaling in sleep microstructure improved). Apart from those findings, blood gas exchange, sleepiness, and quality of life were equally positively improved in the two groups [30].

AVAPS may be a more compatible treatment modality since patients can synchronize to it more easily and in lower pressure support. However, BiPAP is noninferior to it regarding the effect in daytime hypercapnia, nocturnal hypoxemia, quality of life, and sleep.

28.5 CPAP or Noninvasive Ventilation for Obesity Hypoventilation Syndrome

In patients with OHS and severe OSA (AHI ≥ 30), CPAP is considered the first line therapy as already stated, due to its efficacy, simplicity, and lower cost. Previous RCTs failed to show a benefit of NIV over CPAP. However, sometimes CPAP delivery is not enough to improve hypoventilation and reverse the disturbed gas exchange.

Hospital admissions due to acute-on-chronic respiratory failure may also occur despite the use of CPAP. In these cases, BiPAP adjustment is considered to be more effective.

Many trials have been conducted to compare the effectiveness of CPAP versus NIV in patients with OHS. In a randomized controlled trial, 30 patients with OHS were allocated to CPAP, while 27 to BiPAP intervention for 3 months. The percentage of treatment failure was similar between groups (bi-level PAP 14.8% vs CPAP 13.3%, $p = 0.87$). There was no difference in treatment adherence and $PaCO_2$ in wakefulness after 3 months (5.3 h/night bi-level PAP, 5.0 h/night CPAP, $p = 0.62$; $PaCO_2$ 44.2 and 45.9 mmHg, respectively, $p = 0.60$). However, more patients treated with CPAP still had elevated $PaCO_2$ (>45 mm Hg) after 1 month, a difference not evident after 3 months. Finally, there was no significant difference in improvement in sleepiness (Epworth Sleepiness Scale) and HRQoL between the two groups.

Baseline $PaCO_2$ was the only significant predictor of persistent ventilatory failure at 3 months. It was noticed that those with a lower FEV1 and older had a higher risk for respiratory failure and those with more severe OSA had greater improvement of hypercapnia after 3-month treatment [31].

A systematic review of five studies addressed the short-term and long-term effect of NIV compared to CPAP in mortality, utilization of health resources, gas exchange, and HRQoL. Mortality, cardiovascular events, non-adherence to therapy, and healthcare resource utilization were similar in the two groups. Both CPAP and BiPAP delivery similarly improved awake hypercapnia and hypoxemia, need for supplemental oxygen therapy, daytime sleepiness, sleep quality, sleep-disordered breathing, quality of life and breathlessness.

The choice of the most suitable PAP delivery depends mainly on the phenotype of the patient. First, it is important to clarify if nocturnal hypoventilation dominates, or OSA also coexists. In the second case, the severity of OSA (AHI< or >30) should be taken into account.

Without a doubt, CPAP is less expensive than NIV, and less skill and training are required to apply it. As concluded in the study by Masa et al., based on post hoc within-trial cost-effectiveness analysis using the Pickwick study, CPAP was more cost-effective than NIV [32].

Therefore, according to recent evidence, CPAP is a more affordable treatment and should be the first choice in stable patients with OHS, severe OSA (AHI ≥ 30), and chronic hypercapnic respiratory failure [33] (Fig. 28.1).

28.6 Acute Respiratory Failure in (ARF) OHS

Acute decompensation of OHS is a life-threatening complication that represents 8–31% of ICU admissions [34, 35]. The use of NIV in acute respiratory failure attributed to OHS has been a standard clinical practice, although no related RCTs have been conducted [36]. As first demonstrated by Carillo et al., ARF of OHS can be effectively treated with NIV leading to similar or even better short- and long-term outcomes compared to COPD-related ARF [37]. In case of ARF in OHS, the underlying cause should be carefully evaluated and managed, since this is essential for NIV success.

In a retrospective study including 76 patients, where NIV treatment failed in 13, NIV failure was mainly associated with pneumonia, high severity scores, and low HCO_3 level on admission. There was a successful response to NIV in cases of idiopathic decompensation of OHS and elevated $PaCO_2$ and HCO_3 on admission. Also of note, in the NIV success group ($n = 63$), 33 patients (53%) experienced a delayed response with sustained hypercapnic acidosis [38]. In another retrospective cohort of OHS patients, admitted in the ICU, NIV was used as first-line ventilatory support in 36 patients (97.2%) and was successful in 33 patients (91.7%). NIV was

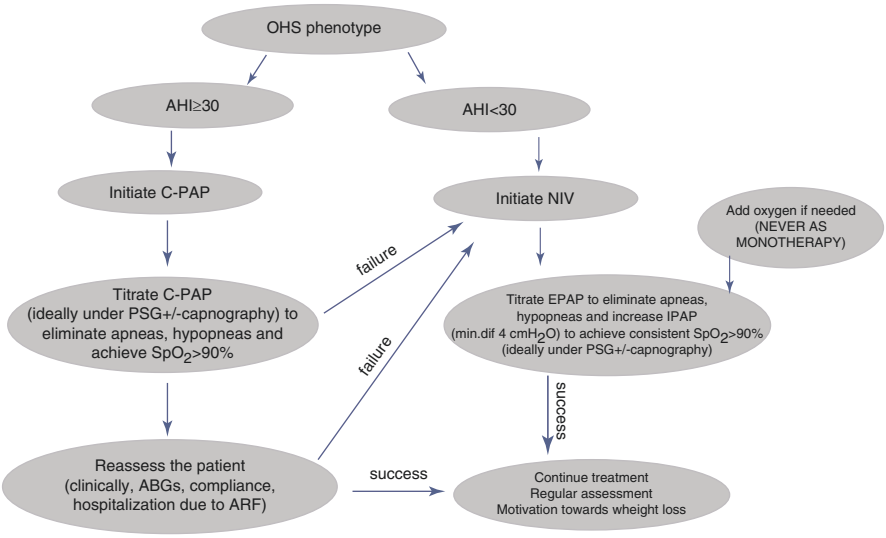

Fig. 28.1 Treatment algorithm for OHS. *ABGs* arterial blood gases, *AHI* apnea hypopnea index, *ARF* acute respiratory failure, *CPAP* continuous positive airway pressure, *EPAP* expiratory positive airway pressure, *IPAP* inspiratory positive airway pressure, min. Dif. minimum difference, *NIV* noninvasive ventilation, *OHS* obesity hypoventilation syndrome, *PSG* polysomnography

successful in preventing intubation or death despite the delayed response in correcting respiratory acidosis (time to correct hypercapnic acidosis median 2.9 (range 1–3 days) [39].

NIV should always be used in an environment with rapid access to endotracheal intubation by well-trained operators. Early application (within 1 h of presentation to the emergency department) seems to be vital. Several ventilatory modes are used with success, such as BiPAP mode, pressure support ventilation (PSV), volume-assured pressure support (aVAPS), and pressure control ventilation (PCV), without differences in performance. In general, high positive pressure levels of pressure (both IPAP and EPAP) are needed to achieve adequate tidal volume and upper airway patency, as well as longer initiation [40]. After discharge, patients with newly diagnosed or suspected OHS should be offered home NIV training until outpatient further evaluation is feasible (ideally within 2–3 months) [8].

Key Major Recommendations

- OHS has increased in recent decades because of the increasing prevalence of obesity. In these patients, the suspicion of the syndrome's existence must be evaluated early, to prevent hospital admissions, severe comorbidities, and mortality
- Further examinations must be conducted to rule out other diseases that also cause hypoventilation. It is also essential for a PSG to be performed to determine the sleep disordered breathing pattern (obstructive or non-obstructive) and choose the appropriate treatment mode.
- CPAP is the first step in the treatment of patients with OHS and concomitant severe OSA (AHI $\geq$ 30).
- NIV is usually chosen when response to previous CPAP treatment is inadequate or when there is mainly nocturnal hypoventilation without severe OSA (AHI < 30). It is often used in obese patients with acute decompensation of OHS who need admission to the hospital.
- AVAPS mode should be applied when the treatment with other PAP modalities has failed.
- Oxygen therapy should be added when needed, but never as a monotherapy.
- NIV is well documented to treat nocturnal hypoventilation and OSA if it co-exists, daytime hypercapnia and nocturnal hypoxemia, improve sleep pattern, gas exchange, utilization of healthcare resources, and HRQoL. It also prevents severe complications such as cardiovascular diseases.

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29 Cardiopulmonary Interventions to Prolong Survival in Patients with Duchenne Muscular Dystrophy

Secil Ozercan

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https://doi.org/10.1007/978-3-031-28963-7_29

Abbreviations

BIPAP	Bilevel positive airway pressure
CPAP	Continuous positive airway pressure
CSA	Central sleep apnea
DMD	Duchenne muscular dystrophy
FEV_1	Forced expiratory volume in 1 s
FVC	Forced vital capacity
IPAP	Inspiratory positive airway pressures
MEP	Maximal expiratory mouth pressures
MIP	Maximal inspiratory mouth pressures
NIV	Noninvasive ventilation
NIV/MPV	Mouthpiece intermittent positive pressure ventilation
OSA	Obstructive sleep apnea
PCV	Pressure controlled ventilation
PEEP	Positive end-expiratory pressure
PFT	Pulmonary function tests
PSG	Polysomnography
REM	Rapid eye movement
RR	Respiratory rate
SDB	Sleep disordered breathing
VC	Vital capacity
VCV	Volume controlled ventilation
VTPCV	Volume-targeted pressure-controlled ventilation

29.1 Introduction

Duchenne muscular dystrophy (DMD) is an X-linked recessive disease and is one of the most common types of muscular dystrophy, with an approximate prevalence of 15.9–19.5 per 100,000 live male births [1].

In the initial stages of the disease, the proximal lower limb muscles are affected followed by the shoulder muscles, the distal limb muscle, and finally the respiratory muscles. The consequences are progressive impairment of motor skills, loss of ambulation, orthopedic complications, cardiac involvement, and breathing difficulties [2].

In patients with DMD, vital capacity (VC) peaks between 9 and 16 years of age, and then decreases by 5–10% per year until ventilatory support is required for survival [3]. Approximately 90% of patients with this variety of disease who do not use ventilatory support die from pulmonary complications associated with respiratory muscle weakness (including progressive restrictive ventilatory defects, chronic hypoventilation, and pulmonary infection between 16 and 19 years of age, or more uncommonly, after age 25 [3]. In fact, the mortality rate due to cardiac insufficiency

may be more common than respiratory failure because of the ability to effectively correct respiratory failure [4, 5].

Currently, there is no cure for DMD; however, recent advances in disease management have altered the natural course of the disease, so it is now possible for most individuals with DMD to live well into their fourth decade [6]. This has led to the belief that denying noninvasive ventilation (NIV) to hypercapnic patients with DMD is unethical [6]. The multisystem complications of DMD require a multidisciplinary team methodology for optimal surveillance and management [5, 6].

29.2 Discussions and Analysis

29.2.1 Clinical Course of DMD

The main muscles of inspiration are the diaphragm and external intercostals. The sternocleidomastoid and scalenes assist in respiration [7]. While expiration during regular breathing is passive, forced expiration and coughing require use of the expiratory muscles, including the internal intercostals and the abdominal wall muscles [7].

As the respiratory muscles get progressively weaker, the weakened diaphragm forces individuals to become more dependent on the chest wall muscles for respiration [1]. Initially, hypopnea, oxygen desaturation, and hypercarbia may occur during rapid eye movement (REM) sleep in individuals with subacute or chronic respiratory muscle weakness [1, 5]. To compensate, those with DMD may exhibit paradoxic breathing and tachypnea [1, 5].

Throughout the progression of DMD, a multitude of sleep disordered breathing (SDB) have been defined, including obstructive sleep apnea (OSA), central sleep apnea (CSA), and nocturnal hypoventilation [1, 5]. Using chronic systemic steroids is commonly recognized as a risk factor for OSA due to their association with obesity. Hypoventilation is often more marked at night and can give rise to nocturnal hypercapnia or elevation of the arterial partial pressure of carbon dioxide, which can result in morning headaches, broken sleep patterns, nightmares, nocturnal confusion, daytime fatigue, mental clouding, and somnolence [1, 5]. SDB without hypercapnia is the first indication of respiratory insufficiency [1, 5]. This develops into SDB with nocturnal hypercapnia and, finally, diurnal hypercapnia [1, 5].

Weakness of expiratory muscles may give rise to decreased speech volume and more importantly, the lack of ability to cough forcefully enough to clear airway secretions. This places individuals at an increased risk of pneumonia [7].

Due to progressive muscle weakness and loss of function, DMD patients may develop thoracolumbar scoliosis, leading to additional restrictive lung diseases, hypoventilation, and risk for progressive respiratory failure with acute illness [1].

Progressive generalized muscle weakness in DMD can induce dysphagia [8]. Decreased tidal volumes cause a compensatory tachypnea to maintain sufficient minute ventilation [8]. Swallowing is only safe during expiratory pauses; however,

tachypnea decreases swallowing time to less than 1 s, thus rendering swallowing unsafe, causing it to occur during inspiratory pauses [8]. The impaired swallowing and hypercapnia can lead to depression and decreased appetite along with malnutrition and weight loss [8].

29.2.2 Assessment of Cardiorespiratory Function

There is no optimal frequency for physician visits for patients with DMD. Objective measures of respiratory function are critical for prognosis and timing respiratory interventions [7]. While there appears to be some debate regarding optimum testing options, spirometry seems to be the best-studied and most standard test available [5, 7]. Spirometry measures the forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1). Maximal inspiratory and expiratory mouth pressures (MIP,MEP), sniff nasal inspiratory pressure, cough peak flow rates, arterial blood gas measurement, end tidal carbon dioxide, oxygen saturation, and polysomnography comprise other beneficial testing options [5, 7].

The 2018 DMD Care Considerations, advised regular (twice per year) visits to a respiratory specialist once the patient is no longer ambulatory. These visits should include measure of VC, MIP, MEP, cough peak flow, FVC, SpO_2, end tidal carbon dioxide, and transcutaneous carbon dioxide [5].

Patients with cough peak flow rates below 160 L/min are felt to be at high risk for mucous plugging and respiratory insufficiency [5, 7]. A cough peak flow of 270 L/min can fall below 160 during an acute infection. Therefore, initiating a series of pulmonary interventions when cough peak flow rates attain a level of 270 L/min is advised [5, 7].

Alveolar hypoventilation is characterized by increased arterial CO_2 [5, 7]. Hypoventilation, atelectasis, or mucous plugging can lead to oxygen desaturation [7]. Patients are advised to begin assisted cough techniques and assisted ventilation if their oxygen saturation falls below 95% [7].

Cardiac involvement is universal in patients with DMD. Cardiac disease is the second most common cause of death in patients with DMD, with 10–20% of patients dying of cardiac failure such as dilated cardiomyopathy; however, this proportion is likely to increase over the coming years in individuals in whom NIV prevents respiratory related mortality. Dilated cardiomyopathy primarily effects the left ventricle, and can lead to dyspnea and other symptoms of congestive heart failure. Conversely, right ventricular failure can result from respiratory failure and pulmonary hypertension. Patients with DMD are also at risk for ventricular arrhythmias [9]. Patients with DMD are evaluated starting at 10 years old by echocardiography and cardiac MRI; and are evaluated longitudinally on a yearly basis, with therapeutic intervention using angiotensin-converting enzyme inhibitors, beta-blockers, and diuretics at the earliest signs of myocardial failure. It is important to look for and treat coexisting nocturnal hypoventilation, which aggravates cardiac dysfunction. In a high percentage of cases, both reverse remodeling and normalization of left ventricle

systolic function and size. Dilated cardiomyopathy occurs in up to 90% of DMD patients >18 years old. The risk of cardiac involvement in carriers of DMD is approximately 10%, and this may occur in the absence of muscle weakness [9].

29.2.3 Nocturnal Respiratory Support in DMD

For DMD patients, the teenage years are often characterized by worsening respiratory reserve and an increased risk for sleep-disordered breathing, including hypopnea, central and obstructive apnea, and hypoxemia [10].

There are four general stages of hypercapnic respiratory failure in DMD patients: Stage 1 is characterized by SDB without hypercapnia; Stage 2 involves SDB with hypercapnia during REM sleep; Stage 3 includes SDB with hypercapnia during REM and non-REM sleep; and in Stage 4, diurnal hypercapnia presents [10]. Intervention with NIV in Stages 2 and 3 can increase quality of life and chances of survival, whereas the average survival at Stage 4 with no ventilation intervention is less than 1 year [10].

Nocturnal NIV using a bilevel positive airway pressure (BIPAP) has been used favorably in the treatment of sleep-disordered breathing and nighttime hypoventilation in patients with DMD [10]. Determining the level of positive pressure required to eliminate obstructive apneas or hypopneas and normalize ventilation and nighttime oxygen saturation is best done in either a sleep lab or through careful bedside observation and monitoring [10]. However, the nasal mask seems to be the first choice of interface for nocturnal ventilation regular evaluation and adjustment of nasal NIV is required as the patient's requirements change over time [10]. NIV can also result in improved quality of sleep, decreased daytime sleepiness, delayed daytime hypercapnia, improved well-being and independence, improved daytime gas exchange, and a slower rate of decline in pulmonary function [10].

Nasal continuous positive airway pressure (CPAP) likely has limited utility in patients with DMD and may be beneficial only in those with obstructive sleep apnea syndrome but with normal nocturnal ventilation [10]. In cases of hypoxemia due mainly or partially to hypoventilation, support with BIPAP or a volume ventilator is recommended. As hypoxemia in DMD is typically an indicator of hypoventilation, treatment with oxygen without concurrent supplemental ventilatory support should be avoided because supplemental oxygen can restrain respiratory drive and aggravate the hypercapnia [5, 10].

Polysomnography can be used with continuous CO_2 monitoring in patients with DMD to assess the sufficiency of home ventilatory support [10]. In areas where polysomnography is not easily available, overnight pulse oximetry with continuous CO_2 monitoring can be employed to observe nighttime gas exchange. Where CO_2 monitoring is not accessible, overnight pulse oximetry can be utilized to detect nighttime oxyhemoglobin desaturation. Because simple oximetry typically provides only indirect information on ventilation, it should only be used to assess the need for ventilatory support when better options are inaccessible [10].

29.2.4 Diurnal Respiratory Support in DMD

Typically, patients with DMD utilizing sleep NIV via either lip cover, nasal, or oronasal interface, eventually develop dyspnea or tachypnea upon discontinuation in the morning, at which point 24-h support becomes a necessity [5, 10]. 24-h NIV is a combination of nighttime ventilation using a noninvasive mask together with daytime NIV ventilation. The most commonly used diurnal noninvasive technique is mouthpiece intermittent positive pressure ventilation (NIV/MPV) [10]. NIV/MPV are mechanisms that force air into the lungs through a mouthpiece rather than an endotracheal tube or tracheostomy tube [7]. Thus, 24-h NIV/MPV represents a safe and noninvasive alternative to tracheostomy [5, 10–12].

NIV/MPV utilizes a commercially available or custom-made mouthpiece placed near the mouth using a flexible gooseneck attached to the wheelchair [10]. MPV may be applied in conjunction with single-limb intentional open circuit ventilators both in pressure controlled ventilation (PCV) and in volume controlled ventilation (VCV) to allow air stacking [9]. The user holds the mouthpiece and based on the possibility of head movements, may continuously use the device or grasp it on demand to obtain passive volume controlled breaths at a given rate or trigger a volume controlled breath, keeping either a part or the entire volume [9]. Alternatively, a pressure controlled breath can be administered corresponding to the patient's need and comfort [9]. This system has been used effectively in patients with DMD with a mean FVC of 0.6 L (5% predicted). Mouthpiece ventilation is well tolerated and does not hinder eating or speaking [10].

While not yet in use for symptomatic hypoventilation, meal-time NIV/MPV was introduced to slow respiratory rate (RR) and increase breath volumes to allow more time to safely swallow food [8]. In some cases, mouthpiece NIV is only used to facilitate eating and speech [8]. A common issue with this, however, is that the lips can become too weak to grab the mouthpiece NIV and so nasal NIV is used with no or very low back-up rate during meals allowing for adequate minute ventilation with only 3 or 4 assisted breaths [8]. Typically, volumes ranging from 1200–1500 mL are administered to enable 6000 mL min ventilation with 12–15 s between assisted breaths, allowing for safe swallowing [8]. The NIV also aids in speech and coughing to help decrease aspiration risk [8].

Although the mechanism is unclear, dysphagia may improve significantly with the introduction of MPV [4]. It is conceivable that, once started, MPV reduces the work involved in breathing, thus resulting in overall improvements in muscle function [4]. It is also possible that there is improvement in oropharyngeal muscle strength or endurance or that the reduction in dyspnea that occurs with MPV allows for easier swallowing and less anxiety while eating [4].

29.2.5 Modes and Monitoring

29.2.5.1 Modes

There are two main types of positive pressure ventilators: volume and pressure support; however, there is no evidence to support whether they are superior to conventional types [9].

Pressure-Controlled Ventilation

During PCV, volume does not remain steady when resistance increased. [9]. However, constant peak inspiratory pressures and the presence of nonintentional leaks, which are compensated for more efficiently compared to VCV, has made PCV the main choice for the majority of patients [9]. Ideal results have been observed when pressure-controlled modes are combined with a bilevel ventilator in vented configuration [9].

Today, the most widespread NIV devices are bilevel pressure cycled units which feature separate inspiratory and expiratory pressures [7]. The level of positive pressure support delivered is the difference between inspiratory and expiratory pressure. Many patients with DMD have central sleep apnea necessitating the use of NIV machines that allow a respiratory rate to be set [7].

Bilevel ventilators today offer both time and flow cycling [9]. Overall, in DMD patients, timed modes are usually preferred over flow-cycled modes because they have a backup rate for definitions (e.g., assist PCV mode) [9]. When using a flow-cycled mode, it should be done in conjunction with a timed mode (e.g., ST mode) [9]. In particular, a minimum and maximum inspiratory time during the flow-cycled breath should be established as the latter can also prevent a prolonged inspiratory phase, which can impair patient–ventilator synchrony [9].

Bilevel pressure support devices may assist upper airway stabilization and reduce atelectasis in DMD, thus increasing overnight arterial blood gas control [9].

Volume-Controlled Ventilation

Volume cycled ventilators, those that administer a preset tidal volume rather than a set pressure, may offer more support than bilevel pressure cycled ventilators and are becoming more favored over BIPAP as muscle weakness progresses [7]. As nocturnal hypoventilation arises before daytime hypoventilation, individuals using NIV during the night eventually move to daytime use as well [7]. During daytime usage, volume ventilators are more desirable as they offer air stacking benefits and have an absence of leak compensations allowing for mouthpiece ventilation on demand [10].

During VCV, the volume remains stable in spite of an increase in respiratory impedance until the maximal safety threshold (set in the alarm configuration) is reached; however, patients with increased respiratory impedance (i.e., scoliosis) may still require VCV [9].

Volume-Targeted Pressure-Controlled Ventilation

Volume-Targeted Pressure-Controlled Ventilation (VTPCV) are hybrid ventilation modes which incorporate the advantages of conventional modes and, at the same time, prevent their possible disadvantages [9]. The fundamental feature of these modes permits the ventilator to maintain sufficient ventilation when respiratory impedance increases, thus precluding needlessly high preset inspiratory pressures [9]. VTPCV was originally used for invasive mechanical ventilation and later introduced in the noninvasive mode [9].

29.2.5.2 Settings

Effective ventilation is easily achieved with low inspiratory positive airway pressures (IPAP) between 10–15 cm H_2O although pressures >20 cm H_2O have been

reported. In DMD patients, the most sufficient setting for volume ventilators was determined to be at a physiologic back-up respiratory rate (RR 12–14/min) and relatively large delivered volumes of 800–1500 mL for daytime support permits the user to take as much of the air as desired, and, thereby, physiologically vary tidal volumes and air stack ad lib; however, parameters may vary greatly among patients [10].

As positive end-expiratory pressure (PEEP) is primarily used to improve oxygenation in patients with reduced functional residual capacity, whether or not associated with hypoxemia, it is not often required for patients with DMD as they typically have normal lungs [9]. However, the presence of an associated obstructive sleep apnea may be a signal for its use. Nevertheless, high levels of PEEP may reduce cardiac output in DMD patients and may cause abdominal bloating [9].

29.2.5.3 Monitoring

Monitoring the effectiveness of nocturnal NIV is a critical facet in the management of DMD with the aim of titrating the ideal ventilator setting to achieve effective ventilation [9].

Once NIV application has begun, ventilatory settings can be precisely calculated to overnight SpO_2 and CO_2 measurements, to avoid overventilation, which is comparatively simple to do for patients with neuromuscular disease as the impedance to inflation is low [11, 12]. Follow-up for DMD patients receiving NIV should be conducted regularly, for example, every 6 months, including oxygen saturation and end-tidal CO_2 levels [11, 12].

While the American Academy of Sleep Medicine suggests using polysomnography (PSG) to monitor NIV in practice, this is not feasible in many countries due to costs and availability [9]. Nowadays, the majority of home NIV ventilators are outfitted with a built-in software that offers data about adherence to the therapy (usage/night), leaks, estimation of the apnea/hypopnea index, and trends of some ventilator parameters [9]. Some more advanced models even provide remote access to flow and pressure waveforms [9].

29.2.6 When to Start NIV?

Despite the fact that NIV is necessary for the treatment of DMD patients, the criteria used to initiate ventilatory support are unclear. One definite indication for NIV initiation is evidence of hypercapnia or hypoxemia during sleep or wakefulness [7].

A slow and steady initiation of NIV in individuals with nocturnal hypercapnia but daytime normocapnia is a logical approach, as waiting for daytime ventilatory failure endangers patients through possible minor chest infections and uncontrolled decompensation [6].

The primary objective of preventive NIV is to lower the unavoidable worsening of VC with disease progression in normocapnic and asymptomatic patients. A study which investigated the effects of preventative NIV use in DMD patients revealed that survival was lower in the experimental group using prophylactic NIV,

supporting the opinion that preventative NIV should not be applied to DMD patients experiencing hypoventilation [10].

The guidelines on the management of DMD patients support earlier onset of NIV compared to previous standards. First, they emphasize the importance of frequent routine pulmonary function tests (PFT) checks. Second, they advise limits to start nocturnal assisted NIV with a backup rate when there are early signs or symptoms of sleep hypoventilation or other sleep-disordered breathing such as abnormal sleep study (these studies include overnight oximetry, capnography, and polysomnography), FVC <50% predicted, MIP <60 cm H_2O, or awake baseline SpO_2 < 95% or pCO_2 > 45 mm Hg [5]. Nocturnally assisted ventilation is also indicated if sleep study results show any of the following: end-tidal or transcutaneous CO_2 > 50 mm Hg for ≥2% of sleep time, a sleep-related increase in end-tidal or transcutaneous CO_2 of 10 mm Hg above the awake baseline for ≥2% of sleep time, SpO_2 ≤ 88% for ≥2% of sleep time or for at least 5 min continuously, or an Apnea–Hypopnea Index ≥5 events per hour [5].

Nevertheless, incorporating all components of PFT assessment rather than relying on a single limit value is prudent. Initiation of NIV with the existence of only nocturnal hypercapnia can delay future daytime hypercapnia, which occurs 4–5 years after NIV initiation [10]. Furthermore, daytime NIV should be included only when daytime hypercapnia occurs, meaning that patients have raised CO_2 levels day and night. In addition, when awake SpO2 is <95%, pCO_2 > 45 mm Hg or symptoms of awake dyspnea are present, daytime NIV should be initiated [5].

However, these criteria have lately been reported as being difficult to reach in symptomatic patients for whom diurnal PCO_2 > 45 mmHg was the significant reason for extending NIV into daytime use. Deterioration of symptoms and daytime dyspnea indicate the high cost of energy expenditure for the maintenance of normocapnia [5].

NIV is suggested for symptomatic nocturnal hypoventilation and for all patients presenting daytime hypoventilation. NIV during sleep may correct daytime hypercapnia, possibly by re-setting chemoreceptor sensitivity to CO_2. In patients with more severe weakness, respiratory failure with hypercapnia can arise during wakefulness as well as during sleep to such an extent that cannot be reversed by nocturnal assisted ventilation alone. For these patient's, daytime NIV is used to relieve symptoms of hypoventilation, improve quality of life, and increase life expectancy [5, 6].

29.2.7 NIV Adherence

Adherence in youth using NIV has been affected by physical, behavioral, familial, and psychosocial factors as identified by recent studies [13]. Previous research on physical factors did not observe a correlation between adherence and disease severity, therapeutic pressure, and NIV therapy type (continuous or bilevel) [13]. Behavioral, familial, and psychosocial influences appear more prominent in NIV adherence [13]. Factors such as embarrassment, forgetting, simply refusing to use, illness, choosing to ignore obstructive sleep apnea, and refusing to transport the

machine out of the home have all been identified as reasons for nonadherence by both parents and patients [13]. There is also a relationship between mask style and age at initiation on adherence [13].

The most common barriers for NIV use are uncomfortable masks, poor sleep with NIV, and simple refusal to use the machine [13].While mask discomfort was the most reported barrier by caregivers and their children, it is also the easiest to solve as another mask can be used or a mask can be custom-made for the patient [13]. Leaking around the mask and/or the mouth is associated with poor ventilation and sleep disruption and is often related to poor mask fit, issues related to ventilation timing, or the excessive use of IPAP. The strategies to reduce leaking include increasing RR (≥23/min), decreasing IPAP (≤15 cm H_2O) or VT (≤13 mL/kg), or increasing the inspiratory/expiratory (I/E) ratio (from 1/1.5 to 1) [10].

The use of microprocessor-based ventilators that compensate for leaks may be a good way to improve mouth leaking and asynchrony. Additionally, either mouth taping using a chin strap or cervical collar or a mouthpiece with lip sealing or a full face mask can also be used to prevent uncontrolled mouth leaks. As gastrointestinal bloating may be a serious complication of NIV, there are benefits to limiting IPAP use [10].

29.2.8 Contraindications and Precautions for NIV

Contraindications, although rare, can include lack of consciousness, lack of patient cooperation, inability to maintain the airway, presence of severe bulbar impairment, and a lack of nasal access. Patients should be instructed in airway clearance techniques before initiating NIV. Training caregivers and families on airway clearance techniques during home NIV is also a critical component in the success of NIV [10].

29.2.9 Efficacy of NIV

29.2.9.1 Quality of Life and Symptoms

Thanks to technological developments in ventilators, ventilator modes, interface design, and secretion removal techniques have made NIV use much more user-friendly and have increased patient comfort and quality of life [9]. Those afflicted with DMD consider home NIV beneficial in order to live a more independent life and as a way to enhance their overall health and quality of life. Nocturnal NIV can reverse symptoms associated with poor sleep quality and full time NIV/MPV can reverse symptoms associated with daytime dyspnea [10].

29.2.9.2 Blood Gas Improvement

Survival

In DMD patients, NIV is generally deemed to provide an additional 5–10 years of life expectancy; however, there is no data to support increased life expectancy

related to the timing of NIV initiation [10]. Research has shown that NIV treatment can prolong life expectancy of DMD patients who use the treatment when compared to those that do not. (When VC falls below 1 L, mean survival is just 3.1 years without the use of assisted ventilation and patients who are left untreated and who become hypercapnic may survive for less than 1 year [6].)

29.2.9.3 Delay Decline in Lung Function

One hypothesis to explain the decrease in both lung volume and maximum airway pressure after initiation of NIV is that this treatment may possibly contribute to the preservation of lung and chest-wall compliance, which results in the slowing of lung volume decreases related to progressive respiratory muscle weakness [5].

There have been conflicting long-term physiological outcomes related to NIV in DMD patients. For example, VC has been shown to either increase, stabilize, or decline at a slower rate or to decline further similar to levels prior to NIV [5, 11, 12]. However, hospitalization rates have been reported to either reduce in number or to remain unchanged after initiation of NIV [11, 12].

29.2.9.4 Improved Cardiac Function

NIV assistance has been shown to positively influence cardiac function by decreasing the cardiac burden [5, 14].

29.2.9.5 Ameliorate Symptoms

As patients with DMD often initially develop ventilatory insufficiency or failure during an acute chest infection, acute NIV can be utilized to diminish the need for intubation and/or facilitate weaning [5, 11]. Symptoms related to sleep hypoventilation such as nocturnal awakenings, daytime sleepiness, morning headache, and vomiting decreased with initiation of NIV [5, 11].

29.2.9.6 Increased Tracheostomy Risk

24-hour NIV/MPV represents a safe and noninvasive alternative to tracheostomy [5, 10–12]. Tracheostomy should only be applied when other noninvasive methods have become ineffective [5, 10, 11]. On the other hand, the benefits provided by a tracheostomy are a more secure patient–ventilator interface, but tracheostomy does have some potential complications. Increased secretion, impaired swallowing, increased risk of aspiration, and by-passed airway defenses can all lead to a greater risk of infection. There is also the greater risk of airway blockage with musos plugs and impaired verbal communication to consider [5, 10, 11].

Tracheostomy requires surgery, hospitalization and the risks of anesthesia, which are increased in DMD patients. The difficult part of invasive mechanical ventilation is that it requires a caregiver to be present 24 h a day [9].

Tracheostomy ventilation becomes necessary in the case of severe aspiration risk, severe respiratory infection, and after onset of severe bulbar weakness that is rarely developed in DMD patients [9].

Tracheotomy in DMD patients may be considered in the following circumstances: patient preference, inability to use NIV, three failed extubation attempts

during a critical illness despite optimum use of NIV and using mechanically assisted coughing to prevent aspiration of secretions into the lungs due to weak bulbar muscles [9].

29.3 Conclusions

Although there is no definitive treatment for DMD patients to date, mortality has decreased in patients with the use of NIV and the average life expectancy is prolonged from the second to the fourth decade. Quality of life of DMD patients using NIV increased and mortality decreased.

Key Major Recommendations

- Patients with DMD should regularly visit a respiratory specialist when they are no longer ambulatory. These visits should include measurement of VC, MIP, MEP, cough peak flow, FVC, SpO_2, end-tidal carbon dioxide, transcutaneous carbon dioxide, and all individuals with DMD require regular cardiac evaluation with annual electrocardiograms and echocardiograms, starting at least by school age.
- In patients with DMD, there is good evidence that NIV can improve symptoms, quality of life, and survival.
- Despite that NIV is necessary for DMD patients, the criteria used to initiate ventilatory support are unclear. One definite indication for NIV initiation is evidence of hypercapnia or hypoxemia during sleep or wakefulness.
- Mask style, age at initiation, embarrassment, forgetting, simply refusing to use, illness, choosing to ignore OSA, and refusing to transport the machine out of the home have all been identified as reasons for nonadherence by both parents and patients.
- Contraindications, although rare, can include lack of consciousness, lack of patient cooperation, inability to maintain the airway, presence of severe bulbar impairment, and a lack of nasal access. Tracheostomy should be considered when contraindications or patient aversion to NIV are present, or when NIV is not feasible due to severe bulbar weakness or dysfunction.

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Noninvasive Ventilation Pressure Adjustments in Patients with Amyotrophic Lateral Sclerosis

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30.1 Introduction

Amyotrophic lateral sclerosis (ALS) is characterized by degeneration of upper and lower motor neurons, leading to progressive paresis of all voluntarily innervated muscles and therefore affecting mobility, communication, swallowing, and breathing [1]. The incidence of ALS is 1–2 per 100,000 of the population, and the age-specific incidence and mortality rates peak at 55–75 years [2]. Failure of respiratory muscles with the occurrence of alveolar hypoventilation typically limits survival to 2–5 years after disease onset. Noninvasive ventilation (NIV) has been shown to improve survival and quality of life in patients with ALS [3]. Pressure support ventilation (PSV) or bi-level positive airway pressure (BiPAP) set to spontaneous mode with backup frequency is the preferred modes for NIV because they are more

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_30

comfortable for the patient and compensate for leaks [4]. The initial pressure settings could be simple, but the progression of the disease, ventilator dependence, presence of excessive secretions, and upper airway involvement sometimes make pressure adjustment of NIV more difficult, with a major impact on survival [5]. The evolving technology led to a new hybrid treatment modality named volume-targeted pressure-controlled ventilation (VTPCV) that is now available on the market. The correct setting of these new treatment modalities is difficult and their effectiveness in the ALS population is uncertain [5].

30.2 Discussion

Since most cases of ALS are complicated by respiratory failure due to diaphragmatic dysfunction, NIV has become the standard of care for respiratory support in patients with ALS [4]. The appropriate time to initiate NIV remains unclear. Generally, NIV is initiated at a stage of daytime hypoventilation [6]. The importance of a referral to specialized pulmonary care, where the reported use of NIV is substantially higher, is fundamental [7]. According to the America Academy of Neurology (ANN), NIV in ALS patients should be started at the presence of symptoms of nocturnal hypoventilation (as orthopnea) and one of the following criteria: reduced peripheral oxygen saturation (SpO_2) < 89% for >5 min on overnight oximetry, increased partial pressure of carbon dioxide ($PaCO_2$) >45 mmHg, reduced predicted forced vital capacity (FVC) <50% predicted, maximal inspiratory pressure (MIP) <60 cmH_2O, or a sniff nasal inspiratory pressure (SNIP) <40 cmH_2O [8]. More recently, diaphragm ultrasound has been shown to detect patients at high risk of hypoventilation [9]. Although the diffusion of this technique is increasing, the ability to assess the diaphragm is the domain of few highly specialized centers. Because of the nature and rapid progression of ALS, three-monthly assessments are necessary to determine the appropriate time to initiate NIV so minimally invasive, inexpensive, and early to perform techniques are to be preferred [8]. New data suggest that early (FVC > 80% predicted) NIV adaption in the disease course may provide additional mortality benefit [10]. However, adherence to early NIV is very poor [11]. The role of early NIV in ALS patients is under debate and not conclusive, further literature on early NIV benefit is welcomed. It is important to note that if bulbar weakness is present or not in patients with ALS is often a major difference at the initiation and toleration of NIV [3]. Sialorrhea and shallowing problems are evident in bulbar-affected patients so it is fundamental to reduce the amount of salivary secretions before NIV is started. No difference in terms of efficacy has been demonstrated between volume-preset (Vol-NIV) systems and pressure-preset (Pres-NIV) systems [12]. However, Pres-NIV is the preferred mode for NIV because it is more comfortable for the patient (even in ventilator-dependent patients), compensates for leaks, and seem to have an impact on survival [13]. When NIV is initiated for the first time, a PSV modality with a low inspiratory pressure support (PS) of 6–8 cmH_2O should be set to assure the comfort of the patient and positive end-expiratory pressure (PEEP) should be initially set at zero. Ventilation with a single-limb circuit with intentional leak requires an expiratory positive airway pressure

(EPAP) setting a minimum of 4 cmH_2O to prevent rebreathing. Semi-controlled pressure modes (spontaneous modes with backup frequency) are preferred, being more effective in ALS than spontaneous modes [14]. A respiratory backup rate of 12–14 is usually set at the beginning. Ventilator settings can then be adjusted gradually to ensure sufficient inspiratory assistance to obtain normal daytime and nocturnal $PaCO_2$. Generally, PS must be slowly increased with a step-up of 1–2 cmH_2O until a target tidal volume of 6–8 mL/kg of ideal body weight (IBW) was reached and tolerated by the patient. A stepwise adaptation of pressure values, breathing rate, and other parameters, according to the continuous feedback of the patient about his or her breathing comfort, is advisable [4]. Sleep apnea is a common phenomenon in ALS and an important context factor of ventilation. Up to 45% of ALS patients often combined sleep apnea with nocturnal hypercapnia [15]. Weakened laryngeal and pharyngeal muscles collapse are the most important factor that leads to obstruction of the upper airways. Obstructive events can lead to insufficient nocturnal ventilation, even under NIV, as reflected by recurring desaturations that lead to a reduced global survival [16]. An incorrect NIV setting can induce obstructive sleep apnea events or worsen a preexisting state. Detecting sleep apnea in ALS by appropriate diagnostic measures is fundamental. An overnight sleep study should be reserved for all ALS patients with a medical history of suspected sleep apnea. In the presence of obstructive sleep apnea events, NIV should be intensified with modification of ventilation parameters to prevent upper airway obstruction. In asymptomatic ALS patients with sleep apnea and without NIV, initiation of NIV seems auspicate. Continuous positive airway pressure (CPAP) should be avoided because respiratory muscles may exhaust during further disease progression and CPAP is not to be considered a NIV modality because does it not support diaphragm dysfunction. A practical approach to adjustment of NIV in stable chronic alveolar hypoventilation syndromes as a consequence of ALS in the presence of obstructive sleep apnea syndrome suggests using ventilator settings in BiPAP or PSV. The inspiratory airway pressure (IPAP) and EPAP levels are adjusted to maintain upper airway patency, and the pressure support (PS = IPAP-EPAP) augments ventilation. NIV titration with overnight sleep study is the recommended method to determine an effective level of nocturnal ventilatory support. In circumstances in which NIV treatment is initiated and adjusted empirically based on clinical judgment, a sleep study should be utilized, if possible, to confirm that the final NIV settings are effective or to make adjustments as necessary. The recommended minimum starting IPAP and EPAP should be 8 cmH_2O and 4 cmH_2O, respectively, with the minimum and maximum incremental changes in PS of 1 and 2 cmH_2O. IPAP and/or EPAP should be increased until apneas, hypopneas, respiratory effort-related arousals, and snoring are eliminated. The PS should be increased every 5 min if the tidal volume (TV) is low (<6–8 mL/kg). The PS should be increased if the arterial PCO_2 remains 10 mmHg or more above the PCO_2 goal at the current settings for 10 min or more. The PS may be increased if the SpO_2 remains below 90% for 5 min or more and TV is low (<6–8 mL/kg). A backup rate should be recommended starting with a setting equal to or slightly less than the spontaneous sleeping respiratory rate (minimum of 10 breaths per minute). The IPAP time (inspiratory time) should be set based on the respiratory rate to provide an inspiratory time (IPAP time) between 30 and 40% of

the cycle time. If the patient awakens and complains that the IPAP and/or EPAP is too high, pressure should be lowered to a level comfortable enough to allow a return to sleep. NIV device parameters (when available) such as pressure relief, rise time, maximum and minimum IPAP durations should be adjusted for patient comfort and to optimize synchrony between the patient and the NIV device. The ventilatory pattern is different between day and night in ALS patients, some ventilators have a dual or more setting option so that separate nighttime and daytime ventilation allow the possibility to better adapt pressure adjustment to the ventilatory request by the patient. During the NIV titration mask refit, adjustment, or change in mask type should be performed whenever any significant unintentional leak is observed or the patient complains of mask discomfort. If a mouth leak is present and is causing significant symptoms (e.g., arousals) use of an oronasal mask or chin strap may be tried. Heated humidification should be added if the patient complains of dryness or significant nasal congestion [17]. Close follow-up after initiation of NIV by appropriately trained health care providers is indicated to establish effective utilization patterns, remediate side effects, and assess measures of ventilation and oxygenation to determine if adjustment to NIV is indicated. Ventilator settings are then continuously adjusted over the first hours and days of ventilation with 3–5 days usually needed to achieve optimal settings. The efficacy of ventilation should be evaluated at 1 month and then reviewed every 3 months. NIV optimization requires an individualized approach to respiratory management tailored to the differing needs of each patient and should be adapted based on good quality monitoring of NIV and compensate for further disease progression. If ventilation is not optimized, the benefits are dramatically reduced [18]. The quality and amount of NIV use are very important. When assessing compliance with NIV, the recorded data in the ventilator are therefore very helpful for assessing average daily ventilator use and also for documenting special patterns of ventilator use which may suggest inappropriate settings and patient discomfort (e.g., fragmented nocturnal use, multiple short periods of ventilator use). A minimum of 4 h per day of tolerated NIV demonstrated improved survival post-NIV initiation [19]. The assessment of the quality of NIV care and alignment of care with symptom relief and clinical needs is fundamental. Data provided by ventilator software help the clinician by estimating ventilation, tidal volume, leaks, and the rate of inspiratory or expiratory triggering by the patient, although further validation of these signals by independent studies is needed. In the absence of such validation, information provided should only be considered as indicators of trends without any guarantee as to the linearity of the estimations provided [20]. Oxygen should not be considered a routine treatment for chronic respiratory insufficiency. Delivery of oxygen alone can suppress respiratory drive and lead to worsening hypercapnia. In patients with ALS with acute hypoxemia, management of respiratory insufficiency with NIV needs to be considered first. If hypoxemia remains after optimal NIV pressure is applied, the etiology of the hypoxia needs to be assessed and supplemental oxygen can be considered [21]. The role of secretions management in ALS patients is fundamental. The presence of excessive bronchial secretions can lead to high airway resistance reducing TV during Pres-NIV. Difficulty with secretion management can lead to reduced NIV tolerance and compliance with

reduced global survival [22]. The evolving technology led to the development of a relatively novel ventilatory mode for long-term noninvasive ventilation of patients with ALS named volume-targeted pressure-controlled ventilation (VTPCV). This hybrid ventilation mode combines the advantages of Pres-NIV and Vol-NIV ventilation modalities. The general working principles of VTPCV modes can be described as follows: the controlled variable is inspiratory pressure, which is constrained by the minimum and maximum inspiratory pressures set by the operator. Inspiration is initiated in the pressure-controlled mode, then once the machine receives feedback about the delivered volume, it "decides" whether to stay unchanged or to increase/decrease the inspiratory pressure to reach the dependent variable (the preset VT), before cycling on to expiration. Initially, the target VT value should be set according to ideal body weight (IBW) and pathology. The minimum IPAP is the lowest IPAP level that the patient should receive to maintain ventilation, and it should be at least 4 cm H_2O higher than the EPAP. The IPAP maximum should be the highest pressure the patient needs to maintain ventilation in challenging conditions such as deep sleep stages and supine body position. A minimum per default level of EPAP is always present when using an intentional leak configuration. An appropriate EPAP level should be set according to the presence of concomitant obstructive sleep apnea. Alternatively, some ventilators offer an automatic adjustable EPAP feature. Hereby, a minimal and maximal EPAP level must be set. An alternative approach to define VT and minute volume settings is to use the auto titration function offered by alveolar ventilation (VA)-targeted mode known as intelligent volume assured pressure support ventilation (iVAPS). First, the ventilator estimates the baseline VA following a 20-min learning period during spontaneous breathing under 4 cmH_2O when the patient is awake. Based on the patient's learned parameters, the software automatically defines the ventilator's settings to meet the determined target ventilation. Although the VTPCV modes are especially recommended by the manufacturers for the group of neuromuscular diseases, their application in daily practice still appears to be limited. Special considerations should be taken into account for ALS patients. These patients might be particularly sensitive to NIV and, normally, there is a progressive course of the disease, including diaphragmatic weakness and an increase in NIV requirement. The decrease in muscular effort makes these patients especially prone to desaturations and hypoventilation in cases of important pressure variations. This may lead to glottis closure. Different patented algorithms and set-up variables from different manufacturers create confusion. These factors have most likely hindered the more widespread use of this model in clinical practice. It is advisable to have a more highly trained team to handle these more complex hybrid modes and ensure their proper use in ALS patients [5].

30.3 Conclusion

Pressure-preset noninvasive ventilation is the preferred mode of treatment in symptomatic patients with amyotrophic lateral sclerosis (ALS) because it is more comfortable for the patient and compensates for leaks. The importance of a referral to

specialized pulmonary care, where the reported use of NIV is substantially higher, is fundamental. The initial pressure settings could be simple, but the progression of the disease, ventilator dependence, presence of excessive secretions, and upper airway involvement sometimes make pressure adjustment of NIV more difficult, with a major impact on survival. A stepwise adaptation of pressure values according to the continuous feedback of the patient about his or her breathing comfort and data obtained from diurnal ($PaCO_2$ on awakening), nocturnal (sleep study) respiratory parameters analysis, as well as data provided by ventilator software data are advisable. Close follow-up after initiation of NIV by appropriately trained health care providers is indicated to establish effective utilization patterns, remediate side effects, and assess measures of ventilation and oxygenation to determine if adjustment to NIV is indicated.

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Noninvasive Mechanical Ventilation in Patients with Myasthenia Crisis

31

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31.1 Introduction

Myasthenia gravis (MG) is an acquired illness caused by a humoral and T-cell mediated autoimmune response directed at components of the neuromuscular junction – most commonly the acetylcholine receptor (AChR) or the muscle-specific receptor tyrosine kinase (MuSK). It exhibits an overall female predominance and a bimodal age distribution, peaking in younger females and older males [1].

Clinically, MG manifests as fluctuating hyposthaenia of a variable combination of muscles, including those controlling ocular, bulbar, respiratory and limb movements. Oropharyngeal muscles are critical to maintain upper airway patency, as well as for deglutition and airway secretions management. When dysfunctional, patients often exhibit dysphagia, episodes of regurgitation, and may be at risk for aspiration. Respiratory muscle involvement is also a feared feature of severe MG, as the loss of muscular strength may be enough to produce respiratory failure and warrant ventilatory support [2].

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_31

31.2 Myasthenic Crisis

A significant fraction of patients with myasthenia gravis exhibit episodes of myasthenic weakness severe enough to produce potentially fatal neuromuscular respiratory failure requiring intubation, called myasthenic crises (MC).

In an MC, weakness of inspiratory and expiratory respiratory muscles may occur in variable combinations, the first being clinically apparent by progressive recruitment of accessory muscles, and the latter more obvious by ineffective cough. With respiratory muscle hyposthaenia and decreasing consequential tidal volume, atelectasis begins to occur in the dependent portions of the lung, giving rise to alveolar hypoventilation. This is followed by increasing work of breath and increased respiratory rate, and a ventilation/perfusion mismatch. Patients undergoing an MC typically develop hypercapnia and progress to hypoxaemia, which is frequently severe. Bulbar weakness may also help precipitate respiratory failure, as it may burden the respiratory muscles by upper airway dysfunction and instability. Moreover, as the airway's protection reflexes are blunted and secretions accumulate in the oropharynx, a propensity for aspiration is present, which may also precipitate or aggravate respiratory failure [3, 4].

MCs often occur in the context of a stressor (e.g. infection, pregnancy, taking of precipitating medications), and often progressively increasing muscle weakness is succeeded by respiratory failure. This is not always the case, however, as respiratory muscle fatigue can be disproportional, and rare cases of ventilatory failure have occurred in the absence of flagrant signs of progressive deterioration. Tools for adequate monitoring of patients in MCs are thus paramount, as clinical classifications are suboptimal in distinguishing patients with severely impaired oropharyngeal and respiratory muscle weakness from those in impending respiratory failure. In this regard, arterial blood gas sampling is useful to prove respiratory failure, and progressive vital capacity reduction (which may be demonstrated by the use of a portable spirometer) has been shown to signal the pathway leading from loss of effective cough and sigh mechanisms to atelectasis and ultimately respiratory failure [5].

31.3 Noninvasive Mechanical Ventilation in Myasthenia Gravis

Historically, the cornerstone of ventilatory support during MCs was endotracheal intubation and invasive mechanical ventilation. This was done at the expense of important rates of baro- or volutrauma, ventilator-associated pneumonia (VAP), and atelectasis, length of ICU stays and hospitalisation durations [6].

Noninvasive ventilatory support may unburden weakened respiratory muscles, aid in alveolar recruitment, promote gas exchange normalisation and ameliorate dyspnoea. Furthermore, by supplying positive airway pressure, airway instability and collapse is mitigated. This rationale has substantiated the timely usage of NIV in MC in an attempt to prevent intubation and invasive mechanical ventilation, while MG-targeted therapies operate [7]. Although this is typically referred to

bilevel positive pressure ventilation, reports exist of volume-assured pressure support modes aiming to counterbalance the fluctuating nature of respiratory muscle impairment in MCs [3].

Moreover, findings of comorbid sleep disordered breathing in MG benefiting from continuous positive airway pressure therapy (CPAP) suggest that NIV may play a beneficial role in this aspect, by control of obstructive and central events, improvement of muscle strength and normalisation of gas exchange [8, 9].

Nevertheless, a word of caution is in order regarding the effects of cholinesterase inhibitors used in the treatment of MCs, as these may increase airway resistance and secretions (salivation, bronchorrhoea) and contribute to dysrhythmia, which may prove problematic during NIV. This reiterates the need for intensive monitoring, airway secretion management and respiratory rehabilitation in this group of patients [10, 11].

31.4 Predictors of Failure

Patients undergoing severe myasthenic oropharyngeal and respiratory muscle impairment should be monitored clinically and gasometrically. The presence of hypercapnia (>45–50 mmHg) at onset of NIV has been associated with failure of NIV and with the necessity for endotracheal intubation [4, 12]. Serum bicarbonate was proposed as a gauge of respiratory muscle capacity and levels <30 mmol/L found associated with NIV success. In the same study, an initial APACHE II score <6 was also found to predict a favourable outcome under NIV [13].

Serial functional measurements of the patient's vital capacity and cough peak flow may be helpful indicators of deterioration and need for intubation. Maximal inspiratory pressure acts as a marker for weakness of inspiratory muscles, whereas forced vital capacity (which may also be assessed in supine to identify early decline) and maximal expiratory pressure aid in assessing cough efficiency and secretion management [4].

Finally, severe bulbar dysfunction precluding effective NIV or evidence of aspiration are indications for intubation. This is also the case of decreasing levels of consciousness, potentially fatal dysrhythmias or haemodynamic instability. In the presence of uncertainty, intubation should not be delayed as the probability of better outcomes is greater when performed outside an emergent setting.

31.5 Weaning from Mechanical Invasive Ventilation

Despite endotracheal intubation being a common necessity during MCs, tracheostomy is not usually required. Failure to extubate, however, is a frequent event in the course of MC treatment and is associated with an increase in VAP rates, length of ICU stay and hospitalisation time. Interestingly, an association has also been found between failed extubation and a need for admission to long-term care facilities [4, 14].

Extubation is generally pursued if the patient is stable, does not state complaints of dyspnoea or weakness, and exhibits adequate current volumes, vital capacities and maximal inspiratory and expiratory pressures – the latter having been found particularly useful, as it may yield insight in predicting cough strength. Moreover, in a retrospective study, Thomas et al. reported an age > 50, a pre-intubation serum bicarbonate level ≥ 30 mmol/L and a post-intubation peak vital capacity in days 1–6 < 25 mL/kg as predictors of prolonged intubation [13, 15].

Finally, patients who undergo NIV support have been shown to have lesser reintubation rates and remain under ventilatory support for shorter lengths of time. In one study, reduced intubation rates were observed for some patients undergoing NIV for a relatively short period of time per day (<6 h) [13].

Key Major Recommendations

- A subset of patients with myasthenia gravis exhibits episodes of severe muscle weakness, involving oropharyngeal and respiratory musculature.
- Oropharyngeal muscle involvement promotes airway dysfunction, accumulation of secretions and aspiration.
- Respiratory muscle involvement may produce dyspnoea, atelectasis, alveolar hypoventilation and ultimately, life-threatening alterations in gas exchange.
- Noninvasive ventilation may be used in selected patients to prevent intubation by unburdening the weakened respiratory muscles, promoting alveolar patency and improving gas exchange. Similarly, its application in weaning of invasive ventilation has also been associated with smaller reintubation rates.
- Serial monitoring of clinical, functional and arterial blood gas analysis parameters may aid in the prediction of noninvasive ventilation failure and recognition of the need for intubation.

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Noninvasive Mechanical Ventilation in COPD Exacerbations

32

Lorenzo Appendini

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https://doi.org/10.1007/978-3-031-28963-7_32

32.1 Introduction

Chronic obstructive pulmonary disease (COPD) is one of the diseases with the highest morbidity and mortality [1]. COPD was the fifth cause of death in 2002, and it is projected to be the fourth cause of mortality by 2030 [2]. In the natural history of the disease, episodes of exacerbation of chronic respiratory pathology are frequent [3, 4], the economic and social costs of which are extremely high [5]. The exacerbations of COPD worsen the advanced stages of disease (stage II and III of the GOLD classification) and, in the most severe forms, are associated with high mortality [5]. The risk of death in these conditions is linked not only to comorbidity [6], but, above all, to the onset of respiratory acidosis (acute or acute-on-chronic respiratory failure) resulting in the need for ventilatory assistance [7].

A functional and operationally effective key describing indications and methods of ventilatory care used in the management of COPD patients with acute respiratory failure (ARF) starts from the analysis of the pathophysiological causes that determine their onset.

32.2 Pathophysiology of Respiratory Failure in COPD Applied to the Management of Patients in Need of Ventilatory Care (Why?)

The purpose of breathing is to bring oxygen and remove carbon dioxide to/from tissues [8]. Respiratory and cardiovascular systems contribute to this function. The respiratory system is structured to transfer respiratory gases between air and blood. To accomplish this task, the respiratory system is composed of a gas exchanger (the lungs) and of a mechanical pump (the thoracic wall associated with the respiratory muscles). A functional damage can involve both the gas exchanger and the respiratory pump or both, hesitating respectively in a predominantly hypoxemic or hypoxemic–hypercapnic respiratory failure [9]. The addition of an external mechanical pump (the mechanical ventilator) can be used to assist the respiratory system in restoring gas exchange when the in-built pump (the respiratory muscles) is failing in part or completely.

The equation of motion of the respiratory system (Eq. 32.1) mathematically defines a universally accepted mechanical model of the respiratory system [10].

$$P_{\text{mus}} = E \cdot V_T + R \cdot V' + \text{PEEP}_i \tag{32.1}$$

where P_{mus} is the (de)pressure generated by the inspiratory muscles activity during inspiration, E is the elastance of the respiratory system, V_T is the tidal volume displaced during inspiration, R is the resistance of airways and tissues, V' is the inspiratory airflow, and PEEP_i is the positive elastic pressure present at end expiration when inspiration starts above the relaxation volume of the respiratory system.

It correlates the pressure(s) available during inhalation (term to the left of the equation) with elastic and resistive pressures that must be generated to produce inspiratory flow and volume (term to the right of the equation). The equation of motion is a powerful theoretical tool as it is not only able to make predictions about the mechanical behavior of the respiratory system in the most varied pathophysiological conditions that arise during spontaneous breathing, but also to model and predict what happens by applying the mechanical ventilator support modes currently in use and, in all probability, in the future. Accordingly, it becomes clear how mechanical ventilator assistance works, what ventilation modes are currently most effective, at what stage of illness to apply them, how to adjust settings and when and how to remove the mechanical assistance.

32.2.1 The Load (Respiratory Mechanics)-Capacity (Inspiratory Muscle Strength) Balance

In the presence of an intact neuromuscular control system, patients develop mainly hypercapnic respiratory failure whenever there is an imbalance between the ability to generate pressure by the inspiratory muscles and the respiratory system mechanical load [11–14]. The equation of motion of the respiratory system (Eq. 32.1) quantifies and models this balance.

This is often the case during COPD exacerbation. Coussa et al. evaluated and distributed the inspiratory mechanical load in its components in normal subjects and in COPD patients with severe respiratory failure [15]. They showed that the mechanical load of patients is 2–4 times higher than in normal subjects mainly due to the presence of $PEEP_i$ (absent in normal subjects), and increased respiratory resistance. In addition, subsequent literature has shown that the ability to generate pressures of the respiratory muscles is impaired in COPD patients with ARF. In particular, the static increase of end-expiratory lung volume, coupled with the presence of dynamic pulmonary hyperinflation (DPH) play a key role in limiting their function [16]. In fact, the increase in lung volume impairs the ability to generate pressure of inspiratory muscles because of (i) the inspiratory muscles fibers shortening with respect to their optimal length, and (ii) the alteration of geometric conditions between the diaphragm and the chest wall [17, 18], notwithstanding adaptation of the length of muscle fibers to static and dynamic variations in pulmonary volume induced by COPD have been described [19–21]. In addition, malnutrition [22], electrolyte disorders [23], and steroid therapy [24] usually established for the treatment of episodes of exacerbation can contribute to further impairing the function of the respiratory muscles.

The high mechanical load associated with the reduced efficiency of inspiratory muscles force patients with COPD exacerbation to breathe near or above the fatigue threshold of the respiratory muscles, a causative mechanism of acute respiratory failure [13, 14, 25].

32.2.2 Pathophysiological Rationale of Using NIMV to Treat ARF in COPD Exacerbation

The role of mechanical ventilation in hypercapnic respiratory failure is to add an external pump to support the failing respiratory muscles in providing adequate elastic pressure to generate the tidal volume, resistive pressure to generate flow in the airways, and additional pressure to offset the presence of $PEEP_i$. The effect of mechanical ventilation is represented in the equation of motion by reporting the pressure generated by the ventilator in the airways (P_{aw}) in its left term (Eq. 32.2):

$$P_{mus} + P_{aw} = E \cdot (V_T) + R \cdot (V') + PEEP_i \tag{32.2}$$

It is clear from Eq. (32.2) that mechanical ventilation is not designed to modify the mechanical characteristics of the respiratory system, but it is used substantially to re-equilibrate the imbalance between mechanical load and respiratory muscle performance.

32.2.2.1 NIMV and Inspiratory Muscle Effort

COPD patients in respiratory failure demonstrate unsustainable levels of activation of inspiratory muscles [12–15, 25, 26]. Mechanical ventilator assistance significantly reduces the effort required of inspiratory muscles. For example, the diaphragm time pressure product, a recognized index of diaphragm energy expenditure [27], decreases significantly with the application of noninvasive CPAP, PSV, and with a combination of CPAP and PSV in COPD patients with ARF [28]. Interestingly, CPAP and PSV, assisted mechanical ventilation modes, are both effective in reducing the energy cost of diaphragm contraction, in agreement with evidence that the presence of $PEEP_i$ associated with high pulmonary resistances contributes to a large part of the pathological mechanical load in patients with COPD [12, 15]. Particularly, CPAP is indicated to counterbalance the presence of $PEEP_i$, while PSV assists the respiratory muscles in generating volume flow in the presence of a pathological elastic and resistive load [28, 29]. The above physiopathological argumentations, confirmed by numerous experimental data [28, 30], justify the well-established use of CPAP and PSV in combination for the treatment of ARF during COPD exacerbation.

32.2.2.2 NIMV and Respiratory Neuromuscular Control

Assisted ventilatory modes, the most widely used during COPD exacerbations, are effective provided that the patient's neuromuscular control is intact, since its impairment can result in hypoventilation.

Respiratory neuromuscular control can be clinically assessed by measuring occlusion pressure at the airways opening in the first 100 ms from the start of an occluded inspiration ($P_{0.1}$) [31–33]. Repeated observations show that COPD patients in acute respiratory failure have high levels of neuromuscular activation, demonstrating the competence of respiratory centers in this condition [31, 34, 35]: they

want to breathe, but they cannot because of respiratory mechanical constraints [36]. This makes it unlikely that altered neuromuscular control is a prevalent cause of ARF in COPD exacerbations, at least at its inception, and justifies the use of assisted ventilatory modes in the treatment of these patients.

Respiratory centers respond to increased ventilator support with a progressive reduction in neuromuscular activation [12, 37]. This has been demonstrated in ventilator-dependent COPD patients [13] and in patients with acute respiratory failure [38]. However, an excess of ventilator support may exceed the adaptability of the nervous ventilation control system resulting in the appearance of dyssynchronies between the patient's respiratory activity and the operation of the ventilator [12] (see below).

32.2.2.3 NIMV and Pulmonary Gas Exchange

The hypoxemia found in episodes of respiratory failure during COPD exacerbation depends on first instance by the typical morphological alterations found at the pulmonary level. They basically consist of a widespread chronic inflammation of the respiratory tree associated with thickening of the bronchial walls, the presence of excessive secretions that obstruct the bronchial lumem, a hypertrophy/hypertonus of the bronchial smooth musculature [39], and a variable destruction of the alveolar walls [39, 40]. All these morphological alterations cause important functional alterations, including (i) an increased physiological dead space which is responsible for the increase in ventilatory demands, (ii) a reduction in the alveolar exchange surface due to the presence of pulmonary emphysema, and (iii) regional differences in the distribution of ventilation and pulmonary perfusion [41]. The latter mechanism, recognized as the main culprit for hypoxemia found in these patients [41, 42], is associated during the exacerbations of COPD with a marked alveolar hypoventilation induced by changes in the respiratory pattern (rapid shallow breathing) in determining important oxyhemoglobin desaturations [43].

Extrapulmonary factors are also added to the intrapulmonary mechanisms that induce hypoxemia. These include PO_2 of inhaled air, minute ventilation, cardiac range, and consumption of O_2 [44].

The application of noninvasive mechanical ventilation (NIMV) in patients with hypoxemic respiratory failure secondary to exacerbation of COPD increases arterial oxygen partial pressure (PaO_2) and decreases the carbon dioxide arterial partial pressure ($PaCO_2$) [28, 45, 46], notwithstanding intrapulmonary causes of hypoxemia and the consumption of O_2 cannot be manipulated by this treatment [47]. Conversely, the inspiratory fraction of O_2 can be easily modified on the ventilator to correct hypoxemia, as well as the respiratory pattern and minute ventilation can be modified by NIMV application to obtain an increased alveolar ventilation [47].

Altogether, the above data confirm that NIMV can improve gas exchange by acting mostly on extrapulmonary mechanisms, and not on intrapulmonary causes of hypoxemia in COPD patients [47].

32.3 Timing to Start NIMV (when?)

The severity of acute COPD exacerbations (AECOPD) ranges from a modest increase in symptomatology to overt acute respiratory failure (ARF) [48], represented by an increase in $PaCO_2$ over 45 mmHg or compared to the previous chronic hypercapnia, resulting in the onset of respiratory acidosis (pH < 7.35) [41, 49]. In ARF patients, maximized drug treatment and adequate oxygenation may be insufficient; therefore, mechanical ventilatory assistance may be required in the presence of intolerable dyspnea at rest, signs of respiratory distress (tachypnea with respiratory frequency of more than 30 acts/min, obvious use of the accessory respiratory muscles, paradoxical breathing), and laboratory evidence of worsening hypercapnia and acidosis [50].

NIMV may be used with different indications according to the severity of respiratory failure: (i) at an early stage, when mild respiratory acidosis is present and respiratory muscle failure is impending, to avert the need for endotracheal intubation, (ii) as an alternative to invasive ventilation at a more advanced stage of acute respiratory failure, and (iii) to prevent the occurrence of impending (but not established) acute or post-extubation failure, or to facilitate the process of weaning from mechanical ventilation [51].

As a matter of fact, in patients with "mild" AECOPD without respiratory acidosis (pH >7.35), NIMV did not prove to be more effective than standard medical therapy in preventing the occurrence of ARF, and in improving mortality and length of hospitalization. Furthermore, >50% of the patients did not tolerate NIMV [52, 53]. Conversely, in patients with mild-to-moderate ARF, as indicated by pH levels 7.30–7.35, NIMV was successfully administered in different settings, including on the ward, to prevent endotracheal intubation (ETI) [54].

In more severely ill patients (pH <7.25), the rate of NIMV failure was inversely related to the severity of respiratory acidosis, rising to 52–62% [55, 56]. Finally, the use of NIMV as an alternative to ETI did not affect the mortality rate and the duration of ventilatory support, but the patients treated with NIMV experienced a lower rate of complications (VAP, difficult weaning).

32.4 Where Should NIMV be Delivered (Where?)

The stratification of NIMV efficacy according to severity of ARF suggests that the clinical setting for NIMV delivery should be adapted to guarantee adequate resources (availability of a trained team, of noninvasive/invasive monitoring, and of prompt intubation and switch to invasive ventilation) to maximize its success [57]. Available data suggest that NIMV can be safely employed in the Medical Ward in the management of patients with moderate acidosis (pH <7.36 >7.30) and hypercapnia ($PaCO_2$ between 45-60 mmHg) [58, 59]. Intermediate or high-dependency respiratory units fit better for patients who present moderate-to-severe acidosis (pH < 7.30), provided that the facilities for rapid endotracheal intubation and institution of conventional IMV are promptly available. An Intensive Care Unit should

be available for patients with severe respiratory acidosis (pH <7.25) [54]. In this setting, NIMV may be as effective as conventional mechanical ventilation to reverse acute respiratory failure due to COPD [55]. ICU settings also fit for post-extubation failure or difficult weaning [60, 61].

The above strategy of NIMV setting allocation would not only optimize outcomes but also reduce health care costs, the considerable pressure on ICU beds in most countries, and avoid undue distressing experiences for some patients admitted to ICU [62].

32.5 Ventilatory Strategies and Modes in COPD Exacerbation (How?)

The choice of ventilation mode depends on the patient's clinical conditions. Basically, in a COPD patient in whom mechanical ventilation seems to be indicated, there are four levels in the decision-making process to address: (1) whether to ventilate the patient in noninvasive or invasive mode, (2) whether to use assisted or controlled ventilation modes, (3) what ventilatory mode to use, and (4) which parameters to select for each mode.

32.5.1 Choice between Noninvasive Versus Invasive Mechanical Ventilation (IMV)

The general purposes of mechanical ventilation, irrespective of the methods used and their adjustments, consist in (i) supporting the overloaded respiratory muscles, (ii) improving gas exchange and pH, (iii) reducing/resolving dyspnea and, fundamentally, (iv) enabling the patient to survive by ensuring adequate alveolar ventilation, until the causes of respiratory failure have been resolved by pharmacological treatment.

Mechanical ventilation can be applied in two different ways: (1) noninvasively (NIMV) using interfaces applied externally to the body surface and (2) invasively (IMV) through an endotracheal tube that bypasses the upper airways (naso-orotracheal tube, tracheotomy). NIMV can be delivered either in the form of positive pressure ventilation (NPPV) using nasal or oro-nasal masks and helmets, or in the form of negative pressure ventilation (NPV) by placing the patient inside an iron lung or by using ponchos or semi-rigid armors at chest wall level [63]. In expert hands, the NPV seems to have the same performance as the NPPV [64, 65], but, at present, the size of the iron lungs, the technological backwardness of the equipment, the lack of confidence with this technology by most operators, and the consequent reduced diffusion of the technique make NPV a prerogative of a few specialized centers [63]. An exhaustive description of noninvasive NPV is provided in Chap. 8 of this book.

The indication to start some form of ventilatory assistance and the choice between NIMV compared to conventional IMV depends not only on the severity of

COPD exacerbation and the consequent respiratory acidosis, but also on many other factors such as the timing of the intervention, the characteristics of the patient, the skills of the health personnel, the availability of monitoring, etc. [66–68].

Despite the complexity of this clinical problem, there is currently strong scientific evidence that NIMV is an effective treatment of respiratory failure in COPD exacerbations, since numerous randomized and controlled clinical trials, as well as at least four meta-analyses, support this evidence [69–72]. In fact, NIMV has proved effective in reducing the need for ETI and the use of IMV, with a concomitant improvement in survival, a reduced incidence of complications, and reduced stay in intensive care (ICU) and hospital [70–72] compared to conventional medical therapy. Furthermore, the evidence of a greater number of infectious complications related to the use of IMV compared to NIMV [73–76] is remarkable, since the latter can play an important role in influencing survival and length of stay in the ICU.

Based on the scientific evidence published in the literature, it has therefore been suggested to consider NIMV as the reference mode of ventilatory support for the treatment of hypoxemic–hypercapnic respiratory failure during COPD exacerbations, leaving on the back burner ETI and IMV [62].

However, ETI and IMV are still recognized as of paramount importance in the presence of several clinical conditions concomitant to COPD exacerbation to suggest their use either as frontline or second line intervention after NIMV failure.

32.5.1.1 IMV as Frontline Intervention

For many years IMV has been the only mechanical ventilation mode available for the treatment of respiratory failure, thus making discomfort and potential side effects related to the use of invasive methods inevitable [77].

Currently, both IMV and NIMV are available for the treatment of COPD patients who develop respiratory failure because of the failure of conventional medical therapy, the latter being considered the first choice of treatment (see above). However, several clinical conditions preclude the use of NIMV in favor of IMV as frontline intervention: (i) comatose patient in respiratory arrest, (ii) factors preventing the correct positioning of the patient–ventilator interface (recent maxillofacial surgery, nasopharynx deformity, etc.), (iii) severe obesity, (iv) the elective indication to the protection of the airways from inhalation (coma, neuromuscular pathology that prevents valid swallowing, recent gastro-esophageal surgery, risk of vomiting, etc.), (v) the need for frequent bronchial aspirations due to excessive and tenacious bronchial secretions associated with ineffective cough.

A randomized and controlled prospective study of Conti et al. compared the performance of IMV and NIMV in this clinical condition [55]. This study showed that COPD patients treated with either IMV or NIMV had a similar ICU stay, the same days of mechanical ventilation, the same incidence of complications and mortality in both ICU and hospital. These results suggest that IMV can be used without increasing the overall risk to patients, demonstrating the same probability of success as NIMV, when it is applied in the general population of COPD patients with ARF. To sum up, whenever there is an elective indication of endotracheal intubation in combination with the need for ventilator assistance during a COPD exacerbation

episode, IMV still remains the first-choice treatment due to its proven efficacy and sufficient safety [55].

For the sake of completeness, in clinical reality, even an urgent indication to endotracheal intubation and the consequent invasive mechanical ventilation can be sometimes inappropriate if one considers the resulting quality of life, the prognosis, the probability of obtaining short- and long-term benefits, the prospect of becoming a ventilator-dependent patient, the point of view of families, and the expectations of the patient and family members regarding the proposed treatment. There are currently no precise guidelines on these important aspects. In this context, it seems useful to identify within the health team a manager who can carry out an integrated assessment, mediate the various positions, make authoritative and shared decisions and act as spokesman for all interested parties.

32.5.1.2 IMV as Second Line Intervention

NIMV studies used as ARF treatment in COPD patients report varying failure rates ranging from 5 to 40% [56, 74, 78–83] and which can reach 52–62% in patients with pH < 7.25 [55, 56]. An assessment of NIMV's risk factors of failure in the treatment of ARF in COPD exacerbation episodes provides useful guidance for the timely transition to IMV [84]. A comprehensive description of predictive indices of NIMV outcome is provided in Chaps. 20 and 21 of this book. The finding of both early and late failure of NIMV invariably requires the switch to invasive ventilation, excluding patients who die during treatment with NIMV [83]. An exhaustive dissertation of NIMV failure is provided in Chap. 22 of this book. Briefly, early failures are defined as the need for intubation and recourse to IMV due to a worsening of arterial gases or pH in the first 1–2 h of NIMV or their failure to improve after at least 4 h [85], and late failures as a clinical deterioration hesitated in tracheal intubation during hospitalization [83]. Data on the effectiveness of IMV as second-line ventilation after late NIMV failure were reported by Moretti et al. [83]. The authors showed that more than 20% of patients treated with NIMV for a first episode of COPD exacerbation undergo a second episode of exacerbation during hospitalization. Among them, mortality is particularly high (91.6%) if treatment with NIMV is continued compared to those who undergo ETI and IMV (52.6%).

In conclusion, both the NIMV and IMV seem to empower each other if used with an integrated approach associated with COPD exacerbations. Further efforts and research must, however, be carried out in the future to define the indications and limits of use to obtain the best results in terms of patient survival and quality of life.

32.5.2 Choice between Controlled and Assisted Ventilatory Modes

There are countless ventilation modes available on modern commercial ventilators (see Chaps. 2 and 5 in this book). Basically, they differ according to the degree of freedom that the patient has in controlling the operation of the ventilator (Table 32.1). In controlled modes (volume control ventilation: VCV; pressure control ventilation:

Table 32.1 Modes of mechanical ventilation used in COPD exacerbations

Type	Mode	Patient-controlled variable(s)	Aims of mechanical ventilation	Clinical presentation of the eligible patients
Controlled	VCV	– None	– Gas exchange improvement – Breathing pattern optimization – Respiratory muscles rest	– Comatose – Respiratory arrest, or – Gasping – Low NMD
Controlled	PCV	– Tidal volume, to some extent	– Gas exchange improvement – Breathing pattern optimization – Respiratory muscles rest	– Comatose – Respiratory arrest, or – Gasping – Low NMD
Assisted	A/C volume controlled	– Respiratory rate	– Gas exchange improvement – Breathing pattern optimization – Respiratory muscles unloading	– Obtunded – Rapid shallow breathing – Low NMD
Assisted	A/C pressure controlled	– Respiratory rate – Tidal volume, to some extent	– Gas exchange improvement – Breathing pattern optimization – Respiratory muscles unloading	– Obtunded – Rapid shallow breathing – Low NMD
Assisted	VC-SIMV volume controlled	– Respiratory rate – Allows spontaneous breathing between mandatory breaths	– Respiratory muscles unloading – Gas exchange improvement	– Obtunded – Rapid shallow breathing – Low NMD
Assisted	PC-SIMV pressure controlled	– Respiratory rate – Tidal volume, to some extent	– Respiratory muscles unloading – Gas exchange improvement	– Obtunded – Rapid shallow breathing – Low NMD

Assisted	PSV fixed inspiratory pressure	– Respiratory rate – Tidal volume – Inspiratory time	– Respiratory muscles unloading	– Alert, worried – Clinical signs of respiratory distress – High NMD
Assisted	PAV variable inspiratory pressure	– Respiratory rate – Tidal volume – Inspiratory time	– Respiratory muscles unloading	– Alert, worried – Clinical signs of respiratory distress – High NMD
Assisted	NAVA variable inspiratory pressure	– Respiratory rate – Tidal volume – Inspiratory time	– Respiratory muscles unloading	– Alert, worried – Clinical signs of respiratory distress – High NMD

A/C assist control, *NAVA* neurally adjusted ventilatory assist, *NMD* neuro-muscular drive as assessed by $P_{0.1}$ measurement [31–36], *PAV* proportional assist ventilation, *PC-SIMV* synchronized intermittent mandatory ventilation, volume controlled, *PCV* pressure control ventilation, *PSV* pressure support ventilation, *VC-SIMV* synchronized intermittent mandatory ventilation, volume controlled, *VCV* volume control ventilation
Modes are listed (from top to bottom) according to the increasing patient's freedom to control ventilatory parameters

PCV), the patient completely undergoes the operation of the ventilator, which is regulated by an external operator. The latter has the task of choosing all the ventilation parameters, since the ventilator is the only mechanical pump that provides all the necessary energy (P_{aw}) to generate a predefined volume, inspiratory flow or pressure as described in Eq. (32.3):

$$P_{aw} = E \cdot V_T + R \cdot V' + \text{PEEP}_i \tag{32.3}$$

where Paw is the pressure applied by the ventilator to the airways and, hence, to the respiratory system; other symbols as in Eq. (32.1).

In the assisted ventilatory modes (Assist/Control, SIMV, PSV, PAV, NAVA), the patient's control on the ventilator progressively increases (Table 32.1, from top to bottom) both in terms of the number of ventilation parameters controlled and of the mechanical result of his inspiratory muscle effort, since the activity of the respiratory muscles becomes increasingly successful in adding its mechanical effects (respiratory rate, inspiratory duration, flow, and volume generation) to the action of the ventilator (Eq. 32.2). It is clear from this description that the indications and purposes of the controlled modes differ to a large part from assisted modes. In fact, the controlled ventilation modes are mainly designed to ensure fixed and adequate alveolar ventilation and, hence, good gas exchange, whereas the assisted modes are designed to reduce the energy cost of ventilation to maintain an efficient function of the respiratory muscles (Table 32.1) [29].

In summary, due to the wide variability of the clinical condition of the COPD patient in respiratory failure, both controlled and assisted methods may be indicated: the selection criterion is based on the competence of the ventilation control system and the capability of the respiratory muscles to match an increased workload, which in combination determine the amount of pressure available for inspiration (Pmus) (Table 32.1).

32.5.2.1 Controlled Mechanical Ventilation (CMV)

The primary objective of this mode of ventilation is to maintain acceptable oxygenation ($PaO_2 > 60$ mmHg) and to correct respiratory acidosis [68], while keeping the respiratory muscles at rest [86].

Basically, the controlled ventilation modes have indications for the treatment of ARF in COPD exacerbations which partly overlap with those suggesting the use of invasive ventilation. In fact, CMV is indicated in patients with ongoing or imminent respiratory arrest [7, 77], in those who have absolute contraindications to NIMV use, and in those where NIMV fails [68, 85].

In controlled ventilation modes (volume control and pressure control, Table 32.1), the ventilator completely takes charge of the patient's respiratory workload, leaving the respiratory muscles completely at rest. Usually, sedation is necessary to facilitate the rest of respiratory muscles, and greater patient comfort [87]. Because of the critical conditions of these patients, CMV seems indicated only in the Intensive Care setting, where full respiratory monitoring is available and ETI is promptly available [87].

The duration of controlled (and, perhaps, invasive) modes may vary in patients depending on the severity of clinical conditions [86], but, in general, they should be used for a short time (24–48 h) to avoid the onset of muscular damage and atrophy [88–90]. On the other hand, ventilation periods of less than 24 h may prove insufficient to solve the causes of functional exhaustion of overloaded respiratory muscles [91].

Since CMV is seldom if never indicated to assist AECOPD patients with NIMV, its details are not provided in this chapter. An extensive review of these aspects has previously been carried out by D Georgopoulos and L Brochard where the reader is referred for further information [86].

In summary, even if CMV is indicated and provided (mostly invasively) the switch of the patient to an assisted mode of mechanical ventilation is desirable as soon as possible.

32.5.3 Choice and Setting of Assisted Ventilatory Modes

Table 32.1 shows that assisted modes of mechanical ventilation differ mainly according to their capability to adapt to the patient's neuromuscular drive, Assist/Control being remarkably similar to Control modes, and NAVA being completely controlled by the respiratory centers through phrenic nerves activity. Thus, the choice of the assisted mode that matches better to the actual stage of COPD exacerbation depends mainly on the level of competence of neuromuscular drive. As examples, an obtunded patient showing rapid shallow breathing and low neuromuscular drive assessed by low $P_{0.1}$ [36] should be better managed by A/C modes or SIMV modes set with high backup respiratory rate; conversely, a conscious, worried, tachipnoic patient with clinical signs of respiratory distress and high $P_{0.1}$ should take advantage of more versatile modes, ranging from PSV to NAVA according to their availability and operator's confidence toward the technique (Table 32.1).

Details about A/C and SIMV modes are discussed elsewhere in this book (Chap. 3).

Among the assisted modes of mechanical ventilation (Table 32.1), the most widely used in clinical practice in general, and in the treatment of hypercapnic respiratory failure in COPD patients in particular, is pressure support ventilation (PSV). This mode is thoroughly discussed in Sect. 32.5.3.1, including indications, settings for COPD exacerbation, monitoring, and adverse effects.

32.5.3.1 Pressure Support Ventilation (PSV)

Given the high degree of control over the ventilator granted to the patient (control on both the start and the end of inspiration, as well as on tidal volume delivered), this mode has as its primary objective the unloading of the respiratory muscles [29]. Its effectiveness in reducing respiratory muscle workload in COPD patients has been repeatedly confirmed [12, 28, 29, 92–94], and has been compared to volume-control assisted mode (AVC) by Vitacca et al. [95]. The two techniques have proven to be similar in their ability to avoid endotracheal intubation, but PSV has been

shown to be superior both in terms of adherence to treatment and reduced number of side effects.

If the secondary adjustments (quality and sensitivity of triggers, pressurization speed, and criterion of cycling between inspiration/expiration) are initially neglected, the only parameters to be adjusted on the ventilator are the inspiratory and expiratory pressure levels. This convinced the clinicians to consider PSV easy to set up and use. However, it is not so easy to correctly set this mode of ventilatory assistance [96], an operation that would require a timely knowledge of the mechanical characteristics of the patient's respiratory system, as previously discussed.

Invasive measurement of esophageal (and gastric) pressure is the reference technique for estimating the inspiratory mechanical load to cope with during spontaneous breathing and assisted ventilation modes [12, 28]. However, this kind of invasive monitoring does not adapt to current clinical practice, due to the laboriousness of the technique, the level of skills required of operators in the data collection and their interpretation, the difficulty in obtaining repeated measures, the lack of time in case of clinical emergency, etc. [25]. Alternatively, Alberti and collaborators have shown that measuring the neuromuscular drive with the occlusion pressure technique ($P_{0.1}$) correlates with changes of respiratory muscle effort [97]. The same authors have suggested that adjustments of PSV settings resulting in $P_{0.1}$ values below 3.5 cm H_2O are a good compromise to maintain an adequate load-capacity balance of the respiratory muscles during assisted ventilation.

In case of unavailability (most cases) of inspiratory mechanical load and $P_{0.1}$ measurements, regulation of inspiratory pressure based on the current volume generated in PSV mode is widely used in the clinical context [98]. Briefly, the goal is to adjust the ventilator support to obtain current exhaling volumes of about 6 mL/kg [98]. This can be achieved either starting from high inspiratory pressure values (e.g., 20 cmH_2O) to decrease according to the current volume obtained and the patient's comfort, or starting from low pressure values (e.g., 8 cmH_2O) to rise [99]. The first strategy aims to relieve the patient's respiratory distress early, while the second favors the minimization of air leaks in case of noninvasive ventilation to obtain the best possible tolerance and comfort of the patient [99]. This way of operating has proven effective in minimizing asynchronies between patient and ventilator [98]. However, there is some doubt as to the accuracy of regulation strategies based solely on current volume, given the wide variability of patients' subjective response to changes in pressure support [37].

About the regulation of expiratory pressure, see the dedicated paragraph of this Sect. (32.5.3.2).

PSV secondary adjustments are not less important and have a major impact both on the efficacy of this mode of ventilation, and on the optimization of patient–ventilator interactions. The inspiratory trigger phase accounts for no more than 10% of the entire respiratory effort [100] but contributes substantially to the autocycling of the ventilator if too sensitive, or to the presence of patient's unsupported efforts [101]. The flow trigger is preferred for its lower energy cost [100] and adjustments around 1-3 L/min (range 0.5-10 L/min) were considered a good compromise [99]. The inspiratory pressurization speed may also be insufficient or excessive. In the

first case, part of inspiration results under-assisted, while in the second case, overpressure may occur, which may cause nonintentional air leaks and discomfort in the patient [102]. Finally, the standard algorithm controlling the switch from inspiration to expiration (based on cycling to expiration when the inspiratory flow has decayed to 25% of the peak inspiratory flow) is sometimes largely inadequate for COPD patients in mechanical ventilation, being the result of an abnormal extension of mechanical inspiratory time (see section: Patient–ventilator interactions). In the latest generation ventilators, the cycling criterion can be varied (5–70%), thus offering the possibility of modulating the inspiratory time. Experimental data have shown that shortening the insufflation time by manipulating the cycling criterion (e.g., 40–50% of the peak flow), improves coordination between patient and ventilator, reduces the percentage of ineffective efforts without negatively affecting the energy cost of the diaphragm and alveolar ventilation in COPD patients [103].

Patient–Ventilator Interactions

It has been shown that at levels of PSV excessively high compared to the actual patient's inspiratory workload, the inspiratory activity of the patient ends early compared to the mechanical respiratory act supported by the ventilator [12, 37]. In this case, the respiratory system continues to be passively inflated by positive inspiratory pressure [12, 37]. Under these conditions, the duration of inspiratory time and the consequent increase in lung volume are determined either passively by the increase in the elastic return of the respiratory system, or by the recruitment of expiratory muscles [37]. Passive pulmonary hyperinflation generated by high PSV levels has two consequences. First, the higher the V_T, the longer the expiratory time required to reach a complete exhalation. Second, part of the patient's expiratory time is "occupied" by the mechanical inspiratory time. Under these conditions (shortened expiratory time), one or more inspiratory efforts may occur early during exhalation without being able to cycle the ventilator (ineffective inspiratory efforts) due to high operational pulmonary volume and consequent elevated elastic recoil pressure [12, 104]. That is to say, the PSV level can be set incorrectly in such a way as to provide not only insufficient, but also excessive, support [12]. This last condition is associated with the presence of ineffective inspiratory efforts in ventilatory dependent COPD patients [12]. A diaphragmatic pressure time product higher than 150 $cmH_2O \cdot min$, a $P_{0.1}$ around 1.5–2.5 cmH_2O, or a V_T lower than 8 mL/kg, all obtained with the application of comfortable PSV levels, have been shown to protect against the onset of this major and clinically relevant patient–ventilator dyssynchrony [12, 98].

32.5.3.2 PEEP/CPAP

Since the effects of positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) application during spontaneous breathing depend on the resulting pulmonary distension, their use has traditionally been questioned for the treatment of acute respiratory failure in patients with COPD. The reason for this prejudice is based on the fact that pulmonary hyperinflation (DH) is a common phenomenon in these patients. In the presence of DH, it was believed that CPAP

could (i) worsen the dysfunction of the respiratory muscles by further reducing their contractile capacity for dynamic increase in lung volume, (ii) be responsible for barotrauma, and (iii) cause hemodynamic impairment against modest advantages, since in these patients, hypoxia is usually resolved by administering low oxygen concentrations even during episodes of exacerbation. However, in contrast to this dated point of view, recent evidence shows that CPAP applied either invasively [105] or noninvasively [28] is beneficial in patients with COPD exacerbation.

The presence in these patients of pulmonary dynamic hyperinflation associated with expiratory flow limitation (EFL) [26, 106–109], may explain the apparent contrast. The presence of $PEEP_i$ abnormally challenges the inspiratory muscles as it acts as a "threshold load" that must be compensated for and subsequently maintained throughout the inspiration by inspiratory muscle contraction before negative pressure in the central airways can be generated to produce airway flow and tidal volume increase [110]. This additional load imposed on the respiratory muscles can be exceedingly high. The presence of $PEEP_i$ can account for up to 40% of the entire energy cost of breathing in patients with exacerbation of COPD [12–15].

EFL is defined as the loss of relationship between alveolo-atmospheric pressure gradient and exhalation airflow: at pressure gradient increments the flow does not vary and the apparent resistance increases due to dynamic airway compression [111]. In this condition, the exhaling flow is determined by the difference between alveolar pressure and critical transmural pressure present at the point where the airways collapse [16, 112]. In the presence of EFL, the application of positive external pressure to the airway opening (CPAP/PEEP) does not affect the alveolar pressure (and therefore end-expiratory volume) until a critical value is reached or exceeded, just below the $PEEP_i$ value [105, 111, 113]. This particular feature allows CPAP to work during inspiration by counterbalancing the threshold load (i.e., $PEEP_i$), thus reducing inspiratory workload, without showing any negative effects related to a reduction in the alveolo-atmospheric pressure gradient during expiration [111, 113]. These mechanisms were demonstrated in patients intubated with COPD during the ventilator weaning phase [105] and confirmed during noninvasive mechanical ventilation [28]. PEEP, being applied only during expiration, if applied in conjunction with inspiratory pressure assisted modes, can only increase the sensitivity of the inspiratory trigger [111, 114, 115] and reduce its energy cost [12, 115], and improve patient–ventilator interaction by reducing the percentage of ineffective breathing efforts to cycle the ventilator [12, 104]. By contrast, PEEP cannot counterbalance $PEEP_i$ during inspiration since the driving inspiratory pressure results reduced by the PEEP amount [12]. Therefore, the choice between these two methods cannot be separated from a careful assessment of the physiopathological objectives to be met. In particular, the application of PEEP is best suited in combination with volumetric assisted/controlled modes, while CPAP is indicated for pressure assisted modes.

Some limitations suggest not applying CPAP indiscriminately. First, $PEEP_i$ can also be present in the absence of EFL [26, 111]. For example, some patients may show $PEEP_i$ in the absence of EFL [106]. In this case, the end-expiratory lung

volume increases with the application of any level of positive exhalation pressure applied to the opening of the airways [111].

Second, the level of $PEEP_i$ can vary greatly among COPD patients with EFL [45, 105, 109, 116]. Accordingly, the standard levels of CPAP applied (e.g., 5–10 cm H_2O), may be inappropriate both in excess and in defect: high levels of CPAP (i.e., above $PEEP_i$ levels resulting in increased lung volume) are not justified. However, on the other hand, excessively low levels of CPAP only marginally reduce the adverse effects of $PEEP_i$ and, therefore, could be of limited benefit, if any. A measurement of $PEEP_i$ values on an individual basis would be desirable to define the level of CPAP or PEEP needed to optimize benefits and minimize negative effects [28, 117].

Finally, it should be noted that the measurement of $PEEP_i$ during spontaneous breathing may be overestimated due to the presence of activity of the expiratory muscles [28, 118], adding uncertainty about the choice of CPAP values to be set unless appropriate corrections are applied [28, 119]. An empirical rule of approach to PEEP/CPAP levels in COPD exacerbation patients requiring ventilatory assistance is to apply a positive pressure of about 5 cmH_2O, since most of these patients have EFL, and that the average $PEEP_i$ values measured in multiple previous studies in these patients amount to 4.9 cmH_2O.

32.5.3.3 Proportional Assist Ventilation (PAV)

PAV is a form of partial pressumetric ventilator assistance that deviates from the common forms of mechanical ventilator assistance [120, 121]. In this mode, there are no pre-set flows, volumes, or pressures and the choice of the ventilator pattern is in theory completely controlled by the patient. From this point of view, PAV grants even greater degrees of freedom to the patient's ventilator choices even compared to PSV, with the declared aim of improving patient–ventilator interaction (Table 32.1).

Physiological studies have demonstrated the effectiveness of PAV in meeting the requirements for treating COPD patients with acute respiratory failure [25, 122–124]. Other studies have compared PAV and PSV without finding substantial differences between the two modes [125–127], other than a better patient-perceived comfort when using PAV [127].

PAV settings require a precise characterization of the mechanical alterations of the patient's respiratory system even more stringently than PSV requires. In PAV mode, the ventilator compensates for resistive workload impairments by providing pressure in proportion to the inspiratory flow generated (FA) and for elastic workload impairments of the respiratory system by providing pressure in proportion to changes in inspiratory volume (VA) [120]. It is therefore necessary to characterize the resistance and elastance properties of the patient's respiratory system to normalize the mechanical load of ventilation with PAV [25].

The intrinsic characteristics of PAV present some problems of use especially in COPD patients. In the presence of $PEEP_i$, PAV cannot compensate for its presence if adequate CPAP levels are not provided, since this mode of ventilation cannot handle this mechanical anomaly due to its principles of operation [25]. In addition, in noninvasive modes, the possible presence of non-intentional leaks can alter the

correct PAV functioning, the latter being based on a precise estimate of changes in inspiratory flow and volume [120, 121]. These implementation problems currently make PAV a ventilator mode of great charm and intellectual stimulus, but of little impact in clinical use.

Recently, PAV has been equipped with an automatic resistance and elastance estimation software (PAV$^{+®}$) that allows the automatic adjustment of the FA and VA gain factors to keep the resistive and elastic faced by the respiratory muscles normal [128]. Both physiological [128] and short-term clinical [129] studies comparing PAV with PSV in acute patients have shown a greater effectiveness of PAV$^{+®}$ than PSV in compensating for sudden changes in patients' mechanical respiratory load [128] and in increasing the likelihood of continuing assisted mechanical ventilation [129]. These promising results await convincing confirmation from larger-scale randomized trials to allow a wide spread of this ventilatory approach in clinical practice.

32.5.3.4 Neurally Adjusted Ventilatory Assist (NAVA)

NAVA is the latest mode of assisted ventilation [130]. This mode generates inspiratory pressures in proportion to the electrical activity of the diaphragm, measured with a series of electrodes applied to an esophageal catheter [130]. Similar to PAV, it guarantees a proportional relationship between ventilatory assistance and the patient's spontaneous inspiratory effort. The only adjustment available on the ventilator is the gain factor that transforms the electrical activity of the diaphragm into pressure applied to the airways. The measurement of respiratory centers activity is direct, so that, in the presence of an adequate diaphragmatic EMG signal, many, if not all, problems related to the presence of asynchronies between the patient and the ventilator are solved [131]. This mode can automatically take charge of the presence of $PEEP_i$ in COPD patients, without the need for any measurement of respiratory mechanics, although its effects have recently been studied in combination with varying PEEP levels in acute sedated and mechanically ventilated patients [132]. Finally, the characteristic of being regulated by a physiological signal (EMGdi) independent of flow, volume and pressure, theoretically makes NAVA the reference mode for noninvasive ventilatory assistance, since it is virtually immune from nonintentional leaks at the level of the patient–ventilator interface. On the other hand, a lot of uncertainty remains about how to adjust NAVA settings [133, 134].

Although this ventilation technique is particularly promising for use in patients with COPD, it is still to be considered in its early days and cannot be recommended for large-scale clinical use.

In conclusion, apart from the controlled and assist/control modes to be used only in the initial stages of ventilation, PSV added with CPAP, between the purely assisted modes (PSV, PAV, and NAVA), results the most common (and effective) choice for ventilatory management of respiratory failure in patients with COPD exacerbation. PAV has not yet shown a cost-benefit ratio substantially higher than the reference mode to be a viable alternative, although some improvement is expected with the spread of PAV$^{+®}$ soon. Even more futuristic seems to be the NAVA mode that only discounts its initial diffusion, the need to position an esophageal electrocatheter, and the uncertainties that still exist regarding the adjustment criteria.

32.5.4 NIMV: Role of Interfaces

Even though NIV is an effective and safe means of treating ARF in COPD patients [46, 56], its effectiveness may depend to a large extent on how it is implemented. Key points include patient selection, ventilator regulation, and choice of the interface. Literature suggests that most NIV failures are due to interface-related technical problems such as nonintentional air leaks, discomfort in wearing the interface, and compression skin lesions [135]. Skin lesions occur in the areas of greatest pressure of the mask on the skin and can be found even after a few hours of ventilation. Their frequency varies from 2 to 23% depending on the published case studies [136]. The continuous use of noninvasive mask ventilation also seems to favor the appearance of compression skin lesions. In a study in which NIV was prolonged for over 48 hours, the frequency of skin lesions was reported in approximately 70% of treated patients [137]. To overcome the problems related to comfort and the risk of skin lesions, structural changes have been made to the masks by increasing the surface of the inflatable bearing, reducing the thickness of the material with which the bearing is made, and increasing the number of attachment points of the mask fixing cap with discrete results [136].

Given the wide variability of patients' faces conformation and particular anatomical situations (e.g., edentulism), it seems particularly difficult for a single mask to adapt satisfactorily to each patient. It is more likely that the availability of different models in several sizes will facilitate the choice of the most efficient interface.

Recently, the use of transparent plastic helmets has been introduced for the application of NIV both in continuous positive pressure mode (CPAP) [138] and in pressure support mode [139, 140]. Unlike conventional masks, the helmet allows greater comfort and does not present pressure points on the face, avoiding the risk of skin lesions at the expense of the nasal pyramid and allowing ventilator assistance in those who already have mask injuries [139, 140]. The potential problems related to the helmet are its high internal volume and the distensibility of the walls (especially the sealing collar) that predispose to the re-breathing of CO_2 and to a not optimal interaction between patient and ventilator when partial ventilator assistance modes are used, respectively. In this latter condition, the helmet interferes negatively with the algorithms of recognition of the beginning and end of the patient's inspiratory effort based on variations in pressure or flow in the airways [141]. Re-breathing of CO_2 accumulated inside the helmet and the presence of important dyssynchronies between patient and ventilator have been associated with a lower efficiency of PSV in reducing the energy cost of ventilation and dyspnea compared to the same mode delivered by face mask [141]. In conclusion, the helmet should be considered as a second choice in the management of ventilated COPD patients in noninvasive mode due to hypercapnic ARF. In case the choice of interface falls on the latter option, close monitoring of the patient's response in terms of reduction of $PaCO_2$ is indicated, turbine ventilators equipped with single circuit, and an intentional leak should be preferred, this latter being mounted just before the expiratory PEEP valve [142].

Non-intentional leaks through the contact surface between the mask and the patient can also adversely affect the ventilator's cycling algorithms. A

non-intentional leak from the noninvasive interface during support pressure assistance simulates the presence of an inspiratory flow generated by the patient and forces the ventilator both to provide autocycled inspiratory support within the patient's respiratory cycle, and to continue the duration of the inspiratory support itself even during the patient's exhalation [143]. These induced dyssynchronies can be so marked to cause ineffectiveness of ventilatory assistance in reducing the energy cost of breathing and increased discomfort on the part of patients [143]. In this case, to avoid the risk of NIV failure, it may be useful to use timed pressumetric inspiratory assistance methods that have proven effective in correcting the above problems [143].

Different types of masks have varying effects on the efficiency of noninvasive mechanical ventilation. Navalesi et al. compared the effects of three types of masks (facial, nasal, and nasal pillows) and two modes of mechanical ventilation (assisted volume vs assisted pressure) in patients with hypercapnic respiratory failure [144]. All the conditions tested proved to be efficient in improving gas exchange and minute ventilation compared to spontaneous breathing. However, the application of the nasal mask was the best tolerated, although the less effective in removing CO_2. No difference was found between the two ventilator assistance modes in terms of mechanical ventilation tolerability, gas exchange, or ventilator pattern. These data suggest that the type of interface may affect the result of noninvasive mechanical ventilation more than the chosen ventilation mode [144].

In conclusion, the patient–ventilator interface is far from being a secondary item in the process of implementing effective noninvasive ventilatory care in COPD patients. The correct choice of interfaces, the control of non-intentional leaks, the optimization of patient–ventilator interactions, and the prevention of side effects associated with their use must be part of the wealth of knowledge of operators dealing with noninvasive mechanical ventilation in COPD exacerbation.

32.6 Conclusions

Indications and choices of mechanical ventilation in patients with COPD exacerbation are based on documented pathophysiological mechanisms that cause acute, acute-on-chronic respiratory failure. Noninvasive mechanical ventilation represents the gold standard in this context, even if invasive mechanical ventilation still has a precise role in selected patients, especially as rescue ventilation when NIMV fails. In acute conditions, mechanical ventilation aims to reduce respiratory workload and to support gas exchange and alveolar ventilation. Among the ventilatory modes, pressure assisted combined with CPAP represent the best current choice for the treatment of ARF in COPD exacerbations. Finally, since pathophysiological alterations of COPD affect every aspect of the application of mechanical ventilation in these patients, regular clinical-instrumental monitoring is essential to obtain the best results and to avoid complications related to this method.

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33 Noninvasive Mechanical Ventilation in Acute Exacerbations of Chronic Obstructive Pulmonary Disease: Key Determinants of Early and Late Failure

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Abbreviations

AECOPD	Acute exacerbation of chronic obstructive pulmonary disease
AHRF	Acute hypercapnic respiratory failure
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
$FİO_2$	High-fractionated oxygen
HES	Hypercapnic encephalopathy
ICU	Intensive care unit
IMV	Invasive mechanical ventilation
NIV	Noninvasive ventilation
OR	Odd's ratio

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_33

33.1 Introduction

An acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is defined as an acute worsening of symptoms that results in the need for additional therapy. Exacerbations should be assessed properly as they inversely affect the course of the disease. AECOPDs are categorized as mild (treated with short acting bronchodilators only), moderate (treated with short acting bronchodilators plus antibiotics and/or oral corticosteroids) or severe (patient that requires hospitalization or visits the emergency room, may be associated with respiratory failure) [1]. AECOPDs are a very common reason for admission to hospital. Approximately 20% of patients hospitalized for chronic obstructive pulmonary disease (COPD) develop acute hypercapnic respiratory failure (AHRF) leading to acute or acute-on-chronic respiratory acidosis when the respiratory muscles fail to achieve adequate alveolar ventilation and also hyperinflation during exacerbation also contributes to respiratory muscle compromise. With excess load on respiratory muscles, an abnormal breathing pattern develops which is characterized by a high respiratory rate with lower tidal volumes. As a consequence, the level of arterial carbon dioxide (CO_2) rises and respiratory acidosis ensues [2]. Estimates of in-patient mortality range from 4 to 30%, but patients admitted due to AHRF have a higher rate, in particular elderly patients with co-morbidities (up to 50%) and those requiring the intensive care unit (ICU) (11–26%) [3].

What triggers the abnormal breathing pattern of the patient remains unclear [4]. The key element during decompensation seems to be the shortening of the inspiratory time, inducing both a decrease in tidal volume and an increase in respiratory frequency. Because this is associated with, or is secondary to, excessive respiratory loads, treatment should be directed at reducing the loads imposed on the respiratory muscles. When hypoventilation becomes so severe that several organ dysfunctions occur, there is no choice other than to provide artificial ventilation to avoid a fatal outcome despite medical therapies [4]. The traditional way of artificial ventilation was invasive mechanical ventilation (IMV), but nowadays, the role of noninvasive ventilation (NIV) in the management of acute hypercapnic respiratory failure secondary to COPD is well established [5]. Several randomized controlled trials have demonstrated that adding NIV to standard medical therapy improves dyspnea as well as reduces mortality, intubation rate and hospital length of stay [5, 6]. A previous study using NIV in respiratory failure secondary to exacerbations of COPD demonstrated reductions in respiratory rate and transdiaphragmatic activity with increases in tidal volume and minute ventilation. Thus, NIV not only rapidly improves gas exchange but also allows respiratory muscle rest reducing respiratory muscle work in respiratory failure [7].

33.2 Discussion and Analysis of Main Topic

NIV is essential in AECOPD to prevent acute respiratory acidosis, endotracheal intubation and invasive mechanical ventilation in mild to moderate acidosis and respiratory distress and to prevent invasive ventilation in severe acidosis and more

severe respiratory distress [2]. The strongest evidence to support NIV is based on patients with a pH of 7.25–7.35, in the absence of a metabolic cause for the acidosis. An improvement in either pH or respiratory rate, or ideally both, is a good predictor of a successful outcome with NIV; in those that will respond, response is seen within the first 1–4 h [8].

"How NIV works?" question has three important characteristics.

The first is ventilation. The success of NIV is based on the ability of assisted ventilation to improve alveolar ventilation by increasing tidal volume. Pressure targeted modes support in synchrony with the patients' inspiratory efforts, which usually results in an increase in tidal volume, subsequently associated with a reduction in the load on respiratory muscles [9]. As the volume that reaches the lung is improved, alveolar functions, gas exchange abnormalities, and clinical deterioration are resolved.

The second characteristic is its intermittent mode of support. NIV is usually delivered periodically for only a few hours during a 24-h period (usually 6–12 h). A stimulated and active respiratory drive still works and can therefore sustain prolonged periods of spontaneous breathing. However, the treatment should provide a reduction in the amount of effort needed and intermittent support seems to be adequate. When the need for ventilatory support becomes permanent, tolerance of the mask becomes a limitation and is frequently a cause of failure.

The third characteristics is the availability of a face mask instead of endotracheal tube. Although the use of face masks has some limitations such as leaks and limited clinical tolerance, they have been confirmed to be superior to endotracheal tubes as a first-line treatment [4].

However, NIV is not successful in all cases of acute or chronic respiratory failure due to COPD when compared to usual medical care with reported failure rates of between 9% and 50%. There has also been concern that NIV may delay endotracheal intubation and mechanical ventilation resulting in a worse outcome [10]. Prediction of outcomes, specifically negative predictors, following acute NIV is essential to assist the physician with decisions regarding the use of NIV in the acute setting.

Patient selection is the main stone in NIV. Three temporal moments and the main patient related predictors or risk factors, based on data from randomized controlled trials, were defined as:

1. Immediate failure (within minutes to <1 h) (15% of all failures)
2. Early failure (1–48 h), (68% of all failures)
3. Late failure (after 48 h), (17% of all failures)

Patient related risk factors:
Immediate risk factors:

1. Weak cough reflex and/or excessive secretions
2. Hypercapnic encephalopathy (HES) and coma
3. Intolerance and psychomotor agitation

4. "Fighting with the machine": Patient–ventilator asynchrony

Early risk factors:

Hypoxemic ARF

1. Baseline arterial blood gas and inability to correct gas exchange (pH < 7.25)
2. Increased severity of disease
3. Increased respiratory rate (>35 breaths/min)
4. Miscellaneous: Poor nutritional status, increased heart rate, higher baseline C-reactive protein/white blood cell count, lower serum potassium, airway colonization by non-fermenting gram-negative bacilli

Late risk factors:

1. Sleep disturbance
2. Functional limitation
3. Possible initial improvement in pH
4. Hyperglycemia

Immediate NIV failure: Immediate NIV failure is defined as the failure within minutes and not beyond the first hour. Approximately 15% of all NIV failures were immediate independent of the cause of respiratory failure.

Weak cough reflex and/or excessive secretions: Ineffective clearance of secretions with an inadequate cough reflex is a relatively common cause of immediate failure. The patient should have the capability of spontaneous secretion removal as it is a relative contraindication for NIV, especially in patients with impaired consciousness and depressed cough. Some physiotherapeutic techniques have been shown to modulate mucociliary clearance during NIV; intrapulmonary percussive ventilation is a technique that delivers small bursts of high-flow respiratory gas at high rates for mobilization of secretions. The use of fiberoptic bronchoscopy in the early period is another intervention that may minimize the burden of respiratory secretions [11].

HES and coma: HES is often considered a cause of immediate NIV failure because of poor compliance due to confusion and/or agitation. Additionally, it is viewed as a relative contraindication because of the increased risk of aspiration. The risk of aspiration has been shown to be minimized by the rapid improvement of neurological status under NIV, and NIV failure rates were reported to be comparable among patients with and without HES. The use of a relatively high back-up rate and/or pressure control ventilation may also help to "capture" the patient better. Another key factor in patients with HES is the rebound effect of high-fractionated oxygen (FiO_2) on the $PaCO_2$ and pH, known as the "Haldane effect." This effect can be prevented by a simple intervention: decreasing the FiO_2 level [11].

Intolerance and psychomotor agitation: Patient tolerance has been shown to be critical for NIV success, especially in the first few minutes while the patient adapts to this "new mode" of breathing. The use of judicious sedation may be valuable to achieve a sedation level that keeps the patient awake, easily arousable, and comfortable. Ideal sedatives should be short acting and have no significant effects

on respiratory drive and hemodynamics. It has to be kept in mind that over sedation during NIV can be potentially dangerous. Thus, close monitoring with evaluation of arterial blood gas, cardiopulmonary and ventilator parameters, adverse events, and the level of sedation is mandatory [11].

Patient–ventilator asynchrony: Asynchrony has rarely been cited as a direct cause of NIV immediate failure. Asynchrony can easily be detected by a physical examination (e.g., number of spontaneous breaths vs. ventilator-delivered breaths, accessory muscle use) of the patient and symptoms (e.g., dyspnea). Two main causes of asynchrony are a high level of ventilator support and an increased number of leaks. A number of strategies can be implemented to avoid "gross asynchronies," such as optimization of ventilator settings using the screen ventilator waveforms, adjusting trigger sensitivity, increasing positive end-expiratory pressure, minimizing leaks, using different modes, or more sophisticated ventilators. New modes of ventilation, such as neutrally adjusted ventilator assist, have been documented to reduce asynchrony [11].

Early NIV failure: Nearly 65% of NIV failures occur within 1–48 h of NIV use. This time interval has received more attention in assessments of predictors of failure. It has two main subtypes, i.e., hypoxemic and hypercapnic respiratory failure, and we will discuss the hypercapnic one in detail as it is our main concern.

Although AHRF covers respiratory failure due to neurological disorders (such as neuromuscular disorders) or other acute or chronic lung disorders (such as restrictive lung disease), most of the studies done in this field have involved patients with AECOPD [11].

Baseline arterial blood gas and inability to correct gas exchange: The pH level, which is an indicator of the severity of hypercapnia, has been reported to be a critical factor in determining the success of NIV. Although some reports failed to show any relationship between baseline arterial blood gases and the success of NIV, a large body of evidence clearly indicated that a lower baseline pH is a risk factor for NIV failure in COPD patients. In nearly 50–60% of patients with a baseline pH of <7.25, NIV was unsuccessful. A subgroup analysis of COPD patients with mild to moderate acidosis revealed that NIV improved patient outcomes only if the baseline pH was ≥7.30. Three studies with 320 patients were included in the 7.35–7.30 subgroup and five studies with 221 patients in the <7.30 subgroup. Studies in both pH subgroups showed treatment failure to be significantly less with NIV (RR 0.63; 95% CI 0.43, 0.95 and RR 0.37; 95% CI 0.25, 0.54, respectively). There were no significant differences between the two pH subgroups [7].

In addition to baseline levels, pH values 1 h after the application of NIV were shown to be strong predictors of the success of NIV, with high sensitivity and good specificity (93% and 82%, respectively) [9]. In a study of more than 1000 COPD patients, Confalonieri et al. pointed out that a pH <7.25 after 1 h of NIV use was associated with an increased risk of failure and that the risk of failure was even greater than when the pH levels were <7.25 at admission. For the abovementioned reasons, we do not recommend routine use of NIV in patients with a pH <7.25 outside a "protected" environment [11].

Increased severity of disease: The relationship between NIV failure and the severity scores, including APACHE II and SAPS II, has been documented in a number of reports. Several researchers found an association, whereas others failed to find any association.

Increased respiratory rate: An initial high respiratory rate and its reduction after 1 h of NIV have been shown to be associated with successful NIV outcomes in COPD patients. A respiratory rate of 30–34 and ≥35 breaths/min at admission were demonstrated to lead to NIV failure, with an Odd's ratio (OR) of 1.83 and 2.66, respectively, whereas the ratios increased to 2.67 and 4.95, respectively, for the same breathing frequency after 2 h of NIV [11].

Miscellaneous risk factors of NIV failure: Miscellaneous risk factors for NIV failure in hypercapnic ARF are poor nutritional status, a high white blood cell count, low serum potassium, and an increased heart rate. Two additional issues may merit specific consideration. Old age has never been shown to be a negative variable in determining NIV outcomes, and older patients with hypercapnic ARF may respond even better than younger ones to NIV [11].

Late NIV failure: Although the definition of late NIV failure has not been standardized; it is usually defined as failure that occurs 48 h after initiation of NIV, following an initial successful response. Actually, it occurs in a considerable subset of patients (about 15% of NIV failures).

The occurrence of late failure in COPD patients admitted with hypercapnic ARF to ICUs when NIV was used >24 h was found to be associated with functional limitation before admission, the presence of hyperglycemia, and a lower pH at admission. $PaCO_2$ and pH values improved gradually and similarly within the first 24 h in both success and late failure groups. This is of particular importance because initial good responses to NIV may decrease attention and monitoring by clinicians in the following hours. During a hospital stay, pneumonia was more frequently observed as a complication in a late failure group compared to a success group (12.9 vs. 0%). The mortality of a late failure group was extremely high compared to a successful group in another study (68 vs. 0%). In a recent study, sleep disturbance (classified as an abnormal electroencephalographic pattern, greater circadian sleep-cycle disruption, and less nocturnal rapid eye movement sleep) and increased delirium during an ICU stay were also associated with late NIV failure in hypercapnic patients. NIV patients should be continuously monitored (including their sleep patterns and state of delirium), even if their initial clinical and arterial blood gas responses are good because late NIV failure can lead to high mortality [11].

The global rise in obesity has impacted on the COPD population. Of further interest, obese COPD patients were protected from adverse outcomes and were less likely to develop late NIV failure or require hospital readmission at 1 year. Patients with COPD and obesity are also more likely to receive long-term ventilatory support in the form of either NIV or continuous positive airway pressure (CPAP), to treat COPD–obstructive sleep apnea overlap syndrome. It is unclear from the data whether the improved outcomes in obese COPD patients are a reflection of enhanced interaction between opposing pulmonary mechanics or whether it simply reflects

the higher incidence of home NIV and CPAP as a treatment, which increases overall healthcare support.

In the decision to start NIV, the presence of co-existing pneumonia can be confusing from time to time in the practice of clinicians. In current clinical practice, community-acquired pneumonia (CAP) and pneumonic exacerbation of COPD are not exclusive diagnoses for NIV. A recent study revealed that the presence of pneumonia does not appear to be a deterrent to providing NIV, which is consistent with literature data [12, 13]

To foresee the failure risk, patient-related risk factors were summarized up to now. Non-patient related risk factors will be discussed from here on.

The timing of the application of NIV is a critical factor. A longer delay between admission and NIV use was shown to be an independent risk factor for NIV failure probably due to the progression of the underlying disease. Therefore, early use of NIV is recommended. It is also critical not to unduly delay the decision to intubate a patient with failed NIV, because the risk of unanticipated respiratory or cardiac arrest could lead to increased morbidity and mortality [7, 11].

The location of the NIV therapy is another important determinant in the success of NIV. The decision about where to perform NIV should be based on matching the capabilities of the units and teams with the patient's clinical severity and the need for monitoring. Five studies with 414 patients were conducted outside the ICU and three studies with 127 patients on ICU. Both subgroups showed significant improvements in treatment failure with NIV, with the results being slightly better in the ICU subgroup. However, the difference did not reach statistical significance, as can be seen with the overlapping 95%Cis for the two-point estimates [7].

The experience and the skills of the staff are other key components of NIV success. Training in NIV implementation is an important factor in reducing nosocomial infections and improving survival in critically ill patients with COPD [11].

Although much attention has been paid to the development of new interfaces to increase tolerance and patient comfort, mask intolerance remains a major cause of NIV failure. An oronasal mask is generally the most commonly preferred one in ARF, followed by nasal masks, helmets, and mouthpieces [11].

33.3 Conclusion and Discussion

The main aim of AECOPD is to prevent the negative effect of exacerbation and development of adverse events due to exacerbation. The management can be established either in outpatient or in-patient settings. The main pharmacological treatment options are bronchodilators, corticosteroids, and antibiotics. While talking about the treatment of AECOPD, high flow nasal therapy should not be mentioned as its benefits such as improvement in oxygenation, ventilation, hypercapnia, health-related quality of life have not been confirmed [1]. NIV is preferred over invasive ventilation at first line to treat AHRF in AECOPD. Randomized controlled studies determined the success rate as 80–85% [14, 15]. NIV works through improving oxygenation and respiratory acidosis as well as decreasing respiratory rate, work of

breathing, and dyspnea. NIV is also preferred to lower the complication rate such as ventilator-associated pneumonia, prolonged hospital stay, etc. Rapid weaning is also possible with NIV. As a result, NIV decreases the need for intubation and mortality against the debate of delay of endotracheal intubation [1].

With NIV, the risk of treatment failure was reduced by greater than 50% and the number needed to treat was five. For every ten patients treated with NIV, we would avoid one death. With admission pH less than 7.30, risk reduction was 49%, with admission pH between 7.35 and 7.30 risk reduction was 55%. With NIV, the risk of endotracheal intubation was more than halved (59%), and by treating four patients with NIV, we would avoid one patient being intubated. Length of hospital stay was significantly reduced by more than 3 days with NIV. Acidosis has been shown to be an important prognostic factor in survival from respiratory failure in COPD, and thus early correction of acidosis is an essential goal of therapy [7].

Key Recommendations

NIV has become the first-line treatment modality for patients hospitalized for AECOPD with AHRF with better outcomes than either medical treatment alone or ICU management with endotracheal intubation. Three complementary interventions can therefore now be proposed in a stepwise approach to these patients, and their combination should become a new standard of care with consideration of high flow nasal therapy in the near future. The first step is based on drug treatment and on appropriate management of oxygen. The second step is the early use of NIV to prevent further worsening and clinical deterioration. How soon this treatment should be applied remains a matter of debate and may be difficult to base solely on objectively quantified criteria. Endotracheal intubation and artificial ventilation should be reserved for patients with certain criteria that do not fit NIV indications.

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Noninvasive Ventilation in Patients with Acute Exacerbations of Asthma

34

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34.1 Introduction

Asthma exacerbation is defined by acute or subacute progression of respiratory symptoms and a decrease in lung function compared to patients' usual state [1]. It can develop over the span of more than a week, which is more characteristic of adult patients [2]; however, it may be both rapid and severe, even in patients with mild asthma, i.e., well controlled with low dose inhaled corticosteroids (ICS) [1]. It is estimated that 5–10% of the population with asthma will experience a severe exacerbation at least once each year, of which 10% will require admission to the intensive care unit (ICU) [3]. Hospitalization in the ICU, along with invasive mechanical ventilation (IMV), has been associated with increased mortality [4] ranging from 6.5 to 10.3% [5]. However, this increase in mortality cannot be solely attributed to

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_34

complications arising after admission to the ICU [5]. One of the most significant risk factors of poor survival in these patients is out-of-hospital cardiopulmonary arrest and subsequent cerebral anoxia [5]. On the other hand, IMV, which affects 2–4% of all hospitalized asthma patients [4], can be complicated by: ventilator-associated pneumonia, barotrauma, hypotension, and myopathy [5]. All of the above in turn are connected with prolonged hospital stay [6].

34.2 Noninvasive Ventilation's Effects on Lung Function in Asthma

In spite of the lack of robust evidence, there has been a growing trend, as shown by large retrospective studies [4, 7], to utilize noninvasive ventilation (NIV), i.e., CPAP (continuous positive airway pressure) or BiPAP (bilevel positive airway pressure), in patients with asthma exacerbation. This might have been encouraged by effectiveness of NIV in treating acute respiratory failure (ARF) due to chronic obstructive pulmonary disease (COPD) exacerbation [8, 9], which shares some pathophysiological similarities [3]. As in COPD, increasing airflow limitation promotes ventilation-perfusion mismatch and raises intrinsic positive end-expiratory positive pressure (iPEEP) of which the latter increases work of breathing [3]. Furthermore, a growing usage and, in turn, familiarity with NIV might have also contributed to trialing NIV outside its proven indications [10].

As stated in the guidelines [9] the primary goals of NIV in asthma exacerbation would be to decrease the work of breathing, increase ventilation, and, in turn, to avoid IMV. The former can be achieved by offsetting iPEEP with expiratory positive airway pressure (EPAP) or CPAP and by unloading respiratory muscles with inspiratory positive airway pressure (IPAP) [3, 6]. Respiratory exchange on the other hand improves with EPAP/CPAP positive effect on ventilation-perfusion mismatch and, in case of respiratory muscle fatigue, with IPAP sustaining tidal volume, and thus alveolar ventilation [3, 6]. Moreover, it is postulated that applying EPAP/CPAP might also facilitate sputum clearance [11]. The other advantageous effect of NIV in asthma would be its potential direct bronchodilating effect. In their study in patients with asthma exacerbation without ARF, Soma et al. showed that corticosteroids with BiPAP set at 8 cmH_2O IPAP and 6 cmH_2O EPAP increased FEV_1 and reduced breathlessness compared to corticosteroids alone after 80 minutes of treatment [12]. Similarly, Galindo-Filho et al. in their randomized controlled trial (RCT) in adults with asthma exacerbation showed that, compared to jet nebulization alone, nebulized bronchodilators with BiPAP, set at 12 cm H_2O IPAP and 5 cm H_2O EPAP, improved, among others, FEV_1, FVC, PEF, and IC [13]. This difference, however, could not be explained by improved deposition of aerosol with BiPAP because it was similar to jet nebulization, as shown by DTPA-Tc^{99m} inhalation scintigraphy [13]. Furthermore, BiPAP set at 12 cm H_2O IPAP and 8 cm H_2O EPAP was noninferior to albuterol regarding FEV_1 and IC recovery after bronchoprovocation with hypertonic saline in asthma patients [14]. In addition, 10 cm H_2O CPAP was shown to limit exercise-induced bronchoconstriction both when it was applied solely

during exercise or in the recovery period only [15]. Moreover, nasal CPAP at 8 cm H_2O, compared to sham pressure, increased $PD_{20}FEV_1$ by one doubling dose during the methacholine challenge test in patients with asthma [16].

34.3 NIV in Adult Asthma

Despite these pathophysiological premises, a Cochrane review of NIV efficiency in adult patients with asthma exacerbation was unable to identify enough RCTs to reach firm conclusions on the review's primary outcomes, i.e., mortality and endotracheal intubation (ETI) compared to usual care. Low quality data acquired from two studies with a total of 86 participants showed relative risk of ETI in the NIV group equal to 4.48 with 95% CI ranging from 0.23 to 89.13 [6]. However, none of the aforementioned studies classified ETI as a primary endpoint [17, 18]. In addition, only one of the studies, by Gupta et al., included hypoxemia as an inclusion criterium [17]. Unsurprisingly, no ETI were reported in the second study, by Soroksky et al., where mean p_aO_2 in BiPAP group was equal to 82.85 ± 38.72 mmHg [18]. On the other hand, in a study by Gupta et al., 2 patients out of 28 in the BiPAP group were intubated [17]. It is worth underlining that in both cases, ETI was not a result of NIV failure per se but due to NIV intolerance – authors did not provide information whether sedative drugs were used. In the same study, 4 patients out of 25, who failed conventional treatment, subsequently responded to BiPAP and did not need IMV. Failure was defined as lack of improvement in both clinical and gas exchange variables at 1 h [17]. Mortality, however, could not be assessed in both studies because no deaths were reported [17, 18]. The Cochrane review eventually included 5 studies with a total of 206 participants [6]. The gathered data, though low and very low quality, suggested that NIV increased FEV_1 (7.73–20.32%) and FVC (4.38–20.16%) compared to conventional treatment.

34.4 NIV in Child Asthma

As hospital-treated asthma exacerbations per 100,000 population are highest in the pediatric population [19, 20], it is to no surprise that a separate Cochrane review of NIV efficiency in children was also performed [21]. Nonetheless, conclusions were similar. The review included two RCTs', both conducted in an ICU setting, on a total of 40 patients, of which 20 were randomized to BiPAP, whereas the other 20 were treated conventionally, i.e., with nebulized bronchodilators, intravenous steroids, and supplemental oxygen [22, 23]. Both trials reported a significant decrease in symptom scores. Thill et al.'s symptom score assessed accessory muscle usage, wheezing and dyspnea [23], whereas the score used by Basnet et al. assessed respiratory rate, accessory muscle usage, intensity of breathing sounds, wheezing, and prolongation of exhalation [22]. Due to those differences, meta-analysis was not possible. No data on blood gases was collected. Nevertheless, in both studies NIV usage was associated with significantly smaller oxygen requirement [22, 23]. No

deaths or serious adverse events were reported. Nonetheless, Thill et al. excluded 4 patients from the analysis in their cross-over study: 1 due to ETI and 3 because of NIV intolerance. Furthermore, the observation period was 2 h after which patients were crossedover for another 2 h [23]. In contrast, the Basnet et al. study period was 24 h long [22]. The authors of the review concluded that their findings do not permit approval or rejection of NIV usage in asthma exacerbation in children.

34.5 International Guidelines Recommendations

The Cochrane reviews' findings are reflected in international NIV guidelines. The authors of the joint European Respiratory Society (ERS) and American Thoracic Society (ATS) guidelines abstained from providing recommendations in asthma exacerbation citing lack of firm evidence [9]. The same approach was shared by GINA (Global Initiative for Asthma) members [1]. On the other hand, British Thoracic Society (BTS) experts recommend against usage of NIV in asthma exacerbation (grade C) since NIV may unnecessarily delay IMV which has low mortality rate in asthma patients [8]. Nonetheless, both ERS/ATS and BTS guidelines allow for NIV trial in asthma patients with a history of chronic hypercapnia or fixed airway obstruction, which are more typical of COPD (BTS grade D) [8, 9]. The GINA report authors underlined that if the decision to use NIV is made, strict patient monitoring should be started (evidence D), NIV should not be used in agitated patients (evidence D), and sedative drugs should not be given (evidence D) [1].

34.6 Observational Studies Results

Despite a lack of evidence, an increase in NIV usage in asthma exacerbation is evident, as shown by observational studies. In their retrospective cohort study, Stefan et al. analyzed the data of 13,930 asthma exacerbation patients admitted to 97 U.S. hospitals in the period from January 2009 to December 2012 [7]. The analysis showed an increase in NIV usage from 2.3 to 4.7%. Furthermore, compared to IMV, NIV usage was connected with lower mortality (risk ratio, 0.12; 95% CI, 0.03–0.51) and shorter length of hospital stay (4.3 days less; 95% CI, 2.9–5.8). However, most of the patients treated with NIV did not have a primary diagnosis of ARF (i.e., 38.1%) which, along with low risk of NIV failure (4.7%), caused the authors to question whether comparing NIV to IMV in this cohort is truly viable taking into consideration that NIV was most probably employed in a lower severity group than IMV [7]. In their other retrospective study, of cross-sectional design, Stefan et al. analyzed data on 13,558 patients admitted to 58 U.S. hospitals, from 2009 to 2012, for asthma exacerbation [24]. Similar to a previous study, a minority of those treated with NIV had a primary diagnosis of ARF (38.0%) and NIV failure was low (4.9%). Interestingly, data also showed that hospitals with the highest NIV usage did not have lower IMV and mortality rate [24]. Conversely, single center studies, whose staff had high experience in NIV, show different results. Murase

et al. [25] compared patients with asthma exacerbation complicated by ARF, treated at their institution, before and after introduction of NIV. Their analysis showed that after introduction of NIV, a fall in IMV was observed (18.0%, vs 3.5%; $p = 0.01$), whereas NIV failure rate was equal to 12% (2 patients out 17). Furthermore, mortality remained stable with no deaths during both study periods [25]. In another retrospective, observational, single center study, Bond et al. analyzed 265 high dependency unit (HDU) and ICU asthma admissions spanning 15 years [26]; 66.4% of these admissions were initially treated with NIV. In the low GCS group (i.e., GCS $\leq$ 10), 16 out of 33 admissions were initially treated with NIV where initial pCO_2 and pH were equal to, consecutively, 90.0–123.5 mmHg and 6.95–7.06. Out of the other 228 asthma admissions, with GCS > 10, 151 were initially treated with NIV, where initial pCO_2 was equal to 37.5–67.13 mmHg and pH 7.19–7.33. Only 1 patient in the low GCS group failed NIV and required IMV. Altogether, 8 patients, out of which 7 were treated with CPAP and 1 with BiPAP, failed NIV which translated into a failure rate of 4.5%. No deaths were reported during the study period [26]. NIV proficiency in asthma patients with ARF was also confirmed in the largest retrospective cohort study to date by Althoff et al. [4] The authors analyzed administrative data from 682 U.S. hospitals on 53,654 asthma exacerbation patients admitted to the ICUs during 2010–2017. Throughout the study period, the proportion of patients receiving NIV increased from 18.5 to 29.9% ($p < 0.0001$); however, the proportion of patients receiving IMV remained stable ($p = 0.29$), while the proportion of patients receiving neither NIV or IMV decreased from 53 to 43.8% ($p < 0.0001$). This would suggest that, similar to the study by Stefan et al. [7], an increase in NIV usage applies mainly to patients who nonetheless would not be intubated. However, the authors performed a preplanned analysis in an ARF subgroup in which asthma was a secondary diagnosis. In 17,387 ARF patients, IMV use decreased from 63.7 to 38.7% ($p < 0.0001$), while NIV use rose from 29.9 to 35.4% ($p < 0.0001$) without a significant change in mortality ($p = 0.33$). In this subgroup, NIV usage was associated with the lowest likelihood of IMV and in-hospital mortality even after accounting for differences in comorbidities, pharmacologic treatment, or demographic factors [4]. These results suggest that asthma exacerbation patients who benefit from NIV the most are those who develop ARF [4, 25, 26]. Nonetheless, this has not been confirmed in RCTs, which may prove difficult to be carried out due to the already widespread use of NIV in asthma exacerbation [4].

Despite uncertainty regarding NIV effectiveness, its use seems safe in asthma exacerbation. No serious side effects were reported in single-center observational studies [25, 26] and analyzed RCTs [17, 18, 22, 23, 27]. Furthermore, Murase et al. did not observe significant differences between IMV and NIV regarding improvement rate in P_aO_2/F_iO_2 ratio, p_aCO_2, and pH [25]. Bond et al. also reported that the low GCS group was treated without cases of aspiration pneumonia [26]. In an already mentioned Althoff et al. study, an upward trend in NIV usage in the ICUs did not translate into significant mortality change among those who received IMV after NIV ($p = 0.37$) [4]. However, this might be due to the readiness of the ICU personnel to swiftly perform ETI if such need arises. Taking into consideration that

mortality of patients who failed NIV is comparable with those treated initially with IMV [7], the former should only be trialed in a setting where rapid ETI is feasible [8].

The observational studies also reported on factors which were associated with NIV failure. Among those, Althoff et al. listed pneumonia, severe sepsis, and acute renal failure [4], whereas Stefan et al. the number of prior admissions within 1 year, congestive heart failure, diabetes, and pneumonia [7]. Bond et al. in their analysis of high GCS group, i.e., GCS > 10, pointed to higher median age (49 years), higher pCO_2 (87–126 mm Hg), and lower pH (6.9–7.14) values [26]. Interestingly, patients in the low GCS group, i.e., GCS ≤ 10, with similar pCO2 and pH values, were treated effectively with NIV, i.e., failure rate was equal to 6.25% (1 patient out of 16).

34.7 Summary

There are many doubts surrounding the use of NIV in asthma exacerbation. These concerns include the validity of NIV in asthma exacerbation, patient selection, site of initiation and monitoring, risk factors of NIV failure or preferable mode of respiratory support, i.e., CPAP or BiPAP. Nonetheless, the increasing prevalence of NIV in asthma may hinder organization of large randomized controlled trials that could clarify the above [4]. For example, Holley et al. stopped their RCT of BiPAP in asthma exacerbation for selection bias caused by ethical issues [27]. During the course of the study trial investigators became convinced that withholding BiPAP was detrimental to the patients, a notion which later proved unverifiable – analysis of the remaining data showed reduced, yet statistically insignificant, ETI rate and length of hospital stay [27].

Retrospective and limited prospective data suggest that NIV might be safely used in asthma exacerbation. However, NIV should be trialed in a setting where rapid intubation is feasible and the treating team has earlier experience in this mode of ventilation. Furthermore, it seems that the group which benefits the most from NIV are the patients developing ARF in the course of asthma exacerbation. Even so, it is unknown whether NIV could prevent development of ARF. There is no data on the superiority of CPAP or BiPAP in this setting; however, both were reported to be effective. Nonetheless, CPAP should be used cautiously in patients with a low GCS score [26]. The presence of risk factors for NIV failure should prompt further caution if the decision to use NIV is made. Notwithstanding the above, one should keep in mind that recent ERS/ATS guidelines do not support routine use of NIV in asthma exacerbation while BTS experts advocate against use of NIV in asthma outside clinical trials.

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Noninvasive Mechanical Ventilation in Restrictive Pulmonary Disease

35

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35.1 Types of Restrictive Lung Disease

Restrictive lung diseases can generally be separated into three major categories including:

1. Intrapulmonary
   - Intra-alveolar processes
   - Interstitial lung disease
2. Extrapulmonary
   - Pleural diseases
   - Chest wall abnormalities

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_35

3. Neuromuscular diseases
   - Neuropathic
   - Myopathic

A list of common disorders within each category is described in Table 35.1.

To review goals of mechanical ventilation in the category of intra-alveolar processes, the example of acute lung injury/acute respiratory distress syndrome (ALI/ARDS) is used. ARDS is a life-threatening condition characterized by capillary endothelial injury and diffuse alveolar damage resulting in a non-cardiogenic edema. It is one of the most studied areas in intensive care and there is a relatively strong evidence base to draw upon, thus serving as a good example for any lung process involving alveolar filling from either type of edema, hemorrhage or infection [1].

However, it should be noted that the restrictive pathophysiology of ARDS is not limited to alveolar filling defects. Interstitial abnormalities can also be seen in the acute phase of the disease, with fibroproliferative changes developing as early as within a few days and worsen as the disease progresses. Also, abnormalities of the chest wall can be present due to prolonged immobility or concomitant medication that might impair the chest wall musculature [2].

Table 35.1 Restrictive diseases

Intrapulmonary	Intra-alveolar filling defects	Pulmonary edema (cardiogenic and non-cardiogenic)
		Pneumonia (infectious and non-infectious)
		Diffuse alveolar hemorrhage
	Alterations of the interstitium	Idiopathic pulmonary fibrosis (IPF)
		Hypersensitivity pneumonitis
		Sarcoidosis
		Asbestosis
Extrapulmonary	Pleural diseases	Pleural effusion
		Hemothorax
		Pneumothorax
		Mesothelioma
	Chest wall abnormalities	Kyphoscoliosis
		Severe obesity
Neuromuscular	Neuropathies	Myasthenia gravis
		Amyotrophic lateral sclerosis
		Phrenic nerve injury/palsy
		Critical illness neuropathy
	Myopathies	Dermatomyositis
		Muscular dystrophies
		Critical illness myopathy
		Mitochondrial myopathies

Regarding interstitial lung disease, IPF serves as the best model for the unique considerations of mechanical ventilation for interstitial abnormalities in the absence of corresponding alveolar filling defects [2].

The most frequent causes of extrapulmonary restrictive diseases include kyphoscoliosis and post-tuberculosis syndrome [3]. Kyphosis and scoliosis are abnormal curvatures of the spine. Kyphosis is determined by the degree of the spine's anteroposterior angulation, while scoliosis is determined from the extent of the spine's lateral angulation. They are often present in combination and can cause significant disfigurement of the chest wall, impaired lung compliance with restrictive mechanics, leading to progressive hypoventilation and hypercapnia. The extent of scoliosis or kyphosis can be assessed by measuring the Cobb angle from a posteroanterior or lateral radiograph. The magnitude of this angle has been used to predict the likelihood of developing respiratory failure, with an angle of >100° increasing the chance of developing respiratory failure [4]. In addition to a large Cobb angle, patients with vital capacity of less than 1 L, onset of scoliosis before the age of eight, and a high thoracic curve are also at high risk for developing respiratory failure at a future time, usually after the fourth or fifth decade [5].

Regarding neuromuscular diseases, there are three respiratory muscle groups: the inspiratory muscles (diaphragm, pectorals, intercostals, and cervical extensors), the expiratory muscles (predominantly abdominal and upper chest wall) for coughing, and the bulbar-innervated muscles, especially the glottis and tongue for frog breathing and protecting the airways [6]. All three progressively weaken in neuromuscular diseases (NMDs) leading to restrictive lung disease.

Inspiratory and expiratory muscle function can be completely supported, with patients with little to no measurable VC, avoiding invasive mechanical ventilation for many years [6]. However, there are no noninvasive measures to substitute for bulbar-innervated muscles. Bulbar muscle weakness can lead to the inability to swallow secretions, causing suffocation [4]. Total paralysis of bulbar-innervated muscles, however, is not an indication for tracheotomy since patients can be positioned to drool. Tracheotomy becomes necessary when upper airway patency is diminished by stridor or spasticity and continuous aspiration of saliva with an oxyhemoglobin saturation below 95% [4, 6].

35.2 Which Patients Are Likely to Benefit from Noninvasive Ventilation?

Despite the lack of prospective randomized controlled trials, with the exception being a few studies in patients with amyotrophic lateral sclerosis (ALS), most evidence of noninvasive ventilation as treatment for chronic ventilatory failure in restrictive diseases has been obtained from observational uncontrolled studies in patients with neuromuscular and thoracic cage abnormalities [7].

A number of studies have been published in the past several years reporting that NIV in these patients is not only able to improve blood gas parameters but also hemodynamics exercise performance, sleep quality and health-related quality of

life. The mechanisms by which NIV exerts such a positive impact remain nuclear. The proposed pathophysiological mechanisms include respiratory muscle rest, resetting the CO_2 sensitivity of the central ventilatory controller and changes in pulmonary mechanics [8].

The use of NIV in patients affected by restrictive thoracic disorders, in particular in patients with neuromuscular disease, alleviates symptoms of chronic hypoventilation in the short term and may prolong survival [9].

The specific indications for NPPV in these disorders remain controversial. The decision to initiate NPPV is commonly based on the presence of symptoms of hypoventilation, such as daytime hypersomnolence, excessive fatigue, morning headache, cognitive dysfunction and dyspnea, and the presence of at least one physiologic criteria [10]:

1. $PaCO_2 > 45$ mmHg
2. Nocturnal oximetry demonstrating oxygen saturation <88% for five consecutive minutes
3. For progressive neuromuscular disease, maximal inspiratory pressures <60 cmH_2O, sniff nasal inspiratory pressure <40 cm H_2O or FVC <50% predicted.

Because sleep is associated with partial paralysis of the accessory respiratory muscles, hypoventilation and hypercapnia are generally more pronounced at night, initially during REM sleep and later in non-REM sleep as well [4]. As such, the definition of eligible patients may, as to date, be too restrictive and clinically insufficient.

In response to this, German national guidelines [11] for treating chronic respiratory failure have included as indications for NIV:

– Nocturnal $PaCO_2 \geq 45$ mmHg
– Nocturnal $PtcCO_2 \geq 50$ mmHg for over 30 min
– Diurnal normocapnia with a nocturnal rise in $PtcCO_2$ of ≥10 mmHg
– For ALS or other fast-progressing NMDs, a rapid reduction in FVC of >10% of the initial value within 3 months.

Preventive NIV has in fact been successfully accomplished in ALS patients. A retrospective study demonstrated that in a group of ALS patients initiating NIV very early (i.e., with FVC ≥80%) and for at least 4 h/day or 120 h/month, the survival from symptom onset was significantly longer and the crude death rate was significantly lower compared to those patients initiated to NIV later (i.e., with FVC <80%) [12].

35.3 Where to Initiate Noninvasive Ventilation?

Given the increasing demand for home mechanical ventilation in patients with chronic respiratory failure due to NMD or thoracic cage disorder, the setting in which NIV is initiated has also been evaluated. The problem of starting HMV at home encloses the lack of professional supervision in the home environment and nighttime surveillance during sleep. On the other hand, the costs of starting HMV in a hospital setting are substantially higher than at home, there is a significantly higher emotional burden, as well as an increased risk of developing a nosocomial infection.

According to a prospective study performed in the Netherlands, commencing NIV at home in these patients using telemonitoring has proven to be non-inferior to hospital initiation, showing the same gasimetric improvement, as well as in terms of quality of life. In addition, it showed that it is safe, feasible, and cheaper. [13].

35.4 Settings and Titration

35.4.1 Mode

Pressure targeted ventilation (PTV) and volume targeted ventilation (VTV) are the main categories of NIV. These ventilators provide three modes: assist, assist-control, and cycled (control). In control mode, the machine determines respiratory frequency, in assist mode, the machine assists in the patient's spontaneous breathing, and assist/control mode is a combination of the two, where depending on the spontaneous breathing frequency, the patient may either trigger to receive inspiratory support (pressure or volume targeted), or be passively ventilated with the chosen back-up frequency.

In pressure mode, the independent value is pressure and the dependent value is volume, whereas in volume mode, the independent value is volume and the dependent value is pressure. Most of the initial studies in the 1990s used VTV as the preferred mode of NIV in CRF [14]. For various reasons, PTV has been increasingly prescribed in recent years and its usage surpassed that of volume respirators by the end of the 1990s.

The volume mode was extensively used in the past, mainly for restrictive thoracic diseases, specifically neuromuscular disorders, and remains the preferred mode in these patients with severe neuromuscular weakness who can be taught to "stack" breaths to achieve large tidal volumes, enhancing airflow during coughing and aiding in the expulsion of secretions [15].

Hybrid modes such as the volume-assured pressure-support (VAPS) mode combine pressure and volume modes by delivering a targeted volume via a pre-defined pressure range (minimal and maximal inspiratory positive airway pressure) set on the ventilator. A number of clinical studies have evaluated the efficacy of the VAPS mode in correcting hypoventilation in patients with chronic obstructive pulmonary disease (COPD), obesity hypoventilation syndrome (OHS), and restrictive lung disorders. Overall, patients treated with VAPS exhibited improvements in nocturnal gas exchange, although the results on sleep quality were equivocal [16].

35.4.2 Pressure

In routine practice, the pressures in HMV are set according to clinical parameters, such as blood gases, pulmonary function tests, and respiratory muscle pressures. Fanfulla et al. [9] showed that choosing ventilatory parameters, which are to be used during nighttime, in an empirical fashion, based on patient's tolerance when awake and diurnal arterial blood gas variations, is effective in improving gas exchanges, but it may cause patient–ventilator asynchrony during sleep, associated with sleep disruption. These abnormalities can be minimized when a setting that is more physiological is applied, based on recordings of inspiratory muscle efforts.

In published series, EPAP less than 5 cm H_2O is typically used in neuromuscular and scoliosis patients to prevent end-expiratory alveolar collapse and atelectasis. In patients with obesity hypoventilation syndrome, an EPAP of approximately 10 cm H_2O helps to overcome upper airway obstruction. In more severe obesity, IPAPs are more variable, within the range of 15–25 cm H_2O, probably reflecting the need for higher pressures [17].

When starting a patient with neuromuscular disease on NIV, it is important to start with comfortable settings. It is standard to begin with an IPAP of 8–12 cm H_2O and an EPAP of 5 cm H_2O. Over time, the IPAP should gradually be increased, increasing the pressure support gradient, until symptoms of hypercapnia have improved or resolved.

Rise time or pressurization rate consists of the time to reach the maximum inspiratory pressure during the beginning of the inspiratory phase of ventilation, i.e., the time needed to reach IPAP from EPAP. It should be titrated to comfort, although higher values (e.g., >300 ms) should probably be the initial choice for patients with restrictive disorders while lower values might be preferable for patients with obstructive disorders. [18].

35.4.3 Volume

Tidal volume (V_t) is usually set to 8–10 mL/kg of ideal body weight, since using actual body weight in obese patients can lead to volumes that can cause volutrauma.

In patients with restrictive disorders, a higher V_t might be preferable. [18].

In the case of ARDS, the recommended approach is the "lung protective ventilation strategy" or "low tidal volume ventilation strategy," as a way to avoid excessive tidal volumes which can result in alveolar injury. Tidal volumes previously recommended and used, such as 12–15 mL/kg prior to the late 1990s, can cause noncardiogenic edema, which is now referred to as ventilator-induced lung injury. The prevention of this process, with a lower tidal volume of 6 mL/kg of predicted body weight, is believed to contribute to better outcomes in terms of duration of mechanical ventilation and mortality [2].

Low tidal volume has also been a standard approach in patients with interstitial lung disease such as IPF, to keep airway pressures below unacceptably high levels (>40 cm H_2O). [2].

Since pleural diseases with no coexisting parenchymal disease typically do not alter actual lung compliance, the importance of a low tidal volume approach in these patients is unknown. However, caution is advised with the use of tidal volumes larger than 10 mL/kg.

In patients with neuromuscular diseases, the compliance of both lungs and chest wall is normal. As such, the low tidal volume approach is also not as important and may actually be responsible for airway hunger [2].

35.4.4 Other Settings

The back-up respiratory rate (BURR) setting is generally used in NIV to prevent nocturnal alveolar hypoventilation, as such it becomes essential in central hypoventilation syndromes and severe NMDs. In general, BURR is kept slightly lower than the spontaneous respiratory rate. In NMD patients, it is usually set two breaths below the spontaneous rate.

Increasing the I:E ratio to 1:1 (or using inverse ratio ventilation, such as I:E ratios of 2:1, 3:1 and so forth) maximizes the time spent in inspiration, thereby reducing peak and plateau ventilatory pressures.

A shorter inspiratory time encourages lung emptying and a longer inspiratory time improves oxygenation.

A longer T_i (approx. 40% of IPAP time) should be applied due to their decreased lung compliance. This time will optimize the I:E ratio and prevent patient–ventilator asynchrony. The ultimate goals of setting the T_i are to have adequate ventilation, increase the harmony between the patient and the ventilator, and maximize patient's comfort.

A longer T_i range (e.g., T_i min 0.5 s, T_i max 1.5 s) with a lower cycle sensitivity level is preferred for restrictive disorders [19].

35.4.5 Interfaces

Particularly in NMDs, NIV is started first during nighttime to prevent symptoms of nocturnal hypercapnia. As the disease progresses, NIV is often needed throughout the day. In the case of nocturnal NIV, a nasal mask is usually preferred, as it is more comfortable than an oronasal mask. The fitting of the mask takes some time, to ensure that the right mask is being used and the straps have been adjusted to the proper tension, to avoid excessive air leak or pressure sores. When a patient requires daytime NIV, a simple mouthpiece is often effective and allows the most freedom for the patient. If motor control of facial muscles does not permit the simple mouthpiece, then a mouthpiece with lip seal retention can be used [4].

Key Messages

- Restrictive lung diseases are characterized by poorly compliant lungs, chest wall, or both.

- Over time, respiratory impairment progresses to chronic hypercapnic respiratory failure.
- The purpose of NIV in this population is to ameliorate symptoms and arterial blood gases, decrease hospital admissions, and improve health-related quality of life.
- Although it is reasonable to re-assess gasimetric parameters after starting NIV, the primary objective should be to improve symptoms rather than to strictly treat hypercapnia.
- An optimal ventilation strategy for thoracic restrictive disorders has yet to be established.

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Noninvasive Positive Pressure Ventilation in Acute Decompensated Heart Failure

36

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36.1 Introduction

Acute cardiogenic pulmonary edema is one of the most common causes of acute decompensated heart failure (ADHF) and acute respiratory distress in patients presenting to emergency departments and cardiac intensive care units (CICU).

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_36

Hypoxemia, hypercapnia, and respiratory acidemia are common symptoms of the ADHF. Standard medical treatment for patients with ADHF includes diuresis, afterload reduction with vasodilators, inotropic support, and oxygen delivery. In this context, oxygen through nasal cannula or face masks is the primary form of respiratory support. Although many patients respond rapidly to standard treatment, some progress to severe respiratory distress leading to endotracheal intubation and associated complications [1, 2]. As early as 1936, continuous positive airway pressure (CPAP) has been shown to be an effective therapy for acute cardiogenic pulmonary edema [3]. Positive airway pressure can improve respiratory failure and augment cardiovascular function [4]. Multiple actions of noninvasive positive pressure ventilation (NIPPV) can act synergically in the treatment of patients with respiratory distress and impaired cardiac function [2, 5]. In this review, we address fundamental concepts of cardiopulmonary mechanics, the pathophysiology of ADHF, hemodynamics of NIPPV, and the indications for NIPPV in this population.

36.2 Basic Concepts of Cardiopulmonary Mechanics

The cardiovascular and pulmonary systems are complementary physiological processes. Therefore, changes in one system often affect the other [6, 7]. To understand the basic concepts of pulmonary mechanics and its complex cardiovascular effects, it is prudent to know the definitions of pulmonary compliance. At rest, the functional residual capacity is influenced by two factors: (1) the chest wall with a tendency to recoil and (2) the alveoli with a propensity to collapse. During spontaneous inspiration, the contraction of the diaphragm and intercostal muscles make the intrapleural or intrathoracic pressure more negative, with associated hemodynamic effects [8]. Passive expiration occurs through alveoli and chest wall recoil, making the intrapleural pressure less negative. During respiratory distress, the chest wall muscles aid in inhalation and exhalation. Total compliance includes lung parenchymal and chest wall compliance. Lung compliance is defined as the change in alveolar volume over the change in alveolar pressure ($\Delta V/\Delta P$) [9]. Chest wall compliance is influenced by obesity, thoracic cage deformities such as ankylosing spondylitis, kyphoscoliosis, intraabdominal pressure, and medications [9]. Plateau pressure refers to the alveolar pressure at end-inspiration and is the maximal alveolar pressure in the respiratory cycle. Per Ohm's Law (resistance = ΔP/flow), airway resistance is the change in pressure overflow. The airway is related to the diameter of the airways and thus can be influenced by changes in the diameter in cases such as bronchospasm, tracheal or upper airway pathology, mucus plugging, or airway remodeling [8].

In general, lung inflation alters the autonomic tone, pulmonary vascular resistance (PVR), and compresses the cardiac structure. Spontaneous inspiration induces an increase in right ventricular end-diastolic volume. As a result, there is an increase in pulmonary flow, left ventricular end-diastolic volume, and LV afterload, which accounts for systolic blood pressure [10–12]. Under certain pathological states such as cardiac tamponade, acute asthma, ADHF or hypovolemia, this inspiratory blood

pressure fall is exaggerated and referred to as "pulsus paradoxus" [13, 14]. During exhalation, systolic blood pressure rises as a result of the return of LV afterload to baseline, and there is an increase in LV preload from the previous increase in RV output during inspiration, which attributes to increased cardiac output [15].

36.3 Positive Pressure Ventilation and Cardiovascular Physiology

NIPPV works primarily on positive end-expiratory pressure (PEEP), which is the pressure above atmospheric pressure maintained throughout the respiratory cycle to prevent alveolar collapse at end-expiration. Peak airway pressure reflects the pressure required to overcome the airway resistance to generate tidal volume (TV). The key hemodynamics that influences the LV and RV includes transpulmonary or transmural pressure, the pressure difference between the inside of the heart, and the intrathoracic pressure. The net hemodynamic effect of PAP on cardiac output depends on both RV and LV function, volume status, and systemic resistance [16]. PAP reduces venous return (VR) and RV preload [15]. However, the resultant systemic response depends on the afterload-dependent and the preload-dependent states. For example, a decrease in pleural pressure will favor ventricular filling, causing a decrease in LV ejection as it increases afterload. In addition, NIPPV generally augments the inspiratory flow, increases the TV, and unloads the respiratory muscles, thereby decreasing work of breathing. In the context of acute cardiogenic pulmonary edema, it improves alveolar ventilation, re-expands overloaded alveoli, and prevents atelectasis. The effective filling and emptying of the heart are determined by the transmural pressure. In patients with ADHF, the amplitude of inspiratory swings is more significant and results in higher transmural pressure. During systole, NIPPV increases the intrathoracic pressure and reduces venous return, thus decreasing the RV and LV preload; in diastole, NIPPV increases the pericardial pressure, reduces transmural pressure, and thus decreases afterload. It also causes a decrease in the heart rate secondary to increased autonomic tone secondary to lung inflation. These effects of PAP on LV and RV hemodynamics and the concept of ventricular interdependence will determine the net influence on cardiac output.

36.4 Hemodynamics of Acute Decompensated Heart Failure

Acute decompensated heart failure (ADHF) is the most common form of advanced heart failure, accounting for 50–70% of presentations [17–19]. ADHF has a more gradual onset when compared to acute cardiogenic pulmonary edema, and the main alteration is progressive fluid retention responsible for systemic congestion. The objectives of treatment are identification of the potential triggers, decongestion with diuresis and afterload reduction, and correction of hypoperfusion. ADHF and resultant pulmonary congestion most commonly occur due to ischemic LV and diastolic dysfunction, leading to a hydraulic shift of fluid from the intravascular compartment into the lung

parenchyma [20]. The excess of interstitial and alveolar flooding results in significant atelectasis, reduction of gas exchange, and a concomitant shunt effect [21]. In individuals without cardiopulmonary pathology, the fluid between pulmonary capillary endothelial cells is removed by the lymphatic system and returned to the systemic circulation [22, 23]. In acute cardiogenic pulmonary edema, the rapidly increasing hydrostatic pressure in the capillary owing to increased pulmonary venous pressure from elevated LV end-diastolic pressure (LVEDP) cannot be effectively removed and contributes to increased fluid filtration [24]. The elevated LVEDP contributes to the back-up of flow, diastolic dysfunction, and elevated left atrial pressure (LAP). LAP ≥18 mmHg can provide pulmonary edematous change in the peribronchovascular interstitial space [22]. When the LAP increases ≥25 mmHg, the edema fluid breaks through the pulmonary capillary epithelium, resulting in flash pulmonary edema [21]. The flooded alveoli lead to alveolar shrinkage, which provides impaired venous admixture and arterial hypoxemia, resulting in increased PVR. Both the liquid-filled alveoli, higher PVR, and pulmonary hypoxic vasoconstriction will further impair RV impedance and contribute to worsening acute cardiogenic pulmonary edema [15].

36.5 Types of Noninvasive Positive Pressure Ventilation (NIPPV)

NIPPV includes continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), and adaptive servo-ventilation (ASV). CPAP provides continuous NIPPV, and BiPAP provides titratable inspiratory positive airway pressure (PAP) and expiratory PAP, an equivalent to PEEP. BiPAP is preferred in patients with underlying chronic obstructive airway disease (COPD) as it can reduce apnea, increase TV more than CPAP, and improve ventilation. Appropriate NIPPV selection for individuals is paramount to its successful use (Table 36.1). Relative contraindications are summarized in Table 36.2.

Table 36.1 Selection criteria and determinants of success for NIPPV in the acute setting

Selection criteria for NIPPV in the acute setting
Establish need for ventilatory assistance
Moderate to severe respiratory distress
Blood gas derangement: pH < 7.35, $PaCO_2$ > 45 mmHg, or PaO_2/FiO_2 < 200
Determinants of success for NIPPV in the acute setting
Synchronous breathing
Dentition intact
Lower APACHE score
Less air leaking
Less secretions
Good initial response to NIPPV
Reduction in respiratory rate
Reduction in $PaCO_2$
Better neurologic score
Better compliance

NIPPV noninvasive positive pressure ventilation

Table 36.2 Relative contraindication and complications of NIPPV

Relative contraindication of NIPPV
Difficult to cooperate to apply NIPPV
Unstable cardio-respiratory status
Patients with extreme anxiety
Poor consciousness
Excessive secretions
Severe nausea with vomiting
Respiratory arrest
Anatomical abnormalities including trauma or burns
After surgery of face, esophagus, and stomach
Air leak syndrome including pneumothorax
Skin lesions around mask area
Severe right-sided heart failure
Complications of NIPPV
Oral dryness
Eye irritation
Nasal congestion
Drooling
Sinus pain
Gastric distention
Skin lesion: transient erythema, skin ulceration, skin necrosis, especially at the nasal bridge
Pulmonary barotrauma (rare)

NIPPV noninvasive positive pressure ventilation

36.5.1 Continuous Positive Airway Pressure (CPAP)

CPAP is the most widely used PAP therapy in patients with heart failure (HF). It provides a constant positive pressure throughout the respiratory cycle to maintain an open airway during spontaneous breathing. In clinical practice, CPAP is most commonly used to manage sleep disorders such as obstructive sleep apnea (OSA) and obesity hypoventilation syndrome (OHS) via devices for use at home. Some of these CPAP devices are designed to detect various degrees of upper airway obstruction and then adjust the pressure level to maintain airway patency. Furthermore, more recent automated CPAP devices have advanced algorithms to detect central respiratory events such as Cheyne–Stokes breathing. However, patients with HF require lower pressures (<10 cmH_2O) as high pressures can significantly reduce CO. A typical starting pressure for CPAP is 5 to 10 cmH_2O, with titration by 2 cmH_2O. The FiO_2 may start high and be titrated to a goal SaO_2 (e.g., 94% to 98%) while avoiding SaO_2 > 98%. The titration of CPAP level is necessary for patients' demand and comfort. Higher pressures are required in patients with concomitant OSA.

36.5.2 Bilevel PAP (BiPAP)

The major difference of BiPAP compared to CPAP is that BiPAP provides selective pressure support during inspiration as opposed to continuous PAP throughout the respiratory cycle. BiPAP provides two fixed levels of PAP: inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP). The level of pressure support is determined as a difference between IPAP and EPAP. IPAP plays an important role in unloading respiratory muscles, reducing the WB, controlling sleep apnea, preventing microatelectasis, and reducing the partial pressure of carbon dioxide ($PaCO_2$) [25]. EPAP is comparable to CPAP in its resultant hemodynamic affects. Most BiPAP devices have several modes: spontaneous breathing (S-mode), timed back-up ventilation, and spontaneous breathing with timed back-up ventilation (ST-mode). For example, S-mode can be used for patients who require high-pressure CPAP to control concomitant OSA [26]. However, patients with HF generally do not require high pressure as it decreases cardiac output.

Compared to CPAP, the cardiac unloading effects during the respiration cycle are greater in BiPAP due to an increased pressure level during inspiration [25]. Thus, BiPAP may be a better option for the treatment of ADHF [27, 28]. In that context, the purposes of treatment with BiPAP include (1) reducing hypercapnia in ADHF or those with concomitant COPD or OSA and ADHF, (2) keeping ventilation consistent with constant pressure support, and (3) back-up ventilation in patients with central respiratory events. Initial settings are often an IPAP of 10 cmH_2O and an EPAP of 5 cmH_2O. Titration of the IPAP upward by 2 to 3 cmH_2O can be made to improve hypercarbia. However, avoiding IPAP >20 cmH_2O is prudent to prevent elevated abdominal pressure and risk of aspiration [21].

36.5.3 Adaptive Servo-Ventilation (ASV)

ASV is an advanced mode of BiPAP primarily developed for the treatment of Cheyne–Stokes respiration in patients with ADHF and central sleep apnea [29]. ASV devices provide automatically varying pressure support to maintain changing target ventilation determined by the patient's breathing pattern in addition to the back-up ventilation with variable respiratory rates, which is thus called servo-control of ventilation [25]. The goals of ASV are to stabilize abnormal breathing patterns, maintain the $PaCO_2$ level to prevent hypocapnia, and reduce sympathetic tone, which affects RV and LV afterload [30–32]. There are two major ASV devices, volume targeted ASV and flow targeted ASV. In both products, pressure support and auto titration of EPAP are automatically adjusted according to the patient's ventilation. In addition, it provides comfortable pressure support for patients. In the normal heart, SV is mainly dependent on preload, and thus ASV can reduce stroke volume (SV) by decreasing LV filling according to the Frank–Starling mechanism [33, 34]. The decrease in LV filling results from the elevation in intrathoracic pressure by CPAP or ASV. According to Yamada et al., higher PCWP or LVEDP and greater

MR were independent predictors, and a more spherical heart shape might also predict acute beneficial effects of ASV on the hemodynamics in HF patients [35].

36.6 Indications of PAP Therapy in Acute Decompensated Heart Failure

Current guidelines for ADHF recommend using PAP therapy when patients are in respiratory distress, signs of pulmonary edema, hypoxia, or hypoxemia despite conservative treatment with supplemental oxygen via nasal cannula or face mask [36–40]. Several studies have suggested BiPAP is a highly effective technique in patients with acute cardiogenic pulmonary edema from other causes than myocardial infarction [41, 42]. In patients with ADHF as previously described, myocardial ischemia and increased afterload impair LV systolic function and cardiac output, initiating a compensatory sympathetic response that further increases myocardial oxygen requirement and worsens coronary ischemia. RV dysfunction may also occur due to adverse changes in afterload due to hypoxic pulmonary vasoconstriction, changes in RV preload due to hypovolemia, and RV myocardial oxygen supply due to coronary ischemia. The purposes of PAP therapy in this context includes augmentation of oxygenation through patency of alveoli, reversal of microatelectasis, transfer of fluid from the interstitial space to the pulmonary circulation, and intercostal muscle and cardiac unloading (Fig. 36.1).

36.6.1 Acute Cardiogenic Pulmonary Edema (ACPE)

Acute pulmonary edema is related to pulmonary congestion. Clinical criteria for ACPE diagnosis include dyspnea with orthopnea, respiratory failure, tachypnea, >25 breaths/min, and increased work of breathing [43]. The general therapies include oxygen delivery, given as PAP, intravenous diuretics, and vasodilators if systolic BP (SBP) is high. In a few cases of advanced HF, ACPE may be associated with low cardiac output and cardiogenic shock, and therefore inotropes, vasopressors, and/or mechanical circulatory support are indicated for organ perfusion [39].

In patients with ADHF and acute cardiogenic pulmonary edema, it is well established that PAP therapy improves cardiopulmonary hemodynamics, respiratory function, and oxygenation compared with oxygen therapy alone. The selection of CPAP, BiPAP, or ASV is dependent on whether patients require pressure support to ventilate appropriately (Table 36.3). For example, patients with hypercapnia or respiratory muscle fatigue may require BiPAP. One study suggests a beneficial effect of in-hospital BiPAP (with S-mode) therapy for OSA on the improvement of cardiac function following ADHF [44]. Otherwise, CPAP is used because most data suggest no obvious clinical benefits to the use of BiPAP over CPAP [45, 46]. In Japan, ASV is used for patients with ADHF. The advantages of using ASV for patients with ADHF, however still unconfirmed, may include faster initiation due to

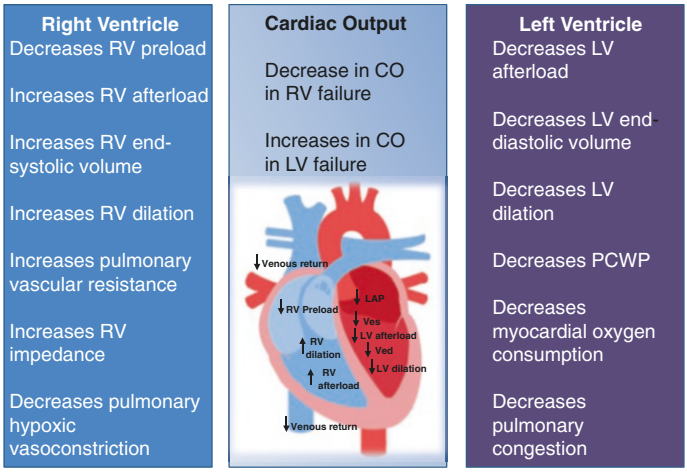
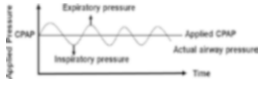


Fig. 36.1 Central illustration of positive airway pressure on the right and left ventricles and cardiac hemodynamics. Positive airway pressure decreases venous return to the right ventricle and thus decreases RV preload. It increases pulmonary vascular resistance due to vascular compression and thus increases RV afterload and therefore RV dilates. Due to the decrease in RV preload, PAP decreases LV preload. The decrease in LV preload, decreases LAP and LVEDP. PAP decreases LV afterload and as such decreases LV end systolic volume and LV size. In a preload dependent state such as RV failure, PAP may decrease CO. In an afterload dependent state such as LV failure, PAP may increase CO. *LV* left ventricle, *RV* right ventricle, *CO* cardiac output; LAP, left atrial pressure, *PAP* positive airway pressure, V_{es} end-systolic left ventricular volume, V_{ed} end-diastolic left ventricular volume, *SV* stroke volume

the fact that devices are small and mobile and better synchronization of patients' respiration compared to BiPAP.

Although a large randomized trial had neutral results, meta-analyses suggest it may improve dyspnea and reduce the need for intubation and mortality compared with traditional oxygen therapy [47, 48]. NIPPV should be started as soon as possible in patients with respiratory distress (respiratory rate > 25 breaths/min, $SpO_2 < 90\%$) to improve gas exchange and reduce the rate of endotracheal intubation [39, 46]. Moreover, the use of PAP therapy in randomized prospective trials was associated with lower rates of intubation and improved 30-day mortality compared with oxygen therapy alone [49–51]. Thus, PAP therapy for ADHF is the universal standard. However, it is paramount to monitor blood pressure as it may also decrease cardiac output and should therefore be used with caution in patients with reduced preload reserve and hypotension. The increase in PVR and RV afterload may also be detrimental in RV dysfunction.

Table 36.3 Summary of functions, advantages, and disadvantages in each NIPPV device

	CPAP	Bi-level PAP	ASV
Differences in applied pressure			
Device function and properties			
Positive end-expiratory pressure	+	+	+
CO_2 clearance	+	++	−/+
Cardiac unloading	+	++	+
Pressure support during inspiration	−	+	+
Backup ventilation	−	+	+
Servo control of ventilation	−	−	+
Advantages	*less expensive	*more significant reduction in the workload of breathing	*synchronizes and stabilizes patients' breathing
	*avoid the incidence of endotracheal intubation	*powerful improvement in oxygenation and CO_2 clearance	*reduces sympathetic nerve activity
	*easy to use	*promoting alveolar ventilation	*decreasing pulmonary and systemic vascular resistance
		*avoid the incidence of endotracheal intubation	*comfortable pressure support
		*provides mandatory respiratory support	*good tolerability
			*dynamically adjusts adequate support pressure
			*avoid the incidence of endotracheal intubation

(continued)

Table 36.3 (continued)

	CPAP	Bi-level PAP	ASV
Disadvantages	* no ventilation support	*sometimes provides discomfort due to square shape pressure waveform	*more expensive
	*minimal support		*less powerful compared to Bilevel PAP (trade-off for comfort)
	*IPAP is lower and EPAP is higher than the applied CPAP level during inspiration		

NIPPV noninvasive positive pressure ventilation, *CPAP* continuous positive airway pressure, *Bilevel PAP* Bilevel positive airway pressure, *ASV* adaptive servo-ventilation, *IPAP* inspiratory positive airway pressure, *EPAP* expiratory positive airway pressure

36.6.2 Mitral Regurgitation

Secondary mitral regurgitation (MR), arising from mitralannular dilation and papillary muscle dysfunction, is a common finding in patients with chronic heart failure. It contributes to the elevation of LVEDP as well as LAP, right atrial pressures, and causes progressive distention of the left ventricle [52]. In patients with CHF, CPAP has been shown to reduce the MR fraction and improve the left ventricle ejection fraction (LVEF), especially in cases of Cheyne–Stokes respiration with central sleep apnea. Moreover, in patients with a dilated LV and high LVEDP in whom functional MR impairs cardiac output, PAP can improve ventricular diameter and decrease MR diameter [53, 54].

36.6.3 Cautions for RV Failure

RV failure is associated with increased RV and RA pressures and systemic congestion. RV failure impairs LV filling and ultimately reduces CO, through ventricular interdependence. The RV is thin-walled and operates as a low-pressure flow pump. In pulmonary hypertension, increased RV impedance induces acute RV dilation [55]. In addition, the combination of systemic hypotension and pulmonary hypertension has an adverse effect on RV myocardial oxygen supply and demand [56].

During NIPPV, increased PEEP and intrapleural pressure decrease venous return and thus RV preload. At the same time, PPV increases RV afterload by increasing transpulmonary pressure causing microvascular collapse and increasing PVR. However, high PAP can cause alveolar overdistension compressing extra-alveolar vessels, increasing PVR leading to hypoxic vasoconstriction [8]. In patients with acute cardiogenic pulmonary edema, lung compliance is decreased due to interstitial edema and fluid-filled alveoli. As PEEP decreases preload and concomitantly creates hydrostatic pressure that forces fluid out of the alveoli, compliance and gas exchange improve, and thus so does PVR. However, in patients with non-compliant lungs, the effect of PEEP on intrapleural pressure and preload is not as significant. In such patients, even small amounts of PEEP can increase RV afterload disproportionally by worsening PVR and impairing pulmonary blood flow [57]. Patients with RV dysfunction are particularly sensitive to this adverse effect on PVR. Therefore, considering each of these potential adverse effects, PEEP should be used with caution in patients with RV failure [58]. Moreover, in patients with RV dysfunction secondary to COPD, monitoring for and preventing auto-PEEP is paramount.

36.7 Conclusion

The net hemodynamic effect of NIPPV is dependent on RV and LV function through ventricular interdependence, preload, and afterload states. NIPPV therapy can recruit collapsed alveoli and increase lung functional residual capacity, thereby

decreasing work of breathing, decreasing venous return, pulmonary vascular resistance, and systemic vascular resistance. Moreover, NIPPV inhibits sympathetic nerve activity, significantly improving pulmonary and systemic hemodynamics. Therefore, there is a resolution of dyspnea, respiratory distress, and metabolic abnormalities in patients with ADHF and ACPE. The administration of early NIPPV can decrease morbidity and mortality, improve clinical outcomes, and thus make the universal standard for management in this population.Conflict of InterestNone.

Funding Dr. Hieda was supported in part by Clinical Research Promotion Foundation. Dr. Hieda was also supported by JSPS KAKENHI Grant-in-Aid for Young Scientists Number 21K17603.

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NIV and Cardiac Diseases with Left Ventricular Mechanics

37

Michinari Hieda

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37.1 Introduction

In 1936, E.P. Poulton et al. reported for the first time that a "pulmonary plus pressure machine" provided by a vacuum cleaner was a valuable therapeutic tool for patients with acute cardiogenic pulmonary edema [1]. To date, noninvasive positive

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_37

pressure ventilation (NIPPV) has been much more sophisticated [2]. In the emergency room or intensive care unit, NIPPV providing positive airway pressure (PAP) has been widely used to manage patients with cardiogenic pulmonary edema [3–12]. The PAP devices, which can be applied without endotracheal airway or tracheostomy, include continuous positive airway pressure (CPAP), bilevel PAP, and adaptive servo-ventilation (ASV) [13, 14].

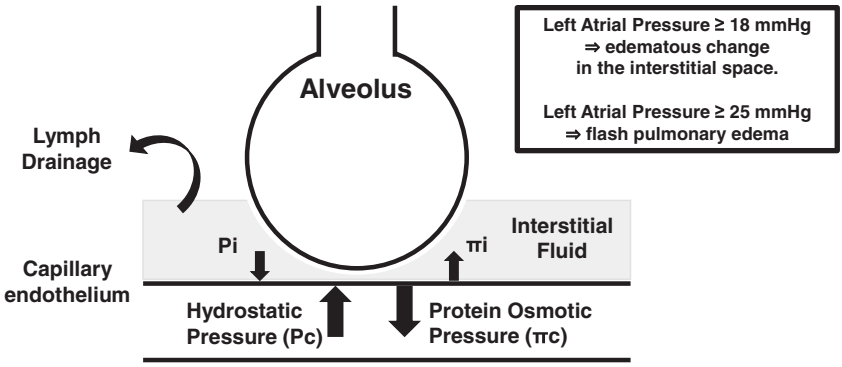
The physiological effects of PAP consist of improved oxygenation and respiratory mechanics, reduced systemic venous return resulting in decreased preload of the right ventricle (RV), decreased RV and left ventricular (LV) afterload due to decrease transmural pressure, and reduce excessive sympathetic nerve activity [15, 16], which eventually augments cardiac output. In this review, we aimed to elucidate the hemodynamic impact of PAP using PV-loop theory to understand its hemodynamic consequences in detail.

37.2 Pathophysiology of Cardiogenic Pulmonary Edema in ADHF

Acute decompensated heart failure (ADHF) is defined as a rapid worsening in heart failure signs and symptoms [17, 18], such as aggressive dyspnea with air hunger, productive cough, and pulmonary edema [19–21]. Cardiogenic pulmonary edema is the most common manifestation of severe dyspnea with oxygenation levels below 92% and is a life-threatening emergency [19–22]. It is characterized by an excess of extravascular pulmonary fluid that causes decreased lung compliance and diffusion capacity, increased pulmonary vascular resistance (PVR) due to arterial hypoxemia, airway resistance, and CO_2 retention [23–25].

Interstitial fluid will move outward from the pulmonary capillaries to the interstitial fluid according to the net balance between hydrostatic pressure and plasma protein osmotic pressure [26], the so-called Starling equation (Fig. 37.1). In normal healthy lungs, leakage occurs through small gaps between pulmonary capillary endothelial cells, and almost all of the excess unwanted fluid is removed by the lymphatics and returned to the systemic circulation [26, 27].

On the other hand, in cardiogenic pulmonary edema, an increase in LV end-diastolic pressure (LVEDP) causes an increase in pulmonary venous pressure, and a sudden increase in hydrostatic pressure in the capillaries disturbs the net transvascular flow balance [24, 27]. The increased hydrostatic pressure in the capillary will provide increased fluid filtration, which is one of the hallmarks of cardiogenic pulmonary edema [28] (Table 37.1; Fig. 37.1). A left atrial pressure (LAP) > 18 mmHg causes edematous pulmonary changes in the perivascular pulmonary interstitium [26].When LAP is 25 mmHg or greater, edematous fluid breaks through the pulmonary capillary epithelium, resulting in flash pulmonary edema [26]. Filling the alveoli with fluid causes the alveoli to contract, leading to impaired venous admixture and arterial hypoxemia, resulting in increased PVR [29, 30]. Alveolar filling with water and elevated PVR triggers a vicious cycle of cardiogenic pulmonary edema.



The Starling equation for filtration of fluid across a semipermeable membrane defines the factors that determine the amount of fluid leaving the vascular space:

$$Q = K [(Pc - Pi) - (\pi c - \pi i)]$$

Q, the net transvascular flow of fluid;
K, the membrane permeability coefficient;
Pc, the hydrostatic pressure in the capillary;
Pi, the hydrostatic pressure in the interstitial space;
πc, the plasma protein osmotic pressure in the capillary;
πi, the protein osmotic pressure in the interstitial space

Fig. 37.1 Physiology of the fluid in the peribronchovascular interstitial space. In the normal-healthy lung, the fluid in the peribronchovascular interstitial space is removed by the lymph drainage and returned to the systemic circulation. On the other hand, in patients with advanced decompensated heart failure or cardiogenic pulmonary edema, the hydrostatic pressure is increased because of increased left ventricular end-diastolic pressure due to left ventricular systolic, diastolic dysfunction, which leads to the increased transvascular fluid filtration

Table 37.1 Chest radiographic and echocardiographic characteristics of cardiogenic pulmonary edema vs. non-cardiogenic edema

Radiographic characteristics	Cardiogenic pulmonary edema	Non-cardiogenic edema
Cardiac silhouette	Enlarged	Normal
Distribution of edema	Central infiltrates	Peripheral or patchy infiltrates
Septal lines	Present	Not usually
Peribronchial cuffing	Present (S6)	Not usually
Kerley's B-lines	Present	Not usually
Pleural effusions	Present	Not usually
Air bronchograms	Not usually	Present
Echocardiographic characteristics	*Cardiogenic pulmonary edema*	*Non-cardiogenic edema*
Pleural effusions	Occasionally/present	Not usually, but possible
Ultrasound comet-tail images	Possible present	Not usually

37.3 Cardiac Mechanoenergetics and Pressure–Volume Loop Diagram

Understanding pressure–volume loop theory is necessary for an essential understanding of hemodynamics. The pressure–volume loop diagram and fundamental equations related to cardiac properties are shown in Fig. 37.2 [31].The pressure–volume loop diagram consists of three key characteristics, including end-systolic pressure–volume relationship (ESPVR), end-diastolic pressure–volume relationship (EDPVR), and effective arterial elastance (Ea).

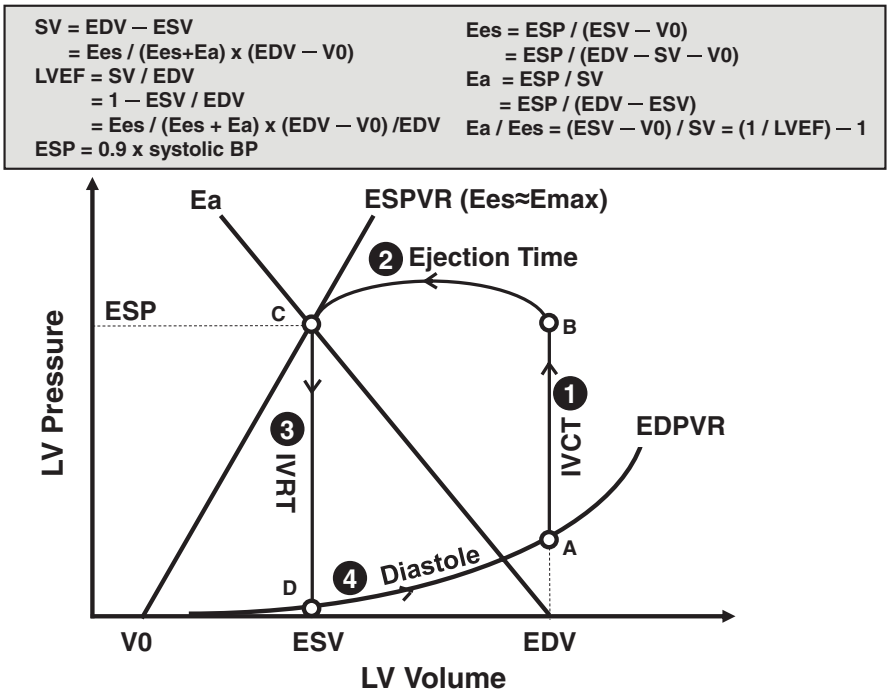


Fig. 37.2 Left ventricular pressure–volume diagram. The LV pressure–volume loop is delineated by the end-systolic pressure–volume relationship (ESPVR) and end-diastolic pressure–volume relationship (EDPVR). The slope of ESPVR passes through the ventricular–arterial coupling point (end-systolic volume and pressure) and the volume intercept (V0), which equates to a state of unstressed left ventricular volume. The end-diastolic pressure–volume relationship represents the left ventricular diastolic property. Ea is depicted with a negative slope connecting end-diastolic volume and end-systolic pressure point. In a cardiac cycle (counter-clockwise), **Point A**, the closure of mitral valves (end-diastole); **Point B**, the opening of aortic valves; **Point C**, the closure of aortic valves (end-systole); and **Point D**, the opening of mitral valves. **Duration 1** (from point A to point B), isovolumic contraction time (IVCT); **Duration 2** (from point B to point C), ejection time (ET); **Duration 3** (from point C to point D), isovolumic relaxation time (IVRT), and **Duration 4**, diastolic time. *SV* stroke volume, *EDV* end-diastolic volume, *ESV* end-systolic volume, *V0* unstressed volume (the X-intercept of the ESPVR), *LVEF* left ventricular ejection fraction, *ESP* end-systolic pressure, *BP* blood pressure

37.3.1 End-Systolic Pressure–Volume Relationship (ESPVR)

ESPVR, representing LV systolic property, is defined by the line connecting the left upper corner of multiple pressure–volume loops under different LV loading conditions (different preload status) [32–35]. It is important to note that this relationship is independent of preload and afterload [36]. The slope of ESPVR represents LV contractility load-independently and becomes steeper when ionotropic drugs are used, while a less steep slope is observed with beta-blockers [36].

37.3.2 End-Diastolic Pressure–Volume Relationship (EDPVR)

EDPVR is indicated by the LV passive filling curve during diastole [37, 38]. The slope of EDPVR signifies the passive LV chamber stiffness, which represents LV diastolic property [39, 40]. The elastin fibers, myocytes, and titin molecules in a sarcomere form LV stiffness [41–43].

37.3.3 Effective Arterial Elastance (Ea)

Ea is a conceptual framework of the total afterload on the LV that integrates arterial stiffness and systemic vascular resistance and is calculated by measuring the ratio of ventricular end-systolic pressure (ESP) to stroke volume (SV) (i.e., Ea = ESP/SV) [44, 45]. The interaction between the ventricle and the aorta is called ventricular–arterial coupling and is essential in the comprehension of LV function. Therefore, the ratio of Ea to ESPVR (Ea/Ees) obtained from pressure–volume loop diagrams is often used to elucidate the mechanical efficiency and performance of the ventricular–arterial system [44, 46, 47].

37.4 Effects of Positive Airway Pressure on Physiologic Effects and Hemodynamics

37.4.1 Impact of PAP Therapy on Cardiac Properties

The LVEDV on the EDPVR curve shifts to the right because PAP therapy decreases the LV preload. In addition, the slope of Ea decreases to decrease the LV afterload due to advantages in transmural pressure and inhibition of sympathetic nerve activity. Because the LV afterload reduction has a more significant contribution to the increase in SV than the preload reduction, SV is consequently increased with PAP therapy. However, the amount of this SV increase depends on the LV contractile properties. Preload reduction by PAP generally reduces LV preload and afterload, and different cardiac properties and volume states determine whether cardiac output is increased or decreased. Thus, the net hemodynamic effect of positive end-expiratory pressure (PEEP) on cardiac output depends on RV and LV systolic

properties, LV preload and afterload [48].When considering how stroke volume changes in pressure–volume loop theory, the behavior of the hemodynamic effects of afterload reduction due to PAP becomes more apparent if we consider whether the LV systolic property is preserved.

37.4.2 Preload-Dependent and Afterload-Dependent Hemodynamics

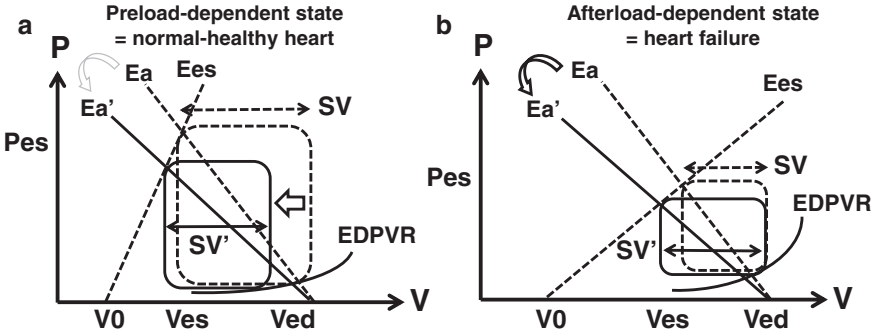
LV with preserved systolic properties (preserved Ees) is highly preload dependent. Daily clinical practice commonly sees patients with normal healthy hearts, severe right heart failure, heart failure with preserved ejection fraction, and under high PEEP.

On the other hand, the left ventricle with reduced contractile properties (reduced Ees) is highly afterload-dependent. In the real world, patients with heart failure with reduced ejection fraction (HFrEF), dilated cardiomyopathy, and severe myocardial infarction are common. PAP reduces LV preload and afterload [49].

As LV preload changes, PAP reduces venous return (VR) and RV preload. In other words, in a preload-dependent state, if VR decreases, stroke volume decreases. On the other hand, stroke volume does not decrease significantly even if VR decreases in the after-load-dependent state. Therefore, the response afterward depends on the afterload-dependent (reduced Ees) and the preload-dependent state (preserved Ees) [3].Therefore, evaluating the hemodynamics and cardiac functions during PAP is important to knowing LV systolic properties [50].

37.4.3 In Predominantly Preload-Dependent State (= More Sensitive to LV Preload, E.g., Normal-Healthy Heart, Severe RV Failure, or Under High-PEEP)

As noted above, if LV systolic properties are preserved, SV becomes preload dependent. PAP decreases VR and RV preload by increasing intrathoracic pressure and afterload dependence [51]. In terms of increased SV, afterload reduction on the LV, which retains its contractile properties, is low; instead, blood pressure is reduced (Fig. 37.3a). Preload-dependent and afterload-dependent hemodynamics are contrasted and summarized in Fig. 37.3. Increased intrathoracic pressure is transmitted to the pulmonary arteries. Subsequently, the intra-alveolar vessels become compressed. The compressed capillaries are lengthened and narrowed, leading to increased PVR (i.e., increased RV afterload). Thus, both the decreased RV preload and the increased RV afterload have the net impact of diminishing the RV stroke volume [30]. At the same time, sympathetic inhibition of activity also can act to decrease PVR. Therefore, the net balance of the effects of PAP in a predominantly preload-dependent hemodynamic state may lead to decreased LV stroke volume, resulting in decreased cardiac output (Fig. 37.3a). This phenomenon is also observed in patients with severe RV failure, Fontan circulation, or tamponade. Thus, too



	Preload-dependent (healthy-normal heart)	Afterload-dependent (heart failure)
RV preload and afterload	↓ RV preload (↑ intrathoracic pressure) ↑ RV afterload (↑ lung volume >> compress pulmonary capillaries)	↓ RV preload (↑ intrathoracic pressure) ↓ RV afterload
RV stroke volume	↓ RV stroke volume	↑ RV stroke volume
LV preload and afterload	↓ LV preload ↓ LV afterload (↓ LV transmural pressure and ↑ pressure gradient between the intra- and extra-thoracic aorta)	↑ LV preload ↓ LV afterload (↓ LV transmural pressure and ↑ pressure gradient between the intra- and extra-thoracic aorta)
LV stroke volume	↓ stroke volume and cardiac output	↑ stroke volume and cardiac output

Fig. 37.3 Pressure–volume loop showing the effects of PAP on stroke volume in the preload-dependent state (**a**) vs. afterload-dependent (**b**). The Ees in the afterload-dependent (reduced Ees) is less steep than those in the preload-dependent state (preserved Ees). Assuming that Ea in both situations has decreased equally by PAP treatment (from broken line to solid line by PAP treatment), the stroke volume in the preload-dependent state will be decreased (**a**) but increased in the afterload-dependent state (**b**). Owing to the difference in the response of RV afterload, whereas PAP can improve stroke volume in the afterload-dependent state, PAP may decrease stroke volume in the preload-dependent state oppositely. *LV* left ventricle, *PAP* positive airway pressure, *P* the pressure of the left ventricular, *V* the volume of the left ventricular, *Ea* effective arterial elastance, *Ees* end-systolic elastance, *EDPVR* end-diastolic pressure–volume relationship, *Ves* end-systolic left ventricular volume, *Ved* end-diastolic left ventricular volume, *SV* stroke volume, *SV'* changed stroke volume by PAP treatment

much PAP should be avoided, if possible or used cautiously, in such patients. Significantly, due to high PEEP, the hemodynamic reaction provided by PAP in the afterload-dependent state may change to that in the preload-dependent state. Therefore, it is necessary to titrate the PEEP appropriately to avoid too much reduction in LV preload. In other words, "More than enough is too much."

37.4.4 In Predominantly Afterload-Dependent State (= More Sensitive to LV Afterload, E.g., Heart Failure with Reduced Ejection Fraction)

If LV systolic properties are reduced (reduced Ees), stroke volume becomes afterload dependent; PAP therapy decreases PVR, so the intersection of Ees and Ea shifts leftward, increasing SV. In addition, the LV preload is increased, but SVR is also decreased due to sympathetic inhibition, increasing SV (Fig. 37.3b).

PAP decreases VR and RV preload by elevating intrathoracic pressure [52]. The reduction of RV preload can normalize the dilated RV with the ventricular septal shift toward the LV, which enables regaining of RV/LV shape and wall motion [53]. In addition, PAP can also improve gas exchange and oxygenation through alveoli recruitment, which will attenuate the elevated PVR due to hypoxic pulmonary vasoconstriction and RV-PA uncoupling [54]. PAP can also decrease LV transmural pressure and increase the pressure gradient between the intrathoracic aorta and the extra thoracic systemic circuit, reducing LV afterload. Reducing sympathetic nerve activity provided by PAP may also decrease both RV and LV afterload. The net balance among reduction in RV preload, more significant decrease in PVR, normalizing RV/LV shape, and reduced LV afterload will improve stroke volume and cardiac output (Fig. 37.3b) [55].

37.5 NIPPV Improves Clinical Outcome

The mechanism by which NIPPV improves hemodynamics is provided by reducing excessive LV preload, preventing alveolar collapse at end-expiration, and reducing LV afterload. In a meta-analysis of randomized trials, NIPPV reduced the need for intubation, improved clinical and laboratory measures of respiratory failure (e.g., heart rate, dyspnea, hypercarbia, acidosis), and improved mortality [11, 56–58]. In addition, in a meta-analysis of 32 studies (2916 patients) that included NIPPV (CPAP and bilevel), NIPPV significantly reduced mortality compared to standard care (RR 0.66, 95% CI 0.48–0.89) [59].

37.6 Conclusions

In this review, the pressure–volume loop theory was applied to detail the hemodynamic effects of PAP therapy. As effects of PAP therapy on cardiac properties, the LVEDV on the EDPVR curve shifts to the right because PAP therapy decreases VR and the LV preload. In addition, the slope of Ea decreases due to advantages in transmural pressure and inhibition of sympathetic nerve activity. Because the LV afterload reduction has a more significant contribution to the increase in SV than the preload reduction, SV is consequently increased with PAP therapy. However, the amount of this SV increase depends on the LV contractile properties. Preload reduction by PAP generally reduces LV preload and afterload, and different cardiac properties and volume states determine whether cardiac output is increased or decreased. Thus, the net hemodynamic effect of positive end-expiratory pressure (PEEP) on cardiac output depends on RV and LV systolic properties, LV preload, and afterload. Among these, stroke volume is mainly dependent on LV systolic property. By considering whether the patient is in a preload-dependent (preserved Ees) or afterload-dependent state (reduced Ees), we can predict the hemodynamic changes brought about by PAP therapy. Thus, owing to the difference in the response of LV afterload,

whereas PAP can improve stroke volume in the afterload-dependent state, PAP may decrease stroke volume in the preload-dependent state.

Conflict of Interest None.

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Home Ventilation for Chronic Obstructive Pulmonary Disease

38

Eda Macit Aydın and Müge Aydoğdu

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38.1 Introduction

In patients with advanced stage chronic obstructive pulmonary disease (COPD), an increased respiratory work load secondary to respiratory muscle fatigue and a decreased sensitivity of the respiratory center to carbon dioxide results in alveolar hypoventilation. In addition to long-term oxygen therapy (LTOT), initiation of long-term home noninvasive ventilation (NIV) can theoretically provide benefits by compensating alveolar hypoventilation, allowing for respiratory muscle rest, improving gas exchange and resetting central respiratory control in response to $PaCO_2$ concentration. In addition, the use of long-term home NIV is expected to reduce the duration of hospital stay, to decrease the frequency of re-hospitalization due to COPD exacerbation and thus result in reduction of cost. However, there are currently limited and conflicting data to support the clinical efficiency and cost effectiveness of

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_38

long-term home NIV in chronic stable COPD patients. In this chapter the indications, principles, and important remarks about home NIV use in COPD patients will be discussed [1, 2].

38.2 Efficacy of Home Type Noninvasive Ventilation in COPD Patients

There are varying results about the benefit of home type NIV use in COPD patients. Several meta-analyses and a Cochrane systematic review concluded that there was insufficient evidence to support the routine use of domiciliary NIV in patients with COPD [3–6]. Although some of these trials have demonstrated an improvement in $PaCO_2$, there was no objective improvement in lung function, hospitalizations or mortality, and a non-significant tendency to improve quality of life (QoL). The RESCUE trial, a multicenter cohort from The Netherlands, compared initiation of domiciliary NIV with standard treatment after an admission with hypercapnic respiratory failure [7]. It reported no mortality benefit and no reduction in admissions or COPD exacerbations in the year after discharge. There was a non-significant trend to improved health-related QoL. A multicenter randomized controlled trial from China compared patients receiving LTOT with domiciliary NIV + LTOT. Although there was a significant reduction in daytime $PaCO_2$ and increase in 6 min walking distance test with domiciliary NIV + LTOT, there was no mortality benefit, improvement in lung function or QoL [8]. In contrast to these studies, a multicenter trial from Germany and Austria comparing domiciliary NIV titrated to reduced daytime $PaCO_2$ with standard care in patients with chronic stable hypercapnic respiratory failure reported a significantly reduced 1-year all-cause mortality in the NIV group [9]. Furthermore, a recent multicenter randomized controlled trial from the United Kingdom, which randomized patients to receive home oxygen or domiciliary NIV + home oxygen, at least 2 weeks after normalization of respiratory acidosis secondary to acute hypercapnic respiratory failure, has reported positive results [10]. The group receiving domiciliary NIV + home oxygen had a significantly longer admission-free survival compared with the group receiving home oxygen alone. This variance among the studies is thought to be due to population selection and it will be important to determine criteria for selecting suitable patients who will benefit from domiciliary NIV. A phenotypic approach can be used to decide for whom home NIV should be started (low exacerbators, high exacerbators, COPD-OSA overlap syndrome etc.). Obesity appears to be a protective factor in this patient group. Patients receiving domiciliary NIV with a BMI >30 kg/m^2 had longer survival compared with those with a BMI 20–30 kg/m^2 [11]. It is recognized that obstructive sleep apnea (OSA) is a common feature in obese patients, and so this protective effect could be due to the effect of NIV of improving the OSA; however, even with adjustment for OSA, obesity appeared to have a protective effect [12]. Furthermore, Murphy et al. excluded patients with OSA from their trial; demonstrating that domiciliary NIV has a survival benefit over and above its effect on treating OSA [8]. The mechanism for this is unclear but is likely to be related to the obesity paradox observed in critical care patients [13, 14].

38.3 Home Noninvasive Mechanical Ventilation Indications in COPD Patients

Stable COPD patients with clinical signs of alveolar hypoventilation despite optimal medical treatment should be evaluated in terms of home ventilator use. The patient's current condition, time required for ventilator support (hours/day), and family support should be considered. The ERS Task force, the Canadian guideline, and the ATS guideline recommends the use of long-term home NIV in addition to usual care for stable hypercapnic COPD patients (conditional recommendation, low certainty evidence) [1]. The definition of stable chronic hypercapnic COPD patients differs in different guidelines. The ATS guideline defines resting $PaCO_2 \geq 45$ mmHg, not during exacerbation; it is $PaCO_2 \geq 52$ mmHg in the Canadian guideline [15, 16]. The ERS task force suggests long-term home NIV be used in patients with COPD following a life-threatening episode of acute hypercapnic respiratory failure requiring acute NIV, if hypercapnia persists following the episode (conditional recommendation, low certainty evidence) [1]. They also noted that long-term NIV should not be initiated during an admission for acute on-chronic hypercapnic respiratory failure, instead reassessment for NIV at 2–4 weeks after resolution is recommended (conditional recommendation, low certainty) [16].

They also suggest that patients with chronic stable hypercapnic COPD should undergo screening for obstructive sleep apnea before initiation of long-term NIV (conditional recommendation, very low certainty). Using an in-laboratory overnight polysomnogram (PSG) to titrate NIV in patients with chronic stable hypercapnic COPD who are initiating NIV is not recommended (conditional recommendation, very low certainty). The NIV should be applied with targeted normalization of $PaCO_2$ in patients with hypercapnic COPD on long-term NIV (conditional recommendation, low certainty) [14]. The ERS 2019 guideline recommends the use of NIV at home and NIV titration to achieve a significant reduction of carbon dioxide levels in COPD patients with chronic hypercapnic respiratory failure [1]. The Canada guideline recommends the use of NIV at home to improve hospital readmission and survival in COPD patients with chronic hypercapnic respiratory failure. For patients who are recommended for home NIV therapy, the initial settings of the mechanical ventilator before discharge should be adjusted according to gas exchange criteria (baseline carbon dioxide values, etc.) and the patient's clinical findings and if necessary high positive airway pressures should be prescribed also [15, 17].

38.4 Home Mechanical Ventilator Settings for COPD Patients

In home type mechanical ventilation applications, it is important to choose the appropriate equipment to maximize the patient's compliance with the treatment. Choosing the appropriate equipment, the ventilation mode (BIPAP-S or BIPAP-ST), and the interfaces (oronasal mask, nasal mask, nasal pillow, total-face mask) should be patient-specific. Fixed pressure modes such as BIPAP-S or BIPAP-ST are generally recommended when using NIV at home in COPD patients compared to the

other modes (volume-assured pressure-preset, adaptive control or auto-titrating pressure modes). Again, although it varies according to the patient, single-circuit, and oronasal masks are often used [1, 17]. However, patient factors and comfort should be considered in mask selection. Nasal masks and nasal pillows have better tolerance and have the advantage of small dead space. However, it should be kept in mind that the use of a nasal mask in a patient who breathes orally due to nasal obstruction may result in alveolar hypoventilation, sleep disturbance, hypoxemia, and/or hypercapnia. Besides, respiratory failure patients have tendency to breathe orally. Therefore, oronasal masks are preferred most commonly for respiratory failure patients. Similarly, a full-face mask should not be the first choice in claustrophobic patients and in patients with abundant secretion, but can be preferred in patients with nasal bridge ulcers or with facial deformities. Despite increasing experience, one or more combinations of the factors such as wrong patient selection, noncompliance of the patient with the treatment and failure in practice are important reasons for the failure of home NIV therapy [16]. Therefore, the device should be tested on the patient and necessary instructions should be given both to patients and their relatives before discharge; required adjustments of pressure support levels should be made according to arterial blood gas results and hemodynamic parameters [15, 17].

High-intensity NIV has been defined as a pressure-limited controlled ventilation option that has come into use recently. This ventilation practice provides control of the patient's breathing with a higher reserve-respiratory rate (typically backup rate of 20/min) and a higher level of inspiratory pressure support (gradual IPAP titration up to 30 cmH_2O). The aim in this mode is to achieve maximum reduction in carbon dioxide levels in a controlled manner by avoiding nocturnal alveolar hypoventilation without sacrificing patient comfort [18]. It has been reported that higher pressure support applied in high-intensity NIV improves compliance with the treatment by improving lung and respiratory muscle functions and is more effective than low-intensity NIV (IPAP of 14–16 mmHg) due to these positive physiological effects. However, in the light of current data, it has not yet become a routine practice due to cardiovascular and pulmonary side effects caused by high IPAP levels.

The use of NIV in COPD patients with hypercapnic respiratory failure has become standard practice in disease management. To improve the results and reduce the failure rate, appropriate patient selection is important, but the bronchodilator, oxygen therapy, and pulmonary rehabilitation program to be added to the treatment are important steps in the use of NIV at home [18].

In the misuse of home-type NIV, inadequate ventilation due to air leak from the mask, sleep disorders, eye irritation, skin abrasions-pressure sores due to mask compression, nasal dryness-congestion-bleeding, and abdominal distension due to air swallowing may develop. For this reason, it is important to inform the patients and their relatives about the complications that may occur due to the use of home-type NIV devices. Proper patient, correct ventilator mode and equipment selection, family support, optimization of ventilator settings are important in treatment success [2].

Table 38.1 Checklist for home NIV in COPD patients

✓ the patient should be called for control after discharge
✓ the patient should be bring the device with him when coming for control
✓ device card should be examined in terms of device usage time, leakage control, and device–patient compatibility
✓ the patient should be evaluated in terms of frequency of attacks, sleep routine, other symptoms, and problems after device use
✓ the patient should be evaluated in detail in terms of treatment (travel, upper respiratory tract obstruction, nasal irritation, etc.) and equipment problems (mask cleaning, drug use during NIV)

As a result, it is recommended that home NIV be used to reduce hospitalization, improve quality of life and survival in selected individuals with chronic stable COPD. Recently, the use of high-intensity NIV, which provides proper functioning of the diaphragm with higher inspiratory pressure support and thus more effective carbon dioxide reduction, especially in the nocturnal period, has come to the fore in stable COPD patients, with caution in terms of side effects. Patients should be assessed individually regarding the duration and time of NIV use, and checklists should be established for follow-up (Table 38.1).

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Nocturnal Noninvasive Mechanical Ventilation

39

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Abbreviations

ABG	Arterial blood gas analysis
AHI	Apnea-hypopnea index
ARF	Acute respiratory failure
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
EPAP	Expiratory positive airway pressure
FVC	Forced vital capacity
MEP	Maximum expiratory pressure
MIP	Maximal inspiratory pressure
MV	Minute ventilation
NIV	Noninvasive ventilation
ODI	Oxygen desaturation index

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https://doi.org/10.1007/978-3-031-28963-7_39

OSA	Obstructive sleep apnea
$PaCO_2$	Arterial carbon dioxide partial pressure
PEEP	Positive end expiratory pressure
PFTs	Pulmonary function tests
PS	Pressure support
PSG + CAPNO	Polysomnography + capnography
RF	Respiratory failure
S/T	Spontaneous over timed mode
SNIP	Sniff nasal inspiratory pressure
SpO_2	Oxygen saturation
T	Timed mode
$TcCO_2$	Transcutaneous carbon dioxide
TV	Tidal volume

39.1 Introduction

It is vital to acknowledge disease specific aspects of nocturnal ventilation that impact the ventilation settings. For example, patients with early-stage obese hypoventilation syndrome (OHS) coupled or not with obstructive sleep apnea (OSA) do not face challenges with diurnal ventilation. Therefore, it is nocturnal ventilation that poses clinical challenges, such as hypoventilation, which may present itself as clusters of desaturations due to subdued breathing. This is why settings should be adjusted during sleep. Capnography might be of great help. The current guidelines of the American Thoracic Society [1] suggest that arterial blood gas (ABG) can serve as a guideline for whether capnography should be performed. For patients who have low or moderate risk of developing OHS (<20%), serum bicarbonate level should be assessed to decide whether to perform capnography: in individuals with serum bicarbonate (HCO^{3-}) levels <27 mmol/L, it is possible to forego capnography, as the diagnosis of OHS seems very unlikely, whereas in individuals with serum arterial oxygen saturation (HCO^{3-}) ≥ 27 mmol/L, it is generally advised to perform capnography to rule out or confirm the diagnosis of OHS.

39.2 Neuromuscular Diseases

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease with a prevalence of about 6 in 100,000. It usually results in progressive hypoventilation stemming from respiratory muscle weakening and is associated with poor survival, cognitive impairment, and poor quality of life [2]. Hypoventilation in ALS patients may worsen during sleep as a result of apneas and hypopneas, hypotonia of respiratory muscles, weakening of the diaphragm, supine position, and probably dysfunctions of the central respiratory drive. In patients with ALS, different muscular parts may be affected in a random way, which means that in some individuals there is

predominance of bulbar muscles weakness, whereas in other cases respiratory muscles weakness may play a major role. In patients with bulbar problems, predominance of obstructive apneas may be expected. To address this pathology, using a mode with auto continuous positive airway pressure (CPAP) is advised. In this case, the ventilator will adjust PEEP based on upper airway measured patency. It is important to avoid a maximal PEEP setting at more than 12 cm H_2O because above this limit there is a large risk of aerophagia which can cause stomachache or even vomiting, which all together would decrease compliance and increase the risk of aspiration pneumonia. On the other hand, in patients with a predominance of respiratory muscle weakness, the home-ventilator should be adjusted in a hybrid mode, in which a target TV is set and the device adjusts pressure support (PS), based on the currently estimated TV. During sleep, in the situation of neuromuscular dysfunction, TV may decrease significantly and unexpectedly; therefore, adjusting settings to a wide range of PS will improve stability during nighttime ventilation. Importantly, VC < 60% predicted value is associated with hypopneas in REM sleep in the course of neuromuscular diseases. VC < 40% and maximum inspiratory pressure <30 cmH_2O are strongly associated with hypoventilation during both REM and NREM sleep phases. Diurnal hypoventilation develops after VC decrease below 25% of predicted value. Nocturnal NIV effectively improves the lowest oxygen desaturation values (nadir SaO_2), apnea-hypopnea index (AHI), and oxygen desaturation index (ODI). Moreover, the occurrence of episodes of desaturation <90% and <80% is reduced [3]. Both nocturnal average end-tidal CO_2 and duration of nocturnal hypercapnea are associated with the severity of nocturnal respiratory symptoms (measured by disease-specific orthopnea-questionnaire scores). Use of NIV may prolong life and positively impact its quality, but only in case of good compliance (NID daily use >4 h). Therefore, for long-term ventilation, it is vital to adjust ventilator settings so that maximal effectiveness is achieved using minimal possible pressures. As respiratory failure is more pronounced at night, disease progression may not be obvious. Therefore, in this patient population, two points of care are essential – reading of both diurnal and nocturnal ventilator reports. This requires assessment of the detailed report downloaded from the ventilator and timely conduction of polysmnography with transcutaneous capnometry (PSG + CAPNO) to assess and optionally adjust ventilator settings. Based on this assessment, it is often necessary to set night and day time device modes to meet different needs at different times of day. Based on this assessment, medical professionals may foresee the need to consider tracheotomy and shifting to invasive ventilation.

39.3 Chronic Obstructive Pulmonary Disease (COPD)

COPD is the third leading cause of *death* worldwide. The disease has two phenotypes, COPD in patients with normal body weight is less frequently complicated by type 2 respiratory failure (RF) (its likelihood increases when FEV_1 is below 0.5 L) – those patients require high PS settings after type 2 RF development, but their diurnal and nocturnal ventilator requirements remain similar. On the other hand, in

obese individuals with COPD, development of type 2 RF is much more frequent. In general, in those patients the ventilator should be set in an auto-EPAP mode, or the level of PEEP should be predefined during CPAP titration. Moreover, in those patients as the respiratory drive decreases, there is an increasing need for assured respiratory rhythm; therefore, the settings should include timed or spontaneous/timed modes for sleep ventilation.

Due to epidemics of obesity in developed countries, the number of obese COPD patients receiving home ventilation is rising. In a cross-sectional observational study on >3500 individuals with COPD, aimed at the assessment of self-perceived sleep quality (SLEPICO study) [4], it was revealed that the COPD assessment test (CAT) and the pulmonary function tests-based disease severity score may predict the decrease in sleep quality as assessed by COPD and asthma sleep impact score – CASIS score. The results of the SLEPICO study reveal that age, disease duration and stage, and most importantly CAT score ≥10 may be indicators for deterioration of sleep quality.

Various factors impact ventilation of individuals with COPD reduced chemo sensitivity, increased resistance of upper airways, and diminished activity of the respiratory muscles. These phenomena are predominant in individuals who report orthopnea during wakefulness and experience shift in ventilation/perfusion ratio and redistribution of body fluids. These changes result in a significant decrease in TV and, consequently, hypoventilation. Nocturnal hypoventilation may lead to retention of carbon dioxide during daytime. Nocturnal NIV is aimed at reduction (or, preferably, correction) of hypoventilation by at least 20% because it was proven than chome NIV may prolong the patient's life only when substantial reduction or normalization of daytime $PaCO_2$ is achieved. Therefore, nowadays, clinical goals are set based on parameters measured during wakefulness. Ventilatory capacities in COPD are impaired due to airway obstruction and dynamic hyperinflation stemming from intrinsic positive end expiratory pressure (PEEP) and because of increased work of respiratory muscles. The capacity of inspiratory muscles is diminished in the course of COPD. Pulmonary hyperinflation leads to a decrease in diaphragm strength. COPD is frequently associated with dysfunction of the diaphragm.

Nocturnal NIV reduces the resistance of upper airways (due to PEEP), reduces nighttime hypoventilation because of PS and PEEP, and results in relaxation of respiratory muscles (due to PS). Therefore, after successful nighttime ventilation, during daytime the patient is able to maintain acceptable spontaneous minute ventilation and obtain improved quality of life and daytime activities.

39.4 Kyphoscoliosis

The severity of the deformity is evaluated by measuring the Cobb angle on an X-ray of the spine. This angle is measured at the intersection of two lines, one parallel to the top and the other parallel to the bottom vertebrae of the scoliotic

curve. The greater the angle, the more advanced the spinal deformity; angles >100 are associated with respiratory symptoms, and angles>120 are associated with respiratory failure. In this setting, the ability to distend is severely impaired, causing restriction, especially when the Cobb angle exceeds. Hypercapnia is initially associated with sleep or physical exercise; as the deformity progresses, it may occur at rest during wakefulness. Nocturnal hypoxemia usually precedes the onset of respiratory failure in kyphoscoliosis. Hypoventilation during sleep is the most common dysfunction and results from a decreased neural drive to the respiratory muscles in the REM phase. Because kyphoscoliotic patients depend solely on diaphragm activity to maintain alveolar ventilation during sleep, they are at risk of developing hypoxemia and hypercapnia. However, the degree of nocturnal desaturation may not always correlate with the Cobb angle. Prevalence of obstructive sleep apnea is similar to that of the general population. OSA further aggravates respiratory failure [5]. Distortion of the trachea may predispose patients with advanced kyphoscoliosis to obstructive sleep apnea occurrence. Kyphoscoliotic patients with RF are often treated with hybrid NIV modalities. This treatment mode has been proven to positively impact both diurnal and nocturnal PaO_2 soon after treatment introduction. Furthermore, unloading of respiratory muscles is reflected in an increase in forced vital capacity (FVC) after 12 months of treatment.

Furthermore, in kyphoscoliotic individuals treated with diurnal mouthpiece pressure ventilation (MPV) and nocturnal NIV, a significant improvement of clinical and ABG parameters (arterial.

oxygen tension (PaO_2)/fractional inspired oxygen (FiO_2) ratio, $PaCO_2$ and pH as well as a significant increase in FVC, FEV_1, maximal inspiratory pressure (MIP), maximum expiratory pressure (MEP), sniff nasal inspiratory pressure (SNIP), TV, and breathing frequency) were noted. The 6-minute walk test (6MWT) distance also improved, but insignificantly. Importantly, quality of life is improved after with MPV + NIV treatment initiation. Although, according to data from clinical trials, NIV is strongly indicated in patients with kyphoscoliosis, as it benefits patients both in terms of CO_2 reduction, as well as outcomes and quality of life, a change in chest elastic recoil in different body positions must be taken into consideration. It may happen that effective minute ventilation may be obtained only in one body position, e.g., on the right or left side. This can be easily observed during daytime, but it may be responsible for nighttime NIV failure. That is why in the case of NV failure, patients with kyphoscoliosis should be observed at different body positions during both wakefulness and sleep. This may be responsible for significant diurnal body position related TV changes in the case of pressure-controlled settings, or for a significant change in inspiratory pressure during volume-controlled settings. This may be suspected in a situation when usually implemented NIV settings are not followed by $PaCO_2$ reduction. In those patients, the best option is NIV set after capnometric and PSG assessment is performed in a respiratory center or sleep lab (Table 39.1).

Table 39.1 NIV disease-related treatment options

	Night time changes in respiration	Position related changes in ventilation (supine/prone)	Acute respiratory acidosis	Chronic respiratory acidosis
COPD	Diminished chemosensitivity, increased upper airway resistance, decreased respiratory muscles' activity, a change in ventilation/perfusion ratio, redistribution of body fluids decrease in TV	**Worsening of airflow obstruction,** increase in hyperinflation and/or atelectasis can cause hypoventilation. Secondary hyperinflation increase in work of breathing, increased arousability and sleep disturbance	Mostly during acute exacerbation	Occurs due to changes in respiratory mechanics; shortening of respiratory muscles (due to hyperinflation) and expiratory airflow reduction, respiratory muscle fatigue
			Hypercapneic in respiratory failure, NIV allows to avoid intubation and mechanical ventilation and decrease mortality, during invasive MV which focus on avoiding ventilator-induced lung injury and minimizing intrinsic positive end-expiratory pressure iPEEP	In less severe bronchial obstruction RF is caused frequently by overlap with OSA. NIV is the treatment of choice
OHS	Hypoventilations, apneas, hypopneas, clusters of desaturation	As OHS usually co-exists with OSA: higher incidence of apneas and hypopneas, positional OSA: 50% increase in AHI in supine sleep position compared to the non-supine position	Leading cause: congestive heart failure, associated with older age, compromised PFTs, low VC associated with ICU admission risk; NIV: first-line treatment	RFis probably underreported, alveolar hypoventilation during sleep → nocturnal hypercapnia and hypoxia → resetting of the respiratory drive → diurnal hypercapnia and hypoxemia
Kyphoscoliosis	Prolonged central apneas, clusters of desaturation mostly in REM sleep, severely decreased TV	Impact of sleep positions on patients with compromised PFTs; clusters of desaturation mostly during REM sleep, inhibited accessory respiratory muscles esp. in REM sleep	May be precipitated by a respiratory infection (pneumonia), blood stream infection, decompensation of pulmonary hypertension (cor pulmonale).The risk of ARF development during infection is associated with the extent of chest deformity and decrease in VC	NIV is first-line treatment due to impaired chest mechanics, improves survival, chronic respiratory failure usually occurs in teenage years/young adults. Body position related differences in ventilation effectiveness and compliance are frequently seen

Neuromuscular diseases	Hypopneas in REM sleep, hypercapnia, nocturnal hypoxemia, sleep atonia, reduced lung volumes, and chemosensitivity, decreased airway dilator contribute to the occurrence sleep-disordered breathing events	Even in normal individuals, the supine position reduces the vital capacity by as much as 19% and the functional residual capacity by about 25%. Diaphragmatic weakness is more pronounced in VC in supine position (>25%). VC and supine VC: crucial criteria for the diagnosis of diaphragmatic function impairment and initiation of NIV	Mostly caused by **Guillain-Barré syndrome and myasthenia gravis** PFTs which predict the need for mechanical ventilation: VC, peak inspiratory pressure, peak expiratory pressure	The most common cause of morbidity and mortality; reduction in inspiratory muscle strength, ineffective alveolar ventilation, expiratory muscle weakness, impaired secretions clearance leading to chronic respiratory insufficiency. Bulbar problems especially in ALS may lead to NIV failure, however intubation is controversial due to poor disease related quality of life and no effective treatment. Cough assist physiotherapy may improve NIV effectiveness and tolerance
Invasive ventilation via tracheotomy	Can be postponed/ avoided thanks to implementation of NIV In some settings should be the first-line treatment, e.g., septic shock-induced ARF in neuromuscular diseases NIV may be used as weaning from invasive ventilation	In invasive MV it is less relevant because prosthesis of the upper airways with the intubation tube protects against apnea occurrence	Tracheostomy is usually performed after 7 day of intubation and mechanical ventilation in the ICU, in patients with poor prognosis for fast decannulation; however, in patients with COPD and OHS weaning from tracheotomy in short period of time (few months) is usually possible with the use of NIV	In patients with neuromuscular disease acute tracheotomy is frequently associated with shifting to chronic invasive ventilation. Chronic NIV may be considered as sealing treatment in ALS; however, occurrence of bulbar syndrome makes NIV extremely difficult and frequently poorly tolerated

39.5 Conclusions

To conclude, it is important to remember spontaneous ventilation during wakefulness and sleep vary. This is more important in chronic respiratory failure, where it is suggested to increase ventilation at night but not necessarily at the cost of patient's quality of life (although large discrepancies are observed in the intensity of NIV settings in different countries). During chronic treatment, it is crucial to restore physiological sleep, sometimes with a slight increase in patient's MV (acceptance of permissive hypercapnia). This will prevent the development of nighttime acidosis. The mechanism of hypoventilation may differ significantly; therefore, chronic home NIV should be performed according to disease-specific recommendations. In acute respiratory failure, the treatment should be targeted at a rapid increase of MV leading to resolution of decompensated respiratory acidosis. In this situation, settings should be adjusted based on the severity of acidosis and the patient's neurological status. This kind of treatment usually lasts for a few hours or days, after which the patient usually requires diminishing of ventilator settings. Therefore in acute respiratory acidosis the ventilator settings are usually based on timed (T) or spontaneous over timed (S/T) modes. Treatment implementation should be performed in a secured setting, optimally aided by multiorgan monitoring (ECG, SpO_2, transcutaneous capnometry T_CCO_2). Those patients should be constantly monitored by a nurse experienced in NIV and mask adjustment. In chronic patients, especially those who have significant diurnal minute ventilation changes (individuals with OHS, neuromuscular diseases), automatic hybrid modes are frequently required. These modalities have the capacity to target optimal minute ventilation even in patients with changing respiratory drive, upper airway patency, and chest compliance. Therefore, in most cases of patients using mostly nighttime NIV, the ventilator settings should be adjusted during sleep. In patients using NIV during day- and nighttime (no matter on the disease leading to respiratory failure) night and day specific settings may increase treatment effectiveness and patient compliance.

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European Models of Home Noninvasive Mechanical Ventilation: What Have We Learned? Evidence and Key Determinants

40

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40.1 Introduction

In the history of mechanical ventilation over the past 100 years, from 1928, when an iron lung was first used at the Children's Hospital of Boston (Massachusetts), through its highest level of use in the 1940s and 1950s during the poliomyelitis epidemics, until our current times, we realize it is a two-speed journey. The fast track was taken in the 1950s, when iron lungs started to be replaced by positive airway pressure through intubation, and the second track started when the facial mask started to be used as a noninvasive ventilation method. Thus, the possibility of avoiding long hospital stays became a reality with the creation of the first home mechanical ventilation (HMV) programs.

The prevalence rate of HMV has considerably increased in Europe in recent years, both in countries that traditionally had low prevalence rates such as

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_40

Switzerland [1] and the Netherlands [2], in those that had the highest rates, such as France (data source is ANTADIR) [3], and also in countries such as Australia and New Zealand (9.9–12/100,000) [4].

In the beginning, most patients (70%) were invasively ventilated with positive pressure mechanical ventilators through a tracheostomy tube, and the rate of patients whose ventilation was noninvasive was low. The interfaces used for these were either mouth or nasal pieces (16%), or negative pressure ventilators (14%). In the 1980s, nasal masks started to be used in patients with Duchenne's disease, and negative pressure ventilators were limited to exceptional use [5].

After that time, the use of noninvasively implemented mechanical ventilators spread quickly as the technique of choice among patients with restrictive respiratory failure. Patients adapted to the ventilator in a hospital setting and there were later followed-up in their homes; this is when the first positive pressure noninvasive ventilation (NIV) home programs appeared. In 1994, Leger et al. [6] published the first series of patients treated with positive pressure NIV at home, with a follow-up of 276 patients during 5 years. In this study, the benefit for patients with kyphoscoliosis or sequelae from tuberculosis or Duchenne's disease was clear. Moreover, the study showed that patients with chronic obstructive pulmonary disease (COPD) and bronchiectasis also benefited from this method. In 1992, the first pressure support ventilator was created and, since then, the technology has improved and different ventilation methods have appeared.

HMV programs have evolved in recent years and, at the same time, technological progress has allowed for an increase in home monitoring of patients on NIV. Moreover, HMV program implementation aims to bring NIV as close to patients' homes as possible.

40.2 HMV Prevalence in Europe

HMV's introduction into Europe has been uneven and has differed according to country. In 2001 and 2002, to assess the pattern of HMV use in Europe, questionnaires were sent to 483 centers in 16 European countries. A total of 329 replied, which amounts to between 62% and 79% of HMV users in Europe. This data was published in the EUROVENT [7] study. The average prevalence in Europe was estimated at 6.6 patients/100,000 citizens, although there was a large variation between countries: France was the country with the highest prevalence (17/100,000), whereas Poland had the lowest (0.1/100,000). Prevalence variation could be related partly to the average years since NIV started to be implemented. Differences in the relative proportion of patients with obstructive disease, rib cage pathology, and neuromuscular disease were also made clear.

In fact, it is highly likely that data obtained from EUROVENT is not up to date. This is the case with Poland, which went from a 0.1/100,000 prevalence in 2002, to 2.5/100,000 in 2010, with a reduction from over 80% of neuromuscular patients in 2002 to 51% in 2010 as a result of the increase in the number of patients with respiratory disease [8].

However, it is not only in countries with low prevalence that there has been an increase in the rate of use of NIV. France, which in 2002 showed the highest rate in Europe (17/100,000) showed a rate of 90/100,000) in 2011 [9]. A similar case is that of the Spanish region of Valencia. Spain showed a prevalence of HMV in 1999 of 4.59/100,000, and of 6.3/100,000 in 2002 according to the EUROVENT study. In a study carried out in 2007 (in the Valencia region [10]), HVM prevalence was proven to have risen to 29/100,000. These data can also be extrapolated to other regions of Spain, such as Madrid, which in 2018 reported a HVM use rate of 74/100.000 [11].

40.3 HMV Models

NIV use in patients with chronic respiratory failure is covered by national health systems; however, only a few countries have clear guidelines about how NIV should be started and in which patient groups. Public national health systems and private insurance companies usually hire private home therapy companies to provide and maintain NIV equipment prescribed by patients' doctors to use when patients are at home. These companies have paramedical staff that can train patients and their families to correctly use NIV. The frequency of visits depends on the type of ventilator prescribed for each patient; the interface type can be adjusted and humidifiers can be provided. In some cases, these companies can also offer other home services, for instance, $SatO_2$ night monitoring can be provided. If problems arise at patients' homes, they are communicated to the prescribing doctor; good coordination with the reference hospital is key [12].

Sometimes, the relationship between these companies and the national health systems is poor and often there is no formal infrastructure. Thus, a European study that was carried out in 16 countries including more than 20,000 ventilated patients showed that, in 62% of centers, an external company carried out services provided to patients. It also showed that the maintenance frequency ranged between 3 and 12 months; that interaction between the service-providing companies and the hospitals was scarce; that the participation of hospitals in the quality control of equipment was poor; and that there were important differences not only between countries but also within the same country [11, 13].

The variability of HVM in the same region is one of the key issues, since HVM requires expert teams and the number of patients seen is a very important element. In fact, a high percentage of centers apply HVM to a small number of patients, and to a higher percentage of less complex patients. This variability can be attributed to the variability of clinical practice, or the lack of resources to perform with quality criteria [12].

In recent years, given the increase in the number of patients in HMV, and the increase in technical complexity in management, the accreditation of NIV Units has been proposed at different levels according to the degree of complexity in the diagnostic and therapeutic approach, as well as in medical research and instruction. The more complex Units are made up of a multidisciplinary team from different health

specialties, to cover complex cases, and provide support to the lower-level Units, allowing the consultation and referral of patients between Units [14, 15].

40.4 NIV Adaptation in HMV Programs

NIV adaptation can take place during a scheduled hospital stay, although it can also be effectively implemented in day hospitals, outpatient settings, and even at the patient's home. Pallero et al. [16] carried out a multicenter, randomized, prospective study to compare efficacy and costs according to whether the HMV program was started in a hospital setting or an outpatient setting, with patients who had stable chronic respiratory failure with NIV indication. The main study variable was the $PaCO_2$ drop 6 months after NIV initiation. They found a significant decrease in both groups, although they did not find significant differences between them. Direct costs of both interventions were estimated. The hospital setting intervention was estimated to have a cost of 2692 euros, whereas the outpatient setting intervention had a cost of 1500 euros. Therefore, the conclusion was that, because adapting NIV in the outpatient setting is equivalent to doing it in the hospital setting from a therapeutic perspective, adaptation in the outpatient setting could lead to cost savings for the health system.

Technology advances rapidly. The most modern ventilators can be equipped with a modem that allows downloading the built-in software data remotely, without the patient going to the hospital or outpatient center. Some offer advanced monitoring capabilities that may include pulse oximetry and capnography, as well as review of pressure/flow curves and other parameters. The COVID-19 pandemic has highlighted the need to avoid admissions for the initiation or optimization of ventilatory support. There are new remote CPAP titration programs in sleep apnea patients that have proven their effectiveness [17]. It is possible that in the future these programs could be transferred to bilevel respirators, facilitating the ambulatory initiation of ventilatory support.

40.5 HMV Programs Follow-Up

There are no data on how frequently patients should see their specialized center doctor, and it depends on different factors such as the patient's pathology, how they adapt to NIV, and how easy it is for them to travel to the hospital. If a private home services company is involved, some of the follow-up can be done in patients' homes. The information can be transmitted to the prescribing doctor who, every 3 months, can systematically check the patients' approximate symptoms, quality of life, ventilation-related side effects, and compliance. After receiving this information, the doctor will be able to determine whatever adjustments are needed.

Some of the tests can only be carried out in the hospital; therefore, it seems that some kind of hospital follow-up is necessary. Generally, the average number of outpatient visits per year is three. Follow-up complementary tests during these visits include arterial blood gas, chest X-rays, and respiratory function tests. The nocturnal evaluation is carried out at home, if possible, or in the hospital to control

ventilation quality during the night, and, if possible, in the 3 months following NIV initiation. Patient nocturnal follow-up during the HMV program's first year includes monitoring O_2 saturation, if possible with capnography, and arterial blood gas first thing in the morning, and in some cases, the respiratory polygraphy and polysomnography. Review of pressure/flow curves and other data offered by the built-in ventilator software has become a basic tool in outpatient evaluation [18].

For many of the more restrictive patients, once they are stable, the supervision required is minimal. Unstable patients or patients who are insufficiently stabilized with NIV need closer follow-up (e.g., those with rapidly progressing neuromuscular diseases such as amyotrophic lateral sclerosis (ALS), and to a lesser extent, patients with muscular dystrophy caused by Duchenne's disease or COPD) [19].

Telemonitoring can be used to check a ventilator's compliance and performance. Although not widely available at the moment, the situation is likely to improve in the future. In 2010, Pinto et al. [20] published a prospective study on 40 patients with ALS who were divided into two groups. In the intervention group, the ventilator data was received by modem, whereas in the control group, compliance and ventilator parameters were checked on official visits. The study did not find differences between groups regarding compliance, although the number of visits to the doctor and to the ER was significantly lower in the group in which telemonitoring was carried out ($p < 0.0001$). Moreover, although there were no significant differences, survival showed a positive trend in the group with telemonitoring ($p = 0.13$), the conclusion being that telemonitoring reduces the need to use health services and probably has a favorable impact on costs, survival, and performance status.

Telemonitoring might also be useful for patients other than those with ALS. In 2015, Borel et al. [21] published a study that observed that an increase in the breathing rate and the percentage of respiratory cycles caused by the patient were predictive of a COPD exacerbation. Both parameters can be registered by NIV software.

40.6 Conclusions

A progressive increase of the NIV prevalence rate by all European Union member states demands cost-effective schemes to manage patients on HMV. Moreover, telemonitoring these patients should be the first option to effectively solve this public health issue, although prospective, multicenter studies that ensure its feasibility are still needed.

Key Major Recommendations

- The exponential and global growth, in Europe, of patients on HMV programs generates a key area for development.
- There is a need for European guidelines on home assistance management models.
- Unique quality indicators for the HMV model are needed.
- The cost-efficiency of telemonitoring programs requires assessment.

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TeleHome Noninvasive Mechanical Ventilation

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Abbreviations

AECOPD	Acute exacerbation of chronic obstructive pulmonary disease
AHI	Apnea/hypopnea index
ALS	Amyotrophic lateral sclerosis
APAP	Automated positive airway pressure
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_41

Sarinc CPAP Continuous positive airway pressure
HMV Home mechanical ventilation
NIV Noninvasive ventilation
NMD Neuromuscular disease
$PtcCO_2$ Transcutaneous CO_2

41.1 Introduction

Home noninvasive mechanical ventilation (NIV) can be used as ventilatory support for hypercapnic respiratory failure, chronic respiratory failure, and nocturnal ventilatory support. The aim of home NIV is to reduce hypoventilation, improve symptoms and quality of life, reduce hospital admissions, and prolong survival. The increasing elderly and obese population contributes to the increase in the number of patients using home NIV. Monitoring of these patients from treatment initiation and long-term follow-up is needed to ensure effectiveness of treatment.

Telemedicine, defined as "the use of information and communication technology to deliver health services, expertise and information over distance, geographic, time, social and cultural barriers," includes various technologies potentially to enhance quality of care and to reduce health care costs, especially in chronic diseases [1]. Telehome monitoring provides close follow-up of patients by ensuring transmission of clinical and physiologic data and by supporting prompt medical intervention before the patient's condition deteriorates [2]. Telehome monitoring should be reliable, noninvasive, and easy to use. Algorithms related to the integrity and security of data need to be enhanced. Moreover, additional evidence regarding health outcomes and cost savings needs to be concluded, the digital data needs to be bridged, and policy changes that support telemedicine reimbursement need to be enacted for the use of telemedicine in common practice [3].

In this chapter, mainly using NIV monitoring systems, the role of telehome NIV for improving the adherence of patients with obstructive sleep apnea syndrome (OSAS) and hypercapnic chronic obstructive pulmonary disease (COPD) to NIV therapy emphasizing the use of telehome NIV in other respiratory disorders will be discussed.

41.2 Discussion and Analysis

41.2.1 NIV Monitoring Systems

NIV monitoring systems include hardware (timer, pneumotachograph, integration of pulse oximeter, transcutaneous capnograph, and cardiorespiratory polygraphy), software and cloud platforms [4].

41.2.1.1 NIV Hardware

All home mechanical ventilators have ventilator timers providing an estimation of daily ventilator use time, and the integrated pneumotachograph showing pressures delivered, flow, the percentage of cycles triggered by the patient, inspiratory and expiratory time, tidal volume, minute ventilation, and the level of leak. These data are available on built-in screens.

Pulse oximetry and capnography are important additional monitoring devices to determine the impact of NIV on gas exchanges. Finger pulse oximeters connected to a dedicated port on the ventilator or through an external adaptor provide monitoring of SpO_2 tracings. Transcutaneous CO_2 ($PtcCO_2$) monitoring integration via an external transcutaneous capnograph will help physicians to determine hypoventilation. Some manufacturers include connectors for integrated overnight cardiorespiratory polygraphy given additional signals such as thoraco-abdominal belts to diagnose sleep related events as in sleep laboratories.

41.2.1.2 NIV Software

Licensed software for data recovery and analysis has been developed with the expansion of home NIV monitoring. Manual data can be transferred from the ventilator to a computer via a memory card or a universal serial bus storage device. The software displays continuous signals such as flow, pressure, and leak for curve analysis and provide an automatic detection of residual apneic-hypopneic events recorded by the ventilator. Moreover, the software can integrate and synchronize the signals communicated by each port from pulse oximetry, or capnography or cardiorespiratory polygraphy recordings.

However, each manufacturer has developed their own software and the presented data vary; therefore, clinicians must be familiar with the interface of the system purchased and presented data.

41.2.1.3 Cloud Platforms

Recently, cloud platforms have been developed to monitor patients more frequently without the need of manual transfer. A summary of pre-analyzed data reducing the amount of data uploaded are usually transmitted once a day when the ventilator is not in use. Secured access codes are used by physicians to access the uploaded data. Data format vary among manufacturers such as NIV software. Remote change of ventilator settings or alarms notifying clinicians about an emergent event can be possible. However, this system has limitations such as overlooked information and lack of close follow up due to transmission of summarized data once a day. Moreover, the number of ventilators that have these teletransmission systems is low. However, integration in all devices and telecommunication progress will overcome these issues.

41.2.2 Telemonitoring for Respiratory Disorders

Respiratory disorders have significant effects and burdens on society. In patients with chronic respiratory diseases, underlying disorders, the level of dependency on

caregivers, the hours spent under mechanical ventilation, the presence of tracheostomy, distance from home to hospital, and hospital access are parts of care burden both for the family and healthcare systems. These patients need education, self-monitoring, and close management to ensure better outcomes and improve survival. Patient, ventilator, or interface oriented problems (such as patient–ventilator asynchrony, re-breathing, or leaks) should be detected to select the most appropriate ventilator settings and interface in patients receiving home mechanical ventilation (HMV). Home telemonitoring presents an alternative tool for close follow-up of patients by ensuring timely transmission of clinical and physiologic data to estimate detrimental events in patients treated with HMV during the day and at night. Subsequent rapid troubleshooting of potential problems may improve adherence to HMV therapy.

41.2.2.1 Telehome NIV for Sleep-Related Breathing Disorders

OSAS a is highly prevalent sleep-related breathing disorder affecting 26% of adults, with high morbidity and mortality leading to cardiovascular, neuropsychiatric and metabolic complications, impotence, and socioeconomic problems [5]. Continuous positive airway pressure (CPAP) is used as the first-line medical treatment in OSAS [6]. CPAP, even in one night, effectively improves sleep architecture, reduces the apnea-hypopnea index (AHI), normalizes oxyhemoglobin saturation, and decreases neurocognitive and cardiovascular impairments.

CPAP adherence is defined as using CPAP for an average of 4 h a night for at least 70% of the nights. Previous studies demonstrated that four or more hours of CPAP use is associated with improvement in daytime sleepiness, quality of life, neurocognitive function, cardiovascular disease, and diabetes in OSAS patients. Targeting longer use will be more effective to achieve further goals such as significantly improved memory and daily functions.

Nonadherence is defined as using CPAP for less than five nights per week. CPAP withdrawal resulted in a rapid recurrence of apneic events, daytime sleepiness, and cardiovascular events.

Adherence can be significantly improved with the use of educational, behavioral, troubleshooting, and telemonitoring interventions. Therefore, it is necessary to increase patients' understanding of the expected benefits of CPAP use, to motivate using this therapy, to determine side effects, and to monitor and promote adherence to CPAP therapy at the beginning of use to improve CPAP adherence.

Previous studies related with different telemonitoring options have demonstrated variable effectiveness in CPAP adherence of OSAS patients. In a recent meta-analysis, the effects of telemedicine interventions on CPAP adherence in patients with OSA were assessed and using telemedicine for up to 6 months was found to enhance CPAP adherence in OSAS, when compared to no intervention [7].

Set-up should be optimized rapidly as the first weeks after NIV initiation are important for long-term adherence. Daily telemonitoring of compliance, leakage, and residual AHI can direct physicians to solve the problems and change ventilator settings in this early period. The impact of telemedicine on the delay to the first technical intervention after CPAP initiation and mean compliance during the first 3 months of treatment in moderate to severe OSAS was assessed in a randomized

trial [8]. This early activation of troubleshooting with telemedicine was found to improve compliance at 3 months indicating the long-term CPAP acceptance.

Significant improvement in CPAP adherence has been demonstrated with telemonitoring when compared with usual care in adult OSAS patients in a recent metanalysis by Patil et al. [6]. Rapid troubleshooting rather than waiting for an appointment to see a clinician and motivation of patients with daily monitoring are potential explanations for the increase in adherence with telemonitoring.

There has been no difference in terms of patient outcomes between initiation of PAP in the home and in-laboratory titration approach in OSA patients [6]. Monitoring nocturnal oximetry and capnography results integrated to NIV software is very useful for initiation of NIV at home. In a recent randomized clinical trial, physiological effectiveness of NIV set-up guided by PSG to limited respiratory monitoring and nurse-led titration in patients with COPD-obstructive sleep apnea overlap was compared and no differences in daytime $PaCO_2$ and adherence at 3 months were found between groups [9]. These findings highlight clinical effectiveness of NIV initiation at home.

41.2.2.2 Telehome NIV for COPD

Home NIV is indicated in COPD patients with chronic hypercapnic respiratory failure.

NIV is usually initiated in the hospital and pursued at the home to correct nocturnal hypoventilation and improve sleep quality, quality of life, and survival. Regular follow-ups are needed to assess the effectiveness of ventilation and adherence to therapy, resolve potential adverse effects, reinforce patient education, maintain the equipment, and readjust ventilator settings according to the changing conditions of the patient. Data related to daily use, unintentional leaks, upper airway obstruction, and synchronization of patient and ventilator can be obtained from NIV [10].

A target threshold of NIV use for COPD patients of at least 5 h per day is associated with significant improvement in gas exchange and prognosis.

An increase in daily hours of NIV use could point to impairment of respiratory status and acute exacerbation onset [11].

The pattern of NIV use during the day and at night should be examined to determine tolerance to NIV and patient comfort. Three or more interruptions per night can indicate patient discomfort due to the interface or inadequate ventilator settings.

Unintentional leaks impair gas exchange and sleep structure. Unintentional leaks lower than 20 L/min are generally tolerable. However, sometimes unintentional leaks as low as 10 L/min can impair patient ventilator synchrony; therefore, the severity of unintentional leaks should be determined to check patient ventilator synchrony. Suboptimal selection, setting, or positioning of the interface, decreased muscle tone during sleep, patient movement during the night, episodes of upper airway obstruction, or suboptimal ventilator settings can be the reasons for leaks. Leak trend examination can highlight the reason for unintentional leaks. Unintentional leaks from initiation of NIV can suggest an unadapt mask, setting, or positioning. Unintentional leaks later in the night can indicate positional leaks or opening of the mouth.

Upper airway obstructions that are dynamic reduction in upper airway patency limiting or interrupting airflow can cause recurrent short leaks. If unintentional

leaks are large and decrease inspiratory pressure, the ventilator cannot compensate for the leaks.

Tidal volume or minute ventilation trend analysis can indicate periods of alveolar hypoventilation.

Predictive value of changes in daily compliance to NIV, leaks, tidal volume, residual respiratory events, or overnight breaks from NIV for detecting severe acute exacerbation of COPD (AECOPD) have been investigated in the study by Blout et al. [12]. They determined that change in the breathing pattern analyzed with data provided by NIV built-in software could predict admission for AECOPD.

Seven-day mean respiratory rate, abnormal values of daily usage, leaks, and tidal volume within the 7-day pre-AECOPD period were found to be potential biomarkers for detection of AECOPD in the retrospective observational study by Jang et al. [13].

Pulse oximetry and capnography are important home monitoring tools to detect efficacy of treatment in terms of gas exchange in patients receiving home NIV. Soon, telemonitoring of home NIV for COPD patients will be a routine management tool to determine efficacy and adherence to therapy, resolve adverse events, strengthen patients' knowledge, and change ventilator settings according to patients' needs.

41.2.2.3 Telehome NIV for Other Chronic Respiratory Disorders

Remote control of NIV settings is very useful in patients with neuromuscular diseases (NMD) receiving NIV. A recent multicenter study demonstrated that HMV initiation at home with telemonitoring was noninferior to hospital initiation in patients with neuromuscular disease and thoracic cage disorder [14]. Improvements in gas exchange and quality of life were similar between HMV initiation at home and HMV initiation in hospital groups. Moreover, home initiation of HMV with telemonitoring in patients with neuromuscular disease and thoracic cage disorder seems to be a cost effective and attractive approach.

Remote NIV monitoring with bi-directional data transmission, which allowed for automatic transmission of NIV data and remote adjustment of NIV settings in ALS patients has been implemented in four previous studies in the literature [15–18].

Reduced need to travel to the clinic for adjustment of NIV settings was the main benefit of telemonitoring for ALS patients in these studies. Lack of robust cost-effectiveness-analysis and issues with reimbursement were the reported barriers to telehealth implementation.

Remote management of ALS patients became more important during the COVID-19 pandemic to detect disease progression and prevent life-threatening conditions. Videoconferencing or home-based self-monitoring as telemonitoring of NIV can effectively reduce morbidity and mortality of ALS patients [19]. An observational study by De Marchi et al. [20] reported their experience with telemedicine at a Tertiary ALS Center from an Italian geographical area with high infection risk during the COVID-19 pandemic and highlighted the importance of a multidisciplinary approach when trying to stabilize the functional and metabolic status. Viewing of patients via video camera to verify any breathing difficulties and to eventually request an urgent pneumological inpatient visit for 2 of 19 ALS patients

who quickly initiated NIV, with stabilization of respiratory function were positive outcomes of telemedicine during the COVID-19 pandemic.

41.2.3 Limitations of Telehome NIV

Telemonitoring has been used for initiation of NIV at home and detection of clinical status to date. Many questions remain before telemedicine can be considered for broad application as most of these studies were single center with relatively small sample sizes, short-term follow-up periods, and driven by expert teams, which limit the representativeness of the results. Data of short- or long-term outcomes of telehome NIV use for management of patients are insufficient.

Lack of real-time data transfer is another limitation of current telemonitoring systems as close follow up is not possible. Rapid progress in telecommunication can overcome this limitation and decrease costs associated with data transfer. Moreover, telemonitoring of NIV parameters needs to become widespread.

Last but not least, detailed examination of comorbidities is essential for patients receiving noninvasive mechanical ventilation. High ventilatory pressures might increase intrathoracic pressure, might reduce right ventricle preload and cardiac output in patients with heart failure. Therefore, close monitoring of blood pressure is needed.

41.3 Conclusion

Recently, telemonitoring via cloud platforms seems to be practical for intervention of problems, improving adherence and outcomes. However large-scale multicentric studies are needed to support effectiveness for outcomes in patients receiving home NIV and to implement these systems in common practice.

Key Major Recommendations

- Telemonitoring integrated with homecare, social services and access to hospital, supporting early identification of deteriorations in patients' conditions, remote control of ventilator settings, and increasing home NIV adherence, represents a promising patient management.
- Basically, daily use of NIV, respiratory rate, and leaks should be recorded by the telemonitoring system.
- Patients should be educated about the telemonitoring program and action plan, and give informed consent.
- Initiation of HMV can be ensured by using telemonitoring to transmit digital data and to provide clinical health care outside the hospital.
- Cloud platforms supply remote change of ventilator settings or alarms notifying clinicians about an emergent event.

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Noninvasive Mechanical Ventilation in Rare Diseases

42

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_42

42.1 Introduction

There are different accepted definitions of rare diseases. Some definitions are based on the number of affected people, while others rely on the availability of effective treatment or the severity of the disease. In Japan, a condition or disease that affects fewer than 50,000 people is approved as a rare disease. In the United States, a disease that affects less than 200,000 patients is considered a rare disease, while the definition of a rare disease in Europe is one that affects less than 2000 patients.

Noninvasive ventilation (NIV) is defined as any mode of ventilatory support that was delivered with a noninvasive interface without tracheal intubation. NIV has been approved to be the first step treatment option for a wide range of sleep and respiratory disorders in pediatric age groups. These disorders include upper airway obstruction, musculoskeletal weakness and chest wall restriction, chronic lung diseases, central nervous system disorders, and other systemic disorders with respiratory insufficiency [1–4]. In recent years, usage of NIV increased in the management of patients with acute respiratory failure. It is a more desirable alternative to positive pressure ventilation via endotracheal intubation for various conditions. NIV can be applied by using positive pressure, such as continuous positive airway pressure (CPAP), bi-level positive airway pressure (BiPAP) and high-flow nasal cannula, or negative pressure.

Since there are numerous rare diseases, it would be impossible to discuss the use of NIV in every rare disease. Unfortunately, there is no adequate number of articles with data solely on NIV use in a specific rare diseases. In this article, the use of NIV in rare diseases that meet the general indications for NIV will be discussed. NIV may be used in patients with neuromuscular diseases and chest wall disorders, anatomic anomalies of the face and/or airway, disease of central nervous system adversely affecting respiratory drive, and some metabolic and genetic diseases that can lead to central nervous system and/or respiratory system problems.

42.1.1 NIV Usage in Patients with Neuromuscular Diseases and Chest Wall Disorders

NIV is commonly used for patients with neuromuscular respiratory failure. Some neuromuscular diseases can require NIV during the disease course, including amyotrophic lateral sclerosis, Duchenne muscular dystrophy, Becker's muscular dystrophy, Steinert's muscular dystrophy, spinal muscular atrophy, and myasthenia gravis [5]. Motor neuron loss in ALS results in atrophy of the corresponding muscle, and consequent weakening of respiratory muscles. Early stages of the disease are usually asymptomatic and respiratory insufficiency manifests in late stage. When muscle function loss becomes pronounced, the patient feels impending respiratory failure.

Available reports indicate that NIV is able to reverse alveolar hypoventilation, improve quality of life, and prolong survival time in neurological patients [6]. When respiratory muscle dysfunction is severe in patients with neuromuscular disease,

respiratory insufficiency occurs and ventilation support becomes mandatory. Weakness is seen in the main three muscle groups (inspiratory, expiratory, and bulbar muscle groups) that achieve the work of breathing. Impairment of inspiratory muscle strength results in alveolar hypoventilation. Insufficient clearance of secretion and cough performance are seen as a result of expiratory muscle impairment. Weakness in bulbar muscles that are necessary for swallowing and increasing the intra-thoracic pressure occur [7]. Also, structural deformities such as kyphoscoliosis in the throrax cavity may occur due to muscle weakness. Weakness of respiratory muscles becomes prominent first during sleep and nocturnal hypoventilation symptoms such as broken sleep pattern, nightmare, morning headache, fatigue, and somnolence occur [8, 9]. Confusion and somnolence result from hypoxemia and respiratory acidosis. Use of accessory muscles of respiration by patients is one of the signs of severe respiratory muscle weakness. Similarly, weakness of the diaphragm is manifested by paradoxical abdominal muscle movements. Neuromuscular diseases can be categorized into slowly progressive and rapidly progressive. This classification is important for to decide NIV timing [10]. Patients with neuromuscular disorders should be monitored using serial spirometry, pulse oximetry, sleep studies, and blood gases. Alveolar hypoventilation can be diagnosed by polysomnography, and polysomnography should be performed every year to identify nocturnal hypoventilation and not to delay the initiation of NIV therapy [9]. Hypoventilation first occurs in REM sleep, but with disease progression sleep disturbances are seen in REM and non-REM sleep, and finally it occurs during the daytime [11]. NIV support should be started in patients with neuromuscular disease as soon as possible after the beginning of respiratory distress symptoms. However, some contraindications restrict the usage of NIV in neuromuscular disease such as anatomical and/or functional obstruction, gastrointestinal bleeding or persistent vomiting, and severe respiratory acidosis (pH < 7.1) [12]. Hypercapnia (>45 mmHg), nocturnal hypoxia (<88%), reduced functional vital capacity (FVC), and sign of respiratory difficulty are indications of NIV initiation [11]. After initiation of NIV, patients should be monitored for improvement of nocturnal hypoventilation and blood gases.

Some chest wall disorders such as scoliosis and kyphosis with severe anatomic deformity may cause severe ventilatory failure. In these situations, the respiratory drive is intrinsically normal but the mechanical problems prevent inflation and deflation of lungs and also reduce respiratory system compliance. The decision to start NIV support in these conditions commonly depends on the severity of hypoxia and hypercapnia that are detected during sleep, and the presence or absence of polycythemia or high pulmonary artery pressure. If hypercapnia is detected during the daytime as well as at night without symptoms or any complications of polycythemia or pulmonary hypertension, the indication for NIV treatment is stronger than with nocturnal hypercapnia alone. Breathlessness on effort, quality of sleep, early morning headaches, and psychosocial and mental function can all be improved by NIV [13].

The post-operative use of NIV may facilitate early extubation in children with neuromuscular diseases. Respiratory movements are reduced during the post-operative period due to sedation and pain. Extubation may be performed in the

operating room in children with neuromuscular disorders but this may be difficult and result in atelectasis and pneumonia. Mechanical respiratory support by NIV has been proven to increase lung volume and expiratory flow and decrease the occurrence of atelectasis in young children with neuromuscular disease [14]. NIV support delivers a positive pressure during the inspiration to increase lung inflation. This lung inflation is followed by an instantaneous switch to negative pressure to the upper airway, and simulating a normal cough. When NIV was used to assist cough in children with various neuromuscular diseases, it generated higher peak cough flows than other classical assisted cough methods [15].

42.1.2 Rare Disease with Anatomic Anomalies of the Face and/or Airway

Children with some anatomic anomalies of the face and/or airway may exhibit a broad spectrum of respiratory problems, which are related to the degree of upper airway obstruction and may be associated with apnea. Achondroplasia, Pierre Robin sequence, Fragile X syndrome, and Goldenhar syndrome are some rare diseases and often present with upper airway obstruction problems. A critical obstruction of the upper airway requires medical and/or surgical intervention. If there is a fatal obstruction, tracheostomy may be considered, although it has mortality and morbidity, especially for neonates and infants [16]. Application of surgery in patients whose condition does not improve despite the use of adequate duration of NIV is important for prognosis and to prevent the worsening of condition. Alternative treatment methods for upper airway obstruction are prone or lateral positioning, palatal plate therapy use of nasal tubes, mandibular distraction, and mandibular traction [17].

Congenital or acquired upper airway obstruction problems cause some respiratory problems that can be supported with noninvasive ventilation such as BiPAP and CPAP. NIV has been shown to be effective for management of obstructive sleep apnea, laryngomalacia, and other congenital upper airways abnormalities [18].

In patients with achondroplasia, upper airway obstruction and obstructive sleep apnea-hypoapnea syndrome (OSA) are caused by associated anatomical abnormalities such as the combination of mid-facial hypoplasia, micrognathia, depressed nasal bridge, relative adenotonsillar hypertrophy, relative macroglossia, a high palate and decreased temporomandibular joint mobility, and nasopharyngeal or glossal muscle hypotonia. NIV can decrease the work of breathing efficiently via providing airway patency in patients with upper airway anomalies because increasing of airway diameter is associated with decreasing of airway resistance that improves breathing. Improvement of nutritional status with NIV was observed for infants with upper airway obstruction problems. These infants have a high prevalence of swallowing difficulties and potential risk of aspiration, usage of NIV also decreases the incidence of aspiration and its complication.

OSA is characterized by recurrent episodes of partial or complete apnea and obstruction of the upper airway during sleep [19]. The pathophysiology of OSA remains controversial. Symptoms of the OSA include excessive daytime sleepiness,

frequent awakenings, unrefreshing and unstructured sleep, difficulty concentrating, and short-term memory loss. Patients with Fragile X syndrome and Goldenhar syndrome may encounter OSA and can be treated with NIV [20, 21]. Facial morphology, anatomical obstruction, connective tissue dysplasia, and hypotonia are the precipitating factors for OSA. In the previous studies, it was shown that continuous airway positive pressure (CPAP) has significant advantages in OSA by improving sleep study parameters such as the apnea-hypopnea index (AHI) and daytime wakefulness, cognitive function, and quality of life [22]. Clinical criteria for starting NIV support depends on symptoms and physiological markers of alveolar hypoventilation such as shortness of breath during daily physical activities, poor sleep quality: insomnia, nightmares and frequent arousals, nocturnal or early morning headaches, daytime fatigue, drowsiness, loss of energy, and decrease in intellectual performance [23].

42.1.3 Disease of Central Nervous System

Central hypoventilation syndrome (CHS) is a rare disorder caused by some congenital or acquired conditions that are characterized by respiratory insensitivity to hypercapnia and hypoxemia during sleep and/or wakefulness. CHS onset time varies according to the course of the underlying disease [24]. Some congenital diseases such as rapid-onset obesity with hypothalamic dysfunction, hypoventilation and autonomic dysregulation (ROHHAD), Prader-Willi syndrome (PWS), Familial dysautonomia, Arnold Chiari malformations, achondroplasia, and disorders affecting mitochondrial metabolism may result in central hypoventilation [24]. The breathing system is regulated by a set of central and peripheral chemoreceptors that are sensitive to changes in partial pressure of oxygen (PaO_2), $PaCO_2$, and hydrogen potential (pH), as well as other factors, such as the stretching of bronchial smooth muscle cells [25]. Polysomnography is the gold standard method to diagnose apnea. Normally, apneas emerge during rapid eye movement (REM) sleep, although in CHS apnea, episodes recur during non-REM sleep due to the impairment of central and peripheral chemoreceptor sensitivity [24]. NIV can provide adequate ventilation for patients with CHS, but this treatment options should be preferred in patients requiring ventilation only during sleep. Traditional BiPAP with spontaneous/timed (S/T) ventilation mode is the most commonly used mode because it provides continuous flow during inspiration and expiration period. In spontaneous/timed (S/T) mode, a backup rate is added to spontaneous mode, and the device starts to deliver breath when the patient's spontaneous respiratory rate decreases below the set backup rate. An inspiratory time is set, and this time is applied to all spontaneous and timed breaths in some devices and applied to only timed breaths in some devices. It is recommended to set the backup rate closer to the physiological respiratory rate during sleep. However, for a patient with CHS, minute ventilation can be significantly different during the course of the night due to variation in the control of breathing during REM and non-REM sleep. This condition results in higher pressure settings during the first half of the night when NREM sleep predominates

and subsequent hyperventilation during the second half of the night when REM sleep is predominant. As children with central hypoventilation syndromes do not trigger the ventilator adequately during sleep, the timed mode with a set respiratory rate is to be preferred.

Recently, the BiPAP intelligent volume-assured pressure support (iVAPS) mode has been proposed for patients with CHS [26]. In this mode of BiPAP, the pressure support is automatically modulated to ensure a constant alveolar ventilation. A potential advantage of this BiPAP mode for patients with CHS would be more homogeneous control of carbon dioxide levels throughout the night. Some manufacturers emphasized that iVAPS is indicated for patients weighing more than >30 kg. Khayat et al. performed a retrospective chart review of CHS patients who underwent both a titration polysomnography (PSG) with standard BIPAP S/T mode and a consecutive follow-up study with BIPAP intelligent volume-assured pressure support (iVAPS) mode [26]. In children with CHS on nocturnal ventilatory support, the use of BIPAP therapy in iVAPS mode when compared to S/T mode resulted in a significant reduction in the peak transcutaneous CO_2($tcCO_2$) in NREM but not REM sleep. Also this reduction trends of mean $tcCO_2$ in NREM sleep can be seen between these two modes. The peak pressures appeared higher with iVAPS when comparing the median IPAP. The significantly reduced peak $tcCO_2$ in İVAPS mode as compared to BIPAP S/T mode during NREM sleep may result from higher peak pressures in iVAPS mode. It is possible to use NIV in average volume assured pressure support mode (AVAPS), which it is similar to iVAPS. This mode of positive pressure ventilation adjusts the inspiratory pressure support to maintain a target tidal volume rather than a target alveolar ventilation and provides less differentiation of the $PaCO_2$ values during sleep and can be used in a younger age group.

The results of this study underline that long-term follow-up by specialists both during therapy and after discontinuation of NIV is necessary in children with associated disorders. Main conclusions of this review are summarized in Table 42.1.

Table 42.1 Main conclusions/future perspective

– NIV stands as a noninvasive primary or adjunctive therapy for neuromuscular diseases and chest wall disorders, anatomic anomalies of face and/or airway, disease of central nervous system adversely affecting respiratory drive, and some metabolic and genetic diseases
– Patients with anatomical abnormalities managed by NIV should be evaluated regularly for failure of conservative treatment and requirement of surgical airway
– Clinicians undertaking the care of patients who have genetic syndromes with anatomical or neurological abnormalities should regularly search for clinical signs and symptoms of obstructive sleep apnea
– Children with genetic diseases who have multiple comorbid conditions may require multiple surgery or procedures to be carried out. During—or in preparation of—any intervention in a child maintained in noninvasive ventilation, adjustment of therapy should be considered according to potential needs and risks, including possible transition to another mode of respiratory support
– When instituting NIV in any patient, end points of therapy should be defined. The clinician should not set incompatible targets at the expense of side effects. Studies should focus on targets of therapy in patients with rare diseases who may have the involvement of more than one organ system by disease process

42.2 Final Conclusions

42.2.1 Learning Points

- Serious obstruction of the upper airway requires medical and/or surgical operation and NIV may be a good adjunctive therapy option.
- NIV is crucial in many rare diseases for safe long-term respiratory support; spontaneous improvement may occur, but most children with anatomical abnormalities require surgical intervention.

42.2.2 Critical Points

- In any patient with decreased lung capacity and chronic need for assistance, even temporary removal of support may result in collapse, which should be foreseen and prevented
- NIV support in neuromuscular commonly depends on the severity of hypoxia and hypercapnia that are detected during sleep, and the presence or absence of polycythemia or high pulmonary artery pressure
- NIV support should be directed solely to the distinctive needs of the particular patients. Fabric procedures should be altered with more tailored approaches

42.2.3 Key Summary

NIV has become an important therapy for children with rare diseases who have sleep and respiratory disorders, including upper airway obstruction, musculoskeletal weakness, chest wall restriction, central nervous system disorders, and other systemic diseases resulting in respiratory insufficiency or failure. NIV is also an important alternative for other invasive therapies (intubation, tracheostomy, or other surgery). Follow-up of children using NIV for a long time should include efficacy, complication, and tolerance of the NIV therapy and the possibility of weaning from NIV.

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Unusual and Emergent New Indications for Noninvasive Mechanical Ventilation

43

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Abbreviations

ACPE	Acute cardiogenic pulmonary edema
ARDS	Acute respiratory distress syndrome
BiPAP	Bi-level positive air pressure
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CPAP	Continuous positive air pressure
FiO_2	Fraction of inspired oxygen

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_43

HEPA	High efficiency particulate air [filter]
HFNC	High flow nasal cannula
HIV/AIDS	Human immunodeficiency virus/acquired immunodeficiency syndrome
ICU	Intensive care unit
NIV	Noninvasive ventilation
PEEP	Positive end expiratory pressure
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SpO_2	Oxygen saturation by pulse oximetry

43.1 Introduction

Noninvasive ventilation (NIV) began during the poliomyelitis epidemics of the early twentieth century, in the form of a negative pressure system called the "iron lung," designed to encase the patient's body from the neck down. Since then, NIV has shifted toward positive pressure ventilation systems similar to those used in invasive ventilation. The main difference between the two lies in the interface. While invasive ventilation requires devices such as an endotracheal tube or a tracheostomy to deliver positive pressure to the lungs, NIV does so through noninvasive interfaces, such as facial or nasal masks, nasal plugs, and helmets. NIV has a well-established role in the treatment of some acute conditions, namely the exacerbation of chronic obstructive pulmonary disease (COPD) and cardiogenic pulmonary edema. Many chronic conditions (e.g., obstructive sleep apnea, obesity hypoventilation syndrome, neuromuscular disorders, and chest wall diseases) also benefit from NIV.

Invasive ventilation requires sedation and intubation, and carries risk of complications such as barotrauma resulting in pneumothorax or pneumomediastinum, infectious complications like ventilator-associated pneumonia, and muscular atrophy from prolonged bed rest. Therefore, the appeal of a noninvasive approach to ventilation has increased. The past two decades have seen a growing interest in expanding the use of NIV to additional etiologies of both hypoxemic and hypercapnic respiratory failure. Moreover, entirely new noninvasive techniques have emerged, such as high flow nasal cannula (HFNC) – initially indicated in neonatal populations, but now increasingly used in adults as well. In this chapter, we aim to describe new and emergent applications of NIV and review the available evidence to support its use in the management of these conditions.

43.2 Brief Overview of Traditional Indications for Noninvasive Ventilation

Historically, up to one-third of patients admitted to hospital for acute exacerbation of COPD died in spite of appropriate therapy, which consisted of bronchodilators, corticosteroids, antibiotics, supplemental oxygen and, when all else failed, invasive ventilation. NIV, more specifically bi-level positive airway pressure (BiPAP), has

changed the paradigm of treatment for this disease, greatly reducing mortality and sparing one-fourth of patients the need for intubation [1]. All patients presenting with COPD exacerbation, hypercapnia, and respiratory acidosis should undergo a trial of NIV [2].

Acute cardiogenic pulmonary edema (ACPE) remains one of the most common causes of respiratory failure, with significant in-hospital mortality. The aims of therapy are to reduce cardiac preload and afterload, remove excess volume and recruit areas of ventilation/perfusion mismatch in the lung. NIV, in the form of continuous positive airway pressure (CPAP) or BiPAP, increases intrathoracic pressure, which reduces both right ventricular preload (by decreasing venous return) and left ventricular afterload (by assisting its contraction). It also recruits poorly ventilated alveoli [2]. Current guidelines recommend the use of NIV early in the management of ACPE because it has been demonstrated to reduce mortality. The data is more robust for CPAP, but BiPAP is also a valid option, especially in patients presenting with hypercapnia [3].

Other established indications for NIV include obstructive sleep apnea, obesity hypoventilation syndrome, neuromuscular disorders and restrictive chest wall diseases, which are discussed in detail elsewhere.

43.3 Expanding the Horizons of Noninvasive Ventilation

43.3.1 Acute Asthma Exacerbation

Asthma is characterized by bronchoconstriction which causes airflow obstruction. Acute asthma exacerbations are classically treated with inhaled bronchodilators, systemic corticosteroids, as-needed supplemental oxygen, as well as other therapies, including aminophylline and magnesium sulfate. Severe asthma attacks may require intubation. Asthma and COPD are similar in that they both cause airway obstruction; the former in a transient, reversible way, and the latter with a fixed, irreversible pattern. It is, therefore, not unreasonable to assume that NIV could play a role in the management of acute asthma exacerbations. Only three small randomized controlled trials (Holley et al., Soroksky et al., and Soma et al.) have evaluated the use of BiPAP in asthma. No patients in these studies, in either the BiPAP arms or the control arms, died. In the first study, three patients required intubation, one in the BiPAP group and two in the control group [4–6]. The available evidence does not show a clear benefit of NIV in the management of asthma exacerbations, and therefore its routine use cannot be recommended for these patients. However, the initiation of BiPAP apparently did not worsen outcomes and a short trial of NIV may be attempted in selected patients. The patient's condition should be closely monitored, and prompt intubation is indicated if it deteriorates [2].

43.3.2 Thoracic Trauma

Blunt chest trauma usually results from motor vehicle accidents, falls, injury with blunt instruments, and physical assault. The most common intrathoracic injury associated with blunt chest trauma is lung contusion, which can cause respiratory failure depending on the extent of pulmonary parenchyma involvement [7]. The available evidence seems to show that the use of NIV in the management of trauma-associated respiratory failure is beneficial, reducing intubation rates when compared with conventional oxygen therapy. However, this benefit is limited to the first 48 h after trauma; therefore, NIV should not be used in chest trauma patients who develop hypoxemia later in the course of their hospital stay [8].

43.3.3 Immunosuppression

Immunosuppressed patients, including those infected with HIV/AIDS, transplant recipients, patients with hematologic cancers, and others, constitute a high-risk group for infectious complications from intubation and mechanical ventilation, and thus stand to benefit from a noninvasive approach. Several studies showed reduced intubation rates and lower or similar mortality rates in immunosuppressed patients treated with NIV, when compared to those treated with intubation [2]. It is recommended to prioritize BiPAP over invasive ventilation in immunocompromised patients with pneumonia and respiratory insufficiency [9].

43.3.4 Before and After Endotracheal Intubation

One of the main complications that occur during intubation is oxygen desaturation. This can be prevented by a period of preoxygenation preceding the intubation, classically achieved with bag-valve-mask ventilation while administering a FiO_2 of 100%. A small trial compared this standard approach to preoxygenation with NIV and found that patients preoxygenated with NIV had fewer desaturations during intubation and higher SpO_2 levels before, during, and after the procedure [10]. However, a subsequent larger trial failed to corroborate these findings. In patients previously under NIV who subsequently require intubation, NIV should not be discontinued in order to perform standard preoxygenation with bag-valve-mask ventilation [11].

According to recent guidelines, NIV is useful to prevent reintubation in high-risk extubated patients (i.e., those over 65 year of age, with underlying cardiac or pulmonary disease) [12].

43.3.5 Respiratory Failure in the Pediatric Population

NIV is the first-line therapy in infants and children presenting with acute respiratory distress and respiratory failure. Over the past decade, there has been a persistent

increase in the use of NIV in children, accompanied by a decrease in invasive ventilation. The success of NIV in preventing intubation depends on the underlying cause of respiratory insufficiency, but overall rates of 77% have been reported, with children presenting with acute respiratory distress syndrome (ARDS) having less favorable outcomes when compared to those with pneumonia, sickle cell disease's acute thoracic syndrome, and various causes of immunosuppression. Children with bronchiolitis also respond well to NIV, with reported success rates of approximately 81–83%. Although it is beyond the scope of this chapter, HFNC has also shown favorable results in this population [13].

43.3.6 End-Stage Acute-on-Chronic Respiratory Failure with Do-Not-Intubate Order

NIV is efficacious in treating hypercapnic respiratory failure of several etiologies. However, its use may seem questionable in patients with end-stage acute-on-chronic respiratory failure, when intubation and invasive ventilation are contraindicated. This dilemma is even further exacerbated if the patient is in hypercapnic coma, or narcosis, and unable of verbally expressing his or her will regarding end-of-life care. On the other hand, in patients with do-not-intubate orders, NIV remains as the ceiling of care, the last therapeutic resort that physicians can offer. Furthermore, NIV has a well-established role as a palliative measure to alleviate dyspnea.

In a French observational study of frail individuals with terminal respiratory failure who presented with narcosis and were treated with NIV, 70% survived to be discharged from the hospital, half were alive 6 months after discharge and 85% of these survivors would be willing to receive treatment with NIV again, should the need arise. The authors of this study postulated that sedation by narcosis helped patients tolerate and adhere to NIV [14]. This may suggest that NIV should be tried in all terminal patients presenting in hypercapnic coma. The same cannot be said about lucid patients, who are capable of refusing NIV and should be consulted first about their wishes. Clinicians should make the decision to start NIV on a case-by-case basis.

43.3.7 Coronavirus Disease 2019 Pandemic

Since it emerged in China in late 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has taken the world by storm. The disease it causes, coronavirus disease 2019 (COVID-19), was declared a pandemic in March 2020 and continues to spread to the present day. Globally, more than 136 million cases and 2.9 million deaths have been confirmed as of April 2021, making it one of the deadliest pandemics in history.

SARS-CoV-2 is mostly transmitted through respiratory droplets and aerosols. The clinical spectrum of COVID-19 ranges from asymptomatic infection to rapidly progressive respiratory failure, ARDS, and death. Retrospective studies have shown

that critically ill patients develop dyspnea relatively late (around 7 days after symptom onset), but then rapidly progress to ARDS over the following 2 or 3 days [15]. When COVID-19 patients develop hypoxemia, support measures are often escalated from low-flow oxygen therapy via nasal cannula up to non-rebreather masks, and then to intubation and invasive ventilation.

Given these patients' rapid progression to respiratory failure and the high rates of infection among healthcare workers during the initial stages of the pandemic, noninvasive techniques such as NIV or HFNC were not widely used. There were concerns that their potential to generate aerosols could result in the dispersal of viral particles in the atmosphere, further spreading the disease to personnel and other patients [16]. The World Health Organization, however, contemplated NIV in their guidelines for management of COVID-19 if adequate safety measures were ensured, such as negative pressure rooms, high efficiency particulate air (HEPA) filters, and personal protective equipment for healthcare workers.

An NIV trial may be adequate in patients with mild-to-moderate respiratory failure due to COVID-19, before proceeding to intubation [16]. However, as the pandemic surged, many countries experienced unprecedented strain on their healthcare systems, with saturation of intensive care units (ICU) and unavailability of invasive ventilators. NIV played a preponderant role, often as the ceiling of care, in the treatment of patients who did not have access to the ICU.

Ideally, a closed double-limb circuit and a non-vented mask should be used, but this is not always feasible, since many dedicated noninvasive ventilators have single-limb circuits with exhalation valves [16]. Furthermore, the use of a non-vented mask increases risk of asphyxia, warranting higher levels of clinical vigilance which are not always available in general wards. The interfaces associated with lesser degrees of aerosol dispersion are full-face masks and helmets. If a vented oronasal mask is used, a surgical face mask can be placed over it as an additional protection measure. Helmets were extensively used in Italy in the early pandemic. Besides having low rates of aerosol dispersion, they can deliver CPAP without a ventilator, provided a high-flow gas source and a positive end expiratory pressure (PEEP) valve are available [17].

43.4 Conclusion

NIV continues to grow and its use has been expanded from the more traditional indications, such as COPD exacerbations, ACPE, and others, into numerous etiologies of respiratory failure, such as asthma exacerbations, respiratory failure secondary to chest trauma, and respiratory failure in immunosuppressed patients. It also has a role to play in the management of respiratory failure in both extremes of age: NIV has proven to be effective in pediatric populations and is useful in terminal patients, not just as palliation but also to treat end-stage hypercapnic respiratory failure. The COVID-19 pandemic has been a major challenge worldwide, and noninvasive measures can allow selected patients to avoid intubation, but, more

importantly, they serve as the ceiling of care for patients who do not have access to intensive care in healthcare systems strained by the burden of this disease.

Key Major Recommendations

- Noninvasive ventilation is recommended to treat respiratory failure developing in the first 48 h after blunt chest trauma and in immunosuppressed patients as a means to avoid intubation and its infectious complications. A trial of noninvasive ventilation is reasonable in selected patients with asthma exacerbation, under close monitoring.
- It is also effective in most etiologies of respiratory distress in the pediatric population (e.g., bronchiolitis and acute thoracic syndrome).
- Noninvasive ventilation can be used for preoxygenation before intubation and is useful to prevent reintubation of high-risk extubated patients.
- In terminal patients with do-not-intubate orders, noninvasive ventilation is effective to alleviate dyspnea and to treat hypercapnic coma.
- Provided adequate safety measures are taken, noninvasive ventilation can be used to treat mild-to-moderate respiratory failure caused by coronavirus disease 2019, and to treat patients without access to intensive care and invasive ventilation due to saturation of available resources.

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Part VIII

Critical Care Applications of NIMV and Related Issues

Equipment Technology for Noninvasive Ventilation in Pre-hospital Setting

44

Steven C. LeCroy

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NIPPV has proved effective in the pre-hospital settings for a variety of cardiopulmonary conditions, from congestive heart failure (CHF) to chronic obstructive pulmonary disease (COPD). In 2011 the National Assocation of EMS Physicians (NAEMSP) publish a position paper stating "The NAEMSP believes that noninvasive positive pressure ventilation is an important treatment modality for the prehospital management of acute dyspnea" [1]. The NAEMSP statement was based on the

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_44

work of Kosowski which concluded that "Prehospital use of CPAP is feasible and may avert the need for endotracheal Intubation (ETI)" [2]. In fact, it is not uncommon to see pre-hospital medical protocols directing EMS clinicians to consider NIPPV for any patient in respiratory distress regardless of underlying pathology. A common technique for NIPPV pre-hospital is continuous positive airway pressure or CPAP. Another option can be the use of bi-level positive airway pressure or BiPAP™ (Philips Respironics). Of the two, CPAP has a proven track record when used pre-hospital; support for BiLevel is growing with significant anecdotal evidence supporting bi-level therapy prehospital. Historically, providing bi-level therapy required more complex devices or ventilators, neither of which was well suited for prehospital use. Fortunately, the first disposable bi-level (FlowSafe II+ Mercury Medical) entered the market in 2018. In contrast, simple disposable and non-disposable CPAP devices designed specifically for pre-hospital have been available for many years, as well as a variety of transport ventilators with NIV capabilities. This chapter will cover the current technology and equipment to provide NIPPV in the out-of-hospital emergency environment.

Historically, NIPPV use in the field was limited by the available technology. Limitations of using hospital NIV devices included size, cost, durability, and oxygen consumption. Over time and with feedback from the field each of these limitations has been addressed with new and innovative technology. Before looking at current devices available for use in the pre-hospital setting and to help determine the appropriate device for a particular agency, a couple of fundamental questions that providers should be asking before selecting a device include: First, what constitutes a good pre-hospital NIPPV device? Second, what capabilities are needed to meet the need of a particular agency? Emergency Medical Services (EMS) agencies share some basic fundamental protocols and equipment types, but if you have seen one EMS agency you have seen one EMS agency; no two are alike.

There are a variety of devices available for clinicians to choose from when providing NIPPV from fully disposable to capital equipment. All medical devices have variations in performance and design. Providers of NIPPV should be aware of these differences and the affect the differences may have on care provided.

44.1 Important Components of a Pre-hospital NIV Device

Patient Interface: NIPPV is only effective if the patient is compliant with the treatment and that starts with patient comfort, a patient is rarely compliant when not comfortable. The choice of interface is a crucial issue in noninvasive ventilation. Available interfaces include nasal, oronasal and facial masks, mouthpieces and helmets, with full face mask being common. Interfaces come in different sizes, having the correct size makes the device more comfortable and improves the seal requiring less pressure from the head strap or harness. Another option to improve comfort is to have some mechanism to take pressure off the bridge of the nose reducing the incidents of pressure sores, a common complaint of NIV patients as well as hospitals due to the increase risk of infection.

Manometer: Applying positive pressure to the airway is not without risk and may lead to a wide range of problems, including pneumothorax, reduced cardiac output,

and even death. As with every therapy, keeping a balance between risk and reward is important. To help manage the risk it is recommended that all patients receiving NIPPV should have the pressure continuously monitored. A manometer also allows the clinician to document pressures used, information that will be valuable in the event of a bad outcome and whether there is a good seal. If the manometer does not register the mask is not sealed. Arguably the most important reason to use a manometer with NIV is to evaluate inspiratory flow rates (forward velocity) of the device. If the inspiratory flow rate is not fast enough to meet the patient's inspiratory demand the manometer reading will drop to zero during inhalation and the patient will experience an increase in work of breathing, air hunger, and will not be compliant with the therapy. This is often described as desynchrony or the effect when the patient's respiratory demands are not being appropriately met by the device.

Few Parts/Compact: EMS units have limited space not only in their vehicles, but in the equipment bags/cases taken to the patient. It is imperative that any equipment designed for EMS be compact, simple, and with minimal parts. Historically, EMS providers have an aversion for any equipment with lots of parts that require assembly before use. As the number of parts increases confusion, application error and reduction in use increases.

Oxygen Consumption: Unlike a hospital, EMS crews or ambulances have a limited supply of oxygen. Many agencies have converted to D cylinders due to their size and weight as a trade-off for less oxygen. Those agencies with longer transport times have to be concerned with oxygen consumption rates.

Nebulizer Capable: With the expanded use of NIV for patients in respiratory distress, including COPD and asthma the ability to provide nebulized medications is no longer an option but a necessity.

Capnography/Capnometry Capable: The measuring of End Tidal CO_2 ($EtCO_2$) should be a standard for any patient in respiratory distress or failure. With current $EtCO_2$ technology all critical patients should be continuously monitored.

Antiasphyxia Capabilities: With EMS's limited oxygen carrying capabilities and potential long transport times or delays, an NIV device should have antiasphyxia capabilities. Antiasphyxia or anti-suffocation protection is commonly provided by an antiasphyxia valve if the device is of a closed design. Open systems do not require an antiasphyxia valve since the device is open to room air.

Adequate Inspiratory Flow Rates: Patients in respiratory distress often require the air/oxygen to be provided at a fast enough speed to meet their demand; it is often not the volume of air/oxygen that is the problem, but the velocity at which it arrives. Inadequate inspiratory flow rates will cause shortness of breath, difficulty breathing, and an increase in work of breathing. Patients in respiratory distress may need flow rates as high as 65 LPM or greater.

Fraction of Inspired Oxygen (FiO_2): Concerns regarding the administration of high oxygen concentrations has been in great debate for several years. The outdated theory that oxygen administration is risk free has been shown to be false. However, at this time, the only way to treat hypoxia is with oxygen. An NIV device with low oxygen concentration capabilities is limited when treating hypoxic patients. Clinicians are left with few options when a device has a maximum FiO_2 of 30% and the patient is still hypoxic but needs the positive pressure to reduce the work of breathing. With increased evidence showing harm due to hyperoxia, EMS agencies

need added oxygen/air blending capabilities during transport at a minimum. Using blenders to control the FiO_2 should become standard for not only NIV patients but to meet current resuscitation guidelines.

Pressure Pop-Off or Relief: Since high airway pressures are dangerous an NIV device should incorporate a mechanism to relieve excessive pressure. Common causes of excessive pressure are blocked exhalation valves or a blocked exhalation opening commonly found with open systems.

Expiratory Filters: With the emergency of the SARS-CoV-2 pandemic there is a renewed interest to consider filters on all aerosol generating procedures. However, in clinical practice, there is no agreement on what procedures should be considered aerosol generating. In response, the World Health Organization has listed noninvasive positive pressure ventilation as an aerosol generating procedure; therefore, filters should be considered [3].

44.2 Types of Prehospital Noninvasive Positive Pressure Ventilation Systems

Commercially available systems provide portable NIPPV through either a conventional external pressure regulator, disposable CPAP system, demand-flow, or a transport ventilator. All four designs contain key features that influence selection and implementation.

Regulator-based portable NIPPV systems generate continuous pressure from oxygen flow, directly controlling inspiratory and expiratory pressure. Regulator-based NIPPV systems allow different inhaled oxygen fractions with reduced oxygen consumption.

Some disposable devices are open systems and use a different NIPPV approach, accelerating oxygen flow through a series of channels to create turbulence. The turbulence acts as a virtual valve, generating positive airway pressure.

Demand-flow devices have a variety of pressure levels and built-in manometers. Transport ventilators may be designed to provide NIPPV. Dependent on the individual brand and model, the process can be somewhat complicated and often beyond standard EMS training.

44.2.1 Conventional external pressure regulator NIPPV systems

Regulator-based portable NIPPV systems generate continuous pressure from oxygen flow, directly controlling inspiratory and expiratory pressure. Regulator-based NIPPV systems allow different inhaled oxygen fractions with reduced oxygen consumption. In 1981, JB Downs invented a new venturi device called the Downs Flow Generators. The flow generators where the first pre-hospital devices used on a large scale and come in two types, adjustable flow and fixed flow. Devices using the downs flow generator design incorporate controls to adjust flow rates as well as the inspired oxygen percentage (FiO_2). Positive end expiratory pressure (PEEP) is determined by a PEEP valve found in the mask.

44.2.2 WhisperFlow® and Vital Signs CPAP System

The first downs flow generator devices were the WhisperFlow (Philips Respironics; http://whisperflow.respironics.com/) and the Vital Signs (http://www.obex.co.nz/Product/Index/137) CPAP systems. Both devices are re-useable flow generators with disposable circuits that attach to the high-pressure side of a flow meter or regulator. These devices are solely powered by gas flow and entrain room air through a venturi. Each produces high gas flow rates ranging from 100–140 L/min. The gas flow leaves the device and enters a breathing circuit exiting through a spring-loaded valve, all pressure adjustments are made by changing valves. Neither unit incorporates a pressure manometer and have high oxygen consumption rates [4] (https://www.medresourcesinc.com/Catalog/Product/26754/Whisperflow).

(Variable Flow Whisperflow, Photograph by Steve LeCroy)

44.2.3 Disposable CPAP Devices

Note: Disposable devices attach to the low-pressure side of the regulator or flow meter, (Boussignac®, FlowSafe®, O-Two Controlled Ventilations™, and BLS Rescuer® Emergency CPAP System), Go-PAP™ Emergency CPAP or to the high-pressure side (O2RESQ™).

44.2.4 Boussignac®

The disposable Boussignac CPAP device (Vygon; https://www.vygon.com/catalog/vygon-boussignac-cpap_572_00557013), first described by Dr. George Boussignac in 1989, was the first completely disposable CPAP device. The principle behind the Boussignac valve is to increase the forward velocity of a gas by narrowing the flow through a cylinder. By increasing the velocity, turbulence is created within the device. It is the turbulence and friction within the cylinder that creates the resistance the patient must breathe against. All pressure adjustments are made by adjusting the flow rate to either increase or decrease the turbulence. This process eliminates the need for valves or moving parts. The valve is open, meaning that it is open to the atmosphere, allowing the patient to breath in room air as needed. The device

incorporates a measuring port to add a manometer if needed. The manufacturer reports that CPAP of 10 cmH_2O can be achieved with approximately 25 L/min of oxygen flow.

FlowSafe II® (Mercury Medical®)

(Photograph courtesy of Mercury Medical)

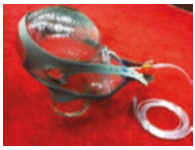
Flow-Safe® is a completely disposable CPAP device featuring a built-in manometer to monitor airway pressure/peak flow and a pressure relief valve for patient safety. There are three versions of FlowSafe® Available: (The original FlowSafe® was discontinued in December 2020), FlowSafe® II, FlowSafe® II ez, and FlowSafe II +. Each device uses the same principle to create pressure. Similar to the Boussignac® the FlowSafe® device changes the velocity of the gas by narrowing the flow. The increase gas flow creates the inspiratory pressure to assist the patient to inhale and also provides the positive end expiratory pressure (PEEP) during exhalation. Pressure adjustments are made by increasing or decreasing the gas flow rate from the flow meter or regulator and monitoring the built-in manometer. According to the manufacturer, the original FlowSafe® achieved pressures from 1.5 to 10 cmH_2O with oxygen flow rates of 10 to 25 LPM, respectively. FlowSafe® II achieves the same pressures as the original FlowSafe® using lower flow rates; however, the trade-off is a slightly lower FiO_2. FlowSafe®II ez incorporates a built-in nebulizer allowing both the CPAP valve and the nebulizer to be powered from a single gas source. FlowSafe II+ is the first disposable bi-level device that allows independent adjustments to the inspiratory positive airway pressure (IPAP) and the expiratory positive airway pressure (EPAP). (http://mercurymed.com/home/).

FlowSafe II + ®	**FlowSafe II ® ez**
	

(Photograph courtesy of Mercury Medical)

44.2.5 O-Two Controlled Ventilations™

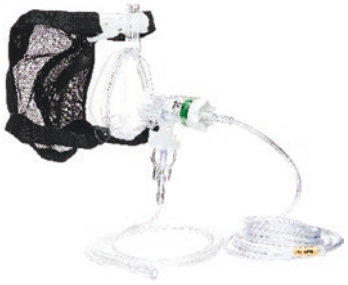
The O-Two Single-Use CPAP device (O-Two Medical Technologies; http://otwo.com/emergency-cpap/o_two-single-use-cpap/) is completely disposable. Adjustment of pressure levels occurs by adjusting the flow rate from the flow meter or regulator. Pressure and flow rate settings are found on the body of the device. According to the manufacturer, the CPAP range is between 5 and 20 cmH_2O at flow rates of 8–25 L/min.



(Photograph by Steve LeCroy)

44.2.6 GO-PAP™

The Go-PAP (Pulmodyne; https://www.pulmodyne.com/go-pap) is a disposable CPAP device with an integrated nebulizer. It operates off of the low-pressure side of a regulator or flowmeter at 10 LPM and delivers approximately 30% FiO_2. There are three options for PEEP 5, 7.5, and 10 cmH_2O. Both the CPAP device and nebulizer can be operated off one gas source with the addition of a proprietary adaptor. The device does not come with a manometer option.



(Photograph Courtesy of Pulmodyne)

44.3 Rescuer® Emergency CPAP System (BLS Systems Limited)

Rescuer Emergency CPAP (BLS Systems; http://blssystemsltd.com/cpap_em.html) incorporates an oxygen reservoir that, according to the manufacturer, allows higher FiO_2 levels with low flow rates, saving oxygen. The device also has filters on both

the inhalation and exhalation side to reduce exposure to airborne pathogens. With the addition of the Rescuer II compact, a smaller version than the original BLS Rescuer, BLS Systems now offer a version with a built-in manometer. The device can also be configured to power a small volume nebulizer directly off the CPAP device.

44.4 O2RESQ™

The O2-RESQ (Pulmodyne; http://www.pulmodyne.com/products/pre-hospital-and-emergency-medicine/o2-resq-product-information/) is an expansion chamber with a venturi air entrainment port. The basic unit provides approximately 30% FiO_2 at a continuous flow up to 140 L/min to meet patient demand. A 3-set CPAP valve with adjustable pressure settings from 5.0, 78.5, and 10.0 cmH_2O provides a constant flow rate of 60 LPM. With the addition of the O2-MAX™ CPAP system, oxygen percentages can be adjusted from 30% to 60% or 90% using the Trio adaptor. CPAP valves that snap onto the anti-asphyxia housing end of the circuit are used to maintain PEEP pressures. There is also a nebulization feature that allows a nebulizer to be added to the closed circuit. The O2-MAX (Guard) provides an option of adding an inhalation and exhalation filter system to the device and was introduced in 2020.

44.5 StarMed Ventumask 30

The Ventumask 30 (Intersurgical; https://www.intersurgical.com/products/critical-care/starmed-ventumask-30-with-venturi-flow-driver-for-cpap-therapy) is a venturi flow driver with an adjustable PEEP valve. The device has a pressure gauge with an adjustable PEEP valve with settings up to 20 cmH_2O. The manufacturer reports the flow driver can produce flows up to 80 LPM and can provide an FiO_2 from 30% to 100%. Dual flowmeters are required to achieve an FiO_2 above 30%. Device comes with a standard cushion mask as a patient interface.

44.6 DIMAR Easy Vent Mask

The Easy Vent Mask (DIMAR; http://peakmedical.eu/wpcontent/uploads/2017/05/2544GB01-EASY-VENT-MASK-2014.pdf) is a venturi device that can supply up to 60 LPM with an adjustable FiO_2 from 35% to 100%. The adjustable PEEP valve can provide pressures from 4 to 20 cmH_2O and has an integrated manometer. Two oxygen sources are needed to achieve an FiO_2 above 35%. The manufacturer offers a nebulizer kit that allows nebulization of medications during CPAP therapy. The device comes with a standard cushion mask as a patient interface.

44.7 Demand Flow

Portable demand-flow CPAP devices require a 50-psi gas source and in most cases a proprietary circuit. Circuits are single limb with a built-in exhalation valve. These devices are generally used for noninvasive ventilation and require a mask with head strap as a patient interface.

44.7.1 PortO2Vent™

The PortO2Vent™ Oxygen Delivery System (Emergent Respiratory Products; http://www.eresp.com/products/porto2vent/) is a gas-powered device that delivers noninvasive positive pressure to spontaneously breathing patients. The device features a non-disposable demand valve that delivers oxygen during inhalation through a disposable circuit at a flow rate determined by the patient's inspiratory effort. A specially designed expiratory valve is pressure balanced to precisely maintain pressure levels and reduce patient effort to open and exhale through the valve.

44.8 MACS CPAP System

MACS CPAP System (Airon; http://aironusa.com/macs-cpap-system/) has infinitely variable PEEP, a built-in pressure gauge, and only flows oxygen during inspiration, for reduced oxygen consumption and easier patient monitoring. The device is non-disposable and uses a disposable circuit. It also incorporates a calibrated knob that sets the CPAP level and a switch selects either 65% or 100% oxygen. MACS is designed to be used with both NIV and endotracheal tube.

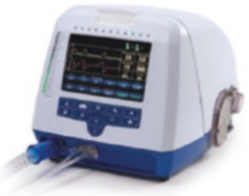
(Photograph Courtesy of Airon Corporation)

44.9 Transport Ventilators with NIV Functionality

Most transport ventilators are complex mechanical ventilation devices and provide most forms of ventilation, including both CPAP and BiPAP. However, many were not designed to provide facemask NIV, and the CPAP/BiPAP modes are for patients

with protected airways. Transport ventilators that do provide NIV have capabilities well beyond those found on other types of pre-hospital NIV devices and are considered capital equipment with an average starting price of approximately $5000 per unit with a disposable circuit and mask. The following is a non-inclusive list of transport ventilators that offer NIV capabilities.

CAREvent® ALS+ CPAP (The O-TWO™ Medical Technologies)
http://otwo.com/wp-content/uploads/O-Two_CAREvent-ALS-CPAP_2012.pdf
Flight 60 (Flight Medical®)
http://www.flight-medical.com/flight-60-3



(Photograph Courtesy of Mercury Medical).
LSP AutoVent™ 4000 CPAP (The Allied Healthcare Products Inc.)
http://www.alliedhpi.com/images/z90-00-0008.pdf
Newport HT70® Ventilator (Covidien™)
http://www.covidien.com/rms/products/portable-ventilation/newport-ht70-plus
Pneupac® paraPAC plus™ (The Smiths Medical)
http://www.smiths-medical.com/catalog/mechanical-ventilation/pneupac/parapac/pneupac-parapac-mri-p200d.html
pNeuton® Model S Ventilator (Airon)
http://aironusa.com/ems-products/ems-pneuton-model-s/

(Photograph Courtesy of Airon Corporation)
Oxylog® 3000 Plus (Drager Medical)
http://www.draeger.com/sites/en_aunz/Pages/Hospital/Oxylog-3000-plus.aspx
Uni-Vent® 731 Series Model EMV + ® and AEV® (Zoll®)
http://www.impactii.com/Vents.html
The ReVel® portable critical care ventilator (CareFusion)
http://www.carefusion.com/medical-products/respiratory/ventilation/revel-ventilator-system/

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Noninvasive Mechanical Ventilation in Pre-Hospital Medicine: Clinical Applications

45

João Rodrigues, Mário Pinto, and Rita Gerardo

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Abbreviations

ACPO	Acute cardiogenic pulmonary oedema
AECOPD	Acute exacerbation of COPD
ARF	Acute respiratory failure
COPD	Chronic obstructive pulmonary disease
COVID-19	2019 coronavirus disease
CPAP	Continuous positive airway pressure
ETI	Endotracheal intubation
HRF	Hypercapnic respiratory failure
NIMV	Noninvasive mechanical ventilation

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_45

PEEP	Positive end expiratory pressure
PHMES	Pre-hospital medical emergency service
WHO	World Health Organization

45.1 Introduction

Over the past few decades, the use of noninvasive mechanical ventilation (NIMV) has increased in acutely ill patients due to its major advantages over invasive mechanical ventilation. The ability of preventing endotracheal intubation (ETI) and its complications and reducing hospital length of stay lead to an expanding usage in pre-hospital and in-hospital care.

Acute respiratory failure (ARF) is a common medical emergency in those with previous cardiac or respiratory conditions. The definitive treatment depends on the management of the underlying cause: pneumonia, heart failure, chronic obstructive pulmonary disease (COPD) or other diseases. Nevertheless, pre-hospital treatment is needed to stabilize the most critically ill patients. For this, a common clinical-decision pathway is generally used. Both Bilevel positive airway pressure (BiPAP) and continuous positive airway pressure (CPAP) may be used to treat ARF [1]; therefore, its implementation in pre-hospital care would be naturally inevitability. Pre-hospital NIMV was evaluated in a series of studies and meta-analysis with favourable outcomes achieved in most of them.

ARF patients tend to be mouth-breathers what leads to the importance of interface suitability. Oro-nasal masks are the most widely distributed for pre-hospital medical emergency service (PHMES) units. Devices for NIMV should be durable, compact size, lightweight, compatible with different kinds of power and have at least one back-up battery. Airway circuits should also be compatible with other respiratory care equipment that might be needed (i.e. piece for inhaled medication) [2]. Moreover, hyperoxia is a usual feature after pre-hospital CPAP when oxygen-driven devices are used with a variable concentration of supplemental inspired oxygen. Hyperoxia is associated with decreased coronary blood flow and induced oxidative stress with the worst outcomes in stroke, COPD and cardiac arrest. In this case, low-fractional supplemental oxygen delivery CPAP avoids hyperoxia and demonstrated improvements in respiratory rate, SpO2, heart rate and blood pressure [3].

Pre-hospital and emergency systems vary widely, for example: some countries are supported by a network of ambulances manned by emergency medical technicians, others have paramedics and others where an emergency physician and nurse are in fast response cars and may help a basic life support team in pre-hospital care when advanced life support is needed. Consequently, cost-effectiveness (adequate and intensive instruction with training, equipment purchase, maintenance, disposable items) of performing NIMV in a pre-hospital scenario must be discussed and balanced in each system and geographic area [4]. There are different data across different systems, some supporting the effective introduction of pre-hospital NIMV and others not [5].

Furthermore, increased distance to hospital care leads to an augmentation in mortality of 1% each 10 km in a straight line to the hospital [6]. Therefore, rural areas would be deprived from adequate medical care if there were no highly competent PHMES.

Nonetheless, it is important to assure that NIMV application in pre-hospital settings should only be sought in cases with absolutely no contraindications for its performance. Resources for complete resolution of problems or clinic deterioration are scarce and the environment is not always in favourable conditions. Advanced airway skills are fundamental for those who apply NIMV in pre-hospital medicine.

45.2 Clinical Applications

45.2.1 Acute Cardiogenic Pulmonary Oedema

One of the most common causes for ARF is acute cardiogenic pulmonary oedema (ACPO). Most studies about NIMV in pre-hospital setting are performed in patients with presumptive diagnosis of ACPO.

Providing NIMV as early as possible delivers earlier improvement and resolution of breathlessness (regularly documented by reduction of dyspnoea in visual analogue scale), heart rate, blood pressure and metabolic abnormality [7]. NIMV reduces left ventricular filling pressure and mitral regurgitation and increases left ventricular ejection fraction. Within 2 h of NIMV administration, systolic function and myocardial energy consumption are enhanced. Most studies regarding NIMV in ACPO are small and heterogenous. The majority of data on mortality, ETI rate and hospital length of stay favours NIMV over standard medical treatment with only supplemental oxygen or late on-set of NIMV at the emergency department [8]. One important indicator for success of NIVM in ACPO is its early implementation in the pre-hospital setting. Even when applied without standard medical treatment, beneficial effects were documented [9].

Since many PHMES units do not have an emergency physician, application of CPAP is simpler than BiPAP, which requires comprehensive ventilatory mechanics. Therefore, the majority of studies involved the use of CPAP, and the first studies about the use of BiPAP suggested a trend towards an augmented risk of myocardial ischemia. However, further data did not confirm it. Moreover, BiPAP has the potential benefit when compared to CPAP of assisting respiratory muscles during inspiration. This feature results in faster improvement of dyspnoea by reducing respiratory muscles workload [10].

The Boussignac CPAP system is a simple, small, lightweight plastic cylinder that is attached directly to a simple mask and provides a FiO2 of 70–100% capable of generating a considerable PEEP effect. In pre-hospital ACPO, Boussignac CPAP improves vital signs and respiratory dynamics. As this device offers an extraordinarily simple strategy, it can be applied by less differentiated personnel and improve clinical outcomes such as an increase in PaO2, decreased respiratory rate and improved haemodynamic status.

45.2.2 Acute Exacerbation of COPD

Acute exacerbation of COPD (AECOPD) is a common cause of acute respiratory distress and hypercapnic respiratory failure (HRF). Owing to hyperinflation, COPD patients are in ventilatory disadvantage since respiratory muscles work at their maximum capacity. Implementation of NIMV reduces mortality rate, hospital length of stay and ETI rates and improves gas exchange. NIMV is commonly used at emergency departments to manage HRF. Although pre-hospital CPAP showed improved ventilatory mechanics and vital signs with lower ETI rates when applied to AECOPD comparing to standard medical treatment [9]. Little evidence is described for pre-hospital BiPAP [11]. This might be explained by the need for highly trained personnel on mechanical ventilation and a lower number of studies and rates for its use. Most devices in pre-hospital medicine only deliver CPAP (mainly oxygen-driven), because it is easier to learn and needs much less instruction time compared to BiPAP.

Portable blood gases analysers are available in some PHMES and prompt for an early identification of HRF. In COPD patients, application of NIMV should be the first mode of ventilation in those who have no absolute contraindication for it [12]. Provided that an adequate ventilator is available, PHMES units should use NIMV in AECOPD with HRF as early as possible.

45.2.3 Acute Asthma Attack

Acute respiratory distress with intense shortness of breath is a common feature of asthma exacerbations. Occasionally, symptoms are so intense that patient cannot go to the emergency department and call for help.

As bronchial hyperresponsiveness is the main characteristic of asthma attack, classic treatment is based on inhaled bronchodilators, systemic corticosteroids, magnesium sulphate, theophylline, and supplemental oxygen. Despite this, some exacerbations need additional care mainly in those patients who develop hypercarbia. NIMV showed beneficial effects on ventilatory mechanics and physiological parameters in this group of patients [13].

Findings of an increase in bronchial diameter, reduced work of breathing and improved respiratory mechanics by off-setting auto-PEEP with an expectable improvement on modified Borg-scale after CPAP implementation reinforces the need for its earlier application [14]. Thus, if no positive clinical evolution is present after standard medical treatment, ventilatory support might be sought. Since PHMES can bring the hospital to the field, NIMV may be started under close monitorization during transportation to the hospital.

45.2.4 Thoracic Trauma

PHMES units are essential in the management of trauma/multiple trauma patients. Chest trauma is responsible for 20–40% of deaths [15]. ARF develops primarily in those with a poorer lung function and in the elderly. Most frequent lesions from

thoracic trauma are rib fractures, pneumothorax and haemothorax, pulmonary contusion and flail chest. Clinical management of less severe patients includes pain relief, oxygen supplementation and general stabilization and immobilization. In those who developed more severe ARF, NIMV showed benefits in reducing ETI rate when compared to standard medical treatment [16]. Albeit published data on this subject is limited and derived from moderate to low quality studies, general findings suggest that early NIMV (BiPAP or CPAP) might be beneficial in those who are at risk for development of ARF after chest trauma since NIMV failure and mortality rates were lower [17]. Every clinical sign must be adequately weighed. If any risks coexist for neurologic, respiratory, haemodynamic deterioration or a long-time to the hospital is needed, probably performing ETI would be more adequate.

45.2.5 COVID-19

The World Health Organization (WHO) declared COVID-19 a pandemic in March 2020. Although most cases are mild infections, there is a substantial volume of patients who develop acute respiratory distress because of life-threatening hypoxemia. Dyspnoea has been the most described main symptom that leads to PHMES unit dispatch. Field observations concluded that initial low pulse oximetry was associated with the need for ventilatory support. The typical patient was middle aged with hypertension, diabetes mellitus, obesity, COPD and chronic renal failure [18].

Independent of a respiratory pandemic, acute respiratory distress is common in pre-hospital care.

Despite what has been discussed earlier, which clinical strategy is best for the management of ARF in COVID-19 patients at the pre-hospital setting remains under debate. It is not uncommon for PHMES units to face concomitant ACPE or AECOPD in the field. Fundamental clinical recommendations for both situations include NIMV application.

Since SARS-CoV-2 is mostly transmitted through respiratory droplets and aerosols, concerns about the most secure ventilatory support emerged. It remains controversial whether treatment of choice for ventilation should be invasive or noninvasive (supplemental oxygen or NIMV). A low rate of NIMV or ETI in COVID-19/suspected patients in pre-hospital setting has been reported. This might be due to fear of contamination, although data on this issue is lacking.

Nevertheless, WHO indicated NIMV in their guidelines if safety measures were ensured. Our personal and small experience suggests that NIMV could be set as a bridge strategy during transportation before ETI at the emergency department in severe ARF with adequate and trained professionals.

45.3 Conclusion

NIMV can be safely performed in pre-hospital medicine since emergency physicians or paramedics are instructed and trained on the basic needs for an adequate ventilatory support when needed. Pre-hospital implementation of NIMV presents

important clinical benefits: improved respiratory physiology, symptomatic control, reduced mortality, and a lower rate of ETI. Although it has a major defined role in ARF due to ACPE and AECOPD, more indications are being investigated and tested with promising results. Generally, most of the trials have a small sample size, but tend to favour an earlier application of NIMV during an ARF. Pre-hospital equipment should be of intuitive use, compatible and interchangeable between different devices.

Even so NIMV presents important empiric positive effects on clinical evolution of acute respiratory failure in pre-hospital management, powered evidence is limited and most of the studies are biased-limited. Good quality investigations are needed so proper instruction for PHMES personnel shall be implemented and widely distributed with fundamental changes for standard ARF care.

Pre-hospital medicine demands a unanimous practice so optimal management is provided, since NIMV provides a safe strategy to improve respiratory mechanics when applied and managed by adequately instructed health professionals.

Key Major Recommendations

- NIMV is effective in treating ARF and should be performed as early as possible in the pre-hospital setting if no contraindications are present.
- Long distances to the hospital increase mortality risk.
- NIMV is an effective strategy in clinical management of ACPE and diminishes the rate of ETI and mortality.
- Data on pre-hospital NIMV is limited and more research is fundamental to establish its role in pre-hospital medicine.

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Noninvasive Ventilation Outside Intensive Care Units

46

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_46

46.1 Introduction

Artificial mechanical ventilation is an integral part of the management of patients with acute respiratory failure (ARF) [1]. Traditionally this has been by invasive mechanical ventilation (IMV), requiring endotracheal intubation (ETI) [2]. Subsequently, noninvasive ventilation (NIV) has been introduced as an alternative means of mechanical ventilation in selected patients as a primary option. Compromising the patient's respiratory tract, or deep sedation, risks the introduction of iatrogenic infection. Thus, NIV can avoid or mitigate such effects, and hence provide better outcomes [3]. To a considerable degree, NIV can offer similar physiological benefits without the deleterious effects associated with the use of IMV [4, 5]. With the growing availability of sophisticated, technologically advanced NIV machines, combined with integrated monitoring facilities and experience, successful application of NIV has become a reality outside the originally critical care domain (Fig. 46.1). The timely initiation of NIV in appropriate patients, even in some emergency or time-critical situations, can greatly simplify care. Once the emergency is over, subsequent management can be continued in an outpatient or lower acuity setting often, reducing ICU stay, and its associated costs and risks [6, 7]. Bypassing high intensity care has the major benefits of reducing costs while providing more comfort for patients and relatives. In this chapter, we shall discuss in detail the indications, applicability, and the strengths, weaknesses, and practicalities, of NIV outside of ICU or hospital settings.

Fig. 46.1 NIV (Trilogy 202 model) for use outside ICU and at home (Published with permission from Philips Electronics UK Limited, Philips Centre, Guildford Business Park, Guildford, Surrey GU2 8XG

46.2 Primary Indications of NIV

ARF is a life-threatening medical condition which may result from several cardiorespiratory and neuromuscular diseases [5, 8, 9]. It may occur de novo or during acute exacerbations of known chronic diseases [10]. ARF is primarily divided into two types. Type I is purely hypoxaemic respiratory failure with normal or low partial pressure of carbon dioxide ($PaCO_2$). This typically reflects a failure of oxygen uptake in the lungs, due to ventilation/perfusion mismatch. Conversely, type II respiratory failure entails both hypoxia and hypercarbia and indicates hypoventilation relative to metabolic production of carbon dioxide. The relevant pathologies can co-exist or overlap.

Some diseases [i.e., Duchene's muscular dystrophy, kyphoscoliosis, obstructive sleep apnoea (OSA) and chronic obstructive pulmonary disease (COPD)] have a chronic course necessitating long-term ventilatory support due to hypercarbia (retention of CO_2) [9, 10]. Such patients need assisted ventilation, often long-term NIV, either with continuous positive airway pressure (CPAP) or, later, bi-level positive airway pressure (BIPAP) [11]. In such conditions, NIV can be continued indefinitely, including in the home, once patients are stabilised, enabling discharge from hospital [10, 12]. Patients with 'do-not-intubate' (DNI) or 'do-not-resuscitate' (DNR) orders can gain comfort through NIV during palliation [13]. Chest wall deformities and neuromuscular disorders are well-known causes of chronic respiratory failure [9, 14]. Recently, the novel coronavirus 2019 (COVID-19) pandemic emerged as an important precipitant of ARF.

The primary aim of any form of mechanical ventilation in ARF is to achieve adequate oxygenation with effective CO_2 elimination and thereby provide symptomatic relief. This can be achieved by assisting ventilation using NIV with CPAP or BIPAP modes. Both have been shown to reduce the work of breathing, and to improve arterial blood gas (ABG) parameters in relevant patients [15]. Some, however, will not tolerate CPAP in the long term as the constant delivery of positive pressure can be distressing as it impedes expiration. They experience this as an obstruction to flow. Such patients may tolerate BIPAP better. It provides dual pressure levels during inspiration and expiration which reduce the work of breathing far more than CPAP [16]. However, it should be recognised that these patients may require return to ICU for IMV at times of exacerbation or complications.

46.3 Essential Requirements for the Safe Use of NIV

The availability of adequately trained staff remains necessary for initiation of NIV, inside or outside of the ICU. Staff should know how to attach and detach the NIV interfaces correctly and rapidly, and appreciate the urgency thereof. They should be attuned to the possible changes in the mental status of patients, of their

interpretation and of how to intervene immediately or seek help when appropriate. They should also know the indications for transfer to ICU for the initiation of urgent IMV [10, 17, 18], and be cognisant of the goals and limits of care for their individual patients.

The use of proper monitoring facilities,during ward or home level NIV care, are very important to detect early failure of NIV. Thus, they may prompt timely intervention to prevent or minimise complications [19, 20]. Close attention and monitoring are needed to detect displacement of the NIV interface and to observe the degree of coordination between patient, mask, and ventilator. Patient-ventilator asynchrony, or poor tolerance of NIV therapy should prompt troubleshooting interventions to optimise the risk/benefit ratio in a dynamic way [7]. While symptoms are useful and insightful guides to practice, there are several invasive and noninvasive methods of monitoring of respiratory gas exchange. They include measuring arterial, capillary, or venous blood gas (ABG, CBG and VBG) samples, peripheral oxygen (O_2) saturation (SpO_2) measurement by pulse oximetry, noninvasive transcutaneous monitoring of partial pressure of O_2 and CO_2 ($PtcO_2$, $PtcCO_2$), end-tidal CO_2 monitoring ($EtCO_2$), and near-infrared spectroscopy. They can be utilised depending on the availability, feasibility, and prevailing logistics [21].

Monitoring of SpO_2 remains the benchmark monitoring modality during NIV therapy. Any alteration in the SpO_2 values warrants urgent review and a call for help if apt. The most pragmatic monitor for this is the pulse oximeter which can noninvasively and continuously monitor SpO_2 [21]. The device has the advantage of being portable, easy to handle, of a rapid response time. It is desirable to have one available whenever a patient receives NIV therapy outside the ICU [22]. It is also desirable to have the means to measure blood pressure noninvasively and to check an electrocardiogram [2, 23].

Of almost equal importance is the measurement of $PaCO_2$ levels. While it can be achieved by the frequent monitoring of ABG, the continuous monitoring of $EtCO_2$ from exhaled gas levels is noninvasive, easier to measure and has comparable value, despite theoretical considerations [6, 10]. The ABG remains the gold-standard for the monitoring of $PaCO_2$ to monitor ventilation [22]. An ABG is generally done before initiation of NIV, as a baseline measurement, and then can be done intermittently if needed to corroborate with $EtCO_2$ values. Values of $EtCO_2$ should be interpreted carefully during NIV therapy. Sometimes patients may need to revert to IMV or assisted invasive ventilation, based on ABG values, changes in conscious state, or progression of their condition [10, 24].

When any patient is being managed with NIV in the ward, there should be a facility to monitor invasive ABG rapidly. Currently various methods of blood gas analysis exist: (i) the gold-standard of course is the ABG analysis, which is obviously invasive and requires arterial puncture or placement of an arterial catheter, (ii) CBG analysis which is less invasive, requiring a simple finger prick, much like blood sugar estimation, (iii) $PtcO_2$ and $PtcCO_2$ measurement using specially designed skin electrodes which constitute a noninvasive technique (Figs. 46.2 and 46.3), and lastly the VBG analysis, which is again invasive but can be done using simple venepuncture or through an indwelling central venous catheter [25]. Among

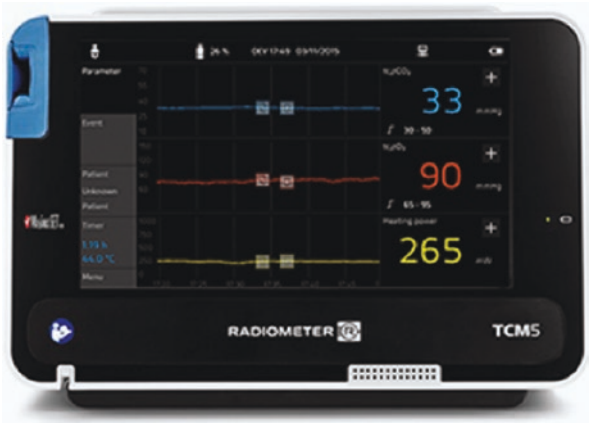

Fig. 46.2 Transcutaneous blood gas monitor (Reproduced with permission from Radiometer Limited, United Kingdom)

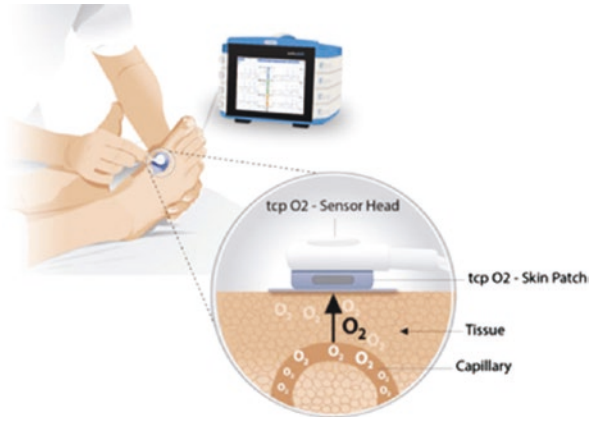

Fig. 46.3 Skin electrode for measurement of transcutaneous blood gas (Reproduced with permission from Radiometer Limited, United Kingdom)

these, the VBG is not widely endorsed due to conflicting results in several studies [21]. The limitation of ABG is that it is available largely in ICU and high dependency unit (HDU) setups, or in operating theatres, but rarely in the general wards or outside of hospital. It is also expensive and an invasive procedure, requiring specialists for accurate interpretation. It is thus not always readily available, or very practical for monitoring patients receiving NIV therapy in the ward or, especially, at home.

The introduction of point of care portable hand-held ABG machines recently has facilitated analysis of blood gas parameters and electrolytes levels using a bespoke cartridge (Fig. 46.4). This does not require the expense of an ABG analyser, as in the ICU/HDU or operating theatres, nor does it require arterial puncture. Only one to two drops of blood are required, easily obtained by fingertip puncture. It has acceptable correlation with the gold standard ABG analysis and can be used where the latter is unavailable [26, 27]. It is easy to learn for relatives and gives a printout of results. They can be faxed or sent electronically for review, and in concert with noninvasive parameters, to assess progress [26, 28, 29].

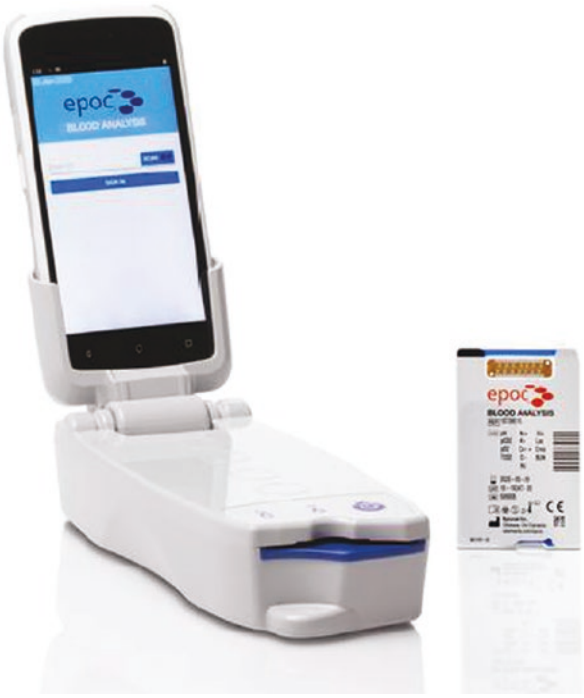

Fig. 46.4 Handheld Blood gas analyser (Reproduced with permission from Cruinn Diagnostic Limited)

The preference for the type of blood gas measurement depends on the availability, type of respiratory support the patient is on, their clinical status, the availability of trained personnel, logistic support, and the location (ICU, medical ward or home, etc.). For example, the reliability of CBG is questionable in low peripheral perfusion, a common clinical scenario in critically ill patients. In these cases, invasive ABG analysis is preferred because most such patients will have an indwelling arterial catheter. However, less invasive CBG is useful in patients with acceptable haemodynamics and in children [21]. Pulse oximetry, introduced in the 1980s has reduced the need for frequent blood sampling. Although transcutaneous blood gas monitoring is noninvasive and innovative modality, it is not always reliable. The frequent need for sensor replacement, as well as calibration, dislocation of adhesive rings, and adverse reaction such as skin burns all need to be balanced against the benefits and utility [21].

Ultimately decisions about the choice of monitor will often be dictated by practical considerations of interpretability, cost, availability, and logistics. The main concern is that the user ought to be familiar with the normal ranges, the meaning of what is measured and the criteria that should trigger expert consultation. With regard to comparison of devices, in a retrospective comparative study [30], the efficacy of different monitoring tools was evaluated in 100 patients who were managed on long-term home NIV therapy. Four different combinations of monitoring tools were considered (i) ABG and nocturnal SpO_2, (ii) nocturnal SpO_2 and $PtcCO_2$, (iii) $PtcCO_2$ and data from built-in ventilator software; and (iv) a combination of all the

above-mentioned tools. Among them, the combination of $PtcCO_2$ and data from ventilator software was found to be the most accurate noninvasive monitoring strategy for assessing the efficacy of home NIV therapy [30]. In routine practice through, with its ready availability and ease of interpretation, the use of a saturation probe is widespread and, essentially, the standard of practice.

46.4 Newly Expanding Indications of NIV Outside the ICU

The scarcity of ICU beds and their cost, coupled with rising populations of diseased and older people have incentivised the establishment of modalities that allow patients avoid such care altogether [2, 6, 10, 31]. Consequently, hospitals benefit from treating respiratory failure on general wards, as do patients, if it can be done safely and effectively. The reduced need for sedation, and its associated complications, has obvious benefits.Patient selection for instigation of NIV, especially outside the ICU, is crucial [32]. As patient cooperation is a prerequisite, consciousness without confusion, disorientation, obtundation or drowsiness define the ideal state. Frequently, however, trials of NIV are undertaken in situations that are suboptimal, with success often reported. This is often while tests and diagnoses are performed, discussions about likely outcomes occur and early responses to NIV are evaluated. Preparations for intubation may be made, even as a contingency.

46.4.1 Role of NIV in the Operating Room

Surgery, with its associated postoperative pain and delivery of anaesthesia can impair diaphragmatic function, worsening ventilatory impairment and aggravating pulmonary atelectasis and hypoxaemia. These effects are exacerbated if the site of surgery is close to the diaphragm. The relevant changes are more prominent in the immediate postoperative period, further challenging any existing impairment of respiratory function [33].

Prophylactic application of NIV has been found to improve preoxygenation during induction of anaesthesia, even, indeed, during the apnoeic period of intubation in cases of pre-existing respiratory failure, in hypoxic and obese patients [34]. Morbidly obese patients often have restrictive pulmonary pathology owing to their body habitus, with co-existing sleep apnea and central obesity hypoventilation syndrome [33, 34] Prophylactic use of NIV in these patients can improve oxygenation while preventing hypoventilation during induction of anaesthesia [34].

Intraoperative use of NIV appears to be safe and beneficial in selected patients, particularly when tracheal intubation is deemed dangerous. Most patients with ARF and baseline respiratory distress will not tolerate recumbent positioning for long, a basic requirement for most significant surgery. Sedation, anaesthesia, minor surgery, IMV, and positioning can exacerbate respiratory distress in such patients. Moreover, neuraxial anaesthesia, although frequently chosen in such patients for its lack of impact on pulmonary function, can reduce or even eliminate the respiratory

contribution of the intercostal muscles. Thus, sedation and/or neuraxial opioids can impair respiratory function further. In these situations, prophylactic use of NIV can offset alveolar hypoventilation, reducing the work of breathing, ultimately reducing atelectasis, and left ventricular afterload [35]. This benefit has been proven ultrasonographically [35].

NIV, in patients with pre-existing respiratory and cardiac failure requiring sedation, neuraxial block and/or peripheral nerve blocks, may permit them to lie supine for an adequate period of surgery. It can allow the administration of additional sedation too, if required. NIV in this scenario has the capacity to allow such patients forego intubation and ventialtion [36, 37]. Conversely, in patients undergoing palliative surgical procedures under regional blocks or sedation, NIV offers no advantage over standard preoxygenation in reducing subsequent organ dysfunction in the presence of hypoxemia [38]. However, in emergency surgery in hypoxaemic patients already on NIV therapy, CPAP is interrupted during standard preoxygenation. This can precipitate further hypoxia in this frail cohort. Many will need a modified rapid sequence induction (RSI), perhaps without positive pressure ventilation. Institution or continuation of either high-flow nasal cannula (HFNC) or NIV has been found to be beneficial in preserving oxygenation. NIV can be a safe and effective preoxygenation method in this scenario [39]. The combined use of HFNC and NIV for apnoeic oxygenation prior to ETI is a novel strategy of preoxygenation in hypoxaemic patients, and has proven effective in reducing the severity of desaturation compared to using NIV alone [40]. Even during fibreoptic bronchoscopy under sedation, prophylactic use of NIV has been found to eliminate the need for intubation and IMV in immunocompromised patients who incur elevated risks from ETI and subsequent IMV [41].

Prophylactic use of NIV in the postoperative period has also been shown to be useful in patients with pulmonary contusions [41]. Up to 50% of such patients undergoing abdominal surgery have episodes of postoperative hypoxaemia and about 10% may ultimately need tracheal intubation [42]. Some 40% to 90% of patients undergoing open-heart surgery suffer from different grades of postoperative pulmonary complications (PPC) [42]. Prophylactic, as well as therapeutic, use of NIV postoperatively in these patients has been shown to improve oxygenation, reduce postoperative pulmonary atelectasis, the need for reintubation, incidence of postoperative pneumonia, nosocomial infection and PPC [42].Prophylactic use of NIV in patients after major abdominal surgeries has also been found to reduce incidences of critical care admission, the length of ICU and hospital stays [40, 42].

The prophylactic and therapeutic application of NIV in post-anaesthesia care units (PACU) and HDU after planned extubation appears beneficial in reducing postoperative respiratory complications, need for re-intubation and IMV, and thus, improves overall outcome [39]. As postoperative respiratory failure is the leading cause of short-term mortality after solid organ (kidney, liver, and lung) transplant surgery, the prophylactic use of NIV may prove beneficial in improving oxygenation, reducing the need for ETI and IMV, with reduced infection rates, morbidity, and mortality [42]. In the postoperative period, NIV can even be used in a 'sequential' manner interspersed with simple oxygen therapy to provide some

ventilator-free time, boosting tolerance while reducing the incidence of postoperative atelectasis. For example, NIV can be prophylactically applied postoperatively for approximately 30–45 min at 2–4 hourly intervals for the first 24-h. If needed, this can be daily increased to 3–12 h daily, depending on the tolerance of patients and the indication for its use (curative or prophylactic) [40]. However, a nasogastric tube after abdominal surgery, which is very commonly required, can affect the overall success and utility by generating an air leak [40].

46.4.2 Role of NIV in Obstetric Care

ARF complicates less than 0.1% of pregnancies [43, 44]. However, it remains one of the leading causes of ICU admission in the obstetric population, accounting for significant morbidity, and maternal as well as foetal mortality (14% and 11%, respectively) [43, 44]. Pulmonary complications constitute about 10% of obstetric ICU admissions [44]. ARF in obstetrics can represent exacerbation of underlying diseases, COPD and asthma, cystic fibrosis for example,which is uncommon, but can occur in parturients. Acute events, such as pneumonia, pulmonary embolism, amniotic fluid embolism, pulmonary oedema, and acute respiratory distress syndrome (ARDS) may also cause ARF in patients with entirely normal lungs and airways [44]. As with non-pregnant patients, NIV has also been found to be beneficial in the management of sleep disorders during pregnancy [44].

In gravid patients with mitochondrial myopathy, NIV has been successfully used for the management of respiratory failure during late pregnancy and postpartum [45]. Severe respiratory failure during pregnancyhas been found to increase the risk of spontaneous miscarriage in the first trimester by 50%, and of preterm delivery by 80% [46]. Moreover, such periods of prolonged hypoxia can lead to foetal morbidity and mortality [46]. This subset of patients can be effectively managed using NIV under close monitoring, if necessary outside ICU. Obstetric patients who require ETI and subsequent IMV have been found to have a fourfold higher risk of a difficult airway, and eightfold increase in failed intubation [43, 44]. Hence, trials of NIV in such patients can be extremely prudent, because of the advantage of avoiding intubation entirely. NIV finds a further, useful application during surgery in patients with different neuromuscular disorders. The prophylactic or therapeutic application of NIV during late pregnancy, either for concurrent surgery or caesarean section under neuraxial blocks, can be of great benefit in obstetric patients unable to lie flat [47, 48].

The benefit of NIV in pregnant women is controversial due to the inherent, perhaps theoretical, risk of aspiration. The decreased tone of lower oesophageal sphincter combined with delayed gastric emptying, and higher intragastric pressures (a parameter which rises as early as week 14) might put these patients at higher risk of pulmonary aspiration. The risk in practice seems very small however, even though during NIV, gastric insufflation of air and aerophagia are well described [49]. Hence, NIV is optimally deployed under strict observation in selected pregnant women provided they are fully conscious with a strong cough reflex to protect their

airway [49]. The strategy ultimately in this setting should be to provide adequate oxygenation and ventilation while avoiding the complications of ETI and IMV, and perhaps avoiding ICU admission with its associated stresses, costs, and risk of infection.

46.4.3 Role of NIV in Emergency Department (ED)

In recent decades, the role of NIV has extended into emergency departments, under the supervision of medical emergency team and anaesthesiologists. This has improved the early acute management of patients with ARF resulting from COPD, cardiogenic pulmonary oedema, and pneumonia [50]. This has gained popularity because of the scarcity and delays associated with accessing ICU beds, where such patients were traditionally managed. Emerging evidence indicates that the early use of NIV in appropriate cases of ARF can reduce morbidity and mortality. Thus, it will obviously reduce the rate of intubation, ventilation, and ICU admission. This has ancillary benefits in terms of the incidence of hospital acquired and ventilator associated pneumonia, infection with multi-resistant organisms, and so on [51]. For the effective and safe use of NIV in ED, logistics and human resource issues should be considered in advance [51]. Emergency physicians and nursing staff should be trained on how to initiate NIV therapy, the common modes, alteration of the NIV parameters, care of patients on different NIV interfaces. They should be able to detect the early signs of NIV failure and of patient-ventilator desynchrony so that an alternative management strategy can be instituted promptly.

While the ready use of ETI and IMV might lead to poor outcomes and resource utilisation, recently emerging evidence suggests that persevering with NIV support for periods beyond 4 h may invite a worse prognosis, with higher morbidity and mortality than early ETI and IMV [52]. Several *scoring systems* have been designed and employed to facilitate early detection of NIV failure in such patients. The HACOR score comprising of five variables (i.e., heart rate, acidosis, consciousness, oxygenation, and respiratory rate) has been found to have a good predictive power in detecting NIV failure in COPD patients within 48 h of admission [53, 54].

Patients suffering from acute exacerbations of COPD, chronic renal failure (CRF), or acute pulmonary oedema who are unable to access ICU beds at present, or perhaps at all, NIV therapy can be continued in the ED. In this situation, management in ED may continue for longer, even until they recover from the acute crisis or until get an appropriate bed. In some cases, depending on the overall course of the disease and its prognosis, they may ultimately be transferred to a long-term care facility or their home, possibly with a long-term need for NIV.

The early empiric use of NIV at ED admission in victims of blunt chest trauma and rib fractures with mild respiratory distress can entirely obviate ETI and IMV. This can decrease the associated risks and complications. Such prophylactic use of NIV reduces the incidence of ARF, improving oxygenation, avoiding tracheal intubation, and hence minimising pulmonary complications, morbidity, and

mortality [42]. However, the utility of NIV in preventing intubation in patients with chest trauma suffering from ALI associated with respiratory distress remains controversial, particularly in more severe cases [55].

46.4.4 Role of NIV in the General Wards

The evidence emerging from recent trials [13, 31, 56, 57] encourages the use of ward based NIV therapy. It appears to be a cost-effective alternative to ICU care and invasive ventilation, a crucial attribute for low-and middle-income countries.When NIV is started in emergency departments or general wards, patients need close monitoring of their progress and intense observation as their early response is both unpredictable and important [58]. Baseline ABG analysis should precede initiation of NIV, and be repeated 1–2 hourly until a stable pattern is discernible. Three patterns of response are typically observed. The patient will improve, the parameters may not change significantly, or further deterioration may be noted. In the latter scenario, the patient should be transferred to ICU promptly, with a view to IMV being commenced [58]. Where the patient improves, NIV therapy can be continued using similar settings. However, if there is no improvement in parameters after, say, 30 min to 1 h of continuous therapy, either a change in the settings of NIV or a transition to IMV become necessary [6, 10, 59]. In the management of such patients with ARF in the wards, close monitoring, early detection of failure of NIV and timely conversion to IMV are key to successful management.

Following an acute crisis entailing ventilatory support in a hospital setting, some will have an ongoing need for such treatment due to progression of their disease. Typically, family members support is of value to institute NIV therapy at home. This will reduce healthcare costs, while making the therapy more convenient and tolerable for patients and their family, logistically. The likelihood of readmission, often attributable to hospital acquired infection, can be reduced in patients suffering from COPD and other chronic respiratory diseases [60–62].

The primary onus for the management of these patients lies with specialised nurses. Often, the typical trained ward nurses will be unfamiliar with NIV machines, the early detection of patient-ventilator asynchrony, and the troubleshooting or escalation necessary in poor responders. They may not detect deterioration at an early stage, for multiple reasons such as high volumes of other hospital activity, poor nurse-patient ratios, or due to inadequate training [20, 63]. Although NIV is well tolerated by most patients, it is clearly not risk-free. Indeed, serious adverse events such as worsening of respiratory failure, hypercapnoea, ventilator-patient asynchrony, pulmonary aspiration, coma, and death have been reported. Importantly, such complications are found to be higher when NIV is initiated in the wards [1, 6, 10, 58, 64].

Problems faced during NIV in the ward: The initial setting up of most NIV machines requires only a short period of training. What is far more important part and challenging is interpreting the progress of the patients, detecting failure, and patient distress and responding to them appropriately. A lack of proper training may

lead to hypercarbia, respiratory acidosis, ventilatory failure and cardiac arrest, through delayed diagnosis and intervention [21]. The ward nursesare often overburdened from their routine workload. Also, it may prove difficult to motivate busy staff to initiate further interventions which require extra training. Understanding and managing NIV therapy and acquiring the skills to troubleshoot that therapy require specialist skills, training, or extensive experience. As discussed above, a patient on NIV needs repeated ABG analysis. This may be difficult with some nurse-patient ratios, or when the logistics of analysing and interpreting such samples are difficult. Any failure to observe ineffective NIV, such as from ill-fitting masks or patient-ventilator asynchrony may lead to more complications and risks. Arguably, this shortcoming can be offset by intermitted ABG analysis or monitoring of transcutaneous $EtCO_2$. This equally requires special training to perform and interpret [23]. Also, the ward nurses may be unfamiliar with the suctioning of oropharyngeal secretions, or with effective and adequate resuscitation if needed in case of emergency. This in turn puts the lives of these patients at greater risk that it might be within the ICU.

For prolonged use of NIV, nasal masks have been found to be more comfortable and tolerable. They are, however, less efficient in the elimination of CO_2. Full tight-fitting oro-nasal facemasks remain the first choice for this purpose. Conversely, of course, they are poorly tolerated by patients in the long-term. Those with claustrophobic tendencies may reject them out-of-hand, or efforts at persistence may be doomed to treatment failure for non-compliance [23]. Also, the feeling of air flowing into one's face, eyes and nose makes some uncomfortable and fearful. Effective and successful NIV therapy mandates proper training of the patient also to achieve cooperation and synchronicity with the machine. Allowing intentional air-leaks solves some of these discomforts, but reduces efficiency.

46.4.5 Role of NIV in the Home Care Setting

The idea of using NIV in home settings became current in the 1980s. Initially trialled in patients with obstructive sleep apnoea, it was later implemented in children with long-term neuromuscular disorders. Nowadays, children comprise approximately 10% of patients being on home NIV support [65, 66] Adults, often suffering from COPD, and typically after hospital discharge following an acute exacerbation, form the majority of those receiving home NIV [15].

(a) **Initiation of home NIV:** For initiation of home NIV therapy, initial trials should be started in the hospital setting before exploring the logistics of sending patients to their home. It should be started intermittently in the wards, for 4 to 6 h daily, to familiarise patients and educate them about it. Once able to synchronise with NIV, exhale with comfort, and tolerate the mask, then the daily duration of NIV therapy is gradually increased to maximise therapeutic benefits [18, 23, 67, 68]. Nocturnal use of NIV should be tried only when one can tolerate daytime NIV comfortably and for long periods. During initial

sessions of nocturnal treatment, ABG analysis should be done the following morning. Once improvements are demonstrated based on ABG and symptomatic grounds, or, at least, no deterioration is observed, the nocturnal NIV sessions can be extended gradually. When the patient gets accustomed to the therapy through the day and night, home NIV therapy can be arranged. The process depends on how patients tolerate, interact, and synchronise with the device and its settings. A further problem remains that of training those who will look after the patient during the changeover process and during home NIV sessions.

(b) **Caring personnel**: The training of those who will provide community care for patients during home NIV sessions is a task that requires dedicated time, particularly as they may lack both relevant baseline knowledge and a scientific background. It is among several logistical obstacles to the smooth transition to domiciliary care. Ideally, the patient would reside near to a hospital to access medical facilities when necessary, something that occurs frequently initially. Either the patient may need to be brought to the emergency department, or a medical team can attend their home. During home NIV therapy, at least in the initial period, the patient may show signs of worsening respiratory distress with features suggestive of failure at any time. This necessitates urgent intervention by trained personnel, for safety and to gain the confidence of the domestic carers [69]. Also, the training of family members of those being treated on NIV at home is crucial, they rarely being familiar with the medical care of serious conditions.

They should be trained to read and interpret pulse oximeter readings, clinical signs indicative of deterioration in the patient's condition, and able to address them temporarily or seek help as appropriate. Careers must be able to assemble, connect and disconnect the NIV mask interface and circuit, to carry out resuscitative interventions and suction of airway secretions when needed. Adequate suctioning facilities must be present as clogging and accumulation of secretions may be catastrophic. Alternative modes of ventilatory support and of power supply should be available in the event of an emergency. Caring relatives should have accessibility to all emergency numbers. Because of these obstacles the initiation of NIV therapy at home is not always feasible and, indeed, ideal conditions are rarely achieved [15].

(c) **Home visit by assigned health care providers:** During the home visit, the nurse or physician should review the details of the ventilatory requirements and the degree of synchronisation by accessing the trends recorded in the device. The amount of data stored depends on themachine's sophistication and the software's capacity [22, 70, 71]. The efficacy of NIV therapy can be assessed by reviewing data on breaths delivered, the correlation between delivered and exhaled tidal volumes, minute volume delivered and the degree of air-leak. Most machines used for home ventilation should be designed to store data on all these parameters for later review, to evaluate progress by direct assessment or tele-medicine access [72, 73].

(d) **Role of telemedicine in management of home-NIV therapy:** Telemedicine can be of enormous value to patients managed outside of hospital non-experts of relatives. Advances in technology (improved sensors, monitors, the internet, and wireless technologies) enable data to be transferred to the base hospital to be viewed, instantly or later, by the relevant physician. The data can be accessed by assigned experts using personal computers, tablets, or smartphones remotely, providing real-time guidance about the status of the patient. Real-time or stored data (video or physiological parameters) can be used for communication between patient, the caregiver in the home, and the assigned health care provider (nurse or physician) using telephone, internet, wireless, Bluetooth or satellite-based tele-communication technology. This can compensate for the limited presence of healthcare workers or physicians in the long-term care of such patients at home. It can also facilitate the changeover of care from hospital to home which is often delayed due to the lack of manpower and facilities in the home. Moreover, it can make healthcare provision outside hospital much safer, less stressful more acceptable to caring relatives [74–76]. Dellaca et al. reporting the conglomerated findings of various studies on the use of telemonitoring in such patients concluded that the use of telemedicine could reduce home visits by nurses by around 15% [75]. The study also found that most physicians (over 80%) found care using tele-health to be useful in primary care services too [75]. More than 90% of patients noted no negative impact on their relationship with healthcare providers, while about 50% of the patients were very satisfied with the approach [75]. Satisfaction among respiratory patients with telemonitoring is generally high therefore, and it has the potential to reduce the number of hospital admissions by around 50% [75]. While home-based NIV using telemonitoring cannot be employed universally at present, due to cost and technological limitations, it nonetheless is feasible and practical proposal for many [75]. The interventions which can be performed remotely, their advantages and limitations, are detailed in Boxes 46.1 and 46.2, respectively [76–79].

In the home setting, pulse oximetry, $EtCO_2$ and clinical monitoring of respiratory parameters remain the mainstay in the evaluation of therapy. The availability of suitably trained personnel is the main obstacle in initiating home NIV, in general. Therefore, in selecting candidates for home NIV support, consideration should be given to the environment, the family or caregiver support base and to the logistics of communication and follow-up at the earliest stages.

Box 46.1 Different Interventions that Can Be Performed Using Telemedicine [76–79]

Interventions
• *Telecommunication:* Communication is possible between the patients, family members, and the health care providers to resolve and ongoing issues.
• *Telemonitoring:* Real-time vitals and ventilation parameters as well as progress can be transferred to the healthcare providers for viewing as well as interpretation for any necessary instruction which needs to be taken. The caregiver can be instructed using voice communication regarding any modification needed which can curtail complications during home-based management of such patients.
• *Tele-consultation:* Assessment, diagnosis, and care from the base hospital.
• *Tele-education and tele-coaching:* Internet-based educational or self-management platforms can be utilized for education and training of supporting staffs as well as caregiver relatives.
• *Tele-rehabilitation:* Even the educational materials can be sent and required physiotherapy exercise training can be instructed when such facility cannot be regularly provided at home. Even physical activity as well as the progress can be monitored, feedback to the caregivers can be given.

Box 46.2 Advantages and Disadvantages of use of Telemedicine in Caring Patient on NIV Support Outside Hospital [76–79]

Advantages and disadvantages
Advantages
• Improved relationships between the patients and the health care providers.
• Greater patient's satisfaction.
• Reduced need for home visits.
• Effective and smooth management of the patients, reduced rate of complications, and improved outcomes.
Disadvantages
• Lack of legal safety in such care.
• Risk of data breech always remains a concern. Thereby, the persons involved in transmission as well as interpretation of data may be vulnerable to legal consequences.
• Patient related factors (i.e., cognitive function, motor and visual abilities, phonation and speech abilities, education, and experience about technological device) can impact the quality of care as well as the outcome.
• Cognitive ability of the patients as well as the family members and comfort with use of advanced technology is of utmost important for effective management and the outcome.
• Higher initial cost.
• Level of consultation may differ.
• Equipment failure may lead to serious consequences.

46.4.6 The Role of NIV Therapy Outside ICU During the COVID-19 Pandemic

The magnitude of the challenge to healthcare delivery, especially to the critically ill, during the COVID-19 pandemic has made the need for respiratory support outside of the ICU environment undeniable and the benefits obvious. Tele-health care has enabled communication with infectious patients with the minimum of risk, and between carers and physicians as a way to get expert opinions or share data. The shortage of the ICU beds and mechanical ventilators is an ongoing reality that was exposed by the pandemic.

Profound hypoxia, often with elevated airway resistance akin to adult respiratory distress syndrome was characteristic of those affected by COVID-19 infection [80]. Early in the pandemic, concerns about aerosolisation of viral particles lead to a virtual moratorium of NIV and an enthusiasm to direct progression to intubation. This, in combination with IMV did not lead to good outcomes, however, while NIV later seemed to reduce many respiratory complications. Ventilating such patients using NIV provided some relief, as CPAP/BiPAP reduce one's work of breathing. NIV has the capacity to at least delay, and sometimes entirely obviate IMV [81]. Used in these patients, it been shown to temporise respiratory deterioration, which can allow more time for decisions to be made, data to be gathered and treatments to be evaluated. Also, lower staff numbers are necessary for the care of conscious patients on NIV. Thus, it is likely that in the pandemic the widespread application of this modality was crucial in limiting the numbers of fatalities, even in countries which offer highly developed healthcare systems [82, 83].

46.5 Summary

Initially the use of NIV was restricted to the critical care areas due to the perceived complexity of its use, the need for monitoring, trained operators, and the lack of safety data on its use elsewhere. However existing data shows that the use of NIV has expanded beyond the domain of ICU, with benefits to both critically, and terminally, ill patients. This may be of enormous value as demographic trends, population expansion and the complexity and expectations of patients put ever greater pressure on our limited critical care resources. As ICU capacity is both expensive and scarce, and with invasive ventilation largely confined there in practice, it has become essential to find a compromise level of support. This can allow decisions about admission to be made, relevant data to be gathered and necessary space to be created. NIV has made this a reality because its simplicity, less stringent monitoring, and general applicability from ICU to the home setting. It should be anticipated therefore that the use of NIV will expand further with technological advancement. We have sought here to delineate key aspects and developments in the use of assisted ventilation beyond the critical care environment, matters which should benefit society at large and be welcomed by all in healthcare.

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Noninvasive Positive Airway Pressure in Acute Cardiogenic Pulmonary Edema

47

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_47

Abbreviations

ACPE	Acute cardiogenic pulmonary edema
AMI	Acute myocardial infarction
BiPAP	Bi-level positive airway pressure
CI	Confidence interval
CO_2	Carbon dioxide
COVID-19	Coronavirus disease 2019
CPAP	Continuous positive airway pressure
EPAP	Expiratory positive airway pressure
IPAP	Inspiratory positive airway pressure
ITP	Intrathoracic pressure
LV	Left ventricle
LVP	Left ventricular pressure
NIPAP	Noninvasive positive airway pressure
$PaCO_2$	Partial pressure of arterial carbon dioxide
PaO_2	Partial pressure of arterial oxygen
PEEP	Positive end-expiratory pressure
RAP	Right atrial pressure
RR	Relative risk
RV	Right ventricle

47.1 Introduction

Acute cardiogenic pulmonary edema (ACPE) is a common cause of acute respiratory failure, which usually requires conventional oxygen therapy or ventilatory support devices, including noninvasive positive airway pressure (NIPAP) and mechanical ventilation with endotracheal intubation. NIPAP, administered either with continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP), has been employed in patients with ACPE, avoiding the need for invasive ventilatory support with endotracheal intubation [1]. However, firm evidence on the effectiveness of NIPAP for patients with ACPE has been scarce, and prior international guidelines have not issued strong recommendations regarding the use of NIPAP for a subset of patients [2–4]. This chapter provides recent evidence and practical applications of NIPAP in the setting of ACPEs.

47.2 What Is ACPE?

Acute cardiogenic pulmonary edema is characterized by increased left ventricular filling pressure due to heart diseases (i.e., acute heart failure and acute myocardial infarction [AMI]), leading to an increase in pulmonary capillary pressure, and eventually fluid overload toward the pulmonary interstitial compartment and alveolar

spaces [5, 6]. In addition, fluid into the alveoli can dilute the surfactant and neutralize the lubricating properties of alveoli, causing a reduction in lung compliance and an increase in work of breathing [6]. All these factors can cause an increase in airway resistance and decrease in lung diffusion capacity and functional residual capacity. Additionally, fluid in the lungs accumulates at the bottom, causing a ventilation–perfusion mismatch, resulting in hypoxia.

ACPE is treated with respiratory support and medical therapies, including diuretics, vasodilators, and morphine [7], while treatment for the underlying cardiac cause of ACPE should be simultaneously performed. The goal of the treatment is to maintain arterial oxygen saturation in the normal range to balance systemic oxygen demand and supply, and ultimately, to prevent hypoxia-induced organ dysfunction. Patients with ACPE may respond to medical therapies and simple oxygen supplementation. However, patients with severe respiratory failure may require additional respiratory support, including NIPAP or mechanical ventilation with endotracheal intubation, which is associated with adverse events, such as ventilator-associated pneumonia, tracheal injury, and barotrauma, all of which could be critical and related to prolonged hospital stay in patients with ACPE [8].

47.3 What Is NIPAP?

Noninvasive positive airway pressure therapy has been established as a noninvasive and effective ventilatory assist therapy that can improve gas exchange and avoid the need for invasive ventilatory support with endotracheal intubation. The application of NIPAP compared to conventional oxygen therapy was associated with faster improvements in clinical markers, such as a decrease in respiratory rate and heart rate, increase in partial pressure of arterial oxygen (PaO_2), reduction in partial pressure of arterial carbon dioxide ($PaCO_2$), and improvement in respiratory acidosis [9, 10].

The superiority of NIPAP over mechanical ventilation with endotracheal intubation, unless it is used for critically ill patients, is that it is less invasive for patients and more resource saving for healthcare facilities in terms of space (i.e., number of beds in intensive care units), cost, and human resources. Practically, there are two main forms of NIPAP: CPAP and BiPAP. CPAP provides a fixed positive airway pressure throughout the respiratory cycle. In contrast, BiPAP provides two different levels of positive airway pressure corresponding to different phases of the respiratory cycle (i.e., during inspiration and expiration). A theoretical advantage of BiPAP over CPAP could be its effect on the clearance of carbon dioxide.

Both types of NIPAPs can reduce the workload of breathing, enhance lung compliance impaired by alveolar edema, and improve cardiac output by reducing both cardiac preload and afterload. Positive end-expiratory pressure (PEEP) can prevent alveolar collapse and force fluid out of the alveoli, resulting in a decrease in pulmonary vascular resistance and improvement in lung compliance and gas exchange. Distinctive features of BiPAP from CPAP derive from pressure support during inspiration, which is the difference between expiratory positive airway pressure

(EPAP) and inspiratory positive airway pressure (IPAP). Pressure support during inspiration (i.e., IPAP) could unload the respiratory muscles, reduce work of breathing, and increase lung volume, leading to improvement in hypoxia and hypercapnia. A recent observational study comparing the effects of pressure support ventilation versus CPAP in 153 patients with ACPE [11] reported that a significantly higher number of patients in the CPAP group developed hypercapnia after initiation of the therapy, requiring endotracheal intubation or shifting to pressure support ventilation, although no difference in mortality rates was observed between the two modalities. Additionally, the reduction in $PaCO_2$ was greater in the pressure support ventilation group than in the CPAP group. Theoretically, patients with ACPE complicated with hypercapnia (i.e., chronic obstructive respiratory disease) or those with hypoventilation (i.e., obesity hypoventilation syndrome) may benefit from BiPAP rather than CPAP.

47.4 Discussion of Main Topics

47.4.1 How NIPAP Works on ACPE and What Are Appropriate Settings of NIPAP?

NIPAP affects both the cardiovascular and pulmonary systems by increasing lung volume, improving lung compliance, and increasing intrathoracic pressure (ITP), which confers beneficial effects on both respiration and hemodynamics (Fig. 47.1).

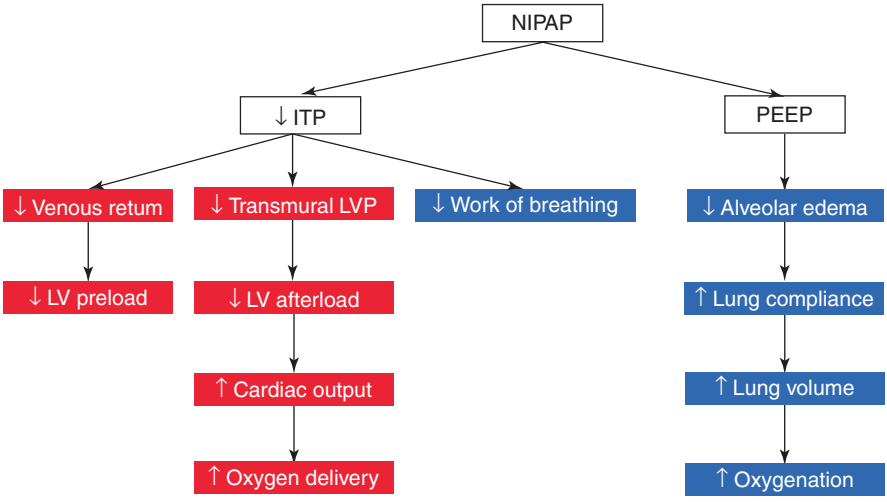

Fig. 47.1 Noninvasive positive airway pressure confers beneficial effects on respiration (written in blue boxes) and hemodynamics (written in red boxes) via positive end-expiratory pressure and increase in intrathoracic pressure. *ITP* intrathoracic pressure, *LV* left ventricle, *LVP* left ventricular pressure, *NIPAP* noninvasive positive airway pressure, *PEEP* positive end-expiratory pressure

47.4.1.1 Effects of NIPAP on Respiration

In patients with ACPE, lung compliance is reduced by interstitial and alveolar edema, leading to an increase in the work of breathing. Positive airway pressure can prevent alveolar collapse at the end of expiration, remove fluid from the alveoli, reduce pulmonary vascular resistance, and enhance alveolar expansion in the inspiration phase, subsequently improving oxygenation, functional residual capacity, and lung compliance [12]. Positive airway pressure also prevents upper airway narrowing and collapse, which are common features of sleep-disordered breathing, which is highly prevalent in patients with ACPE [13]. Other features of NIPAP responsible for the improvement in clinical outcomes among patients with ACPE may be related to an increase in ITP induced by positive airway pressure. The respiratory effects of the increase in ITP can be explained by reduced oxygen consumption due to reduction in the work of breathing [14].

47.4.1.2 Effects of NIPAP on Hemodynamics

From a hemodynamic perspective, ITP alters blood volume from the venous system to the right atrium (venous return), transmural right atrial pressure (RAP), and transmural left ventricular pressure (LVP) [14]. As ITP increases, RAP increases simultaneously, leading to reduction in venous return and right ventricular (RV) end-diastolic volume [15]. Venous return and RV end-diastolic volume are both recognized as preloads of the left ventricle (LV) without a significant pressure gradient between the right heart system and pulmonary vascular system, as well as the pressure gradient between the pulmonary vascular system and left atrium. With an increase in ITP due to positive airway pressure, transmural LVP decreases, leading to a reduction in LV afterload with a subsequent increase in cardiac output [14]. In patients with ACPE, cardiac output increases owning to the increased ITP through reduction in the LV afterload, despite concurrent reduction in the LV preload because the majority of these patients are likely to exhibit a hypervolemic state due to underlying cardiac conditions. Therefore, the reduction in LV preload cannot alter cardiac output as much as the reduction in LV afterload.

In addition to ITP, pressure support may confer additional beneficial effects on hemodynamics. Yoshida et al. reported that BiPAP increased cardiac output and decreased systemic and pulmonary arterial resistance in patients with chronic congestive heart failure [16]. These changes may be attributed to a decrease in sympathetic nervous activity through the neural reflex induced by regular inflation of the lungs with pressure support. This is supported by findings that plasma concentrations of epinephrine, norepinephrine, and dopamine were reduced in patients with ACPE treated with adaptive servo-ventilation [17].

47.5 Evidence on NIPAP

An observational study, involving 1293 patients with ACPE treated with standard oxygen therapy (CPAP or BiPAP), reported that oxygen therapy alone was associated with higher odds of treatment failure, defined as deterioration of clinical status

or death. One in four patients initially treated with oxygen therapy was subsequently switched to NIPAP therapy [18], indicating that NIPAP should be used as the first-line therapy for patients with ACPE.

The latest international guidelines issued by the European Respiratory Society and American Thoracic Society strongly recommend NIPAP for patients with acute respiratory failure caused by ACPE, based on the beneficial effects of decreasing the need for intubation and reducing rates of hospital mortality without increasing the incidence of myocardial infarction, which was raised in one clinical trial [19]. This recommendation is inclusive of both BiPAP and CPAP because the existing evidence has demonstrated significant benefits of both forms of NIPAP over standard care, and insufficient evidence to recommend one form of NIPAP over the other [19]. The recommendation of NIPAP use for patients with ACPE has also been supported by the Japanese Cardiology Society, stating that NIPAP should be promptly employed for patients with acute heart failure when hypoxia or symptoms, such as tachypnea, forced breathing, or orthopnea, sustains [20]. CPAP is the first choice; however, it may be switched to BiPAP in patients with sustained dyspnea or hypercapnia [20].

The Cochrane Library has recently issued a systematic review and meta-analysis of NIPAP in adults with ACPE [21]. The safety and efficacy of NIPAP were compared with those of standard medical care. The primary outcome was hospital mortality, and the secondary outcomes included endotracheal intubation, treatment intolerance, length of stay in the hospital or intensive care unit, rates of AMI, and adverse events. Twenty-four studies with 2663 participants were included in the review. NIPAP was significantly associated with reduction in hospital mortality (risk ratio [RR] 0.65; 95% confidence interval [CI] 0.51–0.82; low quality of evidence). The risk of endotracheal intubation was lower in patients treated with NIPAP (RR 0.49; 95% CI 0.38–0.62; moderate quality of evidence) compared to the standard medical care, while no difference was observed in the length of hospital stay between the two treatment strategies. An increased risk of incident AMI, for those treated with NIPAP, as compared to the standard medical therapy was not observed (RR 1.03; 95% confidence interval [CI] 0.91–1.16; moderate quality of evidence).

Several subgroup analyses for the associations between NIPAP and hospital mortality were performed using the following variables: types of NIPAP (CPAP or BiPAP), types of location of care (emergency room or intensive care unit), and baseline levels of $PaCO_2$ (eucapnia or hypercapnia). Both CPAP and BiPAP were associated with a reduction in hospital mortality when compared to the standard medical therapy (CPAP, RR 0.65; 95% CI 0.48–0.88 and BiPAP, RR 0.72; 95% CI 0.53–0.98; p for interaction = 0.64). Regarding the location of care, mortality benefit was similarly observed for NIPAP in both emergency room (RR 0.66 and 95% CI 0.47–0.93) and intensive care unit (RR 0.52; 95% CI 0.35–0.77; p for interaction = 0.52). The $PaCO_2$ subgroup analysis revealed significant subgroup differences (patients with eucapnia; RR 0.41, 95% CI 0.27–0.63 and those with hypercapnia; RR 0.82, 95% CI 0.65–1.03, p for interaction = 0.005). The systematic review concluded that NIPAP may improve outcomes, such as reduction in hospital mortality and rates of endotracheal intubation, without an increased risk of AMI.

47.6 Tips and Tricks for Practical Use of NIPAP

To minimize adverse events related to NIPAP, experienced health care providers should apply NIPAP without excessive PEEPs that potentially cause pulmonary barotrauma and hemodynamic instability induced by an increase in ITP. Nevertheless, appropriate PEEP varies depending on the degree of pulmonary edema or pulmonary compliance in each patient. In practice, NIPAP should be initiated with a lower level of PEEP (i.e., 4–5 cm H_2O) and careful monitoring is required for both hemodynamic (i.e., blood pressure, heart rate, and cardiac output if available) and respiratory status (i.e., respiratory rate and arterial oxygen saturation) to detect adverse events after initiating the therapy.

Other tips to facilitate NIPAP use involve our efforts to mitigate patients' anxiety and their feeling of discomfort related to NIPAP, which influences the possibility of successful ventilatory support with NIPAP, since patients who are indicative of NIPAP have adequate consciousness levels. Furthermore, NIPAP can potentially impose both physiological and psychological stresses on the patients caused by positive airway pressure throughout their respiration cycles, especially in expiratory phases. Patients may not respond to the treatment or may even drop out of treatment if they have treatment-related concerns and discomfort during the treatment. Accordingly, medical staff should recognize these potential issues and put effort into mitigating such stresses by initiating NIPAP therapy with a relatively low pressure, followed by a gradual increase in the pressure as needed, and simultaneously by building rapport with the patients, which could result in alleviating their anxiety [22]. Other practical ways to address stresses caused by positive airway pressure can be provided by a couple of additional functions that some CPAP devices have. Several types of CPAP devices are designed to detect the degree of upper airway obstruction and then adjust the pressure generated by it to keep the airway open and avoid excessive airway pressure, while other devices can lower pressures during the early expiration phase for patients who experience difficulty in exhaling against positive airway pressure, to alleviate their discomfort.

47.7 Application of NIPAP in Patients with ACPE Complicated by Coronavirus Disease

A newly identified coronavirus disease (COVID-19) pandemic emerged at the end of 2019, affecting millions of people worldwide. COVID-19 infection is characterized by common cold-like symptoms related to the respiratory system, with the risk of developing acute respiratory failure. Presentations of the infection have substantially varied from asymptomatic to acute respiratory failure or with symptoms derived from organs other than the respiratory system. Since the majority of patients have mild symptoms or are even asymptomatic, they do not need any specific treatments. Nevertheless, certain subsets of patients develop respiratory failure requiring oxygen therapy, NIPAP, and mechanical ventilation with endotracheal intubation. Mechanical ventilation requires substantial medical resources, such as isolated space, healthcare workers, and

protective equipment against infection [23], not only for the therapy per se, but also because of a highly contagious feature of the virus with its forms of droplet and contact transmission [24], which increases the risk of nosocomial infection among medical practitioners during medical care for patients. In fact, a medical crisis due to a lack of resources occurred in many countries, including some highly developed countries. In the wake of the medical crisis, emergency departments and intensive care units have increasingly applied NIPAP [25], which can be offered outside the intensive care unit. Since COVID-19 spreads through droplet transmission, aerosolization during medical procedures, such as intubation or bronchoscopy, might expose other patients and healthcare workers to substantial risks of the infection. Aerosolization with nosocomial amplification of the infection can also occur around a face mask of NIPAP during ventilation, as demonstrated in different simulation studies [26]. Accordingly, the efficacy and safety of NIPAP during this pandemic are still debated. A position paper of the Chinese Heart Failure Association and National Heart Failure Committee and Heart Failure Association of the European Society of Cardiology states that hypoxemia cannot be relieved by high-flow oxygen; NIPAP may be considered in patients with COVID-19 and heart failure [27]. To reduce the risk of nosocomial infection during NIPAP therapy, the choice of a helmet as the interface may work by avoiding aerosolization when the helmet is connected to the ventilator without air dispersion between the mask and the patient's face. When facing patients with acute respiratory failure complicated by COVID-19 infection, adoption of helmets and avoidance of face masks as the interface of NIPAP may mitigate subsequent risks of spreading the infection with less medical resources as compared to invasive mechanical ventilation.

47.8 Conclusion

This review provides recent evidence and practical applications of NIPAP in patients with ACPE. Recent clinical practice guidelines recommend NIPAP for patients with acute respiratory failure caused by ACPE, based on the beneficial effects of decreasing the need for intubation and reduction in hospital mortality.

Key Major Recommendations

- NIPAP is recommended as an effective respiratory support in patients with acute respiratory failure caused by ACPE.
- NIPAP confers respiratory benefits through improvement in lung volume, increase in lung compliance, reduction in work of breathing, and hemodynamic effects via reduction in venous return and decrease in intramural LVP, leading to a decrease in the LV afterload.
- The alleviation of potential physiological and psychological stresses in patients due to positive airway pressure is essential to facilitate NIPAP use.
- NIPAP can be an alternative to invasive mechanical ventilation in patients with COVID-19, provided that NIPAP is applied with a helmet as the interface.

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Noninvasive Ventilation in Transfusion Related Acute Lung Injury

48

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48.1 Introduction

Transfusion related acute lung injury (TRALI), one of the most common complications of blood and blood product transfusions, is a clinical syndrome with noncardiogenic pulmonary edema and hypoxemia occurring during or after transfusion. TRALI was first described by Bernard in 1951 [1]. A standardized definition was made at the Canadian Consensus Conference (CCC) in 2004, and standardization

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_48

was achieved in the diagnosis of the disease and in research with the determined diagnostic criteria. [2]. In the conference, it was divided into TRALI and possible TRALI (pTRALI) according to whether there is a risk factor for ARDS. The CCC criteria were reviewed in 2019 by an international expert panel and new diagnostic criteria were published [3]. In the final criteria, the term "possible TRALI" was removed and instead divided into TRALI type 1 (without ARDS risk factor) and TRALI type 2 (with ARDS risk factor or diagnosis).

48.2 Pathogenesis of TRALI

TRALI is mainly caused by the accumulation of neutrophils in the pulmonary vascular bed and their migration to the interstitium. Normally, the passage of neutrophils through the lung capillary network takes place within a certain period of time, as the cells change shape and compress themselves, making their size suitable for passage. Neutrophils must be activated to slow their passage through the lung capillaries and to be sequestered. Activated neutrophils lose their ability to change their shape for passage and become bound to capillary endothelium. However, they can also be activated by stimulated endothelium and subsequently attached to the endothelium. As a result, the attachment of neutrophils to the lung capillary endothelium initiates the development of TRALI. Triggers that activate neutrophils and endothelial cells are human leucocyte antigen (HLA) antibodies, human neutrophil antigen (HNA) antibodies, bioactive lipids, chemokines/cytokines, and neutrophil binding antibodies in the donor blood. Their presence and amount are directly proportional to the probability of TRALI development. However, inflammatory processes that may exist in the patient due to various reasons (such as surgery, infection) significantly increase the likelihood of TRALI development [4, 5].

48.3 Risk Factors

48.3.1 Conditions Associated with TRALI [3]

Sepsis, noncardiogenic shock, massive transfusion, cardiac surgery, increased pretransfusion plasma IL-8, mechanical ventilation with peak airway pressure >30 cmH_2O, chronic alcohol abuse, current smoker, positive fluid balance, higher APACHE II score, increased age, end-stage liver disease, postpartum hemorrhage, liver transplantation surgery, thrombotic microangiopathy, surgery requiring multiple transfusions, and hematologic malignancy.

48.3.2 Transfusion Risk Factors for TRALI [3]

Cognate HLA Class II antibody, cognate HNA antibody, granulocyte antibody positive by granulocyte immunofluorescence test (GIFT), cognate anti-HLA Class I that

activates cells as shown (for example, by granulocyte aggregation in vitro or at least by a positive by GIFT result), higher volume of female plasma.

48.4 Diagnosis and Clinical Manifestations

TRALI remained a clinical diagnosis in the last definition [3]. The 2019 diagnostic criteria, for which the term pTRALI has been abandoned and replaced by the terms type 1 and type 2 TRALI, are given in Table 48.1. Accordingly, type 1 TRALI defines patients without ARDS risk factors, while type 2 TRALI defines TRALI cases in patients with ARDS risk factors or a diagnosis of mild ARDS. Patients with acute onset of hypoxemia (P/F $\leq$ 300 or SpO_2 < 90% on room air) and bilateral pulmonary infiltrates during or within 6 h of transfusion, no signs of left atrial hypertension (even if present, not the main factor) and no temporal relationship with other ARDS risk factors are diagnosed with TRALI type 1. In the presence of respiratory distress and bilateral lung infiltrates (not of cardiac origin) that are stable for 12 h before transfusion and worsen in the next 6 h, TRALI type 2 is diagnosed in cases with ARDS risk factors but without ARDS or in cases with mild ARDS.

Table 48.1 New consensus TRALI definition [3]

TRALI Type I
Patients who have no risk factors for ARDS and meet the following criteria:
1. i. Acute onset
ii. Hypoxemia (P/F $\leq$ 300[a] or SpO_2 < 90% on room air)
iii. Clear evidence of bilateral pulmonary edema on imaging (e.g., chest radiograph, chest CT, or ultrasound) iv. No evidence of LAH[b] or, if LAH is present, it is judged to not be the main contributor to the hypoxemia
2. Onset during or within 6 h of transfusion[c]
3. No temporal relationship to an alternative risk factor for ARDS
TRALI Type II
Patients who have risk factors for ARDS (but who have not been diagnosed with ARDS) or who have existing mild ARDS (P/F of 200–300) (but whose respiratory status deteriorates[d] and is judged to be due to transfusion based on):
(a) Findings as described in categories a and b of TRALI Type I, and
(b) Stable respiratory status in the 12 h before transfusion

[a] If altitude is higher than 1000 m, the correction factor should be calculated as follows: [(P/F) × (barometric pressure/760)]

[b] Use objective evaluation when LAH is suspected (imaging, e.g., echocardiography, or invasive measurement using, e.g., pulmonary artery catheter)

[c] Onset of pulmonary symptoms (e.g., hypoxemia—lower P/F ratio or SpO_2) should be within 6 h of end of transfusion. The additional findings needed to diagnose TRALI (pulmonary edema on a lung imaging study and determination of lack of substantial LAH) would ideally be available at the same time but could be documented up to 24 h after TRALI onset

[d] Use P/F ratio deterioration along with other respiratory parameters and clinical judgment to determine progression from mild to moderate or severe ARDS. See conversion table in Appendix S2 to convert nasal O_2 supplementation to FiO_2

It is important to make the differential diagnosis of respiratory distress developing after transfusion. Before TRALI is diagnosed, other causes of post-transfusion respiratory distress (transfusion-associated circulatory overload (TACO), transfusion-associated dyspnea (TAD), transfusion-related bacterial sepsis, and severe allergic reactions) should be excluded.

48.5 Management

TRALI treatment mainly consists of supportive treatments. Hypoxemia, which is the cause of respiratory distress, should be eliminated with oxygen support, nasal high-flow oxygen therapy, noninvasive ventilation and invasive mechanical ventilation when necessary. However, to prevent secondary damage due to mechanical ventilation, treatment should be arranged in accordance with lung protective ventilation rules. Ventilation should be managed so that the plateau pressure does not exceed 30 cmH_2O.

48.6 Physiological Basis for Noninvasive Ventilation in TRALI

As TRALI causes acute hypoxemic respiratory failure, respiratory support can be provided with noninvasive mechanical ventilation as in other causes of respiratory failure. With the application of noninvasive mechanical ventilation, respiratory effort and work of breathing decrease, lung compliance and tidal volume increase, and alveolocapillary gas exchange and arterial blood oxygen content can improve.

48.7 Evidence for NIV Use in TRALI

Specific clinical studies investigating the effect of NIV use in TRALI are lacking.

Patel et al. [6] investigated the effect of NIV applications (face mask vs. helmet) on intubation rates in ARDS patients. The randomized controlled trial, which was planned to include 206 patients, was terminated early when 83 patients were reached, as it was found that patients who received NIV with a helmet significantly reduced intubation rates compared to patients who used a face mask. Patients with helmets had better results in terms of number of ventilator free days, length of stay in intensive care unit, hospital and 90-day mortality. The 1-year results of these patients were published in a separate article by the same group [7]. In the face mask group, higher rates of ICU acquired weakness and lower rates of functional independence were found at discharge from the hospital. One-year mortality was found to be higher in the face mask group. In the first year, it was determined that the patients in the helmet group had better functional independence and the number of days away from the hospital.

In a prospective, randomized, controlled, multicenter study conducted by He et al. [8], NIV administration in patients with early mild ARDS was compared with

conventional oxygen therapy and the need for invasive ventilation was investigated. In the study in which 21 centers participated and 200 patients were included, no significant difference was found between the groups in terms of invasive ventilation requirement. There was no difference between the groups in terms of intensive care mortality.

Xu et al. [9] reviewed studies comparing noninvasive ventilation and standard oxygen therapy in patients diagnosed with acute lung injury. A total of 1886 patients were evaluated in the meta-analysis, which included 17 studies published between 2000 and 2015. In the studies, noninvasive ventilation modes were applied as CPAP or BiPAP. After the analysis, it was concluded that NIV reduces intubation rates, shortens the length of intensive care stay, and decreases intensive care and hospital mortality.

Coudroy et al. [10] investigated the effect of the difference between NIV administration protocols on the outcome in patients with respiratory failure. Seven hundred fifty patients from 14 studies were analyzed, and they concluded that longer NIV duration did not make a difference in intubation rates. It was concluded that the ventilator type did not improve intubation rates; however, lower intubation rates were obtained in cases with high PEEP compared to low PEEP.

In the multicenter randomized controlled study conducted by Zhan et al. [11], a total of 40 patients from 10 centers were randomized. The effect of NIV and conventional oxygen therapy on intubation rates in early stage ARDS patients was investigated. Intubation rates and organ failure were found to be lower in the NIV group.

48.8 Conclusions

The ICU management of a critically ill patient with TRALI should include a lung protective strategy. Noninvasive ventilation is safe for selected patients with acute lung injury and might have potential beneficial effects by reducing the incidence of organ failure. Early identification, timely NIV approach, and careful hemodynamic monitoring should be warranted in complicated cases.

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Noninvasive Ventilation in Acute Lung Injury

49

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49.1 Introduction

Acute lung injury (ALI) can be defined as a diffuse lung inflammation characterized by sudden onset of oxygenation impairment ranging from mild pulmonary insult to severe respiratory failure requiring mechanical ventilation. The etiologies of ALI can be classified into two main groups, as follows: pulmonary causes (contusion, inhalation injury, pneumonia, aspiration, etc.) and extrapulmonary/systemic causes (severe burns, trauma sepsis, pancreatitis, and blood transfusions) [1]. Diffuse alveolar damage (DAD) is considered as the distinctive histological finding of ALI. DAD is characterized by the exudative phase with alveolar edema and hyaline membrane which is evident within the first week after lung injury, preceded by a reparative phase with interstitial fibrosis.

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_49

To better characterize the severity of the lung injury, the American-European Consensus Conference (AECC) defines ALI with the presence of the following four criteria: sudden onset of impaired oxygenation, bilateral opacities on chest radiography, no clinical signs of left atrial hypertension, less severe hypoxemia (defined as $PaO_2/FiO_2 < 300$). In addition to the first three criteria, more severe hypoxemia (defined as $PaO_2/FiO_2 < 200$) has been considered as acute respiratory distress syndrome (ARDS). The definition of ALI and ARDS has evolved over the years. The most recent definition, which is 'Berlin Definition' published in 2012, reveals three different degrees of hypoxia. These definitions substitute the ALI by categorizing its level of ARDS into three group with mild, moderate, and severe ARDS which is defined by the PaO_2/FiO_2 ratio (severe $\leq$100, moderate $\leq$200, and mild $\leq$300). They also pointed out that ALI and ARDS are the same diseases on the spectrum of progressive respiratory failure. ALI, which previously encompassed the non-ARDS acute lung injury in the AECC definition, was abandoned [2].

The cornerstone of treatment for ALI/ARDS patients is mechanical ventilation support. It is done with endotracheal intubation accompanied by positive-pressure ventilation. However, endotracheal intubation can lead to major complications such as upper airway trauma, barotrauma, and pneumonia. Non-invasive ventilation (NIV) has been developed to prevent the morbidity associated with endotracheal intubation or to serve as an alternative to invasive mechanical ventilation. In addition, it is increasingly used in respiratory medicine.

NIV has revolutionized the treatment of various origins of acute ARF in the setting of exacerbation of asthma and chronic obstructive pulmonary disease (COPD), cardiogenic pulmonary edema, post-operative setting, and as weaning of previously intubated COPD patients [3]. However, the application of NIV in the management of hypoxemic respiratory failure, particularly patients with ALI/ARDS remains unclear [4]. In this chapter, we will take a brief look at the application of NIV in ALI.

49.2 Evidence for Noninvasive Ventilation in ALI

From the physiological point of view, there are indeed strong rationales for applying NIV in the setting of ALI. Lung tissue inflammation and edema generate gas exchange impairment by reducing lung volumes, collapsing alveoli, and causing intrapulmonary shunting. Surfactant deactivation and loss of functional residual capacity result in cyclic recruitment/derecruitment of alveolar units having further lung damage. Moreover, decreased compliance of the lungs leads to increased respiratory work [5].The application of positive airway pressure to the airways recruits collapsed alveoli, increases functional residual capacity, improves alveolar stability, thus decreasing right-to-left intrapulmonary shunt. Their combined impact help to cease pulmonary function and prevent intubation.

The AHRF covers a wide range of diagnostic spectrum and a diverse population. Consequently, it would be misleading to think that NIV is beneficial for all AHRF patients. Numerous studies have been conducted that show advantages of NIV in selected groups with AHRF. Evidence for the benefit in the application of NIV in

patients with community-acquired pneumonia (CAP), cardiogenic pulmonary edema, immunocompromised patients, postoperative surgical patients, chest trauma, pandemic viral illness, and post-extubation has been described [6]. Earlier studies comparing NIV application to standard oxygen therapy reveal that various etiologies have different clinical outcomes. The first randomized study of patients receiving NIV with AHRF due to causes other than COPD was conducted by Wysocki et al. [7]. They concluded that NIV has no benefit in endotracheal intubation or mortality rates in the ICU when used systematically in all types of acute respiratory failure not caused by COPD, contrary to subgroup of hypercapnic patients ($PaCO_2$ > 45 mmHg). Later, Delclaux et al. [8] demonstrated that despite the improvement in oxygenation at early stages, the application of CPAP did not reduce the need for MV and mortality rates compared to patients with AHRF primarily due to ALI. Antonelli et al. looked into the use of NIV for hypoxemic ARF in 20 solid organ transplantation recipients and found that NIV improved oxygenation over conventional invasive ventilation and significantly decreased the rate of intubation and ICU mortality overall, but this decrease was not significant in subgroup analysis of patient with ALI/ARDS [9]. Ferrer et al. [10] conducted another study in which 105 patients with hypoxemic respiratory failure were randomly assigned to receive either NIV or high-concentration oxygen treatment. They found the NIV superior over the control group to reduce the risk for intubation and improve survival overall; however, subgroup analysis indicates the effectiveness of NIV is poor in patients with ALI/ARDS. A meta-analysis of these three studies [8–10] with a total of 111 patients pointed out that applying NIV to routine treatment in patients with ALI/ARDS did not decrease endotracheal intubation rate or ICU survival [11]. However, the total number of studies (3) and patients (111) were relatively not sufficient to draw any firm conclusions.

Contrary to the findings in the meta-analysis of Agarwall et al. [11], two subsequent studies, one involving patients with severe acute respiratory syndrome (SARS)-related ARF [12] and the other involving severe pneumocystis-pneumonia related ARF patients [13], both showed that NIV was effective in avoiding endotracheal intubation in the majority of patients. In a multicenter study involving 147 patients with ARDS, NIV improved gas exchange and reduced intubation rate in over half of the patients [14]. A significant aspect of this study is that the centers that apply NIV as initial treatment for ALI/ARDS patients have a great deal of experience in NIV applications. A second meta-analysis of 13 studies with 540 patients pointed out that applying NIV in ALI/ARDS patients could avoid endotracheal intubation in nearly half of patients and successfully prevent mortality in the majority of cases [15]. Xu et al. [4] conducted another recent meta-analysis of 17 RCTs to comprehensively evaluate the benefit and safety of NIV application for ALI/ARDS patients, by looking at intubation rate, duration of stay, and mortality in ICU. They found that NIV treatment for ALI/ARDS patients had a relatively shorter ICU stay, decreased intubation rate, and improved hospital mortality compared to conventional oxygen treatment.

Few studies have pointed out the efficacy of NIV in patients with AHRF caused by ALI/ARDS, and differences in ARDS severity remain a major cause of

conflicting results. The overall efficacy of NIV in lowering intubation rates or improving clinical outcomes in these patients remains indecisive and still under debate [4, 16]. The first RCT to consider NIV for patients with ALI/ARDS was a study by Zhan et al. [17] that proposed patients receiving NIV for mild ARDS reduced the need for intubation ($p = 0.02$) and the number of organ failures ($p < 0.001$) when compared to standard oxygen therapies. The LUNG-SAFE trial conducted in 459 ICUs worldwide represents one of the largest prospective databases of ARDS patients undergoing either NIV or IMV [18]. NIV use was independently correlated with increased ICU mortality (HR 1.446 95% CI 1.159–1.805). Post hoc analysis of the LUNG SAFE trial found that NIV was used in 15% of patients with ARDS regardless of its severity and the use of NIV was associated with a worse ICU outcome than invasively ventilated patients with a $PaO_2/FiO_2 < 150$ mmHg [18]. These results add further concerns about NIV use in this patient population. In a recent pilot study by He et al. [19], a total of 200 patients with early mild ARDS caused by pneumonia were randomly assigned groups to receive either NIV ($n = 102$) or traditional delivery of oxygen via a venturi mask ($n = 98$). NIV had no effect on the proportion of patients who required intubation ($p = 0.706$), despite earlier improvements of PaO_2/FiO_2 compared to standard oxygen therapy. Du et al. [20] proposed that further studies should integrate mechanical indexes such as higher PEEP and low tidal volume into NIV application to achieve more favorable results. Hence, albeit there appears to be a benefit to using NIV in the more severe patients, this benefit is relatively small.

49.3 Noninvasive Ventilation Failure in ALI

Death or the need for tracheal intubation has been described as NIV failure. The failure rate ranges from 5% to 60%, depending on several factors, including the cause of ARF [21]. A failed NIV attempt was found to be independently predictive of mortality, particularly in patients with de novo ARF [22]. This may indicate the need for vigilance regarding the application of NIV and close monitoring in order to switch immediately to endotracheal intubation when needed.

In clinical practice, although the facemask is the most common initial interface used to deliver NIV, therewithal it may have a role in a large number of NIV failures. The goals of NIV treatment in ALI can be achieved by selecting the appropriate interface (nasal, oronasal, full face, helmet, and mouthpieces) and ventilator mode for the patient. Furthermore, the patients' compliance with long-term NIV sessions can be improved by choosing an optimum interface; to prevent facial skin damage, improve the ventilation tolerance and promote eating, various types of nasal, oronasal/full-face masks, helmets, nasal pillows, and mouthpieces could be applied alternately. A full-face mask has been used as an interface in many of the studies looking into the role of NIV in AHRF. This has a physiologic rationale, as this type of interface reduces air leakage and allows higher airway pressures. Antonelli et al. [14] used helmets or face masks to provide NIV in AHRF and found that the helmet was correlated with prolonged NIV administration ($p = 0.05$). In addition, in the helmet,

no patients were unable to tolerate NIV due to intolerance to the technique, while 38% in the mask group had an intolerance to NIV. Rocco et al. [23] compared the effectiveness of helmet NIV with face mask NIV in 19 immunosuppressive patients with AHRF. The use of helmet NIV was as effective as face mask NIV in preventing endotracheal intubation ($p = 0.37$) and improving gas exchange, but it was associated with less NIV discontinuations in the first 24 h of application ($p < 0.001$) and fewer NIV- related complications (e.g., pressure ulcers, $p = 0.01$). Helmet CPAP reduces the risk of intubation and improves oxygenation better than standard oxygen therapy patients with severe AHRF due to pneumonia [24, 25]. Patel et al. published findings of a monocentrictrial of 83 patients with ARDS who were randomly assigned to NIV through a face mask and a helmet [26]. Treatment with a helmet resulted in a significant reduction of intubation and mortality rates than a face mask NIV ($p < 0.001$). In the study by Patel et al. [26], patients who received helmet NIV, tolerated lower driving pressure and higher PEEP than those using face mask NIV, and these ventilator settings were more consistent with targeted lung-protective ventilation in ARDS. The recent meta-analysis of 25 studies with a total of 3804 patients with AHRF pointed out that there was a statistically significant lower risk of mortality with helmet noninvasive ventilation (RR 0.40) and face mask noninvasive ventilation (RR 0.83) compared with standard oxygen therapy [27]. Hence, the helmet can be a valid alternative to a face mask in patients with AHRH by increasing tolerance and decreasing the rate of NIV-related complications.

Although some of the factors leading to NIV failure in patients with ALI/ARDS are well understood, only a small number of patients have been studied so far. A delay between admission and first use of NIV, high minute ventilation, low baseline PaO_2/FiO_2 ratio, and presence of shock were among the strong predictors of INV failure [19, 28, 29]. Because of the high mortality rate among patients who fail an NIV trail, it is essential to identify patients who will not benefit from NIV as soon as possible.

49.4 Conclusion

Use of NIV for ALI encountered in the ICU remains controversial. The evidence supporting the use of NIV in ALI is fairly weak, and the heterogeneity of the different published studies demonstrates that the effects may differ between different populations. As a result, NIV is not suitable in all patients with severe AHRF. However, given the advantages of NIV, it should be tried early and as the first-line therapy at least in mild cases of ARDS to prevent further deterioration. It would be wise to select patients carefully according to observed pathophysiological changes and NIV failure factors. It is crucial to define factors that predict NIV failure, thereby early intubation can be encouraged rather than NIV maintenance.

More RCTs are required to determine the effectiveness of NIV to avoid intubation and as an alternative to it, and to better understand which patient subgroups can benefit. The challenging issue is determining which patients will benefit most from the NIV application and preventing possible hazards of delayed intubation.

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Noninvasive Ventilation in Acute Respiratory Distress Syndrome

50

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50.1 Background

Acute respiratory failure often determines Intensive Care Unit (ICU) admission due to severe hypoxemia. Direct and indirect lung injuries determine hypoxemia. All these may lead to pulmonary oedema and inflammation [1].

Laennec made recognition of pulmonary oedema without heart failure in 1821. The Acute Respiratory Distress Syndrome (ARDS) was first described more than a century later in 1967 [2]. However, it was only in 1994 that the first criteria on ARDS were announced. Later, a consensus on ARDS was internationally recognized as The Berlin Definition. The last revised and updated version of The Berlin Definition was published in 2012 [3].

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_50

Currently, ARDS is characterized by five variables:

- Timing: onset within 1 week of a recognized clinical insult/new or worsening of respiratory symptoms;
- Chest imaging (Chest X-Ray or Thoracic Computed Tomography) finding bilateral opacities that are not fully explained by nodules, effusions or lung collapses;
- Lung oedema leading to acute respiratory failure not fully explained by fluid overload or cardiac failure;
- Oxygenation, which categorizes ARDS into:
  - Mild ARDS (PaO_2/FiO_2 between 200 and 300 mmHg with PEEP/CPAP $\geq$5 cm H_2O);
  - Moderate ARDS (PaO_2/FiO_2 between 100 and 200 mmHg with PEEP $\geq$5 cm H_2O);
  - Severe ARDS (PaO_2/FiO_2 under 100 mmHg with PEEP $\geq$5 cm H_2O).

Invasive mechanical ventilation (IMV) remains as the standard approach to manage acute respiratory failure due to ARDS. However, the complications related to endotracheal intubation, IMV and the ICU stay must be kept in mind, such as laryngeal trauma, tracheal trauma, ventilator-associated lung injury, ventilator-associated pneumonia, sedation and delirium risk, neuromuscular paralysis and critical care myopathy [4].

50.2 Brief Overview of ARDS Pathophysiology

In ARDS, damage of the endothelium with alveolar flooding due to an impaired protein-rich fluid removal mechanism plays a fundamental role. This results from an increased capillary permeability due to the presence of pro-inflammatory mediators, associated with other mediators such as endothelin-1, angiotensin-2 and phospholipase A-2, which in turn lead to the vascular permeability and distortion of the lung microvasculature. These first stages of lung disease might be followed by the resolution of the lung oedema and proliferation of type 2 alveolar cells, fibroblasts and myofibroblasts resulting in deposition of a new matrix. The outcome is a decreased lung compliance which is usually known as the concept of ‘baby lung’ in ARDS. However, the factors which influence complete resolution or fibroproliferation are not fully understood. It is now recognized that patients who develop consequent pulmonary fibrosis have increased mortality, risk for long-term oxygen and/or ventilator dependence [2].

50.3 General Considerations on Ventilatory Support in ARDS

Since the concept of ‘baby lung’ was introduced in the 1980s, practices of low tidal volume ventilation began to be applied. Several studies identified excessive lung inflammation and hyaline membranes deposition, which caused worsening of

respiratory failure, when implementing high tidal volumes and/or higher inspiratory pressures. Regarding practices of low tidal volume ventilation, favourable results were achieved in several studies. These results were associated with higher survival rates, higher rates of ventilatory weaning and reduced probability of ventilatory barotrauma. Moreover, it reduced the frequency of ventilator-induced lung injury [2].

Nevertheless, respiratory acidosis due to hypercapnia is more likely to happen, and strategies regarding permissive hypercapnia do not seem to result in worse outcomes in ARDS patients.

Another ventilatory strategy commonly used is to perform recruitment manoeuvres. A recruitment manoeuvre comprises a transient increasing in the transpulmonary pressure seeking to promote the opening of collapsed alveoli. Current evidence states that performing recruitment manoeuvres significantly improves oxygenation and might be attempted as a rescue strategy [2].

However, this ventilatory strategy lacks evidence in noninvasive ventilation (NIV).

50.4 The Decision to Perform NIV in ARDS

The role of NIV in the approach of acute respiratory failure has gained interest and is becoming increasingly solid in the literature.

Regardless of hypoxemia severity, NIV is used in ARDS in approximately 15% of patients that are usually older and with lower nonpulmonary *Sequential Organ Failure Assessment* scores compared to the groups with IMV [5].

Since NIV preserves physiological pathways of airway protection such as cough and secretions clearance, advantages related to the application of NIV in ARDS are related to the avoidance of complications of IMV such as sedation, muscle paralysis, ventilator-associated pneumonia, and others. Furthermore, preserving patients' state of consciousness reduces the risk of sedation-associated delirium. Spontaneous breathing also avoids diaphragmatic dysfunction and reduces ventilation/perfusion mismatch by optimizing aeration of the dependent zones of the lung. However, maintaining spontaneous breathing in moderate to severe ARDS may lead to a high inspiratory drive resulting in intense inspiratory effort, and high tidal volumes which in turn may worsen injured lungs with further barotrauma and volutrauma. In addition, a generation of heterogeneous forces within the lung potentiate lung inflammation. Altogether, these mechanisms are known as patient self-inflicted lung injury (P-SILI) [6].

Some data describe that the recognition of ARDS mostly occurs when patients fail an NIV trial. Furthermore, the same data identified a propensity to correct hypoxemia by increasing FiO_2 in those who are under NIV. Comparing to IMV patients, PEEP levels were also lower which is clinically relevant due to the importance of PEEP in patients with moderate to severe ARDS. For example, when applying levels of 10–15 cm H_2O, there is a reduction in the frequency of P-SILI because of the improvement in ventilation homogeneity. This prevents a *pendelluft* effect and reduces dead space and tidal volume [1, 2, 7].

According to the LUNG SAFE study, the success of NIV in mild ARDS is 78% decreasing to 58% in moderate ARDS and 53% in severe ARDS [5].

Although NIV in ARDS lacks ventilation protocols to prevent ventilator-induced lung injury, it is postulated that protective lung strategies should be applied similarly to IMV. Consequently, non-protective settings are frequently used which may cause moments of tidal volumes of 10 mL/kg instead of 6–8 mL/kg. In such patients, when lower tidal volumes cannot be achieved, early IMV is advised [7].

In acute respiratory failure, face masks are the most frequently used interfaces. Both oronasal and full-face masks can be applied with no relevant outcomes between them despite differences in dead space. In addition, they can be replaced by one another to improve patient comfort and tolerance. It must be reminded that air leaks alongside skin injuries limit the use of higher ventilatory parameters such as PEEP during prolonged treatment. Implementing the helmet interface might reduce this issue and should be considered as an alternative to face masks. Rebreathing of CO_2 is a risk while maintaining the helmet interface. Therefore, continuous monitoring is mandatory.

50.5 NIV in ARDS-COVID-19

The COVID-19 pandemic modified the need to introduce and integrate more health personnel in ventilatory management. Due to the overload of health services, intensive care units frequently had difficulties in admitting the total number of patients with acute respiratory failure with the need of permanent monitoring. Therefore, despite the need for more invasive care because of frequent severe ARDS cases, many patients had their respiratory failure managed noninvasively either with NIV or high-flow-nasal-cannula oxygen. Menzella and colleagues found in their retrospective analysis that NIV was effective in almost half of their cohort, which reduced pressure in the intensive care unit and avoidance of intubation with its possible complications. Despite having a high mortality rate, authors hypothesize that it could be by several factors: elevated proportion of do-not-intubate patients who had NIV as a rescue therapy, low PaO_2/FiO_2 ratio and higher SOFAs at admission [6]. Therefore, for those patients who are not candidates to IMV, NIV might be applied with success in patients with the L phenotype regarding COVID-19 pneumonia. One must also be reminded of the need for individual protection equipment when treating COVID-19 patients because of an intensive aerosolization when performing NIV.

50.6 NIV Failure in ARDS

Despite optimization of practices regarding NIV, outcomes on ARDS remain under debate. Currently, NIV has a clear role in the management of hypercapnic respiratory failure; however, when the issue is related to hypoxic respiratory failure, the challenge remains – with the exception for acute pulmonary oedema.

Several reasons are described to explain the possibility of NIV failure when applied to ARDS patients.

In ARDS, patients present with marked tachypnoea and high minute-volume, which results in tolerance and synchronization difficulties in NIV [8].

Moreover, the life-threatening hypoxemia often needs higher PEEP which may predispose to excessive and unacceptable air leaks and discomfort, leading to progressive intolerance and predisposing for NIV failure.

Frequently, ARDS patients have other underlying conditions besides acute respiratory failure. Multi-organ dysfunction and haemodynamic compromise could determinate the need for more invasive procedures and monitoring where NIV should no longer be an adequate option for respiratory failure management.

According to Antonnelli and colleagues, those who fail an NIV trial have much higher rates of ventilator-associated pneumonia mortality rates [9]. These patients could be identified early by a Simplified Acute Physiology Score II greater than 34 and $PaO_2/FiO_2 < 175$ mmHg after a trial of 1 h on NIV [9]. The presence of pneumonia has been associated with failure of NIV, and this finding might be explained by the difficulties in secretion clearance, even more reduced lung compliance and nonhomogeneous gas exchange [10].

Important data from the LUNG SAFE study revealed that patients who fail NIV have a higher risk of mortality while in the ICU. Moreover, according to this data, those who fail the NIV trial have a higher mortality rate than those who have severe ARDS but are managed with IMV from the beginning of its course. Mortality in the ICU was also higher in those who presented initially with a $PaO_2/FiO_2 < 150$ mmHg. NIV failure occurred in more than one-third of ARDS patients; however, more than half had moderate or severe ARDS [5].

The HACOR (Heart rate, Acidosis, Consciousness, Oxygenation and Respiratory rate) score has a solid role while monitoring patients under NIV due to acute respiratory failure. It is well established that delayed intubation increases mortality rates in ARDS. Although invasive ventilation might be more adequate for moderate to severe ARDS, if NIV is implemented, the reduction of HACOR scores more than one point after 1–2 h of NIV is associated with NIV-responders and a reduction of 28-day mortality [11].

Key Messages

- NIV might be used in mild ARDS;
- Clinical monitoring is fundamental, since NIV failure seems to predispose for increased mortality risk;
- There are no current ventilatory protocols on NIV in ARDS; therefore, more research is needed.

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Hypoxemic Respiratory Failure in Solid-Cancer Patients

51

Nazlıhan Boyacı Dündar

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Abbreviations

ARDS	Acute respiratory distress syndrome
ARF	Acute hypoxemic respiratory failure
COPD	Chronic obstructive pulmonary disease
HFNO	High flow nasal oxygen
ICU	Intensive care units
IMV	Invasive mechanical ventilation
NIV	Noninvasive ventilation
OHS	Obesity hypoventilation syndrome
VAP	Ventilator associated pneumonia
VILI	Ventilator associated lung injury

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_51

51.1 Introduction

Acute hypoxemic respiratory failure (ARF) is defined as a clinical worsening in which symptoms and signs such as tachypnea, difficult breathing pattern, and arterial hypoxemia with newly developed pulmonary infiltrates occurs. A high oxygen demand may develop and progress to a critical state requiring respiratory support. ARF is a very common clinical condition associated with increased mortality in solid-cancer patients. In this clinical deterioration, which often requires intensive care support, many clinicians ask themselves whether they will continue more invasive supportive treatments, considering the life expectancy of this patient group. In this respect, noninvasive ventilation (NIV) support has been increasingly used in solid-cancer patients with hypoxemic respiratory failure in recent years.

NIV support is currently used as the first choice for respiratory support in many acute and chronic respiratory failures such as chronic obstructive pulmonary disease (COPD), cardiogenic pulmonary oedema, post-operative ARF and obesity hypoventilation syndrome (OHS) [1]. The success of NIV support in hypoxemic respiratory failure varies according to the underlying disease and the selected patient population. The proven benefits of NIV support in patients with COPD exacerbation are avoidance of intubation and complications of invasive mechanical support including ventilator associated pneumonia (VAP), ventilator associated lung injury (VILI), ventilator dependency, increased morbidity and mortality. Although the results in hypoxemic respiratory failure differ depending on the underlying disease, early NIV support seems to be the first-choice ventilation support in immunocompromised solid-cancer patients, especially to avoid nosocomial infections and long-term complications of invasive mechanical ventilation (IMV) [1]. The most recent meta-analysis on NIV support in ARF has also stated that NIV showed a significant protective effect for intubation in immunocompromised patients [2]. In this chapter of the book, the use of NIV support in solid-cancer patients with hypoxemic respiratory failure will be discussed in the light of the current literature.

51.2 Pathophysiological Basis of Noninvasive Ventilation Support in Acute Hypoxemic Respiratory Failure

Hypoxemic respiratory failure is the most common reason for ventilator support, especially in intensive care units (ICU). The main mechanism of hypoxemia is decreased ventilation/perfusion ratio (V/Q) due to alveolar collapse in ARF [3]. In this situation the applied positive pressure recruits collapsed alveoli and prevent the collapsing of opened alveoli [3]. Hence NIV support decreases intrapulmonary shunt and improves oxygenation. There are different mechanisms of alveolar collapse according to the etiology of ARF. Pulmonary infiltrates in pneumonia, capillary leakage in sepsis of non-pulmonary origin, and pulmonary edema in cardiogenic shock are the most common of those [3]. Therefore, the success of NIV support in hypoxemic respiratory failure varies according to the underlying disease and the selected patient population. It is not possible to conclude that NIV support will be

beneficial in all types of hypoxemic respiratory failure patients due to the heterogeneity of the underlying diseases. The current guideline provides a strong recommendation for the administration of NIV in COPD exacerbation and acute cardiogenic pulmonary edema [1]. It also reports NIV administration as a conditional recommendation in immunocompromised, post-operative, trauma and palliative care patients [1]. According to the most recent meta-analysis published in this field, NIV support, with both a face mask and helmet, was associated with lower risk of mortality and endotracheal intubation when compared to standard oxygen therapy [4]. However, the clinical trials enrolled in this meta-analysis have high risk of bias due to a lack of blinding for intubation [4]. Although NIV support seems like a preventive strategy for avoiding intubation, the ability of NIV support to reduce the work of breathing in ARF is more difficult than in hypercapnic respiratory failure [1]. High pressures are often required to relieve respiratory symptoms, leading to air leaks, gastric insufflation or patient intolerance [1]. Resulting excessive tidal volume with the applied pressure support can exacerbate lung injury, especially in patients with high respiratory drive [1]. Given the risk that NIV support may delay endotracheal intubation and the uncertainty of the evidence, the routine use of NIV support is not recommended for de novo ARF, particularly in pneumonia and acute respiratory distress syndrome (ARDS) [1].

51.3 Basic Practice Principles of Noninvasive Ventilation Support in Acute Hypoxemic Respiratory Failure

NIV is a method of applying positive airway pressure to the patient through an interface without the need for intubation [3]. The main goal of NIV therapy is to alleviate patient symptoms, reduce respiratory workload, prevent respiratory muscle fatigue and improve oxygenation in ARF [5]. To achieve this goal, NIV must be implemented with specific technical aspects, such as selection of optimal settings and interface by an experienced team [5, 6]. Also, the application of NIV support along with careful and rigorous monitoring is vital to detecting NIV failure [6]. Insisting on NIV administration to avoid IMV-related morbidity and mortality is associated with adverse outcomes. In this context, the first point to be considered is whether there are any contraindications for NIV application. Cardiopulmonary arrest, unconscious patient and upper airway obstruction are absolute contraindications for NIV [6]. In the presence of concomitant severe hemodynamic impairment, severe acidosis, previous GIS surgery or bleeding, recent facial surgery, trauma, burn or deformity, inability to protect airway or clear secretions, and changes in consciousness such as drowsiness and agitation NIV application will not be appropriate due to both difficulty in administration and clinically poor results [5]. Another important factor for the effective and successful implementation of NIV support is its application with an experienced team in high dependency or intensive care units. This is also crucial for careful and meticulous monitoring. In this way, close follow-up of the patient in terms of both treatment failure and clinical worsening can be ensured with the protocolized application guidelines. If the patient's clinical

condition worsens despite appropriate initial settings and interface selection, switching to IMV support should be considered. NIV administration should not be insisted upon in conditions such as worsening of acidosis and hypoxia, failure of relieving respiratory symptoms, worsening of consciousness, development of serious facial injury associated with the interface that would prevent NIV administration, or inability to tolerate separation from NIV session. An arterial blood gas sample taken 1–4 h after NIV support should be examined to assess improvement in acidosis or hypoxia. The clinical condition of the patient should also be taken into account when evaluating the blood gas analysis. Less efficient corrections of hypercapnia or pH and failure to improve oxygenation are predictors for NIV failure [5]. Considering the underlying etiology of ARF and comorbidities of the patient, success criteria for NIV support should be well defined. In this respect, the chance of treatment success will increase with an experienced team and well-defined NIV application protocols.

51.4 Acute Hypoxemic Respiratory Failure in Solid-Cancer Patients

In parallel with the developments in chemotherapy and radiotherapy, life expectancy in patients with solid-cancer is gradually increasing [7]. ARF may develop in these patients at any time due to the presence of the primary disease such as lung cancer or metastatic lung lesions or related to the advanced treatment modalities [7]. ARF occurs in approximately 5–15% of solid-cancer patients [7, 8]. Some patients need intensive care support, especially in terms of respiratory support, depending on the severity of respiratory failure symptoms and the level of required oxygen support. In this subgroup of patients, the mortality is as high as 40–67% [8, 9]. The factors associated with mortality are the need for invasive mechanical ventilation, organ dysfunction, older age, frailty or poor performance status, existing comorbidities, delayed intensive care unit admission, acute respiratory failure due to an invasive fungal infection or unknown cause and advanced disease, especially in lung cancer [8]. Although the vast majority of studies on immunocompromised patients have been conducted in patients with hematological malignancies, in the presence of hypoxemic respiratory failure in solid-cancer patients, the similar basic diagnostic and treatment approaches can be used to obtain good clinical results. If ARF due to toxic and infectious pulmonary complications associated with these advanced therapies is diagnosed early and treated appropriately, satisfactory results can be obtained with appropriate respiratory support [10].

51.5 Oxygenation and Ventilation Strategies

In this patient group, the initial oxygenation and ventilation strategy aims to restore gas exchange, reduce respiratory rate, alleviate dyspnea and respiratory distress [8]. In immunocompromised patient, IMV are associated with high mortality [11]. Therefore, it is attempted to avoid intubation and IMV, especially with non-invasive methods,

until the underlying cause is eliminated. Currently available literature supports the use of NIV as a first-line approach for managing mild to moderate ARF in selected patients with immunosuppression of various aetiologies [1]. Although a large observational multicentre Italian survey confirmed the role of NIV as an independent predictor of survival, in a multicentre randomised trial of immunocompromised patients in France and Belgium, early NIV, compared with standard oxygen, was not associated with clinical benefits in mortality, ICU-acquired infections, duration of mechanical ventilation or length of ICU stay [12, 13]. In the study of Azoulay et al., NIV failure was also found to be associated with increased mortality [11]. The main point to be considered when interpreting these studies should be the study population, the underlying cause of deterioration and severity of ARF. IMV as well as avoiding intubation with NIV support will result in increased mortality in a solid-cancer patient with multiple organ failure with severe respiratory failure. In the presence of a reversible etiology such as a pneumonia or pulmonary edema in selected patients, NIV support may of course be effective in improving oxygenation and reducing the patient's work of breathing. The success of NIV support also depends on its implementation with an experienced team [6]. Application of NIV support along with careful and rigorous monitoring is vital to detecting NIV failure. Otherwise, delaying intubation will lead to poor clinical results.

High flow nasal oxygen (HFNO) therapy, which is becoming widespread with the developing technology, is growing as an alternative to standard oxygen therapy [14]. Although it is applied in many diseases, there are also publications indicating that it is superior to NIV support, especially in immunocompromised patients. A post-hoc analysis of a randomised trial by Frat and colleagues, which compared outcomes in immunocompromised patients treated with HFNO, NIV or standard oxygen, the IMV and mortality rates were higher in the NIV group than others [14]. This study showed the age and use of non-invasive ventilation as first-line therapy are the two factors independently associated with endotracheal intubation and mortality [14]. On the other hand, in a retrospective cohort of 178 patients with cancer and acute respiratory failure, the combination of NIV and HFNO was associated with lower mortality rates and was independently associated with higher day-28 survival [15]. In the multicentre, multinational, prospective cohort study of 1611 immunocompromised patients by Azoulay and colleagues, hospital mortality was not affected by the initial oxygenation or ventilation management and also there was a non-significant trend towards reduced intubation in patients applied HFNO [8, 11]. Another interesting finding of this study was the failure of HFNO therapy was associated with increased mortality as with NIV support [11]. As a result, changing technologies and practices in initial oxygenation and ventilation strategies have not yet demonstrated the improved survival in daily practice.

51.6 Palliative Ventilatory Support in Solid-Cancer Patients

NIV was increasingly used in patients with end-stage COPD, heart failure or degenerative neurological diseases as palliative therapy [16]. Similarly, in cancer patients, palliative NIV can be administered to relieve respiratory distress symptoms in dying

patients while maintaining patient communication [17]. The task force of the Society of Critical Care Medicine stated NIV would be effective if it improves breathlessness and respiratory distress without having other negative consequences, such as discomfort from a tight-fitting face mask or an undue delay in the time of death [18]. Nava et al. found NIV was more effective in reducing dyspnea compared with oxygen therapy and required less morphine than oxygen therapy [19]. Although palliative NIV application is a controversial issue in terms of the correct and appropriate use of resources in intensive care units, it is a meaningful application in responding to patients and their relatives who expect symptomatic relief in the presence of end-stage solid-cancer.

51.7 Conclusion

In the presence of ARF, NIV support is currently the first-choice respiratory support for solid-cancer patients. Its main benefit is to avoid the requirement of invasive mechanical ventilation and to reduce associated mortality and morbidity. To achieve this goal, it is very important to identify the cause of ARF and to initiate appropriate treatment in a timely manner. Application of NIV support along with careful and rigorous monitoring is vital to detecting NIV failure. The chance of treatment success will increase with an experienced team and well-defined NIV application protocols. It should be noted that poor performance status, existing comorbidities, advanced disease and high disease severity scores are closely associated with NIV failure. The NIV support is also a meaningful palliative support for symptomatic relief in the presence of end-stage solid-cancer.

Key Major Recommendations

- NIV support is widely used ventilator support in the management of ARF.
- NIV support seems to be the first-choice ventilation support in immunocompromised solid-cancer patients, especially to avoid nosocomial infections and long-term complications of IMV.
- It is very important to identify the cause of ARF and to initiate appropriate treatment in a timely manner for treatment success.
- NIV application with well-defined protocols along with an experienced team is crucial to careful and rigorous monitoring.
- NIV support is also a meaningful palliative support for end-stage solid-cancer.

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Hypoxemic Respiratory Failure in Haematological Critically Ill Patients: NIV in Acute Immunodeficiency Diseases

52

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52.1 Haematological Critically Ill Patients

Haematological malignancy (HM) includes many myeloid or lymphoid diseases, such as lymphoma, acute or chronic leukaemia and myelodysplastic or myeloproliferative syndrome [1].

The improvement of chemotherapy and hemopoietic stem cell transplantation, as well as the innovation of modern targeted immunotherapies, have led to an amelioration of prognosis of these syndromes [2]. Nevertheless, Intensive Care Unit (ICU) admission is often required for many reasons, which include acute respiratory failure (ARF), septic shock or post bone-marrow transplantation monitoring. Patients

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_52

admitted to ICU, in many cases, do not have a good prognosis, with a mortality rate in literature from 33.7% to 58% [3]. The ICU mortality seems to be predicted, as independent variables, by the number of organ dysfunction ≥2 and the requirement of mechanical ventilation [3]. In addition, the Acute Physiology and Chronic Health Evaluation (APACHE) II score at admission in ICU and trends in Sequential Organ Failure Assessment (SOFA) score to monitor patient's conditions and ensure an early support are largely used [4].

52.2 Acute Respiratory Failure in Immunocompromised Patients with Haematological Malignancies

Acute Respiratory Failure (ARF) is the most common life-threatening condition and the leading reason for admission in ICU. It can occur in up to 50% of haematological patients. ARF is defined as arterial oxygen partial pressure (PaO_2) < 60 mmHg or peripheral oxygen saturation (SpO_2) < 90% on room air, or tachypnoea >30/min, with respiratory distress signs or dyspnoea at rest and cyanosis and PaO_2/FiO_2 ratio < 300 [5, 6]. Radiological signs include different patterns of pulmonary infiltrates, often bilateral [7].

As concerns the aetiology of ARF, causes of ARF can be listed in two main categories, such as infectious and non-infectious forms. Pulmonary infections are the most prevalent causes in patients with HM receiving chemotherapy since the defect of humoral or cell-mediated immunity, prolonged exposure to high-dosage of corticosteroids and antibiotics, neutropenia and long hospital length of stay.

Schnell et al. [8] performed a study to evaluate the feasibility of the DIRECT [9] criteria, an acronym to better identify the most probable cause of ARF:

- **D**elay since malignancy onset or HSCT, since symptom onset and since implementation of antibiotics/prophylaxis,
- pattern of **I**mmune deficiency
- **R**adiographic appearance
- **E**xperience and knowledge of the literature
- **C**linical picture (including ongoing chemoprophylaxis and effective antibiotic therapy)
- Findings by HRC**T**.

They applied these criteria to identify causes of ARF in 424 cancer patients admitted to the ICU; 47% of ARF were caused by bacterial infections, 31% by opportunistic pulmonary infections and 22% non-infectious lung disorders. Pulmonary aspergillosis was the principal opportunistic infections, followed by respiratory viral infections and Pneumocystis Jiroveci pneumonia.

Although infectious causes are the most frequent, non-infectious causes of ARF in patients with HM are cardiogenic pulmonary oedema, pulmonary haemorrhage, radiation-induced pneumonitis, aspiration pneumonitis, transfusion-related acute

lung injury (TRALI), venous thromboembolism, leukemic pulmonary infiltrates and pulmonary lysis syndrome [8, 10].

Identifying the cause of ARF is mandatory to establish the prognosis of these patients. Indeed, Gruson et al. [11] in their study proved a prognostic difference between haematological transplanted patients with proven infective pulmonary disease compared to patients with ARF without microbial origin.

Several factors often present in the medical therapy phase can contribute to develop non- infectious ARF. Acute myeloid leukaemia, for example, is characterized by the presence of pulmonary leukostasis with leukemic infiltrates, inducing ARF before the beginning of chemotherapy [12]. Furthermore, tumour lysis syndrome can elicit in lung alveolar proteinosis, worsening the respiratory condition [12]. Chemotherapy can contribute to the releasing of lung inflammatory cytokines by the affected cell, producing a gap endothelial damage with subsequent alveolar oedema. In this context, the use of growth factors to treat chemotherapy-induced aplasia could be involved in the complication of the respiratory condition [13]. Consequently, the neutropenia recovery phase includes an inflammatory response which can lead to the worsening of ARF.

In the literature, as concerns the epidemiology, myelodysplastic syndromes and acute myeloid leukaemia have a higher incidence to develop respiratory complication than lymphoproliferative disorders, such as lymphoma and acute lymphoblastic leukaemia (22–84% vs. 8–18%) [6]. Furthermore, the condition of neutropenia and immunosuppression due to stem cell transplantation predisposes the patient to higher incidence of respiratory events [14].

Allogenic bone marrow transplantation has shown its utility in the therapy of selected patients with HM; however, acute or chronic Graft versus Host Disease (GVHD) may occur, with the development of idiopathic pneumonia, diffuse alveolar haemorrhage and bronchiolitis obliterans [13]. The first step in the management of these patients consists in searching out the most probable cause of the ARF on the basis of clinical examination. It is mandatory to identify patients with cardiogenic pulmonary oedema by using the echocardiography and dosage of natriuretic peptide.

The leading cause of ARF in 90% of haematological patients is bacterial infection; thus, sputum examination plays an important role to detect the cause of infection with a search for bacterial and fungal infections, including opportunistic pathogens and virus. In addition, blood cultures need to be collected. In immunocompromised patients, procalcitonin has a restricted value; galactomannan and beta-d-glucan have to be searched to detect aspergillosis and other fungal infections.

As concerns radiological features, in patients with haematological malignancies, high-resolution CT shows leukemic infiltrates as the most common cause of ARF [15]. Furthermore, lymphoproliferative disorders, especially lymphoblastic leukaemia and lymphoma may start with ARF of infectious nature [16].

The tools for oxygenation strategies to improve patient's respiratory condition have been largely investigated in the literature; the main goal of these strategies is to relieve dyspnoea and respiratory distress by reducing the respiratory rate and guaranteeing an adequate oxygenation to vital organs.

The therapeutic options for haematological patients with ARF include:

- Standard oxygenation strategies, such as low-flow oxygen administered by nasal cannula, reservoir mask, non-rebreathing mask and Venturi mask;
- High flow nasal oxygen, with oxygen flow up to 60 L/min, FiO_2 up to 100%, with humidification system;
- Noninvasive ventilation (NIV) with different types of interfaces, such as full-face mask, oronasal mask or helmet, connected to ventilator in different modalities (continuous positive airway pressure (CPAP) or bi-level positive airway pressure (Bi-PAP);
- Invasive mechanical ventilation (IMV), requiring orotracheal intubation, use of sedative and neuromuscular blocking agents (NMBA) drugs.

Different studies in the past decades have shown how poor the prognosis was of patients with HM and ARF who required IMV, with a mortality of 50–70% [17]. Thus, the need to avoid IMV led to consider NIV strategies to improve the prognosis of this typology of patients.

52.3 Evidence for NIV in Haematological Patients with Acute Respiratory Failure

Noninvasive ventilation (NIV) works through the administration of positive airway pressure by a mechanical ventilator using several interfaces such as a facial mask or helmet. NIV use requires cooperation of patients who need to be alert and able to maintain airway protection on their own.

NIV contraindications include altered consciousness of the patient unless caused by hypercapnia, hemodynamic instability, recent maxillo-facial surgery or facial deformity and upper airway obstruction due to involvement of neoplasm [18].

NIV ventilation modalities include continuous positive airway pressure (CPAP) or bi-level positive airway pressure (Bi-PAP); the treatment is individualized for the patient and gradually titrated in terms of inspiration pressure and positive-end-expiratory pressure (PEEP) with a strict monitoring of the patient's compliance to the interface and oxygenation improvement through blood gas analysis (BGA). The time frame to assess the success or the failure of NIV application should not exceed 4–6 h from the starting of this ventilation strategy in order to consider IMV [19].

The evidence in literature for NIV application in haematological patients with acute respiratory failure is controversial and remains a source of debate.

Benefits of NIV in HM with ARF are shown in several studies. Since 1998, Conti et al. [20] in a pilot study in an ICU setting, proved that NIV reduced the IMV requirement with a rate of NIV failure of 6.6% and ICU mortality rate of 31.3%. Afterwards, this evidence was confirmed by Hilbert et al. [21] in a randomized controlled trial (RCT) in which NIV and standard oxygenation strategies were compared, with a mortality rate in patients treated with NIV of 38% versus 69% of conventional oxygen administration, with a reduction of intubation rate when early NIV was performed.

Squadrone et al. [22], in a randomized controlled trial (RCT), enrolled 40 patients in a ward context comparing NIV and conventional oxygenation strategies; from this trial, NIV mortality rate was 15% versus 75% of standard oxygen administration. They confirmed that the early application of NIV strategy reduced IMV and admission to ICU of those patients.

Gristina et al. [23], in 2011, retrospectively analysed 1302 patients affected by HM with ARF in the ICU setting, comparing NIV and IMV; 21% of these patients received NIV and they reported NIV failure in 46% of patients with consequent IMV requirement. The mortality rate was higher in patients with NIV failure (77%) than in those with NIV success (42%), while the mortality rate in patients with IMV ab initio was 69%. The authors suggested NIV application as first-line treatment in HM patients with ARF.

Recently, Barreto et al. [24] conducted a prospective study in 82 patients admitted to ICU to follow the outcome of patients receiving IMV/NIV/standard oxygen. Rate of NIV failure was 50.8%, due to a higher SOFA score (>7 points), respiratory rate (>34 breaths/min) and sepsis on admission. Mortality was significantly higher in the IMV (83.3%) than in the NIV (49.2%) and standard oxygen (5.9%) groups. Thus, they concluded that NIV was reasonable in haematological patients with ARF, although IMV was recommended when predictor factors of NIV failure occurred.

On the other hand, some studies do not strongly support NIV in the HM population with ARF. Adda et al. [25] retrospectively analysed 99 patients with HM and ARF admitted to ICU with $PaO_2/FiO_2 < 300$ eligible for NIV treatment; of these, 54% failed NIV and required orotracheal intubation due to persistent tachypnoea refractory to NIV, deferred use of NIV from ICU admission, need of vasopressors or renal replacement therapy and ARDS. These factors were identified as independent predictors of NIV failure. The mortality was 79% in patients who failed NIV versus 41% in patients responsive to the noninvasive treatment. The authors suggested using predictive factors of NIV failure to better select those patients who require early intubation. Depuydt et coll. [26], in 2010, found that ICU and hospital mortality of patients who received NIV or IMV or standard oxygen strategies was influenced by the severity of illness instead of the applied ventilatory support. In an RCT, Lemiale et al. [27], in 2015, compared NIV strategies with standard oxygen administration in immunocompromised patients with ARF, concluding that early NIV could not reduce 28-day mortality. In the same way, Liu et al. [1] retrospectively found that NIV failure, which occurred in 74% of enrolled HM patients with ARF ($n = 79$), was linked with higher mortality. Although the aforementioned studies have a wide variability in study protocol, NIV criteria, ICU policy of admission, aetiology of illness and severity of acute respiratory failure, NIV still plays an important role for HM patients with ARF.

The use of NIV should be considered as soon as possible in selected patient to avoid endotracheal intubation and IMV. It could be indicated in HM patients with a mild ARF, presenting $PaO_2/FiO_2 > 200$, RR > 25 breaths/min or $SpO_2 < 90\%$ and in those patients with reversable causes of ARF (COPD, pulmonary oedema, or refuse intubation) [28]. The amelioration of dyspnoea and gas exchange through BGA, as well as the evaluation of patient's compliance to the interfaces without air leaks,

should be followed up within early hours to assess NIV success or early switching to IMV. On the contrary, patients with impaired consciousness, $PaO_2/FiO_2 \leq 200$, hemodynamic instability, RR > 35 breaths/min, ARDS or multiple organ failure should be early addressed to IMV [24, 25]. Furthermore, NIV treatment is to be considered in those patients with 'do not intubate' directive, as stated by international consensus conference on NIV [29], when reversable causes might be involved.

52.4 Conclusions and Perspectives

Acute Respiratory Failure represents the first cause of ICU admission with high mortality rate in patients with haematological malignancies. The main determinants of ARF are bacterial or opportunistic pneumonia and non-infectious lung disorders. A multidisciplinary treatment for this patient is mandatory: cooperation among intensivists, haematologist, radiologist, infectiologist and other specialists leads the patient to a better outcome. The need for endotracheal intubation and invasive mechanical ventilation, in these patients, strongly influences the prognosis and the mortality. NIV in selected patients with HM and ARF, with a strict monitoring of its efficacy in a close time frame, considering when the predictors of NIV failure occur, may improve the outcome of these critically ill patients.

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Noninvasive Positive Pressure Ventilation in Lung Transplant Recipients

53

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53.1 Background

After lung transplant, there is the loss of normal cough reflex and impairment of mucociliary clearance below the tracheal or bronchial anastomosis due to disruption of the nerve supply, as well as impaired lymphatic drainage, and loss of the bronchial circulation. When these are combined with intensive immunosuppressive

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_53

therapy and direct exposure of the allograft to the external environment, lung transplant recipients are at an extremely high risk of respiratory infections [1]. Lung transplant recipients are also at high risk for post-operative ventilatory failure as a result of significant neuromuscular deconditioning due to pre-transplant illness, post-operative pain and immobility, donor/recipient size mismatch, and occasionally due to direct injury to the phrenic nerve during surgery, resulting in further diaphragmatic weakness and/or paralysis.

While improved immunosuppression regimens and monitoring has significantly reduced the incidence of hyperacute rejection in this patient population, approximately 30% of lung transplant recipients experience acute cellular and/or antibody mediated rejection within the first year post-transplant, which can lead to acute respiratory failure as well as increase the likelihood of developing chronic lung allograft dysfunction (CLAD). CLAD, most commonly manifested as bronchiolitis obliterans syndrome (BOS), occurs in approximately 65% of recipients at 10 years, and is the leading cause of mortality in this population after 1 year post-transplant [2]. Further complicating the management of these patients is the severe renal dysfunction that occurs as a result of calcineurin inhibitor immunosuppression regimens and diabetes mellitus due to chronic steroid use [3]. These transplant-associated comorbid conditions further predispose patients to acute respiratory failure from hypervolemia and pulmonary edema, as well as increased risk of cardiovascular disease and greater susceptibility to common and opportunistic respiratory infections.

53.2 Perioperative Period

53.2.1 Bridge to Transplant

The use of NIV in the pre-transplant patient with acute and/or chronic respiratory failure should follow the same principles as those applied to patients who are not deemed to be suitable for transplant, and is detailed in other chapters of this book. It is worth mentioning, however, that chronic hypercarbic respiratory failure is an indication for lung transplant referral in patients with chronic obstructive pulmonary disease (COPD) and for listing in those with cystic fibrosis (CF). Furthermore, increasing number and/or severity of hypercarbic pulmonary exacerbations necessitating NIV use in COPD, as well as dependence on long-term NIV in CF are indications for listing for lung transplant in these disease states, and are thus important for physicians to recognize to facilitate timely transplant consultation and listing [2].

To date, very little data exists regarding the role of NIV in patients with chronic respiratory failure awaiting lung transplant. One small retrospective study examining bilevel positive airway pressure ventilation (BiPAP) in CF patients with chronic respiratory failure awaiting transplant demonstrated improvement in acid–base balance and body mass index with trends toward decreased work of breathing and number of hospitalizations. All patients ($n = 4$) in the BiPAP group were alive with no evidence of BOS at 2 to 8 years post-transplant at the time of study conclusion, compared to 100% mortality ($n = 8$) in the non-BiPAP group at 2 to 10 years. NIV

may thus improve respiratory muscle strength and allow for optimization of nutritional status prior to transplant, leading to more favorable outcomes post-transplantation [4]. Given the small sample size, retrospective nature, and limited generalizability of this study to other populations, one should utilize existing evidence for NIV use independent of transplant eligibility when deciding to initiate NIV in patients with acute or chronic respiratory failure.

53.2.2 Early Extubation

Multiple studies in post-operative patients have demonstrated the benefit of NIV in facilitating early liberation from mechanical ventilation and preventing re-intubation, particularly in those with COPD and heart failure and in those undergoing thoracic surgery [5]. While the respiratory mechanics of the immediate post-operative lung transplant patient differ due to disruption of the nerve supply and neuromechanical uncoupling, changes in anastomotic circulation, and decreased lymphatic drainage, the expected benefits of NIV use in lung transplant recipients are similar to those encountered in NIV use in non-lung transplant patients. Such benefits include unloading respiratory muscles, decreasing respiratory rate and sensation of dyspnea, improving ventilation/perfusion abnormalities, decreasing the heart rate, and improving hemodynamics. Early extubation also has the potential to mitigate some of the risks associated with prolonged mechanical ventilation in this particularly vulnerable population, especially with regard to the development of nosocomial infections, prolonged sedative and analgesic use, airway injuries and anastomotic dehiscence, physical deconditioning, and poor nutritional status, all of which can lead to increased ICU lengths of stay and worse outcomes [5].

One small study examining NIV application immediately post-extubation in 12 lung transplant recipients demonstrated improvement in pulmonary gas exchange, decreased respiratory rate and increased tidal volumes, without the need for re-intubation [6]. It may therefore be reasonable to consider in lung transplant patients who do not fulfill all criteria for extubation. However, passing to NIV assistance should only be considered after careful clinical judgment of graft and patient characteristics. Appropriately trained staff must use optimally individualized ventilator modes with close clinical and physiological monitoring for signs of treatment failure. Patients must be monitored very closely for the ability to protect their airway as aspiration into the transplanted can lead to both early and long-term graft dysfunction. Finally, prolonged dependency on NIV may also limit physical rehabilitation and optimal nutritional support, in which case re-intubation and early tracheostomy should be considered as an alternative strategy.

53.2.3 Early Post-Operative Graft Dysfunction Following Extubation

Respiratory failure in the lung transplant recipient following initial post-operative extubation may develop for a variety of reasons, including primary graft

dysfunction, pulmonary edema, atelectasis, impaired mucociliary clearance and sputum retention, and acute rejection. The need for re-intubation is itself a marker of poorer graft dysfunction, is associated with many postoperative complications, and predicts a greater risk of need for prolonged invasive mechanical ventilator support [7]. Because many of the underlying causes of respiratory failure in this period respond to specific interventions (fluid restriction, diuresis, bronchopulmonary hygiene, relief of abdominal distention, increased immunosuppression), temporizing the lung transplant recipient's respiratory status with intermittent NIV is a reasonable strategy if it does not compromise physical rehabilitation or optimal nutrition delivery. Prophylactic NIV protocols in recipients with dyspnea due to a variety of causes may indeed reduce the need for reintubation among immediate post-operative lung transplant recipients, based on expert experience [6]. By increasing the efficiency of gas exchange, alleviating respiratory distress/fatigue with intermittent trials of NIV, one can prevent further progression of postoperative hypoventilation and enhance effective cough by resting respiratory musculature while other interventions are given time to act.

In a small, prospective study of 21 patient with acute respiratory failure following lung transplantation, Rocco et al. found that NIV improved gas exchange and successfully averted the need for reintubation in 18/21 (86%) of patients. Furthermore, NIV was generally well tolerated with no complications associated with its use. Primary reasons for failure were inability to improve oxygenation and hemodynamic instability [8]. A small case series reporting the addition of prone positioning to NIV in two post-operative lung transplant recipients also demonstrated significant improvement in oxygenation without the need for reintubation after 3–4 days of therapy, suggesting that NIV may be an effective means of facilitating ventilatory autonomy while promoting bronchopulmonary hygiene and re-expanding atelectatic lung [9]. While these results are promising, the overall availability of evidence is limited and thus appropriate patient selection/consideration of clinical trajectory are paramount as to not compromise other aspects of care.

53.2.4 Neuromuscular Weakness

Neuromuscular weakness and alveolar hypoventilation in the post-lung transplant patient is multifactorial, and is a result of pre-transplant illness, post-operative pain and immobility, analgesic use, and, less commonly, disruption of respiratory musculature innervation. Alveolar hypoventilation is further perpetuated by an ineffective cough with subsequent mucus plugging and atelectasis that leads to poor graft compliance, hypoxia, and/or hypercarbia. By unloading the respiratory musculature and enhancing alveolar ventilation, NIV has the ability to support the recipient while many of these acute post-operative issues improve.

NIV may also have a role in those patients who sustain phrenic nerve injury or suffer from diaphragmatic dysfunction due to the surgery itself, situations in which recovery of ventilatory function may by be prolonged. Phrenic nerve dysfunction is a serious complication after lung transplantation, with reported incidence rates

ranging from 3–30%. It can be a result of direct injury, stretch, or hypothermia of the nerve during surgery [10, 11]. Several case reports detail successful weaning of mechanical ventilation and ICU discharge, improvement in exercise tolerance, oxygen saturation, hypercarbia and forced vital capacity with the use of intermittent BiPAP in the setting of unilateral diaphragmatic paralysis, and thus NIV may be a suitable long-term option for such lung transplant recipients even in the absence of phrenic nerve recovery [12, 13].

53.3 Beyond the Perioperative Period

53.3.1 Acute Respiratory Failure

Early application of NIV in immunocompromised patients with acute respiratory failure has been shown in randomized trials to reduce intubation rates, hospital stay and mortality rates primarily by preventing nosocomial infections [14, 15]. Lung transplant recipients represent a unique subgroup of immunocompromised hosts who are at a high risk of both rejection and infection of the lung graft due to a perilous combination of stronger immunosuppression and exposure of the allograft to the environment. Furthermore, disruption of the normal physiological and mechanical properties of the lung parenchyma and chest wall put these patients at much higher risk of respiratory failure than other types of transplant patients.

While previous data suggests that these patients are at higher risk of NIV failure, a recent publication by the authors of this chapter suggests that it is a viable option for many patients presenting with respiratory failure beyond the immediate perioperative period. In a retrospective review of 241 lung transplant recipients presenting with respiratory failure, 54.4% of patients who were tried on NIV were managed successfully without intubation. Severe hypoxemia (pf ratio < 151) and APACHE III score > 78 were found to be independently associated with failure of NIV and subsequent endotracheal intubation. No associations between NIV failure and cause of respiratory deterioration or presence of BOS were noted in the study, and mortality in those who failed NIV was not significantly higher than those who were intubated without a trial of NIV [16]. This suggests that NIV can be utilized in a broad population of transplant recipients with respiratory failure, with careful attention to oxygenation and overall severity of illness. Though exhaled tidal volumes and length of NIV use were not independently associated with NIV failure, careful monitoring and frequent reassessment should be undertaken to identify those who are at risk of volutrauma and/or those who are developing progressive respiratory compromise despite NIV support.

53.3.2 Domiciliary Use: Chronic Respiratory Failure

As previously described, chronic lung allograft dysfunction in the form of BOS is a significant source of morbidity and mortality following lung transplantation,

occurring in up to 65% of recipients at 10 years post-transplant. Similar to other obstructive lung diseases, BOS results in progressive airflow obstruction with subsequent hyperinflation that can cause diaphragmatic flattening and a decrease in the zone of apposition, overexpansion of the rib cage (thereby placing accessory muscles of respiration at a mechanical disadvantage), and creation of a size mismatch between the lungs and chest cavity that limits further expansion of the chest wall. Intrinsic changes in respiratory muscle fibers and the chronic use of steroids may further contribute to neuromuscular weakness. These all lead to a decreased ability to generate inspiratory pressures, thereby limiting inspiratory reserve. Furthermore, as a result of airflow obstruction, intrinsic positive end-expiratory pressure and dynamic hyperinflation ensue during exercise as a result of increased minute ventilation and decreased expiratory times, thereby leading to enhanced mechanical load on inspiratory muscles and creating the sensation of dyspnea. Further increases in respiratory rate due to subjective dyspnea then create a cycle of further hyperinflation, limiting exercise tolerance and leading to further deconditioning.

NIV is thought to counteract these imbalances primarily by decreasing the load on the respiratory system, reducing airway obstruction, and recruiting small airways. NIV may also increase respiratory drive by resetting the CO_2 set point of the chemoreflex receptors, primarily through chronic improvements in hypercapnia and daytime breathing patterns [17]. While no trials have been conducted regarding its efficacy, NIV application in patients with hypercapnia due to BOS has the potential to palliate symptoms, improve exercise tolerance and quality of life, reduce hospitalizations, and serve as a bridge to re-transplant. Based on retrospective reviews, it is generally well tolerated without significant complications, and may actually be underutilized in this population [18].

Because no literature exists with regard to how to initiate and implement NIV in this population, a strategy of high inspiratory pressures with high back-up rates similar to those utilized in COPD could be employed with the goal of improving hypercapnia and abolishing sleep-disordered breathing. Close monitoring and titration should be undertaken to improve comfort and limit patient–ventilator dyssynchrony [19].

53.3.3 Domiciliary Use: Sleep-Disordered Breathing

Very little data exists regarding the prevalence and management of sleep-disordered breathing (SDB) following lung transplantation. In a prospective study conducted by Malouf et al., post-transplant polysomnography was conducted on 25 patients, including 11 who had met SDB criteria prior to transplantation. SDB resolved in 6 of the 11 (55%) patients with prior SDB, but new SDB developed in 4 of 14 (29%) patients without prior SDB findings. The presence of SDB did not impact pre- or post-transplant survival [20]. Another single center cross sectional study of 24 patients at least 1 year post-transplant showed 15 of 24 (63%) to have SDB (defined as AHI $\geq$ 10), with 25% demonstrating predominant CSA. Patients who developed SDB were shown to have elevated systolic blood pressure, greater age, greater

change in BMI, more recent date of transplantation, diagnosis of emphysema, and observed snoring [21]. While it is unclear what effect treatment of SDB breathing has on the lung transplant recipient, is it reasonable to screen for and treat in a manner similar to the non-transplant population.

53.4 Conclusion

Though overall data regarding the use of NIV in the lung transplant population is limited, available literature and physiologic rationale suggest that it is a reasonable treatment strategy for acute and chronic respiratory failure at various times in the course of a lung transplant recipient's history, primarily as a means of liberation from or avoidance of mechanical ventilation and its associated complications. When initiating NIV in the patient with acute respiratory compromise immediately post-transplantation, the benefits of avoiding tracheostomy and prolonged mechanical ventilation should be weighed against the potential delays in rehabilitation and nutrition optimization that prolonged NIV dependence can incur. Particular caution should be taken when employing NIV beyond the immediate perioperative period in recipients with severe hypoxemia and/or a high severity of illness, similar to other populations with acute respiratory failure. NIV may also be useful as a means of providing ventilatory support in recipients with prolonged neuromuscular dysfunction, as a bridge to transplantation, and as a means of symptom alleviation in those with CLAD and sleep disordered breathing.

Funding This chapter did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Noninvasive Ventilation as a Preoxygenation

54

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Abbreviations

APRF	Acute postoperative respiratory failure
ASA	American Society of Anesthesiologists
BiPAP	Bilevel positive airway pressure
COT	Conventional oxygen therapy
EPAP	Expiratory positive airway pressure
FeO_2	Fraction of expired oxygen
FiO_2	Fraction of inspired oxygen
FRC	Functional residual capacity
HARF	Hypoxemic acute respiratory failure
HFNC	High flow nasal cannula
IPAP	Inspiratory positive airway pressure

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_54

NIV	Noninvasive ventilation
OSA	Obstructive sleep apnea
PEEP	Positive end expiratory pressure
SaO_2	Arterial oxyhemoglobin saturation
SpO_2	Pulse oxyhemoglobin saturation
V/Q	Ventilation-to-perfusion ratio

54.1 Introduction

Preoxygenation during induction of general anesthesia and tracheal intubation, or during intubation/re-intubation in hypoxemic acute respiratory failure (HARF), has become a widely accepted safety maneuver designed to counterbalance the effect of apnea with general anesthesia as well as the effect of shunts in patients with acute respiratory distress [1, 2]. The goal of preoxygenation is to increase oxygen reserve and thereby delay the onset of arterial oxyhemoglobin desaturation to achieve safe tracheal intubation conditions for initiation of mechanical ventilation. In a report of the American Society of Anesthesiologists (ASA) Task force on management of the difficult airway, "routine" preoxygenation was endorsed as a new "minimum" standard of care not only during induction of anesthesia and tracheal intubation but also during emergence from anesthesia and tracheal extubation [2].

Conventional preoxygenation techniques intended primarily for patients with healthy lungs consisted of using 100% oxygen gas source and focused on using different breathing techniques (e.g., tidal volume breathing for 3 min, four deep breaths technique, and eight deep breaths in 60 s technique) to wash out the nitrogen gas from the lungs (i.e., denitrogenate the lungs) and to replace it in the functional residual capacity (FRC) with the inhaled oxygen gas [1, 2]. As such, oxygen reserve in the lungs is significantly increased resulting in an initial rapid increase of arterial oxyhemoglobin saturation (SaO_2) between 98% and 99% and a further subsequent slower increase to 100%. However, in a subset of patients such as obese patients, pregnant women as well as in patients with hypoxemic respiratory distress/failure, the conventional preoxygenation techniques of just increasing the fraction of inspired oxygen (FiO_2) to 100% and using different breathing techniques might not achieve adequate preoxygenation and may fail to prevent oxyhemoglobin desaturation during airway instrumentation. The reason for such conflicting responses is mainly due to the pathophysiology for risk of hypoxemia in those patients that include inadequate alveolar oxygenation, severe ventilation to perfusion (V/Q) mismatch, shunt, low venous blood saturation and low cardiac output, and diffusion abnormalities [3]. In such situations, it is essential to restore/augment the lung functional residual capacity, decrease V/Q mismatch, and improve cardiac output by using noninvasive positive pressure ventilation (NIV) in addition to high fractions of FiO_2 to achieve adequate preoxygenation and prevent desaturation during airway instrumentation [3].

54.2 Devices Used for Preoxygenation

Devices used for preoxygenation, whether conventional or non-conventional oxygen delivery systems, are major contributing factors to the success or failure of preoxygenation. Oxygen sources without positive pressure, also referred to as "unsupported ventilation" devices are considered the most conventional and traditional devices (Table 54.1). As some patients with moderate to severe V/Q mismatches and/or diffusion abnormalities do not benefit from the conventional preoxygenation devices and require the use of positive pressure during preoxygenation, several non-conventional devices that provide noninvasive positive pressures will be needed to achieve optimal preoxygenation in such patients (Table 54.1).

NIV preoxygenation is usually provided using a standard pressure cycled positive pressure ventilator (whether a stand-alone ICU or an anesthesia-machine incorporated ventilator) or a specialized BiPAP machine [3]. The therapy can be delivered to the patient using either a full-face mask or a nasal mask. In addition to the clinical benefits, reported adverse effects related to NIV preoxygenation have been relatively mild and most commonly include excessive leaks from around the patient's interface (Table 54.2). Additional concerns of NIV preoxygenation, particularly with full face masks, are the risk of gastric insufflation, distention, and aspiration [3]. Gastric distention has been noted previously with the application of NIV; however, to date no reports document the occurrence of aspiration. In the event of excessive gastric dilation, it may be necessary to decompress the stomach with a naso/orogastric tube.

High flow nasal cannula (HFNC) oxygen therapy is considered as another form of NIV. In addition to stable and high FiO_2 concentrations, HFNC provides a certain level of tonic increase in the airway pressure that functions as positive end expiratory pressure (PEEP) [3].

Table 54.1 Oxygen delivery devices for preoxygenation

Unsupported ventilation	Pressure supported ventilation (e.g., NIV)
1. Non-rebreather mask (NRM)	1. Continuous positive airway pressure (CPAP)
2. Bag-Valve-Mask (BVM)	2. Bilevel Positive Airway Pressure (BiPAP)
	3. High Flow Nasal Cannula (HFNC)

Table 54.2 Benefits and risks of NIV during preoxygenation

Benefits	
1.	Reversal of atelectasis
2.	Increase in functional residual capacity
3.	Provision of stable and high fractions of inspired oxygen
4.	Improvement in alveolar ventilation
Risks	
1.	Gastric insufflation
2.	Air leak around the patient's interface (mask)
3.	Increased risk of aspiration

54.3 NIV and Preoxygenation During General Anesthesia

Before the induction of anesthesia, preoxygenation with 100% inhaled oxygen is recommended to increase the oxygen reserve stored in the FRC and delay the onset of hypoxemia in case of unanticipated difficult airway management. The most conventional and widely used method is spontaneous breathing of 100% oxygen until the expired fraction of oxygen (FeO_2) reaches ≥90%. Compared with spontaneous breathing, preoxygenation with NIV can significantly decrease the time to attain $FeO_2 \geq 90\%$ by almost a minute [4]. Furthermore, at 3 min from initiation of preoxygenation, 47% and 74% of patients can achieve an FeO_2 of 90% or more in the spontaneous breathing and NIV patients, respectively [4].

Oxygen administration via NIV is safe, feasible, and efficient in morbidly obese patients in the operating room and provides a faster preoxygenation than normal spontaneous breathing techniques using a high fraction of inspired oxygen [5–8]. In obese patients, significant improvements in preoxygenation are achieved by the addition of NIV pressures as low as 4 cmH_2O during expiration with an additional 4 cmH_2O during inspiration (i.e., EPAP = 4 cmH_2O and IPAP = 8 cmH_2O) in obese patients undergoing elective surgery [5]. A higher percentage of obese patients can reach an $FeO_2 \geq 90\%$ endpoint with NIV (80%) than with the traditional tidal volume breathing method (60%) [5].

Preoxygenation with high flow nasal cannula (HFNC) in obese patients scheduled for elective surgery provided lower FeO_2 after intubation and a higher rate of desaturation <95% compared to preoxygenation with NIV [6]. In obese patients undergoing elective surgery, preoxygenation with HFNC can result in $FeO_2 \geq 76\%$ while preoxygenation with NIV can achieve $FeO_2 \geq 88\%$ [6]. Furthermore, mild desaturation below 95% can be more frequent with HFNC (30%) than with NIV (12%) with no differences in median lowest SpO_2 during intubation (98% with HFNC vs. 99% with NIV). However, patients may report more discomfort with NIV (28%) compared to HFNC (4%) despite that severe and moderate complications are not different between HFNC and NIV [6]. For emergency tracheal intubation in morbidly obese patients, maximal preoxygenation is essential to counteract the compromised oxygen supply-demand relationship due to decreased FRC, and increased intrapulmonary shunting, associated with increased total body oxygen consumption (VO_2). The immediate use of NIV for preoxygenation in such obese patients can result in a significant decrease in partial pressure of arterial carbon dioxide as well as in a significant increase in oxyhemoglobin saturation in morbidly obese patients scheduled for emergency surgery [7].

The lack of a tight fit between the mask and the patient's face resulting in leaks has been implicated in failure to achieve the desired FeO_2 of 90% or greater during the induction of anesthesia. NIV in the form of bilevel positive airway pressure (BiPAP) counteracts air leaks during induction of anesthesia, fully restoring the effectiveness of preoxygenation [8].

54.4 NIV and Preoxygenation in Acute Post-Operative Respiratory Failure

Acute postoperative respiratory failure (APRF) may be attributed to the residual effect of anesthetics or neuromuscular blockade. Anesthesiologists are vigilant in preventing APRF by the continuous intraoperative management and control of inhaled anesthetics and the use of reversal drugs to counteract the effect of neuromuscular blockers. However, other reasons for APRF that can go unnoticed include atelectasis, pneumonia, and pulmonary edema. In such conditions, poor oxygenation and respiratory failure will ensue postoperatively after extubation and resuming spontaneous breathing activities. Using the conventional techniques of oxygen masks will lead to inadequate preoxygenation and fail to prevent oxygen desaturation and alleviate the signs and symptoms of respiratory distress. No matter how high the FiO_2 is, patients will not achieve an improved oxygenation and the only way to improve oxygenation is to reverse the physiologic shunt resulting from atelectasis, pneumonia, and pulmonary edema by using efficient and adequate positive end expiratory pressure (PEEP) [3].

BiPAP is being used more frequently for APRF as it provides several advantages over traditional invasive mechanical ventilation. BiPAP is a form of NIV support that minimizes the risks of ventilator induced lung injuries, reduces the need for excessive sedation, and preserves the upper airways reflexes and functions for better protection against aspiration and for better humidification of inspired gas. Two separately adjusted pressure levels, EPAP and IPAP, allow the clinician to independently maintain upper airways patency and prevent airway/alveolar collapse/de-recruitment during exhalation, thereby preventing atelectasis and increasing the FRC that is the main oxygen store as well as augmenting tidal volume and alveolar ventilation and subsequently alveolar oxygenation [3]. BiPAP as a preoxygenation method has been shown to be more effective at reducing arterial oxyhemoglobin desaturation than conventional preoxygenation techniques during intubation in hypoxemic patients [9]. Furthermore, the levels of oxygenation achieved with BiPAP are usually sustained for longer duration after intubation than conventional preoxygenation techniques with a non-rebreather bag-valve mask [9].

Following anesthesia, patients with obstructive sleep apnea (OSA) should be extubated in a semi-recumbent position after becoming fully awake with confirmation of airway patency and after verification of complete reversal of neuromuscular blockade. Otherwise, there will be a high risk of post-extubation airway obstruction and severe post-operative oxyhemoglobin desaturation. NIV should be applied as soon as possible after surgery in obstructive sleep apnea patients who exhibit mild to severe postoperative oxygen desaturation. The immediate use of NIV after tracheal extubation can prevent oxygen desaturation and eliminate the need for re-intubation [10].

54.5 NIV and Preoxygenation During Hypoxemic Acute Respiratory Failure

Severe hypoxemia that can occur during endotracheal intubation in patients with hypoxemic acute respiratory failure can result in cardiac arrest, cerebral anoxia and death. Several preoxygenation techniques have been developed to prevent and minimize the incidence of severe hypoxemia during and following the intubation procedure. NIV in the form of BiPAP for preoxygenating patients with severe HARF is associated with less hypoxemia degree and incidence than preoxygenation with oxygen facial masks during intubation procedures as NIV can limit alveolar collapse, reverse atelectasis, and improve alveolar ventilation [9]. Adding HFNC oxygen therapy to NIV for apneic oxygenation prior to orotracheal intubation, may be more effective in reducing the severity of oxygen desaturation than using NIV alone. NIV facial masks need to be taken off after preoxygenation to allow endotracheal tube passage through the mouth. Furthermore, appropriate head positioning and successful endotracheal intubation may take from a few seconds to several minutes in the case of difficult airways. During this period, the hypoxemic patient does not receive oxygen, which contributes to the risk of severe hypoxemia during the intubation procedure. Adding HFNC to NIV preoxygenation will maintain a sufficient supply of 100% oxygen even after removal of the facial mask as the interface for HFNC is a nasal cannula that does not interfere with the oral intubation procedure [11].

In a multicenter, randomized, open-label trial of patients with acute hypoxemic respiratory failure defined as a PaO_2/FiO_2 ratio of ≤300, Frat et al. reported that preoxygenation with NIV compared with high-flow oxygen therapy did not change the risk of severe hypoxemia during intubation or the occurrence of late complications [12]. However, their secondary analyses suggested a possible benefit of NIV over high flow oxygen therapy among patients with moderate-to-severe hypoxemia ($PaO_2/FO_2 \leq 200$) [12]. In a randomized controlled study, Baillard et al. assessed the effect of preoxygenation using NIV before intubation on subsequent organ failures in patients with HARF [13]. They demonstrated no benefits of using NIV as a preoxygenation method to reduce organ dysfunction within 7 days following intubation compared with the usual preoxygenation techniques in hypoxemic, critically ill patients requiring tracheal intubation for invasive ventilation in the ICU. However, their results emphasized that NIV should not be discontinued for preoxygenation in the cases of patients treated by NIV before the decision to intubate, as there was a significant increase in adverse events when face mask preoxygenation was used in patients previously receiving NIV [13].

In the emergency department, NIV can be useful for optimizing preoxygenation in patients who require rapid sequence induction and endotracheal intubation [14]. While 100% oxygen with a non-rebreathing mask increased SpO_2 only from 88% to 90%, converting to NIV increased SpO_2 from 90% to 98–100% at the time of starting endotracheal intubation and maintained SpO_2 between 95–100% until successful intubation [14].

HFNC oxygen therapy is another form of noninvasive ventilatory support. HFNC provides stable and high FiO_2 concentrations along with some level of PEEP via a nasal cannula and subsequently can improve the safety and success rate during manipulation of the airway (e.g., bronchoscopy, tracheal intubation) in both low- and high-risk critically ill patients [15]. Delivering oxygen via HFNC through the nares has several advantages that can prevent or minimize the risks and complications associated with tracheal intubation. HFNC can be left in place during positioning of patient's head and inserting the endotracheal tube, theoretically maintaining some level of PEEP throughout the intubation process, and thereby prolonging the non-hypoxemic apnea time. When compared to bag-valve-mask for preoxygenation before tracheal intubation of ICU patients with mild to moderate hypoxemic respiratory failure, HFNC was feasible and safe and did not result in significant decreases in SpO_2 during the apnea phase before intubation [16]. HFNC significantly improved pre-oxygenation and maintained SpO_2 at 100% during intubation of ICU patients compared to non-rebreather mask (SpO_2 = 94%) [17]. Data from a recent meta-analysis, including 959 patients with acute hypoxemic respiratory failure, confirmed that patients preoxygenated with HFNC had significantly less desaturation episodes than patients preoxygenated with conventional oxygen therapy (COT). Furthermore, HFNC resulted in lower risk of intubation-related complications than COT [18].

54.6 Conclusion

Hypoxemic patients treated with NIV for preoxygenation prior to endotracheal intubation desaturate less than those patients treated with conventional oxygen therapy. The risk of intubation-related complications (aspiration or new infiltrate on post-intubation chest radiograph, hemodynamic instability, and cardiac arrest) are lower with NIV than conventional preoxygenation methods. Among the methods of pre-oxygenation examined, it seems that the combined use of HFNC and NIV is the most effective in minimizing the drop in SpO_2 and maintaining safe conditions for airway intubation.

Key Major Recommendations

- Pre-oxygenation with NIV is safe, feasible, and efficient in the pre- and post-operative period.
- Pre-oxygenation with NIV should be considered over traditional pre-oxygenation techniques whenever atelectasis and/or pulmonary edema are expected and causing oxyhemoglobin desaturation and acute respiratory failure.
- Intensivists and anesthesiologists should be well versed in the initiation and management of all forms of NIV support.

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Noninvasive Ventilation During Bronchoscopy

55

Marta Carvalho Silva

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55.1 Purpose of Review

Noninvasive ventilation (NIV) is the application of ventilatory support without an endotracheal tube (ET) or tracheostomy, so there is no conduit access to the central airways [1]. It is a cornerstone for the treatment of acute and chronic hypoxemic or hypercapnic respiratory failure (RF) of different etiologies and various clinical situations [1, 2]. The absence of an ET decreases the incidence of frequent and serious complications such as ventilation-associated pneumonia [1].

Acute hypoxemic RF commonly affects patients with airway or parenchymal disorders such as pneumonia, interstitial lung diseases and lung cancer that may need to undergo diagnostic or therapeutic procedures such as bronchoscopy (BC) [3]. However, these procedures have risks and are relatively contraindicated in severe hypoxemic patients because they can cause physiological changes in

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_55

respiratory mechanics that can lead to additional hypoxemia, hypotension, arrhythmias, bleeding and blood gas exchanges, aggravating RF [3–5].

A 5.7 mm fiber optic bronchoscope (FOB) occupies approximately 10% of the tracheal cross section in nonintubated patients compared with 40% of a 9.0 mm internal diameter ET and 66% of a 7.0 mm ET [3, 4]. These alterations in central airways decrease lung compliance, increase airway resistance and work of breathing causing significant changes in ventilation such as a decrease in lung volumes, loss of functional gas exchange surface during bronchoalveolar lavage (BAL), bronchospasm and collapse of the upper airways [3, 6, 7]. These mechanisms causes blood gas changes especially during suctioning, such as hypoxemia, with a decrease of up to 10–20 mmHg in PaO_2, hypercapnia with an increase in $PaCO_2$ up to 30% and loss of 200–300 mL of tidal volume during each period, and the normalization of those gas exchanges require from 15 min in normal lungs to several hours in patients with an underlying parenchymal disease [3, 4]. Based on this knowledge, several oxygenation strategies have been used to prevent or correct hypoxemia and RF during BC [3]. Besides the respiratory effects, BC can also cause significant hemodynamic changes such as an increase in intra-thoracic pressure that can affect venous return and afterload, reducing cardiac output and precipitating arrhythmias [3]. These cardiopulmonary risks led to the definition of guidelines that do not recommend BAL in spontaneous breathing patients with hypercapnia and/or hypoxemia with less than 75 mmHg in PaO_2 or $SpO_2 < 90\%$ with supplemental oxygen [8], and before considering the technique all contraindications for both NIV and BC must be considered and evaluated [4].

On the other hand, NIV benefits such as the capacity to decrease the work of breathing, to improve lung mechanics, recruit closed alveoli, improve blood gases and avoid ET and mechanical ventilation in several causes of RF are well known [4]. An oronasal mask is the preferred interface for NIV in acute RF and continuous monitorization with pulse oximetry, heart rate, and transcutaneous CO_2 during the procedure and recovery are recommended [1].

Based on these principles, NIV started to be used as a tool to prevent or treat acute RF or hypoventilation in a wide range of settings outside the intensive care unit (ICU), namely during BC, [9] because patients with acute RF frequently have several comorbidities that increase the risk for BC complications [2].

55.2 Recent Findings

NIV applied during BC was first described in 1996 by Antonelli et al. [10] in a group of immunosuppressed patients with suspected pneumonia and severe hypoxemia. They used NIV 10 min before and 90 min after BC with good tolerance, improvements in gas exchange and eviction of ET [10]. Later studies in immunocompetent patients with hypoxemic acute RF also reported favorable results such as an optimal gas exchange without hemodynamic impairments and low incidence of minor complications using face masks [11].

In recent years, new evidence has become available addressing the use of NIV during BC as well as in more complicated procedures such as transbronchial lung

biopsy, balloon dilatation, electrocautery and argon plasma coagulation with stable oxygenation, good tolerance and minor complications [12]. In non-intubated patients with acute RF, an improvement in oxygenation and a decrease in complication rates during the procedure was found [1, 3, 4], with the advantage of reducing the need for deep sedation or general anesthesia preventing respiratory depression related to the procedure [7]. However, this technique should be done in a setting where intubation and ventilatory support are readily accessible [6].

55.3 Summary

Besides all the benefits announced before about the use of NIV during BC and other complementary techniques in patients with acute RF, there are few studies published and most are observational.

55.4 Main Summary Results

Cabrini et al. [9] performed a systematic review that included 20 papers on the application of NIV during FOB, with the following results:

- All patients successfully completed the procedures;
- There were no relevant intraprocedural complications;
- Only one patient was intubated within the first 6h due to post-procedural acute RF;
- NIV allowed a significantly better arterial oxygenation and a trend toward a lower incidence of post procedural delayed RF requiring intubation;
- High success rates even in patients at high risk of intra-procedural respiratory hypoxemic failure or sedated;
- NIV was mainly used to avoid severe hypoxemia in patients undergoing FOB plus BAL in different scenarios, namely ICU, operating theater and ambulatory, and this was true even when BAL was performed in patients already on NIV due to hypoxemic RF.

Ekren et al. [2] performed a prospective observational study to evaluate the feasibility, safety, and diagnostic efficacy of FOB in patients with ARDS treated with NIV.

They included 28 patients under NIV who require FOB as a diagnostic or therapeutic procedure; used ICU ventilators or other dedicated NIV ventilators; NIV was applied via oronasal or full-face mask; IPAP, PEEP or EPAP levels were titrated to achieve an expiratory tidal volume of 8–10 mL/kg according to ideal body weight, $SpO_2 > 90\%$ and respiratory rate below 25/min. Results:

- The procedure was well tolerated; only 17.9% of patients showed minor complications within 12h after FOB: fever ($n = 2$); hypoxemia ($n = 1$); hypotension ($n = 2$);
- There was no impairment in arterial blood gas/cardiopulmonary parameters after FOB;

– No patient was intubated within 2h after FOB;
– 10.7%, 32.1%, and 39.3% of the patients required invasive mechanical ventilation after 8, 24, and 48h, respectively;
– FOB provided a diagnosis in 96.4% of cases; appropriate treatment was decided according to the results of the bronchoscopic sampling in 71.4% of the patients.

Conclusions: FOB under NIV could be considered as a feasible tool for diagnosis and a guide for treatment of patients with ARDS under NIV.

Sircar et al. [4] performed a study during a 6 years period in an ICU:

They included 27 patients undergoing 28 bedside FOB on NIV(BIPAP) in ICU. Indications for FOB were therapeutic (atelectasis) (*n*=10); diagnostic (*n*=17); 17 patients were under previous NIV (16 on BIPAP; 1 CPAP), and 12 underwent NIV 1 h before FOB; the patient under previous CPAP was put under BIPAP during FB.

Procedure: NIV was delivered through a tight fitting face mask kept in place using adjustable straps and was attached to a catheter mount with a built-in BC port; an oxygen enrichment connector with a built-in expiratory port, single limb NIV circuit and BIPAP-ST30 machine was used; oxygen flow was adjusted to keep $SpO_2 > 90\%$ during the procedure; IPAP between 12–20 cmH_2O; EPAP 4–8 cmH_2O; backup respiratory rate 12/min; arterial blood gas (ABG) was obtained before and 1h after the procedure; all patients received topical anesthesia; sedation was performed in 15 FOB (14 propofol; 1 midazolam); all patients had bedside ECG, pulse oximetry, and blood pressure monitoring during the procedure; FOB was done through nasal passage in 23 patients and oral in 5; FOB had a 6.0 mm outer diameter with a 2.8 mm instrument channel; procedures were performed by experienced pulmonologists and intensivists; chest X-ray was done in all patients 2h after FOB.

Results:

– All 27 patients successfully underwent 28 FOB with NIV;
– Complications: pneumothorax (n = 1); bleeding (n = 4); need for mechanical ventilation (n = 2);
– Procedures performed: collapsed lung/lobes successfully open in all patients; BAL (n = 24); bronchial biopsies (n = 3); brush cytology (n = 4); transbronchial biopsies (n = 7);
– No patient needed ET during the procedure; no hemodynamic instability; sedation was well tolerated;
– There was a significant improvement in oxygenation in post FOB ABG;
– All patients with pre-FOB NIV (n = 17) remained on BIPAP afterward without requiring ET;
– In patients who started NIV for the procedure (n = 11):

  • NIV was discontinued 1–2h after FOB (*n*=8);
  • One patient developed acute RF 6h after transbronchial biopsy as a consequence of pneumothorax, requiring tube drainage and invasive mechanical ventilation, but he was extubated 2 days after;
  • In one patient with diffuse lung disease on NIV for FOBNIV could not be discontinued after the procedure and he needed mechanical ventilation 6h later for acute RF, but could be extubated later;

- One patient with bilateral traumatic lung contusion submitted do BAL needed ET and mechanical ventilation within 24 h of BOF, but was extubated after.

Che et al. [12], in a retrospective study evaluated the efficacy and security of therapeutic FOB assisted with NIV in hypoxemic patients with central airway obstruction under sedation ($n = 15$), comparing with patients through artificial airway (ET) or laryngeal mask under general anesthesia ($n = 14$).

Procedure in the NIV group: patients with contraindications for NIV were excluded (low consciousness level, facial or esophageal surgery and inability to tolerate the face mask); patients initiated NIV at the bronchoscopy center; dezocine (2.5–5 mg) was given intravenously 10 min before the exams and midazolam (1–3 mg IV) immediately prior to FOB; 2% lidocaine was used as topical anesthesia and a swab with 1% ephedrine and 2% lidocaine was retained in one nostril 5 min before FOB insertion; NIV mode was delivered via a full-face mask; PEEP was set at 5 cmH_2O, pressure support at 10 cmH_2O, and FiO_2 at 30%; parameters were adjusted during the procedures to maintain $SpO_2 > 90\%$ and tidal volume > 8 mL/kg; a T adapter was attached to the face mask for the insertion of FOB via nasal route and if the initial insertion failed, a mouthpiece was placed for oral insertion; pulse oximetry, heart rhythm, and blood pressure were continuously monitored during the procedure;

Results:

– Patient's characteristics were comparable between groups (age, gender, diseases, including hypertension, coronary heart disease, and COPD); there were no significant differences between groups in lesion's characteristics including malignant rate and site of obstruction;
– The success rate, procedure time, and oxygenation improvements had no significant differences between groups;
– The lowest SpO_2 during the procedure and improvements in PaO_2 were similar in both groups;
– A less reduction of the systolic blood pressure and heart rate during the procedure was seen in the NIV group;
– The NIV group showed shorter admission time before the procedure than the control group;
– Procedure fees in the NIV group were significantly lower than in the control group.

Conclusions: FOB assisted with NIV was safe, efficient and an economic method for therapy in selected hypoxemic patients with central airway obstruction.

Skoczunski et al. [13] performed a retrospective analysis of NIV-FOB performed in 20 consecutive months to evaluate the risk factors for NIV-FOB complications.

NIV-FOB were performed in 50 patients with multiple comorbidities, acute or chronic RF, substantial tracheal narrowing or after a unsuccessful FOB attempt; patients were ventilated using Astral 150 with dedicated full-face masks with a bronchoscopic elbow; patients were on NIV 5–15 min before FOB and finished NIV immediately after or several minutes after becoming stable; most patients who

were previously on NIV required prolonged NIV; most FOB were performed in the bronchoscopy theater and a few procedures took place in the ICU.

Results:

- Major indications for NIV-FOB were RF or a previous unsuccessful attempt to perform FOB, most of them related to severe hypoxemia;
- Five cases were reported as having complications or death;
- Complications: hypotension (n = 1); bradycardia (n = 1); pulmonary edema (n = 1);
- Two patients were transferred to the ICU where they passed away due to ventilator-acquired pneumonia and irreversible RF more than 48h following the procedure;
- In a single variable analysis statistical relevant factors found as predictive of NIV-BC complications or hospital death were:
  - Hypoxemia before and after NIV-FOB, as a predictor of complications/hospital death;
  - Increased leukocytosis was predictive in terms of foreseen complications;
  - Left heart disease indicated unfavorable NIV-FB outcome;
- No other factors were found predictive of complications such as anthropometric characteristics; urgent FOB; blood gases; pulmonary function tests.

Conclusions: The procedure was safe and beneficial for borderline high-risk patients.

Patolia et al. [5] recommended the following parameters during BC to achieve an optimal ventilation and oxygenation:

- Ventilatory mode set to pressure support;
- IPAP range from 10–25 cmH_2O and PEEP from 5–10 cmH_2O;
- Simple full-face masks with a swivel connector secured to patients' face with elastic straps;
- BC size from 4 to 6.4 mm external diameter;
- Both nasal and oral routes are equally safe;
- 2% lidocaine solution for topical anesthesia and short-term sedation according to respiratory and hemodynamic status;
- Patients should be supplied with 100% FiO_2 during BC;
- Several procedures can be performed: BAL, brushing, biopsies, therapeutic aspiration;
- Following BC, NIV should be continued in all patients for at least 2h to minimize the risk of intubation;

End Practical-Key Messages

- Bronchoscopy is an essential diagnostic and therapeutic technique in respiratory medicine;
- NIV during BC in hypoxemic patients is safe, well tolerated, and effective in preventing or treat acute RF;

– NIV during BC ensured stable oxygenation even with extended procedures, allowed compensation of the extra-work load and was able to avoid invasive ventilation;
– NIV during BC helped in diagnostic and therapeutic procedures in hypoxemic patients, including relief of atelectasis, performing BAL, bronchial biopsies and brushing safely, with low rates of intubation needed;
– Several interfaces can be used for FOB on NIV support including oronasal, full-face, nasal mask and helmet, allowing both oral and nasal route with an interchangeable connector between the ventilator tubing and the mask, but there are no studies comparing different types of masks.

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Noninvasive Ventilation in Preoperative Use

56

Carmen Pascale and Maria Vargas

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56.1 Introduction

Noninvasive mechanical ventilation (NIV) is a ventilation method that allows the patient to be provided with partial or total ventilatory support without resorting to endotracheal intubation or tracheotomy, by using various devices defined as interfaces. The main purpose of NIV is to avoid endotracheal intubation and the consequent complications: nosocomial pneumonia, sinusitis, otitis and lesions of the tracheal mucosa (inflammation, submucosal hemorrhagic edema, and ulcerations). Furthermore, the use of NIV has the following objectives: (1) to reduce the work of breathing, (2) to recruit alveoli with better gas exchange (oxygenation and ventilation), and (3) to improve hemodynamics by reducing left ventricular afterload. The main recommendations for the use of NIV are represented by hypercapnic

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_56

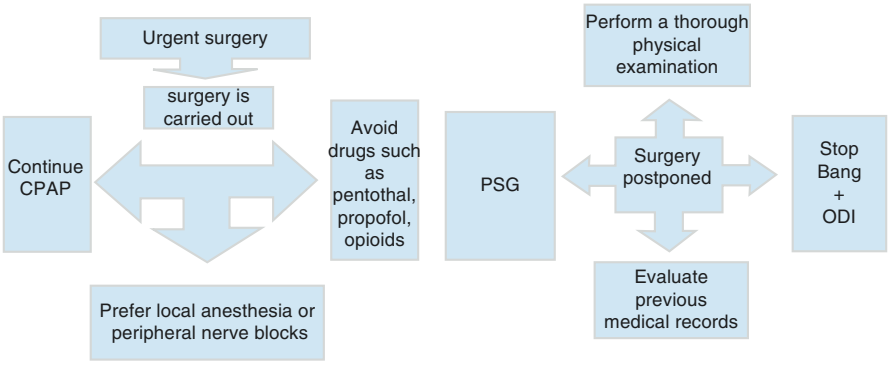
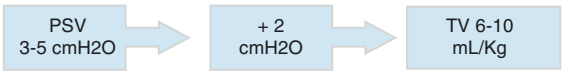


Fig. 56.1 Respiratory assistance during surgery

Fig. 56.2 Settings for mechanical ventilation



hypoxemic states such as COPD exacerbations and cardiogenic pulmonary edema [1, 2]. However, the proposed use of NIV in the preoperative period is to prevent complications related to endotracheal intubation and the use of anesthesia drugs. Anesthesia, pain and surgery, particularly when it comes to procedures involving areas close to the diaphragm, induce changes in the respiratory mechanics of patients with an increased risk of postoperative pulmonary complications. These complications correlate both with factors relating to the type of surgery (A), and with factors relating to the characteristics of the patient (B), and to the anesthesia itself. General anesthesia reduces oropharyngeal tone and airway reflexes. The use of anesthetic agents and opioids reduces respiratory rate, with reduced VT and MV. This causes an increase in CO_2 in the blood and a reduction in functional residual capacity (FRC). During general anesthesia, small airways are closed, resulting in atelectasis and an increase in physiological dead space. These changes in respiratory mechanics under general anesthesia, together with invasive mechanical ventilation, are among the main causes of postoperative lung injury. Summary in Figs. 56.1 and 56.2 [3–5].

56.2 Discussion

After a surgery in which endotracheal intubation is required or after a period of invasive mechanical ventilation, the main pulmonary complications are related to ventilation mechanics itself and any post-surgery reintubations. NIV, therefore, plays a vital role in the prevention of these complications. Patients most at risk of postoperative complications are patients undergoing major abdominal surgery,

traumatized and ICU patients, and bariatric patients with OSAS. Therefore, the use of NIV should be part of a preoperative protocol. This protocol begins with a preoperative anesthetic visit that looks for all the factors listed above that could lead to the onset of pulmonary complications following surgery; continues in the preoxygenation phases during the induction of anesthesia, together with adequate postoperative pain relief therapy and post-operative nausea and vomiting prophylaxis. It then continues with physiotherapy and breathing exercises in the convalescence phase. Approximately 50% of patients undergoing major abdominal surgery will experience respiratory complications, especially in the case of patients with undiagnosed OSAS; 8–10% of these will have need for tracheal intubation. Hypoxemia may occur during the induction of anesthesia, hypercapnia, arrhythmia, myocardial ischemia and delirium, up to unplanned admission to intensive care. Such occurrences can be even more likely and serious if you are dealing with a bariatric patient with OSAS. Unfortunately, 20% of the adult population suffers from OSAS, and in 70% of cases, it remains undiagnosed before surgery. These are blockages of breathing that last for about 10 s during the inspiratory effort due to the collapse of the upper airways. This, in turn, causes micro-awakenings during sleep that are aimed at restoring a patent airway. All this can cause daytime sleepiness, but above all episodes of desaturation with hypercapnia and harmful effects on the cardiovascular system. Anesthesiologists should work with surgeons to develop a protocol whereby patients in whom the possibility of obstructive sleep apnea (OSA) is suspected based on clinical data are observed and evaluated for a sufficiently long time before proceeding with the intervention surgical. In fact, these patients in addition to a high risk of ventilation and difficult intubation, can undergo a series of post-operative complications linked to other pathologies that often coexist. Typically, these are arterial hypertension, systolic or diastolic myocardial dysfunction, insulin resistance, pulmonary hypertension, stroke, coronary artery disease, and cardiac arrhythmias. The preoperative evaluation of a patient should aim to improve or optimize the perioperative physical state. A complete review of previous medical records should be performed, if available, a thorough interview with the patient and/or their family, a thorough physical examination. Particular attention should be paid to the history of previous airway management difficulties during anesthesia, hypertension or other cardiovascular problems, other congenital or acquired medical conditions. In particular, recently the ASA has also recommended a careful evaluation of patients at risk of OSA (STOP-BANG scoring system) and, furthermore, suggests that the severity of the patient's OSA, the invasiveness of the diagnostic or therapeutic procedure and the need for postoperative analgesics should be considered in determining whether a patient is at high perioperative risk due to OSA. Other studies say they take into account the preoperative ODI (oxygen desaturation index): average number of oxygen desaturations per hour. Patients with ODI greater than or equal to five have an increased risk of postoperative complications, including respiratory, cardiovascular, gastrointestinal and hemorrhagic complications. Based on these assessments, you can choose to postpone the procedure or to proceed if the procedure is truly urgent (diagram 1). If surgery can be postponed, then a PSG should be done to determine any new preoperative treatments and choose an appropriate anesthetic

plan. If, on the other hand, the surgery cannot be postponed, it should be explained to both the patient and their family what risks they might run due to their underlying condition. The ASA recommends the preoperative use of CPAP in patients with severe OSA). Patients diagnosed with OSA during preoperative investigations should be advised to use CPAP prior to surgery, including to familiarize themselves with its use after the surgical procedure. If, on the other hand, the patient was already using home CPAP, they should be asked to bring the CPAP and mask for admission. The anesthetist and surgeon will then assess the adequacy of the aids in the patient's possession. The ASA also states that the potential for postoperative respiratory compromise should be considered in the selection of intraoperative drugs and in the choice of the type of anesthesia the patient should undergo. For superficial procedures, it is always advisable to consider the use of local anesthesia or peripheral nerve blocks, with or without moderate sedation and, if patients are already on CPAP, to continue it during sedation in the operating room. If, on the other hand, it is necessary to proceed with general anesthesia, it must be taken into account that this can lead to worsening of the already present anatomical alterations of the upper airways of patients with OSA, causing the pharyngeal collapse already present during the patient's physiological sleep. Anesthetics also reduce physiological arousals from sleep, which is an important defense mechanism useful for overcoming airway obstruction. Drugs such as pentotal, propof, opioids, benzodiazepines, and inhaled halogenated agents reduce pharyngeal muscle tone and/or depress ventilation and decrease the ventilatory response to carbon dioxide. Summary in Fig. 56.3.

To date, there is no clear guide on the pressure settings to be used with NIV in the perioperative period, nor on the overall optimal duration of NIV therapy for individual conditions. It is imperative that both the patient and the family are adequately informed about the purpose of NIV, in the hope that it will have a higher success rate. It is possible to perform an intermittent or continuous NIV. Certainly the intermittent mode is better tolerated by patients. In fact, it allows for breaks to communicate and eat. If you choose to use the intermittent mode, however, it is imperative to establish a clear strategy that outlines the periods of NIV, the rest intervals, and the total daily duration of the NIV. There are two most commonly

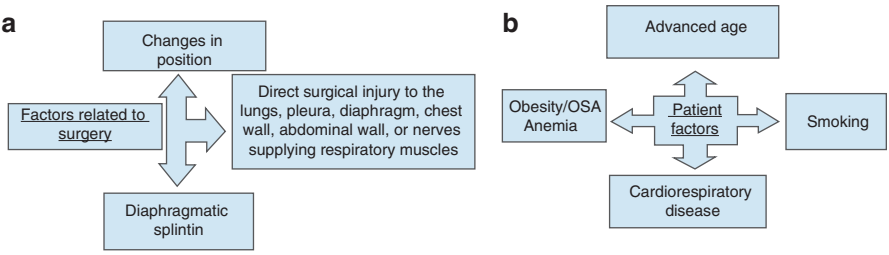


Fig. 56.3 Respiratory and ventilstory response to different stimuli

used modalities of NIV: CPAP and PSV. They have the objectives of improving dyspnea, reducing respiratory rate and $PaCO_2$ values, and optimizing PaO_2 values. CPAP prevents collapse and atelectasis of the airways and alveolar, reduces left ventricular afterload with increased cardiac output, and maintains residual functional capacity. It provides a constant positive pressure during inspiration and exhalation, also managing to balance an inspiratory threshold load imposed by intrinsic PEEP in some patients (for example COPD), thus reducing the work of breathing. In PSV, the patient controls both the respiratory rate and the inspiratory–expiratory times. The patient's spontaneous inspiratory effort triggers the ventilator to deliver a variable flow of gas that increases until the airway pressure reaches a selected level. Once the selected pressure is reached, the patient continues to breathe until their inspiratory flow falls below a threshold level (typically 25% of peak flow). To increase the patient's acceptance of NIV therapy, it is possible to set the ventilation first only with a value of PEEP and then gradually increase the PS (scheme 2). PEEP can be gradually increased up to 10 cmH_2O. The applied insufflation pressure (PSV + PEEP) must be less than 25 cmH_2O.

56.3 Conclusions

In clinical practice, NIV is still used almost exclusively in cases of acute respiratory failure or following surgery. Good results were also obtained in patients with contusive thoracic trauma who undergo acute respiratory failure. In these patients, NIV improves oxygenation, prevents orotracheal intubation, and reduces mortality. However, it is now clear that preoperative NIV has positive effects on the symptoms of patients with OSA and in preventing postoperative pulmonary complications. Proper use of NIV as a therapy before and immediately after surgery appears to have the best potential for reducing postoperative complications. Observational studies have shown a lower frequency of severe postoperative complications (ICU transfer, urgent respiratory support, death) when preoperative CPAP, already started at home, is compared with no preoperative CPAP. However, the reason for the effectiveness of preoperative CPAP is still not fully understood. CPAP appears to cause a decrease in inflammation and edema of the upper airways, a reduction in the size of the tongue, as well as an increase in the volume and stability of the upper airways. These positive effects of a preoperative CPAP are enhanced by pre-oxygenation with 100% O_2, positioning the patient's head tilted 25% upwards. The latter are now common practices in bariatric surgery operating theaters. Overall, therefore, the number of postoperative pulmonary complications is reduced by the correct use of CPAP, which also reduces hospitalization times. The efficacy on cardiovascular events, however, remains to be clarified. The literature, on the other hand, is still too scarce to evaluate the effect of using NIPPV in the preoperative period or to evaluate the effectiveness of weight loss.

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Intraoperative Noninvasive Ventilation

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57.1 Introduction

Over the past two decades, the use of noninvasive ventilation (NIV) has dramatically increased, and it has been proven to be effective in treating both acute and chronic respiratory failure by numerous studies. NIV is considered as a lifesaving

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_57

application in acute care settings such as acute exacerbation of chronic obstructive pulmonary disease (COPD) [1], severe asthma [2], acute cardiogenic pulmonary oedema [3], acute respiratory distress syndrome, community-acquired pneumonia and acute respiratory failure in immunocompromised patients [4]. NIV has also become an integral tool in different chronic care settings which includes restrictive thoracic disorders (chest wall deformities and neuromuscular conditions [5]), chronic stable COPD, cystic fibrosis and disorders associated with nocturnal hypoventilation. NIV has been extensively used in facilitating weaning from invasive ventilation. Recently, NIV has been used as an alternative therapy in terminally ill patients with advanced disease who have developed ARF and with do-not-intubate orders. In such patients, an NIV trial could be beneficial in end-stage chronic respiratory failure, even in the case of extreme respiratory acidosis with hypercapnic coma [6–8].

Review of the literature also suggests the application of NIV in the management of perioperative ARF [9]. Perioperative NIV may reduce the incidence of postoperative complications in high-risk surgery or patients with significant respiratory disease [10]. Noninvasive ventilation (NIV) has an important role in the prevention and treatment of postoperative pulmonary complications (PPC) as it would prevent patient deterioration, reduce the incidence of hospital-acquired pneumonia, length of stay in critical care unit, and need for mechanical ventilation (MA) and also confer mortality benefits in selected patient groups.

In the literature, to date, no randomized trial has evaluated the efficacy and safety of NIV intraoperatively compared to other forms of mechanical ventilation (MV) or no MV. Less invasive methods of airway management, such as the supraglottic devices, have been described [11–13]. However, the application of NIV for airway management has not been studied in detail, and hence no specific guidelines exist for use of NIV intraoperatively. According to European Respiratory Society (ERS) and American Thoracic Society (ATS) guidelines on the application of noninvasive ventilation (NIV) in acute respiratory failure, NIV is effective in the post-operative period for the treatment of both impaired pulmonary ventilation and gas exchange [14], but its intraoperative use has been anecdotally reported in the form of two review articles and a few case reports. In this chapter, we will review in brief the pathophysiological rationale and current evidence stating the successful use of NIV intraoperatively.

57.2 NIV Versus Invasive Ventilation Intraoperatively

Noninvasive ventilation has been used as a replacement for invasive ventilation, and its flexibility allows it to be a valuable component in patient management. Although NIV does not assure a patent and protected airway and has its own limitations, it offers several advantages over invasive ventilation in certain clinical settings, which has been discussed elsewhere in the text book.

Endotracheal intubation is associated with myriad complications such as airway trauma, and considerable patient discomfort and, moreover, requiring the use of sedatives. These complications result in longer hospital stay, higher mortality rates,

and increased health care burden. Evidence has been compelling enough to establish that NIV can safely support ventilation, without endotracheal intubation even in conditions such as ARF, acute exacerbation of COPD and patients with neuromuscular disorders with chronic ventilatory insufficiency. However, NIV is contraindicated in respiratory arrest, unable to fit the mask, unmanageable secretions, uncooperative patient, or in patient with sepsis.

57.3 Principle of NIV in ARF, Acute Exacerbation of COPD AND Acute Cardiogenic Pulmonary Oedema

NIV helps in resting respiratory muscles by reducing diaphragmatic pressure swings [14]. Furthermore, when positive end-expiratory pressure (PEEP) is applied during pressure-supported ventilation (PSV), PEEP helps offset auto-PEEP, thus reducing the work required to initiate inspiration [15].

The use of NIV in the therapeutic management of ARF caused by COPD exacerbation has been successful and has been studied more than any other disorder leading to ARF. Several studies of patients with COPD during acute exacerbations have shown that NIV reduces inspiratory muscle activity and the respiratory rate and increases VT and minute volume, which allows better gas exchange and respiratory muscle rest [16]. During surgery, the benefits of avoiding GA in COPD patients has been quantified by a large data sample matched by Hausman et al. [17, 18] They concluded that the use of regional anaesthesia in patients with COPD is associated with a reduction in incidences of composite morbidity, pulmonary infections, ventilator dependence, and unplanned postoperative intubation.

An observational study done by Tsai et al. [19] indicated it seemed safer to use NIV compared to invasive MA in the setting of acute exacerbation of respiratory failure in COPD patients [19]. The strongest evidence from randomized control trials has confirmed that using NIV with a face mask significantly reduces the need for intubation, shortens the duration of hospital stay, and reduces complications and the mortality rate [20–23].

Based on the above rationale, though the shreds of evidence are limited, NIV seems beneficial and promising when used in the prevention of ARF, specifically in patients at a higher risk (severe COPD [24]) of PPC or after surgery at higher risk of postoperative ARF.

57.3.1 The Rationale for Use of NIV with Neuraxial Anaesthesia (NA) in Conditions Such as COPD

NA technique includes spinal, epidural and combined spinal-epidural technique in which, a higher and faster motor blockade is produced in spinal anaesthesia (SA). A study by Freud et al. [25] found that SA causes a greater decrease in inspiratory capacity and expired reserve volume (ERV) compared to epidural anaesthesia [25]. Generally, in normal patients during NA the diaphragmatic function is preserved unless there is sensory blockade of low cervical dermatomes [26]. However, high

thoracic epidural anaesthesia (TEA) may interfere with the function of the intercostal muscles and a significant reduction in the ventilatory response to hypercapnia is observed [27]. Though the concept of 'permissible hypercapnia' can be beneficial in COPD patients [28], it can alter the state of alertness/vigilance blunting the protective airway reflexes and increasing the risk of aspiration, and hence should be used carefully in patients who already have a compromised respiratory system and the mechanical impairment of ribcage muscles by TEA causes disruption in breathing pattern [29]. This can be detrimental in COPD patients, as ribcage muscles play an important role in generating sufficient flow in these patients. If not used cautiously, NA can lead to ARF in COPD patients with respiratory muscle dysfunction and wasting. However, the pathophysiological rationale of using NIV with NA is highlighted in Table 57.1.

In the supine position, the abdominal viscera are pushed against the diaphragm increasing the pulmonary venous pressure, decreasing the pulmonary compliance, and thereby increasing the respiratory workload. This affects the diaphragmatic function and also increases myocardial work. During surgery, changing patient's position from upright to supine induces a decrease in FRC by 20–25% [30] and a decrease in vital capacity (VC) and FEV_1 between 7% and 23% [31, 32]. These effects are more pronounced after neuraxial anaesthesia (Table 57.2). Ferrandière and colleagues [33] observed an obese patient with severe COPD under transurethral resection of the prostate after spinal anaesthesia in the lithotomy position and found a significant reduction (−30%) in the diaphragmatic excursion during inspiratory capacities (M-mode sonographic study of right diaphragm). Hypoxemia and a profound decrease of FVC associated with alveolar hypoventilation and V/Q mismatching were also seen during surgery. These events were successfully treated with NIV with NA.

Table 57.1 Pathophysiological goals/rationale of intraoperative NIV use with neuraxial anaesthesia

(a)	Reversal of alveolar hypoventilation due to GA agents or inadvertent spread of anaesthetic drug up to cervical dermatomes in patients without respiratory compromise.
(b)	Prophylactic or therapeutic management of acute respiratory failure in patients who are considered "at risk candidates" of respiratory deteriorations due to NA (COPD or chest wall disorders and/or NMDs)
(c)	to prevent the worsening of gas exchange in patients who are affected by chronic respiratory failure preoperatively (i.e., home oxygen therapy and/or domiciliary nocturnal or 24 h NIV/CPAP)
(d)	To make palliative surgical procedures in end-of life debilitated patients with do-not-resuscitate and intubate orders feasible.

Table 57.2 Summary of adverse effects of NA on respiratory function

(a)	loss of contribution of accessory muscles of respiration (active expiration—COPD patients)
(b)	blunted ventilatory response to variation of arterial blood gas
(c)	reduced chest wall expansion due to supine positioning
(b)	relative hypovolemia

57.3.2 The Rationale of NIV Use in Sleeping Disorders During Anaesthesia (Sedation or NA)

Anaesthetizing patients with severe obstructive sleep apnoea (OSA) is quite challenging. According to the Society of Anaesthesia and Sleep Medicine Guideline on Intraoperative Management of Adult Patients (2018), it is recommended that whenever applicable, regional anaesthesia should be preferred over general anaesthesia in patients with OSA [34]. However, the regional anaesthesia techniques require good patient cooperation, which demands use of sedation during surgery. Unfortunately, in OSA patients, even with mild sedation life-threatening complications such as complete airway obstruction and respiratory arrest can occur. In OSA, the depressive effects of drugs such as opioids, benzodiazepines, propofol and even dexmedetomidine on respiratory drive may be exacerbated in an already compromised airway. Owing to fear of losing the airway, these patients are mostly under-sedated and subsequently become uncooperative during regional anaesthesia. Also, the supine position needed for achieving adequate block in NA can deteriorate obese patients with severe OSA. Other intraoperative complications during anaesthesia include hypoxia, acidosis, exacerbation of pulmonary and systemic hypertension and hypercarbia, which tend to continue in the postoperative period as well [35].

Home-based nasal CPAP therapy for sleep has been widely used in patients with nocturnal hypoventilation disorders [36]. The technique of Nasal CPAP or BiPAP prevents upper airway obstruction by creating a positive transmural pressure that functions as a pneumatic splint at the level of the soft palate. Based on the same principle, intraoperative NiPPV can provide a good quality of sedation in a patient with severe OSA even for longer duration surgeries under regional anaesthesia with or without sedation or local anaesthesia with sedation. Planning before surgery and having a BiPAP machine with the appropriate mask available inside the operative room can be beneficial and allow using sedatives to make these patients comfortable under regional anaesthesia. Preoperative counselling and patient's cooperation is mandatory in these cases. There is a possibility to safely sedate OSA patients with intraoperative BiPAP, but many more trials are still required before we can reach this conclusion.

57.3.3 Use of Intraoperative NIV in Patients with Respiratory Muscle Weakness and Restrictive Lung Disorders

The use of NIV to treat chronic ventilatory failure caused by chest wall deformities, progressive neuromuscular disorder (NMD), muscular dystrophies and mitochondrial disorders has been well advocated for many years. In such patients, especially those with respiratory compromise when posted for surgeries, exposer to anaesthetic agents further reduces respiratory muscle strength, increases retention of airway secretions, reduces ventilatory drive and worsens hypoventilation due to central apnoea. Moreover, after administration of anaesthetic drugs, these patients are at potential risk of life-threatening reactions and prolonged mechanical ventilation and respiratory complications postoperatively. Arguments are in favour of the use of

regional or local anaesthesia having the advantage of reducing PPC, especially in NMD patients with reduced pulmonary function [37]. Many of these patients are mostly on chronic ventilatory support in the form of domiciliary NIV. In a case series done by Bach and colleagues [38], NiPPV was used with local anaesthesia and sedation during open gastrostomy in 69 patients having NMDs. It was concluded that such palliative procedure for adequate nutrition can be performed safely without invasive MV or general anaesthesia for patients with little or no autonomous breathing ability. Patients with rare autosomal recessive disorders such as cystic fibrosis and limb-muscle girdle dystrophy who were on domiciliary NIV during pregnancy have been reported to undergo LSCS under NA with the assistance of NiPPV throughout the surgery.

57.4 NIV Modalities and NIV Ventilators Which Can Be Used Intraoperatively

NIV is mostly a blanket term that includes noninvasive positive airway pressure (also termed as 'bilevel'/BiPAP) devices consisting of a higher inspiratory positive airway pressure and lower expiratory pressure as well as continuous positive airway pressure (CPAP) delivered using a nasal, oronasal or facial interface or newer flow-dependent nasal interface. NIV works much better in relaxed patients and those who are counselled preoperatively. The common modes of NIV successfully used during surgery in reported cases are CPAP, BiPAP and PSV. There are several ventilators commercially available, in which not only CPAP but also bi-level positive airway pressure (BiPAP) can be triggered by spontaneous breathing – which is similar but not identical to pressure support ventilation (PSV).

In CPAP mode, a constant positive pressure (5–10 cm of H_2O) is delivered throughout the respiratory cycle either by use of a flow generator with a high-pressure gas source or by utilization of a portable compressor to spontaneously breathing patients. When CPAP is applied with positive inspiratory PSV, it is referred to as PEEP.

BIPAP refers to the association of PSV + PEEP. This mode is activated by changing the CPAP levels at the inspiratory and expiratory phases and is also referred to as noninvasive positive pressure ventilation (NIPPV). The BiPAP mode is more widely used by physicians for patients with a variety of acute or chronic respiratory failures. Noninvasive positive pressure ventilation via face mask has been accepted as a first-line intervention in patients with acute hypercapnic and hypoxemic respiratory failure [39].

In a pilot/preliminary study done by Iwama (Table 57.3), CPAP versus BiPAP was evaluated for the same group of ASA I & II patients undergoing lower extremities surgery under epidural anaesthesia plus sedation with propofol 5 mg/kg, and it was found that CPAP 8 cmH_2O resulted in a high RR, a marked increase in $PaCO_2$ and a slight depression in PaO_2, even when the upper airway seemed to be open. Whereas BiPAP 14/8 cmH_2O resulted in no change in RR, only a slight increase in $PaCO_2$ and no change in PaO_2. A comparison of NIPPV and CPAP in the treatment of acute cardiogenic pulmonary oedema (ACPE) showed that patients treated with NIV demonstrated more rapid improvements in $PaCO_2$ and pH and the mortality

Table 57.3 Studies evaluating elective intraoperative NIV use during deep sedation in patients without respiratory compromise in lower abdominal, lower extremity and shoulder surgeries

Authors of journal article	Year of publication	No. of patients included in study and surgery and position	Anaesthesia during surgery	NIV interface	NIV mode and ventilator used	Intraoperative course and study outcome
Iwama [40]	2002	213; Elective ASA I and II (<80 years) patients undergoing elective lower extremity or lower abdominal gynaecological surgeries in supine or lithotomy position	EA plus propofol sedation with different doses in divided groups, additional muscle relaxant also given in 10 patients	Nasal strip (Breathe Right) attached to nasal bridge to obtain dilation of nasal cavity	CPAP vs. BiPAP evaluated in 10 Pts.	55 patients managed with ephedrine for hypotension.
				Nasal mask	Remaining pts.—BiPAP studied.	No patients had respiratory complication, aspiration, regurgitation or aerophagia.
					Ventilator for BiPAP used like Philips Respironics and other	
Iwama et al. [41]	2003	265; elective ASA I and II undergoing elective surgeries same as prior study.	EA plus rapid and slow induction with propofol in three different ventilators	Nasal mask with nasal strip	BIPAP	3 patients excluded from study as they had malventilation after propofol induction and desaturation due to airway; one resolved by increasing EPAP to 10 cmH_2O, second by insertion of nasal airway, third by LMA insertion. Rest 262 pts. successfully managed with NiPPV.
		Patients divided in six groups.			Three Ventilator used-BiPAP S/T (Respironics), KnightStar 335 and BiPAP Vision (Respironics)	6% patient complaint of slight intranasal pain.

(continued)

Table 57.1 (continued)

Authors of journal article	Year of publication	No. of patients included in study and surgery and position	Anaesthesia during surgery	NIV interface	NIV mode and ventilator used	Intraoperative course and study outcome
Ohmizo et al. [42]	2005	23 adult patients; ASA I and II undergoing inguinal hernia repair.	Spinal anaesthesia with sedation	Nasal mask with nasal strip	BiPAP:	No patients had respiratory complication, aspiration, regurgitation or aerophagia.
					IPAP-14 cmH_2O	one patient complaint of slight intranasal pain.
					EPAP-$8H_2O$	
					NiPPV ventilator-BiPAP Vision (Respironics)	
Soberón et al. [43]	2021	Retrospective case control study	20 pts- deep sedation+ interscalene block+ NiPPV	Portable disposable device- SuperNO2VA nasal PAP ventilation device/mask (Vyaire Medical) applied with strap to nose	Fresh gas flow set on anaesthesia machine at 10–15 L/min and anaesthesia circuit connected to the mask. APL valve set to 10 cmH_2O, hence nasopharyngeal pressure applied.	No patient in deep sedation converted to GA.
		ASA II & III- 60pts with OSA who underwent Shoulder surgeries.	40 pts- GA+ interscalene or cervical plexus block			NIV group compared to GA group intraop had-
		Position- lateral or lazy beach chair position (30° head elevation)				• lower non-surgical time
						• ease of positioning
						• less episodes of hypotension
						• decreased need for vasopressor and i.v. fluid
						• no major adverse events.
						Post-op course same in both groups.

and intubation rates were similar. It is noteworthy that though NIV and CPAP are equally effective in managing respiratory failure associated with ACPE, CPAP is more cost-effective and easier to set up. The current recommendation is to use CPAP (10 to 12 cmH_2O) in the initial treatment of acute cardiogenic pulmonary oedema; NIV should be used in patients who continue to be hypercapnic and dyspnoeic thereafter [39, 44]. Portable ventilators such as BiPAP S/T (Respironics) have been used in studies to deliver NIV intraoperatively.

Newer modes of ventilation such as the S/T (spontaneous/time triggered) mode have also been used intraoperatively in cases reported. In this mode, an inspiratory time (e.g. IPAP %) is also set along IPAP, EPAP and respiratory rate and patient-initiated breaths are supported to the IPAP level, similar to the PSV mode. Additionally, the machine triggers inspiration to the set IPAP level if the patient fails to make an inspiratory effort within a set interval and the IPAP then cycles to EPAP based on the IPAP% period. Average volume-assured pressure support (AVAPS), a relatively newer technology available on Respironic Philips BiPAP devices (e.g. V-60 ventilator), is useful in patients with COPD, NMD, OSA and chronic hypoventilation. AVAPS devices automatically adapt pressure support according to patient's ventilatory needs and deliver an average tidal volume (200 to 1500 mL) depending on patient's pathology.

57.4.1 Patient Interfaces Used Intraoperatively

The primary goal of NIV is to avoid endotracheal intubation. Having an interface that is properly sized, well-fitted and comfortable for the patient is crucial when it comes to success rate of NIV. Each interface has its own advantages and disadvantages [16] and the anaesthesiologist must choose a proper mask depending on the type of surgery, patient comfort and compliance during NIV. The nasal mask has been most commonly used for intraoperative NIV. Modification to the face mask for endoscopy port insertion and nasal mask for TEE probe insertion could be done to deliver NiPPV in various diagnostic and therapeutic interventional procedures under sedation with local anaesthesia.

Recently, Semhar G et al. used a portable disposable device – the SuperNO_2VA mask [45] (Vyaire Medical), which is a flow dependent positive pressure ventilatory device, requiring 10–15 L/min of oxygen to provide expiratory pressure to maintain airway patency [46] – during procedural sedation in a retrospective cohort study.

Limited evidence suggests that NIV improved preoxygenation of patients before intubation, both in hypoxaemic patients in the ICU [47] and bariatric patients in the operating room [48]. Baillard et al. compared NIV to standard preoxygenation with a non-rebreather bag-valve mask (standard method) and concluded NIV was more effective in reducing arterial oxyhaemoglobin desaturation in hypoxaemic and critically ill patients. In their RCT Delay concluded that preoxygenation via a face mask with NPPV in the operating room is safe, feasible and efficient in morbidly obese patients, as it delivers more rapid O_2, achieving a higher ETO_2 (considered as an appropriate surrogate marker for denitrogenation). It has been shown that 5 min of preoxygenation with NIV with moderate levels of PSV (8 cmH_2O) and PEEP (6 cmH_2O) using $FiO_2 = 1$ provides a higher end-tidal of oxygen (ETO_2) than spontaneous ventilation [48].

57.5 Use of Therapeutic or Prophylactic Intraoperative NIV in Different Types of Surgeries (Tables 57.3, 57.4, 57.5, 57.6, and 57.7)

NIV seems promising when used prophylactically in patients undergoing surgery who have chronic severe respiratory limitations due to different diseases. In addition, the use of prophylactic noninvasive mechanical ventilation before surgery that involves significant alterations in the ventilatory function may decrease the incidence of PPC.

NIV permits greater anaesthetic depth without deterioration of oxygenation and ventilation of patients. Airway obstruction intraoperatively induced by profound sedation with benzodiazepines and opioids combined with NA causes obstruction apnoea or snoring which are also accompanied with decreases in arterial oxygen saturation. In deep sedation or mild sedation in OSA patients, nasal CPAP prevents upper airway obstruction and corrects desaturation [49]. There are case reports indicating the use of NIV in severe OSA patients who were on domiciliary NIV and NiPPV) used prophylactically during surgery under NA plus sedation (Table 57.5) without any complications. However, constant monitoring of $EtCO_2$ through NIV interface and continuous assessment of sedation score needs to be done in such cases along with sequential blood gas analysis.

Upper abdominal surgery is usually performed with GA and ETI. However, residual effects of both general anaesthetic agents and pain related to surgery by itself interfere with the functions of the respiratory muscles, increasing the risk of postoperative atelectasis and other pulmonary complications [77]. Anaesthetic agents used for GA, except ketamine, cause a loss of static muscle tone, with a reduction in chest wall outward recoil to counteract the inward elastic recoil of the lung [78, 79], decreasing FRC by 0.4 to 0.5 L under GA. In the case of the limited respiratory functional reserve, the incidence of potential pulmonary complications increases [80]. Unlike GA, lumbar and low thoracic NA produces fewer respiratory complications, while high thoracic anaesthesia causes a reduction in vital capacity and FEV1 up to 20%. Therefore, NIV is considered relatively safer in lower abdominal surgeries under NA. Studies performing application of CPAP and BiPAP along with regional or local anaesthesia have shown that NIV can be a safe option in neonates and paediatric population intraoperatively [81–84].

Older techniques of noninvasive ventilation such as negative pressure ventilation, which requires a special type of device such as Hayek oscillator (high-frequency chest cuirass ventilator), have given satisfactory results in some case reports when used during micro laryngeal surgeries, Nd-YAG laser photo resection and in case of failed intubation fibreoptic intubation [85–89]. Owing to the scarce availability of such devices, nowadays these techniques are not routinely practised and hence not further discussed in this chapter.

Table 57.4 Case reports on the therapeutic use of NIV intraoperatively in abdominopelvic and lower extremity surgeries

Authors of journal article	Year of publication	No. of patient in the study	Surgical procedure done and length of surgery	Patient's age and main comorbidities	Position during surgery	Type of anaesthesia	Preop domiciliary NIV or O_2 therapy	Interface for NIV	NIV mode and ventilator used	Any intraoperative events with NIV	Postoperative course
Nozaki et al. [49]	1995	20	Lower abdominal surgery	None	Supine	SA with midazolam sedation (causing airway obstruction)	No	Nasal mask	CPAP	Uneventful	Not reported
Ferrandière et al. [33]	2006	1	TURP	54-years, severe COPD, Obesity Hypoventilation in response to O_2 therapy in previous surgeries	Lithotomy	SA	No	Mirage Full Face Mask Series 1; Res Med	NiPPV, O'NYX Plus; Mallinkrodt SEFAM; pressure support ventilator with a proximal expiratory valve	Uneventful, Intraoperative correction of hypoxemia	NiPPV continued in PACU in 45 head-up position until SA wore off (total = 150 min.) and discharged from PACU, uneventful postoperative course.
Thys et al. [50]	2007	1	Intramedullary nailing for femoral fracture fixation, length- 75 min.	77-years, chronic smoker, COPD, kyphoscoliosis, CCF, HTN, Hyperthyroidism. Pt. was refused GA d/t severe respiratory acidosis	Supine	SA	Long term home O2 therapy @ 1lt/min for 16 h per day. NiPPV started 15 h Before surgery.	Not reported	NiPPV	Uneventful, intraoperative transient worsening of $PaCO_2$. Respiratory assistance maintained with two-level NiPPV.	NiPPV continued in ICU, discharged from ICU after 4 days, subsequently from hospital on postop day 11 to a nursing facility.

(continued)

Table 57.4 (continued)

Authors of journal article	Year of publication	No. of patient in the study	Surgical procedure done and length of surgery	Patient's age and main comorbidities	Position during surgery	Type of anaesthesia	Preop domiciliary NIV or O_2 therapy	Interface for NIV	NIV mode and ventilator used	Any intraoperative events with NIV	Postoperative course
Bach et al. [38]	2010	62	Open (Stamm) gastrostomy for adults with severe neuromuscular weakness	Total 62 patients (44 pts wit ALS, 10 with muscular dystrophies, 8 with other NMDs).	Supine	Local anaesthesia and sedation with ketamine & midazolam	59 pts. on domiciliary NIV (through nasal and mouthpiece interface)	Oronasal mask	Assisted control-mode ventilation (volumes of 700–1500 mL) OR pressure control mode (pressures of 18–25 cmH_2O with backup rate of 10–12/min).	Desaturation due to airway secretion cleared with suctioning OR mechanically assisted coughing using mechanical insufflation and exsufflation (cough assist, Respironics)	No patients except 13 ALS patients with advanced bulbar underwent tracheostomy.
				51 pts. with						All desaturation <95% reversed.	Mean post-gastrostomy survival- 38.8 ± 6.2 months.
Alonso-Inigo et al. [51]	2012	2 (Both pts. 110 kg)	Retropubic radical prostatectomy	Case 1: 66-years, Obesity (BMI- 38.5 kg m^{-2}, COPD in hypercapnic respiratory failure (FEV_1 1.77 L- 57% predicted; FEV_1/FVC-54%), HTN, Cerebrovascular disease.	Case 1-Supine with 10° head down tilt.	Lumbar epidural plus i.v. sedation with continuous Remifentanyl infusion	No	Oronasal face mask	Initial settings- spontaneous/time triggered (S/T) mode with IPAP/EPAP OF 15/5 cmH_2O with BiPAP Vision ventilator (Respironics)	Uneventful	Uneventful.
				Case 2: 63-years, obesity (BMI- 39.4 kg m^{-2}), moderate COPD, HTN					Both cases- IPAP and EPAP adjusted		Discharged home on POD5 and POD7 respectively

Yurtlu et al. [52]	2016	1	Emergency open cholecystectomy, length- 1 h	46 years old male, severe COPD (preop FEV1- 0.7 L-21.3% predicted), SPO_2-70% with 2 L O_2/min through nasal cannula). Pt. in Hypercapnic respiratory failure.	Supine	TEA in T8-T9- sensory block till T4 Dermatome	Domiciliary NIV device	Not reported	BiPAP- (IPAP- 25 cmH_2O, EPAP- 6 cmH_2O) FiO_2- 35% Patients own home NIV ventilator device used.	Improvement in blood gas values					Transferred to ICU on intermittent NIV, SPO_2-94%, PaO2-71 mm hg, shifted to ward on POD3, discharged to home on POD5 on his regular respiratory therapy
											pH	PaO_2	$PaCO_2$	SPO_2%	
										Preop	7.37	41	49	74	
										Intraop	7.39	48	42	83	
										Postop (ICU)	7.38	71	48	94	

Table 57.5 Case reports on the prophylactic use of NIV patients with impending respiratory failure during abdominopelvic and lower extremity surgeries

Authors of journal article	Year of publication	No. of case, surgical procedure and length of surgery	Patient's age and main comorbidities	Position during surgery	Anaesthesia given	Preop domiciliary NIV or O_2 therapy	Interface for NIV	NIV mode and ventilator used	Intraoperative course with NIV	Postoperative course
Iwama and Suzuki [53]	2003	1, Vasectomy Length- 1 h	42-years, Obesity, Sleep apnoea syndrome	Supine	Sedation with propofol infusion plus additional local anaesthesia (day care surgery requested by patient)	Domiciliary nocturnal NIV	Nasal mask	BiPAP	Uneventful	Uneventful Same day discharge 2 h post-surgery
Bapat et al. [54]	2006	1, local resection of Ca Rectum. Length- 1 h	74-years, Severe COPD, Bilateral leg oedema for 2 years suggestive of cor-pulmonale, orthopnoea, angina pectoris, alcoholic liver disease and macular degeneration	Lithotomy position, 10° Head down tilt.	SA with motor and sensory block at T10 Level	Home oxygen at 2 L min^{-1}	Facemask	CPAP of 7.5 cmH_2O; Dra¨ger CF800 machine	Uneventful	After surgery CPAP discontinued, Nasal o2 @ 2.1 min^{-1} and semi-sitting position resumed as preop. Discharged home on POD2
Warren and Sharma [55]	2006	1; dilation and curettage and b/l tubal ligation. Length-1 h	26-years, 12 weeks intrauterine pregnancy, severe Myasthenia Gravis with chronic respiratory insufficiency, central sleep apnoea, orthopnoea	Semi-lateral position	Local anaesthesia with conscious sedation	Domiciliary nocturnal BiPAP	Not reported	BiPAP with Home settings	Uneventful	Uneventful, discharged home on POD3.
Kinoshita et al. [56]	2007	1; replacement of right femoral head	69-years, Exacerbation of COPD	Not reported	SA with light sedation (BIS = 70 to 80) by continuous i.v. propofol infusion	Bilevel positive pressure ventilation via portable NPPV prescribed by attending physician and started immediately before surgery.	Nasal mask	NiPPV: Portable NPPV ventilator IPAP- 14.5 cm H_2 EPAP- 4 cm H_2	Uneventful. Reliable capnograph trace obtained via sample line attached to nasal mask for NPPV to detect apnoeic events during NIV	Not reported

Leech et al. [57]	2007	1; Insertion of dynamic hip screw	76-years, obesity (BMI-37 kg m^{-2}), advanced COPD, cor-pulmonale, Pulmonary HTN, orthopnoea	Supine with slight head-up tilt	SA with sensory block at T10 plus target controlled sedation with propofol	Trial of BiPAP immediately before SA- to check tolerability and adequacy of assisted ventilation	Not reported	BiPAP: IPAP- 16 cmH_2O EPAP- 5 cmH_2O	Uneventful	Post-op BiPAP gradually reduced over 3 hrs period; O2 via nasal sponge @ 2 L/min over next 24 hours in HDU. Discharged home POD7.
Kapala et al. [58]	2009	1; elective sigmoid resection for Ca sigmoid. Length- 4.5 h	63-years, severe OSA (apnoea-hypopnea index- 146), paralyzed left hemi diaphragm CABG before 5 months, NIDDM, GERD, CRF	Lithotomy, upper body raised to 30°	Combined spinal- epidural anaesthesia plus sedation with fentanyl, midazolam and ketamine.	Domiciliary nocturnal BiPAP	Type of mask not reported (Patients own mask)	BiPAP: IPAP- 12.5 mmHg EPAP- 8 mmHg	Comfortable, conscious, and communicative throughout procedure	BiPAP temporarily discontinued and then reapplied overnight. Nocturnal BiPAP continued, discharged POD5.
Dawson et al. [59]	2012	1; total knee arthroplasty	66-years, childhood poliomyelitis with partial paralysis and significant kyphoscoliosis and subsequent restrictive lung disease, orthopnoea, past H/O spinal fusion surgery	supine	Continuous SA after CT study of lumbar spine	Domiciliary Nocturnal NIV	Not reported	BiPAP	Uneventful	NIV continued post-op, discharged home POD11.
Singh et al.	2015	1; right total knee replacement	55-years, Obesity (41 kg m^{-2}), severe OSA (Apnoea-hypopnea index- 35), dyspnoea NYHA-II, moderate pulmonary HTN (MPAP-40 mmHg with RVH)	Semi reclined position	Combined spinal- epidural Level of block- T10 Plus midazolam and fentanyl sedation	Home CPAP therapy with poor compliance	Not reported	BiPAP: IPAP- 12 cmH_2O EPAP- 4 cmH_2O	Stable, comfortable throughout surgery	Uneventful. Postop BiPAP continued for 48 h Patient recovered well and discharged POD5.

Table 57.6 Case reports of NIV Noninvasive ventilation (NIV) use during thoracic surgery, neurosurgery, intervention cardiology and other diagnostic procedures

Authors of journal article	Year of publication	Number of cases, procedure done, duration	Patient's age, gestation and main comorbidities	Type of anaesthesia given	Position during surgery/ procedure	Preop domiciliary NIV or O_2 therapy	Interface for NIV	NIV mode and ventilator used	Postoperative/ postprocedure course
Rubowitz et al. [60]	2001	1; phacoemulsification and intraocular lens implantation	40-years, myotonic dystrophy and severe orthopnoea	Local anaesthesia	Supine	CPAP overnight, O_2 during day	Facemask	CPAP	Not reported
Yamamoto et al. [61]	2003	2 cases	Case 1: 25-years with visual disturbance, tumour in right frontal lobe.	Case 1: Local anaesthesia+ sedation with continuous inj. Propofol infusion+ inj. Fentanyl top up	Supine	No	Nasal mask	Case 1: BiPAP	Not reported
		Case 1: Awake craniotomy with intraop motor function mapping	Case 2: 43-years, headache with difficulty in speech, brain tumour, Hyperthyroidism, DM, OSA	Case 2: Supraocular and occipital nerve block with LA+ Sedation with Continuous infusion inj. Propofol+ inj. Fentanyl top up				IPAP-10–12 cmH_2O	
		Case 2: Left temporal craniotomy with intraop speech mapping						Case 2: NiPPV with proportional Asist ventilation	
Reber et al. [62]	2003	1; phacoemulsification	63-years, OSA	local anaesthesia and sedation	Supine	Domiciliary nocturnal CPAP	Nasal mask	CPAP	CPAP continued for 1 h after procedure.
Guarracino et al. [63]	2008	1; Lt side VATS for pleuropericardial window procedure for recurrent pleural and pericardial effusion	72-years, carcinoma breast with metastasis to thoracic vertebrae and jaw bone, CRF	EA plus sedation inj. Propofol	Right lateral position	No	Facemask	BiPAP: IPAP-12 cmH_2O EPAP-6 cmH_2O	BiPAP continue 5 h after surgery in ICU, shifted to ward on POD2

Huncke et al. [64]	2008	1; Awake Craniotomy with intraop language mapping	62-years, Refractory seizure disorder, OSA, Morbid obese(BMI-45.8 kg/m^2), asthma, IHD, NIDDM, GERD, CRF	MAC+ Scalp block+ sedation with dexmedetomidine and remifentanil	Rt semi lateral position	Nocturnal CPAP	Not reported	CPAP	Not reported
Guarracino et al. [65]	2010	3; Percutaneous aortic valve implantation	83, 84, and 88-years. All having severe aortic valve stenosis, belongs to NYHA class-3, Orthopneic	Local anaesthesia + Sedation with remifentanil infusion	Supine	No	Oro-Nasal mask With vertical hole on the anterior part for TEE probe insertion	BiPAP: IPAP-8–12 cmH_2O EPAP-4–6 cmH_2O	Shifted to ICU, on BiPAP for 2 h.
Zangrillo et al. [66]	2019	22, 11 pts. in janus mask group 11 pts. in GA group Left atrial Appendage closure	All pts. > 65-years, mild to moderate MR, on beta blocker, multiple comorbidities.	Sedation with propofol, fentanyl and remifentanil	Not reported	Not reported	Janus mask- designed to permit endoscopic procedure on Airway and GIT with NIV	NiPPV	3 pts. in Janus mask group had transient apnoea – managed with reducing level of sedation All pts. shifted to cardiology ward

Table 57.7 Case reports of prophylactic NIV use in ARF during lower Caesarean Section (LSCS)

Authors of journal article	Year of publication	Patient's age, gestation and main comorbidities	Anaesthesia given	Position during surgery	Preop domiciliary NIV or O_2 therapy	Interface for NIV	NIV mode and ventilator used	Any intraoperative events with NIV	Postoperative maternal outcome	Newborn outcome
Bose et al. [67]	1997	27-years, primigravida at 24 weeks of gestation, cystic fibrosis and pancreatitis orthopnoea	Lumbar EA and sedation with ketamine	Semisiting and tilted to left	Fully dependent on NiPPV by 24 weeks	Nasal mask	NiPPV	SpO_2 gradually worsening despite increase in FiO_2 100%	Mother developed pneumonia on POD8 and required tracheal intubation. She expired on the tenth day.	Baby wt.- 790 g; NICU stay-7 weeks for respiratory distress, intraventricular haemorrhage & Septicemia. Transferred to another hospital on nasal oxygen & caffeine
Cameron et al. [68]	2005	29-years at 29 weeks of gestation, cystic fibrosis with end stage respiratory failure, domiciliary oxygen therapy throughout day, cor-pulmonale, orthopnoea	Combined spinal - Epidural anaesthesia	Supine left lateral tilt	From 24 weeks of gestation nocturnal BiPAP, then fully dependent on BiPAP	Not reported	BiPAP	Uneventful	On POD10 Pt developed pneumonia, transferred to respiratory unit. On POD26 discharged home requiring nocturnal BiPAP.	Baby wt.- 1505 g with Apgar scores 9 at 1 min & 10 at 5 min shifted to NICU
Allen et al. [69]	2007	28-years at 34 weeks of gestation, autosomal recessive limb-girdle muscular dystrophy, orthopnoea, PFT showing severe restrictive lung ds	Combined spinal - Epidural anaesthesia	Supine with 15-deg head-up tilt with 15 degree let lateral tilt	34 weeks of onward NiPPV 11 h in day and throughout night started	Facemask	NiPPV	Uneventful	Required NiPPV for 1 h on POD1. Discharged home on POD7 with advice to use nocturnal NiPPV. Uneventfully recovered and discontinue NiPPV after 6 weeks.	Female baby wt- 2435 g, Apgar score 9 at 1 min and 10 at 5 min.

Terblanch et al. [70]	2008	28-years at 24 weeks of gestation, congenital myasthenia syndrome	SA	Supine with left tilt.	On Nocturnal BiPAP since age of 15 years.	Not reported	BiPAP	Uncomplicated	Postoperatively BiPAP titrated to prepregnant baseline setting and discharged on POD12	Male baby wt-2270 g Apgar score 8 at 1 min and 9 at 5 min. Required CPAP for 12 h.
Yuan et al. [71]	2009	22-years at 33 weeks of gestation, mitochondrial thymidine kinase 2 deficiency, chronic respiratory failure on NiPPV, preeclampsia	EA	Not mentioned	By the age of 12 years on NiPPV, before pregnancy on NiPPV 22 hr./ day, during pregnancy on NiPPV 24 hr./day	Not reported	NiPPV	Not reported	Not reported	Female baby wt-1349 g, with Apgar scores 7 at 1 min and 9 at 5 min discharged home on day 28
Erdogan et al. [72]	2010	28-years at 34 weeks of gestation, obese (BMI-41.5 kg/m^2), severe preeclampsia with pulmonary oedema, asthma, orthopnoea	SA	Semi-fowler position	Pre-op SPO_2-70% to 80% with 10 L/min O_2, before LSCS on BiPAP (IPAP/ EPAP-16/8)	Not reported	BiPAP with preop setting. SPO_2- 98%	Uneventful	BiPAP intermittently continue for next 24 h, discharged home on same day	Female baby wt-2630 g, apgar score 5 and 8 at 1 min and 5 min respectively.
Fujita et al. [73]	2014	32-years at 23 weeks of gestation with quadruplet pregnancy, threatened preterm labour, acute pulmonary oedema due to tocolytics	SA	Not mentioned	Immediate before LSCS SPO2-80% with 15 L O_2/min via reserved face mask	Not reported	NiPPV with S/T mode (IPAP/ EPAP-10/8 cmH_2O)	Dyspnoea improved with SPO_2-100%	Shifted to ICU, NiPPV continued for 22 h post op, On POD1-transferred ward and POD6 discharged home	

(continued)

Table 57.7 (continued)

Authors of journal article	Year of publication	Patient's age, gestation and main comorbidities	Anaesthesia given	Position during surgery	Preop domiciliary NIV or O_2 therapy	Interface for NIV	NIV mode and ventilator used	Any intraoperative events with NIV	Postoperative maternal outcome	Newborn outcome
Polin et al. [74]	2015	Case series of 3 pt. with super morbid obesity Case 1: 29-years at 37weeks, BMI-73 kg/m^2, OSA on home BiPAP, HT, DM, asthma	Combined spinal - Epidural anaesthesia	Semi-recumbent with ramp of 20 to 40 degree	Home BiPAP	Not reported	BiPAP	Required intraop BiPAP with her own home setting, developed PPH required blood transfusion	Shifted to surgical ICU. Discharged on POD7	Apgar score 2 & 9 at 1 and 5 min respectively
Ranjan et al. [75]	2015	27-years at 38 weeks of gestation, Limb Girdle Muscular Dystrophy	EA	Not mentioned	Preop PFT-Restrictive pattern not on O_2.	Not reported	NiPPV	Uneventful	Shifted to surgical ICU for 24 h, and afterward to ward	Healthy Female child, with Apgar score 8 and 10 at 1 and 5 min respectively
Kock et al. [76]	2018	25-years at 32 weeks gestation, Amyotrophic lateral sclerosis, dyspnoea, orthopnoea	Combined spinal - Epidural anaesthesia	Semisitting	On BiPAP 2 h before LSCS	Oro-nasal mask	BiPAP	Continued BiPAP	Shifted to ICU, slowly weaned from 24 h NIV to night-time NIV, Discharged home on long term BiPAP	Male baby, Apgar score 8 and 8 at 1 and 5 min respectively. NICU-intubated due to grade 2 respiratory distress Distress syndrome, receive surfactant, extubated & treated for 2 days on CPAP.

57.6 Summary

Although NIV application in the operation theatre is not a usual practise, its use in the operation theatre, as in high-risk cases with risk of PPC carries the advantage of the presence of an anaesthesiologist, who can detect any complications and intervene at the earliest to provide further respiratory support. Proper patient selection for NIV depends on the type of surgery, patient compliance and comorbidities, and managing physicians/anaesthesiologists need to determine the type of interface and mode to use for noninvasive ventilation.

Although the number of case reports describing the use of NIV together with regional anaesthesia and deep sedation has increased in recent years, these reports are mostly in the form of case reports or case series. At present, it is difficult to decide when NIV with NA would be preferable to oxygen delivered via nasal cannulas or a face mask plus NA or to invasive ventilation with GA because there is no comprehensive list of patient's clinical criteria.

Future RCTs are necessary to determine basic recommendations and specific guidelines to formulate a cautious approach to using intraoperative NIV specially in high risk, orthopneic patients (such as those with cor-pulmonale and COPD) undergoing lower extremities or lower abdominal surgery. A larger comparative study of higher quality needs to be done to evaluate local or neuraxial anaesthesia with deep sedation and intraoperative prophylactic NIV versus general anaesthesia with tracheal intubation (control group). Such studies could quantify/evaluate reduction in PPCs, length of ICU stay, hospital stay and mortality with the use of NIV during surgery.

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58 Use of Noninvasive Ventilation in Postoperative Patients in Cardiac Surgery

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Abbreviations

ARDS	Acute respiratory distress syndrome
BiPAP	Bilevel positive airway pressure
CABG	Coronary artery bypass grafting
COT	Conventional oxygen therapy
CPAP	Continuous positive airway pressure
CPB	Cardiopulmonary bypass
ExtF	Extubation failure
FiO_2	Fraction of inspired oxygen

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_58

FRC	Functional residual capacity
HFNC	High-flow oxygen therapy through nasal cannula
ICU	Intensive care unit
IMV	Invasive mechanical ventilation
NIPPV	Noninvasive positive pressure ventilation
NIV	Noninvasive ventilation
$PaCO_2$	Partial pressure of arterial carbon dioxide
PaO_2	Partial pressure of arterial oxygen
PEEP	Positive end-expiratory pressure
PPD	Postoperative pulmonary dysfunction
PSV	Pressure support ventilation
RCT	Randomized controlled trial
RSBI	Rapid shallow breathing index
TV	Tidal volumes
VC	Vital capacity

58.1 Introduction

Cardiovascular diseases still represent the leading cause of death globally; fortunately, cardiac surgery had made remarkable progress over the years, successfully treating most heart diseases (coronaropathies, valvulopathies, and congenital disorders). Approximately 1.5 million open-heart surgeries are performed each year worldwide, with 500,000 procedures in Europe as well as in the United States.

Cardiac surgery is often performed under general anesthesia through a median sternotomy and with the support of cardiopulmonary bypass (CPB). An uneventful recovery certainly requires an adequate tissue oxygenation, which is essential in preserving organ function and is also pivotal for wound healing [1]. The main issue of this chapter is to explain the rationale of and to analyze the current evidence about the use of noninvasive ventilation (NIV) in postoperative patients in cardiac surgery.

58.2 Alterations in Pulmonary Function After Cardiac Surgery

Cardiac surgery, as a major surgery, is quite commonly followed by changes both in gas exchange and lung mechanics, namely postoperative pulmonary dysfunction (PPD). Its clinical manifestations encompass a spectrum, from the more frequent mild respiratory derangements, i.e., hypoxemia associated with atelectasis and/or pleural effusion, to more rare and severe overt pulmonary complications, among which are pneumonia and acute respiratory distress syndrome (ARDS) [2].

PPD pathogenesis is multifactorial, including patient baseline features and surgical-related factors. Patient advanced age, preoperative respiratory disease,

severity and urgency of underlying cardiopathy, American Society of Anesthesiologists class of II or higher, smoking habit, obesity, and anemia may contribute to increase the risk of PPD development [1]. As mentioned above, cardiac surgery is performed under general anesthesia: the upward shift of the diaphragm, due to the supine position, together with relaxation and impaired compliance of the chest wall contributes to exacerbate the ventilation–perfusion mismatch. Moreover, the institution of CPB leads to an interruption of pulmonary ventilation (which is associated with loss of surfactant and alveolar collapse, favoring development of atelectasis and retention of secretions) and of pulmonary circulation, in turn, causing pulmonary ischemia and injury to capillary walls, with consequent release of inflammatory cytokines. Furthermore, median sternotomy incision, harvesting of the internal mammary artery, pleural dissection, topical cooling for myocardial protection (with inherent risk of phrenic nerve injury), ischemia-reperfusion injury, blood products transfusion and postoperative pain are surgical-related factors that synergistically affect respiratory performance. The consequent systemic inflammatory response adds to the well-known effects of invasive mechanical ventilation (IMV), namely the ventilation-induced lung injury resulting from mechanical and biological trauma. Mechanical stress involves barotrauma, the lung damage due to the high airways pressure, and volutrauma, the overdistension of alveoli related to the use of high tidal volumes (TV). Biotrauma results from the cyclic alveolar opening and collapse: the shear forces applied to the collapsed units may directly damage the airway epithelium, causing pulmonary edema—due to increased microvascular permeability—or may be mechano-transduced, thus initiating local or systemic inflammatory reactions, by means of leucocyte recruitment or cytokine release, respectively [2].

All these combined factors result in a wider alveolar–arterial oxygen gradient and in increased pulmonary microvascular permeability, as well as vascular resistance and shunt fraction, with reduction of vital capacity (VC), functional residual capacity (FRC), and lung compliance, both static and dynamic [2]. Since such complications threaten the surgical success and the patient's recovery, also implying increased healthcare costs, their prevention, early identification, and effective treatment are strictly advisable. Shorter times of CPB, possibly utilizing circuits coated with low-inflammatory-response-stimulation materials, a protective ventilation strategy with low TV and positive end-expiratory pressure (PEEP) to prevent alveolar collapse [2], early extubation, judicious blood- and pain-management, and early use of antibiotics may all reduce the risk for pulmonary complications following open-heart surgery.

58.3 Weaning from IMV: The Risk of Post-Extubation Failure

Choosing the right time to start separation from IMV is essential to the success of cardio-surgical procedures and represents a key step toward patient recovery. It must be as soon as possible, since early extubation (within 6–8 h from surgery)

reduces both incidence of complications and length of ICU stay, whereas a premature or a delayed extubation can lead to the need for reintubation.

Weaning from the ventilator represents a step-by-step transition from need of total ventilatory support to spontaneous breathing. Patient readiness is ascertained by assessment of: neurological function and fluid balance, hemodynamic parameters (e.g., heart rate, main arterial pressure, central venous pressure, serum lactate, and cardiac index), cough strength, amount of tracheobronchial secretions and pulmonary exchanges (e.g., pH, PaO_2/FiO_2 ratio, $PaCO_2$, bicarbonate, and rapid shallow breathing index (RSBI), namely the ratio between respiratory rate and TV) during unassisted breathing, a trial that simulates the post-extubation setting by removing PEEP. Unfortunately, these usual weaning predictors perform poorly in predicting late extubation failure (ExtF), probably because the spontaneous breathing test only evaluates the patient respiratory status, not his/her mental status or the ability to clear secretions after extubation.

Nowadays, several clinical parameters are considered risk factors for ExtF: diminished neurological function, markedly positive fluid balance, low hemoglobin and high bicarbonate levels, low serum urea and albumin concentrations, insufficient cough strength, increased tracheobronchial secretions, high RSBI, advanced age, and anamnesis of chronic obstructive pulmonary disease [3].

Extubation failure (ExtF), namely the need to restart mechanical ventilation after extubation by means of unplanned NIV or reintubation with consequent IMV, occurs in about 13% of postoperative open-heart surgical patients [3]. Its pathogenesis usually includes respiratory and cardiac dysfunction: residual muscular blocking or respiratory muscle fatigue, poor diaphragm excursions due to postoperative pain, upper airway obstruction, excessive secretions, hypoxemia and hypercapnia cumulatively increase the respiratory rate and decrease the TV, with a sharp increase in the RSBI that exacerbates ventilation–perfusion mismatch and alveolar hypoventilation; concomitant failure to increase cardiac output enhances tissue oxygen extraction.

A pivotal study by Rady and coworkers disclosed that in the individual risk for ExtF, patient frailty, depicted by baseline diseases (e.g., chronic obstructive pulmonary disease, pulmonary hypertension, left ventricular dysfunction) and by hematological/biochemical disorders (e.g., anemia, hypoalbuminemia, increased serum urea and creatinine), adds up to adverse intraoperative factors, such as redo procedures or aortic arch interventions, and need for long CPB time, massive blood transfusion, or intra-aortic balloon pump [4].

All in all, ExtF represents a major complication, since reintubation comes with several drawbacks: loss of airway protecting mechanisms, airway trauma, deep sedation, and the potential for aspiration predisposes to the need of tracheostomy or to ventilation-associated pneumonia. Reintubated patients have a poor prognosis, with longer times of ICU and hospital stay and increased mortality [3]. Moreover, rescue NIV once ExtF has occurred is often ineffective [5]. Patients with high risk of reintubation seem to be the ones who most benefit from planned application of early NIV [3].

58.4 Post-Cardiotomy NIV: Principles and Rational for Use

NIV represents a noninvasive modality of mechanical ventilation that emerged about four decades ago to treat acute respiratory failure (ARF) due to exacerbations of chronic obstructive pulmonary disease and cardiogenic pulmonary edema. A noninvasive interface allows applying a positive intrathoracic pressure (PIP) in conscious patients, which increases oxygenation and decreases the work of breathing.

There is a deep anatomical and functional relationship between heart and lungs. In turn, heart-lung interactions are affected by positive pressure, with both hemodynamic and respiratory consequences (Table 58.1). A tendency to reduce cardiac output, due to reduced left ventricle preload and afterload, is balanced by a reduction in respiratory workload, since PIP prevents alveolar collapse thus increasing FRC and arterial oxygenation [6]. PIP reduces ventricular filling and consequently its preload through multiple mechanisms: it reduces both pressure gradient for venous return and, by external compression, ventricular distensibility during diastole; furthermore, compression of pulmonary vessels may hamper venous return to the left atrium or right ventricular ejection. The same external compression on the left ventricle enhances its emptying during systole, thus also reducing its afterload. Of note, in patients with elevated left ventricle preload and afterload due to acute heart failure, PIP may increase cardiac output, whereas it may have drawbacks in patients with isolated right ventricle dysfunction, since it increases right ventricle afterload.

Although IMV represents the cornerstone in severe ARF treatment, it is well known that mortality associated with postoperative pulmonary disease mainly depends on the consequences of reintubation. Anesthesiologists must prevent the occurrence of postoperative pulmonary overt complications; once ARF occurs, they must prioritize achievement of adequate oxygenation and carbon dioxide removal while avoiding intubation. Rationale for NIV use in the postoperative period

Table 58.1 Main physiologic effects of positive intrathoracic pressure (PIP)

Cardiovascular
↓ Venous return → ↓ RV preload → ↓ LV preload
↑ Pulmonary vascular resistance → ↑ RV afterload → RV enlargement → ↓ LV compliance
↓ LV afterload (↓ systolic wall stress)
↓ Systemic blood pressure → ↓ Cardiac output
Respiratory
Recruitment of collapsed alveoli → ↑ Functional residual capacity
Maintenance continuously opened alveoli → Gas exchange during the whole respiratory cycle
Intra-alveolar pressure against edema
↓ Work of breathing
↑ Oxygenation

RV right ventricle, *LV* left ventricle
Modified from [6]

encompasses post-extubation support and management of PPD, whose impact is maximal in the first hours after surgery and tends to regress in a couple of weeks. With this mindset, cardio-anesthesiologist use of NIV, both to prevent respiratory failure (prophylactic NIV) and to treat ARF without reintubation (curative NIV), is nowadays well established.

58.5 Current Evidence

58.5.1 NIV Modalities and Interfaces

Noninvasive respiratory support techniques include conventional oxygen therapy (COT), high-flow oxygen therapy through nasal cannula (HFNC), continuous positive airway pressure (CPAP), and bilevel positive airway pressure (BiPAP), also known as noninvasive positive pressure ventilation (NIPPV). COT delivers a low stream of oxygen (≤15 L/min), either by nasal cannula or face mask, whereas with HFNC up to 60–80 L/min of heated and humidified oxygen-gas mixture is deliverable. In common practice, CPAP and BiPAP are the two mainly used NIV modalities. CPAP delivers constant positive airway pressure during the whole respiratory cycle: it increases intrathoracic pressure, preventing alveolar collapse and atelectasis and maintaining FRC, whereas it reduces left ventricle afterload. BiPAP represents the association of pressure support ventilation (PSV) with PEEP: the ventilator, triggered by each spontaneous inspiratory effort of the patient, provides a gas stream giving to him/her a pressure-support breath (PSV). Once airway pressure reaches a set threshold, the patient can continue breathing until their inspiratory flow rate drops below the 25% of the peak flow: at that time, pressure support returns to the pre-set level of PEEP, enabling spontaneous expiration. With this modality, TV depends on patient respiratory compliance and effort and on ventilator's support, while the patient can control their respiratory rate, as well as inspiratory and expiratory times [7]. CPAP, which is simpler to use and available without a ventilator, should be preferred in hypoxemic patients, whereas BiPAP requires a ventilator and should be preferred in hypercapnic respiratory failure. In addition, daily practice takes advantage of a combination of modes [1]. As outlined in an elegant article by Jaber and colleagues, while CPAP improves oxygenation and carbon dioxide removal by reducing atelectasis and increasing ventilation/perfusion ratio, BiPAP relieves dyspnea and unloads respiratory muscles work besides ensuring alveolar ventilation [7].

All in all, NIV efficacy depends on: patient-tailored titration, in terms of ventilation modality; patient collaboration (NIV works better in relaxed and trained patients); adequate interfaces. NIV can be administered through masks, hoods, or high-flow nasal cannulas. The tight fitting of the mask is crucial to minimize patient–ventilator interface leaks (often ranging between 20% and 40%), the helmet is noisy, unable to humidify the gas and delivers CPAP only, whereas nasal cannulas provide a high stream of warmed and humidified oxygen, but the PEEP effect completely disappears with an open mouth. Optimizing trigger levels and

pressure settings, as well as patient cooperation and interface fit, could improve treatment success.

58.5.2 NIV Limitations and Untoward Effects

NIV is absolutely contraindicated when the patient refuses this support, in the case of cardiac/respiratory arrest, and when there is immediate need for tracheal intubation. Relative contraindications are patient's reduced level of consciousness, agitation and/or poor collaboration, hemodynamic instability or arrhythmias, upper airway obstruction or excessive respiratory secretions, uncontrolled vomiting or upper gastrointestinal bleeding, multiple organ failure, facial trauma, and rapidly worsening respiratory failure [1].

Among NIV complications, treatment failure, delayed intubation, barotrauma, pulmonary aspiration/pneumonia, and hemodynamic compromise are the most threatening. Gastric insufflation, discomfort and/or claustrophobia, facial skin lesions, ocular damage, mucosal dryness/nasal congestion, arm edema, exacerbation of delirium, and carbon dioxide rebreathing (especially if device uses a common inspiratory and expiratory line) are also described [1].

Moreover, NIV increases the workload for both nurse and physiotherapist. A widespread implementation of NIV allows better familiarity with this respiratory support, whose related workload does not exceed the patient benefit anyway.

58.5.3 Locations

Most of the studies published so far, evaluating both prophylactic and curative use of NIV in cardiac postoperative settings, took place in the ICU. As previously mentioned, treating patients in the ICU allows a constant control and thus a safe application of the technique. Nevertheless, the nadir oxygenation values have often been observed 48–72 h after surgery, when most of the cardio-surgical patients have already been discharged from the ICU. On these bases, Olper and colleagues carried on a prospective RCT to evaluate whether NIV preserved its safety and efficacy in treating ARF even when performed in the ward [8]. Patients with mild to moderate hypoxemic ARF, namely with a PaO_2/FiO_2 ratio between 100 and 250, were randomized to perform cycles of CPAP on top of standard treatment with oxygen, early mobilization, diuretics, and deep breathing exercises. The improvement in oxygenation was significantly greater in the CPAP group, and only a few cases of hypotension were registered: after reduction of CPAP pressure or administration of low dose dopamine, blood pressure values turned back to normality, without need for treatment discontinuation. However, the authors did not report about baseline respiratory function or type of surgery. CPAP may extend its future indications to treatment of mild to moderate postoperative ARF, since it is cheap and easy to apply, and it remains safe and effective also in the main surgical ward, where the nurse–patient ratio and the experience of the staff in NIV management are lower than in the ICU.

58.5.4 Clinical Scenarios

Because it is simpler, requires lower sedation, and is prone to fewer complications than conventional IMV, NIV has been more widely used after cardiac surgery during the past few decades.

Earlier prophylactic use seems more effective in preventing reintubation than curative use once post-extubation respiratory failure occurs. A European survey reported satisfactory outcomes for preventive NIV use in selected high-risk patients: today, this represents postoperative NIV main indication. The curative approach seemed ineffective to most centers, reaching a 90% success rate only in the case of early application for mild-moderate respiratory failure [5].

Several reviews and meta-analyses updated the current evidence in this setting, with sometimes conflicting results [9–11]. In a work assessing the prophylactic NIV effectiveness in cardio-surgical patients, comparing it to conventional physiotherapy or oxygen therapy, the former failed to significantly reduce the risk for atelectasis, pneumonia, reintubation rate, and time of ICU stay [9]. Of note, patients preventively treated with NIV had higher arterial oxygenation and lower incidence of ARF than controls [9]. Similarly, in a review comparing prophylactic NIV plus standard therapy to the latter alone, the former failed to prevent cardiac/pulmonary complications and reintubation, although it could shorten the length of both ICU stay and hospital stay [10]. Interestingly, another study comparing NIV with conventional pulmonary-care strategies claimed that prophylactic NIV was capable of significantly reducing atelectasis and reintubation rate, mostly in patients older than 60 years and affected by preoperative hypoxemia [11]. Since a standardized and homogeneous use of this ventilation modality is lacking, results of the studies could be affected by ventilation settings and by the types of support administered in the control groups. Atelectasis incidence is known to be higher in patients undergoing internal thoracic artery harvesting and pleural drainage positioning. Many reports failed to acknowledge the relative percentage of patients undergoing CABG in intervention groups and control groups: this might be a further explanation for the contrasting results among studies in terms of pulmonary complication reduction, mainly atelectasis.

Although randomized controlled trials (RCTs) have been performed during the past few years, optimal timing, settings, and duration of postoperative NIV remains uncertain.

A recent Brazilian RCT found NIV performing better when administered immediately after rather than 24 h after orotracheal extubation [12]. In a population of patients undergoing on-pump CABG, immediate NIV decreased the loss of functional capacity (better results on 6-minute walk test), improved gas exchange (higher PaO_2/FiO_2 ratio), and reduced reintubation rate. Better functional capacity depends on blood oxygenation and tissue perfusion: consequently, better performance in the walking test is due to optimized lung function and cardiac output [12]. Another study focused on effects of prophylactic BiPAP after myocardial revascularization

in patients with preoperative left ventricular dysfunction. Although cardiac output was not directly evaluated, the authors speculated that enhanced tissue perfusion was at least in part due to an increase in cardiac performance, inferred by lower levels of arterial lactates and higher central-venous oxygen saturation values [13]. Because the oxidative capacity of respiratory muscles is compromised in heart failure patients, NIV-induced drop in respiratory work may represent another possible explanation for this outcome [13]. Of note, the study made no mention of concomitant support with either inotropic drugs or intra-aortic balloon pump.

Also, NIV strengthening with recruitment maneuver, namely the administration of higher PEEP for a short time during conventional NIV treatment, seemed safe and effective in reducing atelectasis (up to 94% of cases) and improving oxygenation in patients undergoing on-pump CABG [14].

Optimal duration of the treatment is also controversial. Some studies speculated NIV administration for a longer period could be necessary to obtain better results [10, 13], others argued that it was uncomfortable and reduced patient adherence to therapy, thus tipping the balance toward shorter treatments [14]. Furthermore, in a recent single-center observational study, prolonged NIV was associated with worse outcomes, in terms of morbidity and length of ICU/hospital stay. A preoperative impaired respiratory performance, i.e., a residual volume to TLC ratio greater than 46.5%, and the occurrence of stage 2–3 acute kidney injury within 48 h after surgery, as independent predictors for prolonged NIV, could be helpful to anesthesiologists in identifying high-risk patients [15].

Interestingly, a multicenter trial showed the noninferiority of high-flow nasal oxygen therapy (HFNC) to BiPAP in terms of treatment failure [16]. The study was not specific for cardiac surgery, since the population included patients undergoing thoracic interventions. Despite being noninferior to BiPAP with low levels of PEEP in reducing reintubation rate and switch/premature discontinuation of treatment, HFNC failed to improve oxygenation. Furthermore, prophylactic and curative use of both the treatments were not assessed separately; therefore, the results may be affected by poor outcomes of curative NIV.

All in all, according to the 2020 European Guidelines of Anesthesiology and Intensive Care Medicine, NIPPV may be preferred to CPAP to reduce the risk of atelectasis (class II, level C) and either NIPPV or CPAP may be considered to prevent further respiratory deterioration (class II, level B) in hypoxemic patients after cardiac surgery [17].

Although NIV is gaining acceptance also in pediatric patients after cardiac surgery, there is still little experience and few studies have been undertaken in this setting [18, 19]. Postoperative NIV is not associated with relevant complications, being viable and safe also in this population. The reported success rate ranges from 62% [18] to 85% [19], whereas its failure seems associated with the use of higher-pressure gradient and higher oxygen concentration [18]. The use of NIV in pediatric patients as alternative ventilator support following extubation failure is not well established so far.

58.6 Five Practical Rules for Successful Implementation of NIV

- Identify Who Most Benefits From Prophylactic Use
  - Perform a correct patient selection, focusing on individuals older than 60 years, smokers, with a low cardiopulmonary and renal physiologic reserve, obese or with a poor nutritional state. Despite that prophylactic NIV is safe and effective, its routine use in all patients undergoing cardiac surgery to prevent ARF cannot be recommended, since it has no clinical impact on hard outcomes.
- Detect Early Dysfunction in Curative Use
  - Detect pulmonary deterioration early and promptly administrate NIV, since poor oxygenation and respiratory fatigue due to difficult spontaneous breathing are known predictors of treatment failure. NIV also demonstrated its efficacy in treating mild to moderate ARF.
- Choose the Best NIV Modality for the Patient and Your Team
  - Start with low levels of PSV and PEEP (3–5 cmH_2O), then gradually increase them until therapeutic targets are achieved. Total inspiratory pressure (PSV + PEEP) must not exceed 25 cmH_2O. CPAP is easy to apply, also in the ward, whereas BiPAP requires a ventilator and thus the ICU location: prefer the former in hypoxemic patients and the latter in hypercapnic patients. The more relaxed and trained the patient is, the better NIV works: inform him/her properly to achieve a good synchrony with ventilator, correctly fit interface, and use mild sedation when necessary.
- Monitor the Patient
  - Close monitoring of the patient is mandatory. Frequently check level of dyspnea, respiratory rate, comfort, collaboration, and level of consciousness. Evaluate hemodynamics (by means of ECG and continuous blood pressure wave), oxygen saturation (with continuous pulse-oximetry) and values of oxygen, carbon dioxide, and pH.
- Recognize When to Stop NIV
  - Once a satisfactory recovery has been achieved, switch to COT. Conversely, in case of clinical worsening (altered mental status, poorer levels of pH, PaO_2 and $PaCO_2$, respiratory fatigue), intolerance/asynchrony with NIV, need to protect airways, persistent hemodynamic instability, or cardiac/respiratory arrest, immediately intubate and switch to invasive support. Remember that a late intubation carries higher risk of worse outcomes and mortality.

58.7 Conclusions and Future Perspectives

A certain degree of PPD virtually affects all the patients undergoing open-heart surgery. Since IMV carries life-threatening drawbacks [2, 3], weaning from the ventilator represents a key step toward ICU discharge and patient recovery. ExtF

represents a major clinical complication, since unplanned curative NIV seems to be suboptimal, whereas reintubation is known to have a poor outcome [3]. Several studies and meta-analyses validated that the prophylactic respiratory support with NIV in postoperative patients in cardiac surgery is safe and effective in preventing the onset of overt pulmonary complications [9–16]. Thus, its main usefulness is appreciated in the early treatment of patients with high risk of developing such complications, i.e., older subjects, with multiple co-morbidities and an intrinsic frailty. Further refinement of patient selection, identifying who is more likely to benefit from prophylactic NIV, as well as the patient-tailored choice of NIV modality, in terms of ventilator settings, fitting of interfaces and location to perform the treatment, are necessary to achieve the goal of minimizing IMV in the postoperative period.

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Use of Noninvasive Ventilation in Postoperative Patients in Abdominal Surgery

59

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Abbreviations

ARF	Acute respiratory failure
BIPAP	Bilevel positive airway pressure
COPD	Chronic obstructive pulmonary disease
COT	Conventional oxygen therapy
CPAP	Continuous positive airway pressure
EPAP	Expiratory positive airway pressure
HFNC	High flow nasal cannula
IPAP	Inspiratory positive airway pressure
NIPPV	Noninvasive positive pressure ventilation
NIV	Noninvasive ventilation
PEEP	Positive end-expiratory pressure
PPCs	Postoperative pulmonary complications

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_59

59.1 Introduction

Noninvasive positive pressure ventilation (NIPPV) has become the standard for treating acute respiratory failure (ARF) in the intensive care unit [1, 2]. However, to date the role of the noninvasive ventilation (NIV) in patients with acute pulmonary complication after surgery is not defined. In general, 5–10% of all surgical patients develop postoperative respiratory failure and up to 40% of those who underwent abdominal surgery [3]. Jaber et al. [4] describe acute respiratory failure as a severe respiratory distress with dyspnoea, a respiratory rate of more than 25 breaths/min, contraction of accessory inspiratory muscles, paradoxical abdominal motion, peripheral oxygen saturation less than 92% while breathing at least 10 L/min of oxygen, or partial pressure of arterial oxygen (PaO_2) less than 60 mmHg on room air or less than 80 mmHg while breathing supplemental oxygen. The pathophysiological effects of anaesthesia and abdominal surgery on the respiratory system include prolonged lung volume reductions, diaphragm dysfunction, alveolar collapse and reduced mucociliary clearance. All of these increase the likelihood of development of postoperative ARF. Several strategies to maintain alveolar patency in such patients are available and may assist in postoperative pulmonary complications (PPCs) prevention. In addition to the NIPPV, other types of postextubation respiratory support have been proposed and compared for management of pulmonary complications and prevention of re-intubation [5]. Continuous positive airway pressure (CPAP) and high flow nasal cannula (HFNC) benefit hypoxaemic patients with acute peri-operative/peri-procedural respiratory failure [6]. Therefore, we can say that there is a universal agreement to the use of NIV, CPAP and HFNC for patients at high risk of re-intubation, but the specific circumstances in which each therapy should be used are unclear.

59.2 Current Evidence and Discussion

Several studies suggest a reduction in PPCs after high risk abdominal surgery may be achieved with use of postoperative NIV [6]. The definition of high risk has varied in the literature, but most clinicians would agree that patients with a history of chronic obstructive pulmonary disease (COPD) or congestive heart failure, body mass index >40 kg/m^2, age > 65 years, multiple spontaneous trial failures, excessive secretions and upper-airway obstruction meet the definition. Eighty patients, who had previously received a COPD diagnosis from a pulmonologist, undergoing elective abdominal surgery (hepatectomy, Whipple procedure, incisional hernia repair, splenectomy cholecystectomy, omentectomy and nephrectomy) were randomly allocated into four group to compare the effects of high/low- flow CPAP (Respironics BiPAP Vision device and flow generator HAROL, Italy), bilevel positive airway pressure (BIPAP) and spontaneous ventilation with oxygen support [7]. All patients were transferred to the recovery room following extubation. In the first group, prophylactic BIPAP was applied for 60 min with the parameters (with Respironics BIPAP Vision device), FiO_2 40%, IPAP (inspiratory positive airway pressure)

12 cmH_2O and EPAP (expiratory positive airway pressure) 5 cmH_2O; in the second group prophylactic CPAP was applied for 60 min with the parameters CPAP (flow generator HAROL, Italy), CPAP level 5 cmH_2O and FiO_2 40%; in the third group prophylactic CPAP was applied for 60 min with the parameters (with Respironics BIPAP Vision device) CPAP level 5 cmH_2O and FiO_2 40%; in the fourth group 6 L min^{-1} oxygen was applied with a face mask for 60 min, deep breathing exercises and respiratory physiotherapy were conducted on the patients. No statistically significant difference was found between the groups in terms of $PaCO_2$, PaO_2 and SpO_2. Nevertheless, the authors concluded that CPAP ventilation with a mechanical ventilator in high risk patients could be a valid prophylactic respiratory support. Jaber et al. [8] conducted a multicentre randomised clinical trial of NIV in surgical patients who developed hypoxemic acute respiratory failure after abdominal surgery. In accordance with the Declaration of Helsinki, the trial was conducted between May 2013 and September 2014 in 20 French intensive care units among 293 patients that were randomly assigned to receive standard oxygen therapy (up to 15 L/min to maintain SpO_2 of 94% or higher) or NIV delivered via facial mask (inspiratory pressure support level 5–15 cmH_2O; positive end-expiratory pressure 5–10 cmH_2O; fraction of inspired oxygen titrated to maintain $SpO_2 \geq 94\%$). Patients had undergone laparoscopic or non-laparoscopic elective or non-elective abdominal surgery under general anaesthesia. The outcomes were tracheal reintubation within 7 days following randomisation, gas exchange, health care-associated infections rate within 30 days, invasive ventilation-free days at day 30 and 90-day mortality. Noninvasive ventilation improved the primary outcome of the 293 patients included in the intention to treat analysis; reintubation occurred in 49 of 148 patients (33.1%) in the NIV group and 66 of 145 (45.5%) in the standard oxygen therapy group at 7 days after randomisation (absolute difference, −12.4%; 95% CI, −23.5% to −1.3%; $p = 0.03$). Noninvasive ventilation was associated with significantly more invasive ventilation-free days compared with standard oxygen therapy (25.4 vs. 23.2 days; absolute difference, −2.2 days; 95% CI, −0.1 to 4.6 days; $p = 0.04$), while fewer patients developed health care-associated infections (43/137 [31.4%] vs. 63/128 [49.2%]; absolute difference, −17.8%; 95% CI, −30.2% to −5.4%; $p = 0.003$). At 90 days, 22 of 148 patients (14.9%) in the NIV group and 31 of 144 (21.5%) in the standard oxygen therapy group had died (absolute difference, −6.5%; 95% CI, −16.0% to 3.0%; $p = 0.15$). The findings of the randomised clinical trial support use of NIV, because compared with standard oxygen therapy, it reduced the risk of tracheal reintubation within 7 days. Faria et al. [9] compared noninvasive positive pressure ventilation versus standard oxygen therapy in the treatment of acute respiratory failure after upper abdominal surgery. This review included two trials involving 269 participants [10, 11]. The authors concluded that CPAP or bilevel NIPPV is an effective and safe intervention for managing postoperative lung complications. They also reported that NIPPV may be considered in patients with acute respiratory failure after oesophageal surgery, when the insufflation pressure level was less than 12 cmH_2O. In 2019, a pilot study was conducted with 130 patients randomly assigned for usual care of continuous high-flow nasal oxygen therapy for 48 h following extubation or usual care plus additional early intermittent

NIV [12]. The eligibility for therapy was defined using the Melbourne Group Scale; PPCs is diagnosed when four or more of eight screening criteria are present in a 24-h day. Although NIV is well tolerated by most patients, it is not entirely free from serious adverse side effects. This randomised controlled trial clearly describes the NIV-complications. The absolute contraindications are cardiac or respiratory arrest, severe agitation or encephalopathy, untrained pneumothorax or intraoperative pneumothorax with intercostal catheter, uncontrolled vomiting, inability to protect airway, severe upper gastrointestinal or haemoptysis, need for immediate intubation and facial trauma. Anatomical leak and severe hypotension are the major adverse event. The problems related to interface–ventilator interaction during NIV and remedies, or arm oedema, CO_2 rebreathing, claustrophobia, discomfort, nasal skin lesions and noise, are reported extensively in the literature. High-flow nasal cannula has the distinct advantage over NIV and CPAP of being more comfortable and least likely to fail because of patient tolerance, but it should not be the choice of therapy when specific and high levels of PPEP are required or when ventilation is needed. CPAP and HFNC have been advocated for the treatment of hypoxemic respiratory failure; however, if the failure is a result of atelectasis, then CPAP is again the therapy of choice because PEEP (positive end-expiratory pressure) is indicated and can be applied at a precise level. Patients who are hypercarbic require ventilation, hence NIV is indicated. In patients with hypoxemia who require either CPAP or HFNC, the choice is dependent on the need for precise and high PEEP levels. The OPERA (Optiflow for prevention of post-extubation hypoxemia after abdominal surgery) trial is the first randomised controlled study powered to investigate whether early application of HFNC following extubation after abdominal surgery prevents against postoperative hypoxemia and pulmonary complications [13]. High-flow nasal cannula oxygen delivers a flow-dependent positive airway pressure and improves oxygenation by increasing end-expiratory lung volume. This ventilatory support, which delivers high-flow heated and humidified oxygen and air via nasal prongs at a prescribed fraction of inspired oxygen and a maximum flow of 60 L/min, is an attractive alternative to conventional oxygen therapy. Between 6 November 2013 and 1 March 2015, 220 patients were randomly assigned to receive either HFNC (n = 108) or standard oxygen therapy (n = 112). Participants were provided with high-flow nasal oxygen therapy postoperatively for a median duration of 15 (IQR 12–18) h following extubation. HFNC oxygen therapy is delivered via the Optiflow™ system (Fisher & Paykel Healthcare Ltd., Auckland, New Zealand) using an MR850 heated humidifier and an RT202 breathing circuit. The primary endpoint was absolute risk reduction for hypoxaemia at 1 h after extubation and after treatment discontinuation. Secondary outcomes included occurrence of postoperative pulmonary complications within 7 days after surgery, the duration of hospital stay and in-hospital mortality. Although prophylactic use of HFNC may have potential therapeutic advantages over conventional oxygen therapy for respiratory support after extubation, evaluation is limited in the early post-extubation surgical period and benefit remains to be established. No difference in the absolute risk reduction of postoperative hypoxaemia 1 h after extubation [21% vs. 24%, absolute risk reduction −3 (95% CI −14 to 8)%, P 1/4 0.62] were reported. Several

confounding factors, such as postoperative pain management, intraoperative fluid administration and respiratory chest physiotherapy, can be suggested. The authors concluded that the routine use of postoperative HFNC after extubation does not seem to be justified in similar patients. A single French study used the FreeO_2 system (Oxynov, Quebec, Canada) in the post-anaesthesia care unit in a patient population admitted for major abdominal and thoracic surgery [14]. FreeO_2 is an innovative device for treatment of hypoxemia during the immediate postoperative period. The system, using artificial intelligence closed-loop adjustments and predictive analytics, can perform frequent and rapid O_2 variations. FreeO_2 is equipped with a SpO_2 monitor and an electronically controlled valve that automatically adjusts O_2 flow from 0 to 20 L/min on a per-second basis, with a 0.1 L/min precision, according to a closed-loop algorithm to reach the predetermined SpO_2 target. Primary outcome is the percentage of time spent in the target zone of oxygen saturation during a 3-day time frame. The target zone of oxygen saturation is SpO_2 = 88–92% for patients with COPD and 92–96% for patients without COPD. Automated O_2 administration is not the standard of care for postoperative patients. Although this study supports the FreeO_2 system, more quality studies are needed to confirm these findings. The European Respiratory Society/America Thoracic Society clinical practice guidelines recommends the use of NIV and/or CPAP for patients with postoperative ARF6. No guidelines recommended the use of any of these therapies in patients at low risk of re- intubation. Leone et al. [15] reported the guidelines that The European Society of Anaesthesiology and European Society if Intensive Care Medicine developed for the use of NIV in the hypoxaemic patient after surgery. Among 19 recommendations, the two grade 1B recommendations state that: in the peri-operative/peri-procedural hypoxaemic patient, the use of either NIPPV or CPAP is preferred to COT for improvement of oxygenation; and that the panel suggest using NIPPV or CPAP immediately post-extubation for Hypoxaemic patients at risk of developing acute respiratory failure after abdominal surgery. The expert panel outlined five clinical questions regarding treatment with noninvasive respiratory support techniques: What goals of therapy? Which patient populations? What monitoring, laboratory, radiological tests during treatment? Prevention complications? Location of care? Specifically, after upper abdominal surgery for hypoxaemic patients, the authors suggest CPAP or NIPPV rather than COT (conventional oxygen therapy) to reduce the risk of hospital-acquired pneumonia and its associated complications, with level of evidence 2A. In general, the first query determined the target of therapy with NIV and the panel concluded either NIPPV or CPAP to improve oxygenation, to prevent the risk of reintubation, to reduce the mortality rate, as compared with COT in the surgical patients with acute respiratory failure. The second query identified patients may benefit from the use NIPPV or CPAP. With level 1B the noninvasive support is suggested immediately post estimation for hypoxaemic patients after abdominal surgery. Periodic clinical assessment, continuous monitoring (pulse oximetry, noninvasive blood pressure, electrocardiography) and periodic sampling for partial gas pressures were recommended based on indirect evidence. Semirecumbent positioning in patients at risk of aspiration, helmet versus face mask are tips to keep in mind. No recommendation regarding the location of care is in

these guidelines due to the scarcity to date. The authors also highlight the gaps in the evidence, in particular, no information regarding surgical complications in perioperative patients. NIV with high pressures has traditionally been contraindicated after major gastric and oesophageal surgery due to the theoretical risk of gastric dilatation and disruption of surgical anastomoses.

59.3 Conclusion

Abdominal surgery is most often followed by diaphragmatic dysfunction and a marked decrease in vital capacity, which often leads to respiratory failure or massive atelectasis. Mechanical ventilation with reintubation is necessary when any of the following major criteria or three or more of the minor criteria are met. Major criteria are: respiratory arrest, respiratory pauses with loss of consciousness or gasping respiration, encephalopathy and cardiovascular instability. Intolerance or discomfort to NIV, a decrease in PaO_2, or $PaCO_2$ by 20% or more, an increase in the respiratory rate, difficulty in removing airway secretions are minor criteria that must always be kept in mind. Certainly, NIV is an efficacy treatment for pulmonary complications. This result should, however, be interpreted with caution [16].The ability to anticipate and to provide early treatment to potentially modifiable adverse clinical events such as postoperative hypoxemia is of critical importance to prevent the development of subsequent complications. In surgical patients, the choice between NIV,CPAP or HFNC is influenced by the PEEP levels needed. HFNC is an appropriate alternative to NIV in patients who do not need high levels of PEEP. Patient compliance is absolutely essential and the most determining factor of success or failure of noninvasive ventilation. Our findings support the use of NIPPV for management of ARF after surgery. As enthusiastic supporters of using NIV in postoperative patients, we acknowledge that one of the greatest barriers to its more widespread application is the uncertainty that exists over which mode of support should be used in which patients. Future studies should investigate developing a specific protocol for patients at high risk for ARF.

Key Recommendations

- Post operative pulmonary complications following surgery are common and associated with increased morbidity and mortality and hospital length of stay
- Incision site pain, residual anaesthetic effect, abdominal surgery and lying position decrease lung compliance and cause lung atelectasis and diaphragm dysfunction
- NIPPV can be effectively used in the first-line intervention for treatment and prevention of ARF following abdominal surgery. NIPPV reduces the risk of reintubation
- HFNC should be considered in the management of post-extubation respiratory failure after surgery

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60.1 NIMV in Thoracic Surgery

After lung resections, respiratory dysfunction lasting for a few days can be observed due to the loss of lung volume [1]. This impairment in respiratory function may develop due to many reasons such as thoracotomy pain, anesthesia, reflex inhibition of the phrenic nerve, closure of the distal airways, and loss of parenchymal functions [2]. Surgery, anesthesia, postoperative pain or pain relievers such as opioids cause hypoxemia and hypercapnia by increasing respiratory workload, decreasing lung volume, weakness of respiratory muscles and deterioration of diaphragmatic activity. Surgery adversely affects abdominal, thoracic and diaphragmatic muscle strength, reduces phrenic nerve stimulation and induces pain. Pain also causes a decrease in functional residual capacity by suppressing the cough reflex [3]. Risk factors for the development of postoperative respiratory failure vary according to the patient and the operation. Advanced age, impaired functional status, smoking

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_60

history, obesity, presence of comorbid diseases such as chronic obstructive pulmonary disease (COPD), low albumin, and high blood urea nitrogen are the most well-known reasons for the patient. The urgency of the surgery, the type of lung resection, and the chosen anesthesia method (general or spinal) are also reasons related to the surgery.

Pulmonary gas exchange is impaired due to reasons such as lung parenchyma lost after lung resections and respiratory depression caused by narcotics. The presence of pleural air leakage may also increase the workload spent on breathing and cause deterioration of pulmonary gas exchange. All of these factors cause pulmonary complications such as secretion accumulation, atelectasis, pneumonia, and acute respiratory distress after long-term mechanical ventilator-dependent lung resection surgery, and contribute to the complication rate up to 24–41% [4]. This increases the length of hospital stay, cost, and mortality. Acute respiratory failure (ARF) is a common and severe complication that is frequently associated with pulmonary complications after major surgeries, especially after lung resection [5]. The risk of postoperative ARF development is generally defined as an increase in respiratory rate (>25/min), use of auxiliary respiratory muscles, paradoxical respiration, and deterioration in arterial blood gases (PaO_2 < 60 mmHg in room air, PaO_2/FiO_2 < 250, $PaCO_2$ > 50 mmHg) [6, 7]. In many studies, it has been shown that PaO_2 decreases and PCO_2 increases after resectional lung surgery [8].

High mortality rates have been reported in patients who developed ARF after lung resection and underwent tracheal intubation and mechanical ventilation [9]. These high mortality rates are often due to complications of postoperative intubation and prolonged mechanical ventilation [10]. In addition, mechanical ventilation is clearly associated with many vital complications such as pulmonary infection, bronchial stump separation, prolonged parenchymal air leak, and bronchopleural fistula (BPF) [11]. Therefore, it has been shown that mechanical ventilation should be avoided as much as possible after lung resection and conservative treatment (noninvasive ventilation–NIV) should be applied primarily in selected cases [12]. Although preventing the development of ARF in patients undergoing surgery is an important goal, preventing invasive mechanical ventilation as much as possible in patients with ARF will positively change the prognosis in these patients.

NIV is generally accepted as an effective respiratory support in case of acute respiratory failure, and its use is increasing in postoperative patients. Studies examining the use of NIV in intensive care units show that the use of NIV has increased from 16% to 24% in the past 5 years [13]. In an 8-year retrospective study, Carlucci et al. reported their NIV experience in patients with chronic obstructive pulmonary disease (COPD), and stated that the treatment was successful even in more severe patient groups with the experience increasing over the years [14]. Although the use of NIV in non-surgical ARF has been well described in many randomized controlled studies, there is no consensus for its use before and/or after surgery [15]. NIV application has been reported in obese patients after gastroplasty, in the treatment of atelectasis after upper abdomen surgery, for prophylaxis before and after thoracic surgery, and as postoperative prophylaxis after coronary artery surgery [16].

60.1.1 NIV Initiation Criteria and Application Procedure: In the Post-Operative Process

1. Respiratory rate greater than 25/min,
2. Active work of auxiliary respiratory muscles,
3. Paradoxical abdominal movement,
4. PaO_2 is 60 mmHg and below in room air,
5. PaO_2/FiO_2 being 250 mmHg and below in oxygen support,
6. $PaCO_2$ being greater than 50 mmHg,
7. Those who have at least three of the criteria for abnormality in the chest X-ray (such as alveolar consolidation, atelectasis, or interstitial pulmonary edema) can be considered as ARF.

In addition to these findings, NIV treatment can be applied in a patient who is conscious, can communicate, is hemodynamically stable, and can protect the airways. Absolute and relative contraindications for postoperative NIV therapy are shown in Table 60.1.

In ARF after lung resection, NIV can be applied as continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP) [17]. Care should be taken to ensure that the mask covers the nose and mouth (oronasal or facial mask). Since the leakage from the mouth will be reduced with the facial mask used, the best benefit will be achieved even during sleep. In a patient breathing spontaneously with CPAP, a constant positive pressure is applied throughout the entire respiratory cycle, while BiPAP is associated with a higher inspiratory airway pressure (IPAP–inspiratory positive airway pressure) and a lower expiratory airway pressure ventilation (EPAP–expiratory positive airway pressure) is provided. IPAP and EPAP

Table 60.1 Absolute and relative contraindications for postoperative NIV therapy

Absolute
1. Cardiac or respiratory arrest
2. Multiple organ failure
3. Severe agitation and encephalopathy
4. Copious secretions
5. Uncontrolled vomiting
6. Inability to protect airway
7. Severe upper gastrointestinal bleeding or hemoptysis
8. Immediate endotracheal intubation necessary
9. Facial trauma
10. Hemodynamic instability or unstable cardiac arrythmia
Relative
1. Mildly decreased level of consciousness
2. Progressive severe respiratory failure
3. Uncooperative patient who can be calmed or conformed

settings valid for non-ICU ventilators are similar to pressure support ventilation (PSV–pressure support ventilation) and positive end-expiratory pressure (PEEP) for intensive care ventilators. A positive pressure of 7–10 cmH_2O for CPAP is sufficient to keep the tracheal pressure positive during the entire respiratory cycle. At the same time, this pressure level is well tolerated and no significant hemodynamic effects are observed. BiPAP mode, on the other hand, should be started with EPAP, that is, PEEP, and then the respiratory rate and comfort of the patient should be considered, with IPAP 2 cmH_2O above PEEP, at a maximum of 20–25 cmH_2O, or with an expiratory tidal volume of 6–10 mL/kg. This should be taken into consideration when increasing the settings.

Riviere et al., in their study of 135 patients who underwent NIV after lung surgery, stated that pressure support was increased over time and that while it was 8 cmH_2O at the beginning, the exhaled tidal volume was adjusted to be 8–10 mL/kg and the respiratory rate to be less than 25/min. In the same study, PEEP was initially set to 4 cmH_2O [13]. Previously published publications have stated that in most cases, target blood gas values can be reached with inspiratory 8 cmH_2O and expiratory 4 cmH_2O pressures [18]. The importance of appropriate pressure support is related to the stage and type of respiratory distress as well as respiratory compliance. Postoperatively applied CPAP can increase functional residual capacity to preoperative values, improve oxygenation, and protect respiratory muscles. The use of CPAP is a technique that has features such as reducing postoperative atelectasis, improving gas exchange, reducing the need for intubation, and providing rapid recovery. Although CPAP has been shown to be more effective than routine respiratory physiotherapy, when CPAP is interrupted, deterioration in functional residual capacity occurs within a few minutes.

Noninvasive positive pressure ventilation (NPPV), also known as BiPAP, has been accepted as a therapy in acute hypercapnic and hypoxemic ARF [19]. Compared to CPAP, BiPAP uses a relatively high inspiratory pressure. Thus, ventilation with BiPAP is ensured to reach all areas with alveolar collapse. BiPAP minimizes the respiratory workload. The theoretical benefit of BiPAP, combining PEEP and inspiratory pressure support results in increased lung ventilation, reopening or improvement in atelectatic alveoli, and thus an improvement in gas exchange. Another benefit of applying BiPAP is that this process can also be performed under service conditions. In the first 24 h, preventive (prophylactic) NIV should be administered for about 30–45 min at 24 h intervals, and therapeutic (therapeutic) NIV for about 60–90 min at 2-to-3 h intervals, and the total administration should be 3–12 h a day. After lung surgery, therapeutic NIV should be administered intermittently every 3 to 4 h and preventive NIV at least 5 times per h each day.

60.1.2 General Benefits and Possible Harms of NIV

NIV is a safe method that improves gas exchange as effectively as intubation in cases with various ARF patterns, and it has been shown to be a very good alternative to invasive mechanical ventilation. It has been stated that NIV clearly reduces the

need for intubation, lower respiratory tract infection and pneumonia risk, thus reducing hospital stay and mortality/morbidity, and dealing with airway secretion will be more successful [20]. It is generally believed that NIV improves pulmonary gas exchange by opening previously closed lung sections.

The most important physiopathological mechanism underlying the effectiveness of NIV in the treatment of postoperative ARF is increased intrathoracic pressure. With intrathoracic positive pressure, collapse in the airways and alveoli is prevented, FRC increases, atelectasis development is prevented, interstitial edema decreases, and gas exchange increases. In addition, the afterload of the heart decreases, diaphragm activity improves, and respiratory workload decreases [21]. NIV applied with positive pressure provides re-expansion of microatelectatic areas, which facilitates recovery in blood gas. In addition, it has been stated that it may prevent a decrease in cardiac output and oxygen transport to organs by reducing venous return [22]. However, these issues are controversial. In addition, it has been reported that NIV administration is a relative contraindication in the case of postoperative hypercapnic ARF [13]. Some studies support the opposite view and have shown that NIV is effective in postoperative hypercapnic ARF [23].

The use of preventive and/or therapeutic NIV before and/or after lung resection is still a controversial issue despite many clinical studies. Perrin et al. [8] in randomized controlled and prospective studies have shown that NIV administered before and after surgery has benefits. In this study, patients were required to receive standard therapy without or with NIV at home for 7 days before surgery and for 3 days after surgery. In this randomized controlled study, 32 patients with an FEV1 < 70%, who were planned for elective lobectomy due to lung cancer, were included in the study and randomized control group (n = 18, standard treatment) and study group (n = 14, 7 days preoperatively in addition to standard treatment and NIV administration for 3 days postoperatively). It was observed that arterial blood gas, FVC, and FEV1 in room air decreased significantly in both groups in the first postoperative hours compared to preoperative values, but PaO_2, FVC, and FEV1 were significantly higher in the study group. It was observed that using NIV significantly improved arterial blood gas data (pH, $p = 0.0003$; PaO_2, $p = 0.0006$; $PaCO_2$, $p = 0.04$) and respiratory functions (FVC, $p = 0.03$; FEV1, $p = 0.02$) when compared with the control group. The rate of atelectasis was 14.2% in the NIV group and 38.9% in the control group ($p = 0.15$). Arrhythmia and drainage time were not different between the two groups. The length of hospital stay was statistically higher in the control group than in the study group (19 ± 3 days vs. 12 ± 1 day, $p = 0.04$). In another study, it was shown that NIV, which is used as a preoperative and postoperative prophylactic, accelerates the recovery of early postoperative hypoxemia after lung surgery and corrects the deterioration in respiratory functions [8]. In a study involving cases with acute exacerbation of COPD it was shown that AFR was more easily treated in cases who had previously used NIV at home, which suggests that preoperative NIV administration should be kept in mind in selected cases [24]. In their prospective randomized controlled study of 48 cases, Auriant et al. compared standard oxygen therapy (n = 24) and additional NIV administration to standard treatment (n = 24) in patients who developed ARF after lung resection [6]. This study

was discontinued due to the fact that intubation requirement (20.8% vs. 50%, $p = 0.035$) and mortality (37.5% vs. 12.5% vs. 12.5%, $p = 0.045$) were higher in the standard treatment group than in the NIV-administered group. It has been shown that in selected cases developing ARF after lung resection, NIV reduces the need for invasive mechanical ventilation and mortality without causing an increase in the frequency of side effects. In their review, Jaber et al. examined the clinical results and indications of NIV application in cases with ARF after surgery [24]. The results of this study stated that the application of NIV in thoracic, cardiac and abdominal surgery, facilitates postoperative ARF management and reduces postoperative complications.

60.2 NIMV in Neurosurgery

Respiratory failure is a serious complication after neurosurgical procedures. The major patient group in the neurosurgery population is patients with traumatic brain injury and spinal cord injury. The incidence of RF in these patients has been reported as 4.7/1000/year [25]. It is thought that the high mortality after respiratory failure may be related to age, localization of procedures, and neoplastic disease. In surgical procedures, resection of infratentorial mass lesions has a higher risk of postoperative respiratory failure due to several factors [26]. In their study evaluating 1699 patients, Flexman et al. reported respiratory failure in 3.8% of supratentorial procedures and 6.6% of infratentorial procedures. There are limited studies on the use of noninvasive ventilation support in neurosurgical procedures. Studies have mostly focused on the use of NIV in neuromuscular diseases [27]. The main physiopathology in these patients is respiratory failure due to loss of airway protective reflexes or decreased respiratory drive. Consequently, they are at risk for pulmonary complications such as pneumonia and acute respiratory distress syndrome (ARDS) [28].

Mechanical ventilation options used after neurosurgical procedures ensure reliable oxygen delivery, control arterial carbon dioxide rise, and also modulate cerebral hemodynamics [28]. However, it can also have deleterious effects on the brain due to the complex physiological interactions between the intrathoracic, central venous, and intracranial compartments [28]. Therefore, there is no consensus on its use. No recommendation has been made regarding the use of noninvasive positive pressure ventilation in patients with hypercapnic or mixed hypercapnic/hypoxemic respiratory failure. Components such as volutrauma, atelectrauma, oxygen toxicity, and biotrauma have been shown to contribute to ventilator-induced lung injury in mechanically ventilated patients [29]. Therefore, patients should adopt a ventilation approach based on the principles of minimal tidal volume, the use of high levels of positive expiratory pressure (PEEP), and the avoidance of high inspired oxygen concentrations [29]. On the other hand, there are concerns that using PEEP in brain-damaged patients reduces cerebral blood flow, resulting in an increase in ICP as well as a decrease in mean arterial pressure [29]. However, administration of mild to moderate levels of PEEP does not appear to cause any clinically significant effect on ICP [30]. There are also newer modalities such as prone positioning,

high-frequency oscillatory ventilation, high-frequency percussion ventilation, and extracorporeal lung support, but these treatment options have only been explored in neurocritical patients and may be considered in patients refractory to standard ventilation therapy modalities [30].

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Noninvasive Ventilation in Solid Organ Transplantation

61

Vasileios Michailidis

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Abbreviations

ALI	Acute Lung Injury
ARDS	Acute Respiratory Distress Syndrome
ARF	Acute Respiratory Failure
CMV	Cytomegalovirus
COT	Conventional Oxygen Therapy
HFNC	High Flow Nasal Cannula
HPS	Hepatopulmonary Syndrome
ICU	Intensive Care Unit
IMV	Invasive Mechanical Ventilation
NIV	Noninvasive Ventilation
NPPV	Noninvasive Positive Pressure Ventilation

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_61

OLT	Orthotopic Liver Transplantation
PEEP	Positive End Expiratory Pressure
PRC	Postoperative Respiratory Complication
RCT	Randomized Controlled Trial
SOT	Solid Organ Transplantation

61.1 Introduction

SOT has become an established and practical definitive treatment option for patients with end-organ dysfunction. With the advent of surgical skills, newer technologies, and the use of innovative immunosuppressive strategies, the rate of SOT has increased significantly over the past decades. The survival rates after SOT have dramatically improved as a direct consequence of the extension of the applicability of SOT to an increased number of patients suffering from end-stage failure of various organs. However, these patients are at high risk of a number of life-threatening complications, either related to their immunosuppressive regimens and infectious events or to other types of complications. Pulmonary edema, primary graft dysfunction, diffuse alveolar hemorrhage, drug-related pulmonary toxicity, or acute interstitial pneumonia from various causes are the most frequent complications [1, 2]. Respiratory complications, especially ARF, are the principal cause of morbidity, together with acute organ rejection, and one of the main causes of mortality [3]. Approximately 5% of patients undergoing renal, hepatic, cardiac, or pulmonary transplantation develop pneumonia in the period after transplantation, with an attributable mortality of 37% [3]. During the immediate postoperative period, pneumonia is generally caused by Gram negative germs that often colonize patients in the ICU, while in the late postoperative phase, Cytomegalovirus (CMV) is one of the most common causes of pneumonia [4, 5]. Pneumocystis carinii is also a cause of pneumonia occurring at least 3 months following transplantation. Once these patients develop ARF, they often require ICU admission and intubation for mechanical ventilation. In these cases, mortality of immunocompromised patients is particularly high, ranging from 50% to 70% [6, 7]. Therefore, NIV, which is administrated without the use of an endotracheal tube, can be used as an alternative to invasive mechanical ventilation (IMV) in treating immunocompromised patients. Applying NIV can avoid side effects directly related to endotracheal intubation and IMV, such as ventilator-associated pneumonia, excessive sedation, upper-airway injuries and tracheomalacia, and can also lead to a better clinical outcome [8]. The beneficial effects of NIV in ARF include lung recruitment with proper use of positive end-expiratory pressure (PEEP), improvement in hypoxia and dyspnea, and relief of respiratory muscle fatigue [9].

61.2 Noninvasive Ventilation and Solid Organ Transplantation

61.2.1 Liver Transplantation

Orthotopic liver transplantation (OLT) is currently the only definitive treatment for patients with acute liver failure and end-stage liver cirrhosis. However, postoperative respiratory complications (PRCs) are frequent after liver transplantation and their incidence is reported to be between 44% and 87% [10–15]. Persistent pulmonary edema, pleural effusion, and atelectasis have been reported to be major independent predictors of post-transplant pneumonia [12]. All of these respiratory disorders can affect lung compliance and alveolar gas exchange and, when severe, may necessitate tracheal intubation and mechanical ventilation. Thus, PRCs after transplantation negatively impact mortality [10, 11, 13], with recent data showing a mortality rate of 40% [16]. In the early stages after transplantation, pulmonary complications may prolong intubation time and increase the risk of systemic infectious complications. Prolonged mechanical ventilation due to refractory respiratory failure is a marker of poor recipient recovery, predisposes a recipient to long-term ventilator dependency, and predicts further complications. Rapid extubation followed by an immediate NIV application should be considered in this setting to shorten and accelerate the weaning process.

Several factors are involved in the onset of PRCs and many preoperative and intraoperative variables have been associated with different degrees of severity of respiratory impairment after OLT. Chihara et al. [17] found that controlled preoperative infection, ABO blood type incompatibility, and postoperative pneumonia prior to the start of NIV in patients with liver transplantation were early predictors of NIV failure and independent risk factors for reintubation. Investigators proposed that if patients do not show improvement in the PaO_2/FiO_2 after NIV, early endotracheal intubation with mechanical ventilation should be considered as an alternative therapy. Reintubation often becomes necessary in the postoperative period of a complicated liver transplant, either within the first few days or at any time later.

Hepatopulmonary syndrome (HPS) is defined as a defect in arterial oxygenation induced by intrapulmonary vascular dilations. HPS is an independent risk factor for long-term mortality in patients with cirrhosis and liver transplantation is the only effective therapy. NIV therapy in patients with severe HPS immediately after extubation might protect them from severe hypoxemia after transplantation and from complications necessitating reintubation and might improve their prognosis [18]. Cirrhotic patients diagnosed with HPS had higher mechanical ventilation time, more need of noninvasive ventilation, as well as longer intensive care unit and hospital stay [19].

61.2.2 Kidney Transplantation

Kidney transplants account for about two-thirds of all solid organ transplants [20]. In particular, renal transplant recipients may be at increased risk for acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), most notably in the event of graft failure or antilymphocyte globulin therapy for rejection [21]. In the early posttransplant period (<1 month) cardiogenic pulmonary edema accounted for one-half of the diagnoses, while opportunistic fungal infections and drug-related pulmonary toxicity were mostly diagnosed in the late posttransplant period (>6 months). Moreover, opportunistic pneumonia is among the leading causes of death in kidney transplant recipients [22, 23]. In these patients, ARF is associated with high mortality and graft loss rates and accounts for one-half of the ICU admissions. NIV efficacy has been retrospectively compared to that of high-flow nasal cannula (HFNC) in renal transplant recipients with hypoxemic ARF secondary to severe pneumonia and the approaches reached similar outcomes in mortality and length of ICU stay [24]. Twenty patients received HFNC and the other 18 received NIV as the initial respiratory support. The ICU mortality in the HFNC group was 5% compared with 22.2% in the NIV group ($p = 0.083$). The median length of the ICU stay was 12 days in the HFNC group, compared with 14 days in the NIV group ($p = 0.297$). The number of ventilator-free days at day 28 was significantly higher in the HFNC group than in the NIV group (26 ± 3 vs. 21 ± 3; $p = 0.001$). The incidences of both pneumothorax (0% vs. 22.2%; $p = 0.042$) and skin breakdown (0% vs. 22.2%; $p = 0.042$) were significantly lower in the HFNC group.

61.2.3 Lung Transplantation

As with any other type of surgery, respiratory complications such as atelectasis, pneumonia, pulmonary edema, and ARF due to different causes, can arise in the postoperative period of lung transplantation. Furthermore, prolonged intubation has been considered one of the main predisposing factors for developing nosocomial pneumonia after transplantation, and it has been associated with increased length of ICU. NIV is a choice to shorten weaning time and avoid reintubation following lung transplantation. The expected benefits of NIV are increased lung gas volume, improved gas exchange, reduced atelectasis, reduced respiratory effort, and reduction in the incidence of nosocomial infections. Small non-controlled studies in patients receiving lung transplantation (single or bilateral) have reported the efficacy of NIV in preventing endotracheal intubation, and treating ARF [25–27]. Rocco et al. [28], in a prospective non-randomized study, evaluated the application of noninvasive positive pressure ventilation (NPPV) in a group of 21 patients developing postoperative ARF after bilateral lung transplantation. NPPV administration was well tolerated, improved gas exchange, and the large majority of patients (86%) avoided intubation and were discharged from the ICU.

Even though NPPV is a viable option for lung transplant recipients with ARF, extreme caution should be exercised when used in patients with high severity of

illness (APACHE III >78) and/or severe hypoxemia ($PaO_2/FiO_2 \leq 151$) owing to the previously mentioned factors associated with NPPV failure. Wiles et al. [29] found that ICU lung transplant recipients with ARF who failed NPPV application had higher hospital mortality, similar to those intubated from the outset (48.3% vs. 38.6%, $p = 0.37$).

61.3 Noninvasive Ventilation Efficacy in Solid Organ Transplantation

ARF is a life-threatening complication that affects immunocompromised patients, including solid organ transplant recipients, accounting for 62.5% of ICU admissions [6]. Several noninvasive respiratory support methods are available, such as NIV, HFNC, and conventional oxygen therapy (COT), but NIV is often ordered as the first-line ventilation strategy in immunocompromised patients with ARF.

European Respiratory Society and American Thoracic Society guidelines recommend NIV before IMV in immunocompromised patients with hypoxemic ARF [30] based on initial beneficial outcomes of NIV compared with standard oxygen therapy [31, 32]. However, this recommendation remains controversial as it is based on only two small early randomized controlled trials (RCTs) [31, 32].

Antonelli et al. [31] studied solid organ transplant recipients with hypoxemic ARF and compared NIV delivered through a face mask with standard treatment using oxygen supplementation to avoid endotracheal intubation and decrease duration of ICU stay. Forty patients with a PaO_2:FiO_2 of less than 200 mmHg while breathing oxygen and active use of accessory respiratory muscles were randomized to receive either NIV or treatment with supplemental oxygen via a Venturi mask. Within the first hour of treatment, 70% of patients in the NIV group and 25% in the standard treatment group improved their PaO_2/FiO_2. Over time, a sustained improvement in PaO_2/FiO_2 was noted in 12 (60%) patients in the NIV group but only in five patients (25%) randomized to standard treatment ($p = 0.03$). Using NIV was associated with a significant reduction in the rate of endotracheal intubation (20% vs. 70%; $p = 0.002$), rate of fatal complications (20% vs. 50%; $p = 0.05$), length of ICU stay (5.5 ± 3 vs. 9 ± 4 days; $p = 0.03$), and ICU mortality (20% vs. 50%; $p = 0.05$). However, no significant difference was found in the in-hospital mortality rate. In this randomized trial, the early application of NIV was well tolerated and associated with a rapid and sustained improvement in gas exchange.

In a prospective, randomized, controlled study, Hilbert et al. [32] compared the efficacy of NIV delivered intermittently through a face mask with that of standard medical treatment with supplemental oxygen and no ventilatory support in patients with immunosuppression from various causes, including SOT. Patients suffered from hypoxemic ARF, which had been precipitated by pulmonary infiltrates and fever. Periods of NIV delivered through a face mask were alternated with periods of spontaneous breathing with supplemental oxygen. In the NIV group, the mean values for levels of pressure support and PEEP during the study were 15 ± 2 cmH_2O and 6 ± 1 cmH_2O, respectively. The early use of NIV during episodes of

pneumonitis and hypoxemic ARF helped avert the need for endotracheal intubation and improved the outcomes in immunosuppressed patients. Compared to standard oxygen therapy, the group treated with NIV had lower rates of endotracheal intubation (12/26 vs. 20/26 patients, $p = 0.03$), serious complications (13 vs. 21, $p = 0.02$), ICU mortality (10 vs. 18, $p = 0.03$), and in-hospital mortality (50% vs. 81%, $p = 0.02$).

In contrast to previous studies, the trial of Lemiale et al. [33] showed neither benefits nor harms from NIV in critically ill immunocompromised patients, at 28 ICUs in France and Belgium. Immune deficiency is defined as hematologic malignancy, solid tumor, solid organ transplant, and long-term or high dose immunosuppressive drugs medication. Enrolled patients were randomly assigned in a 1:1 ratio to receive either NIV or oxygen therapy alone throughout the ICU stay. This trial powered the primary outcome to reducing patient mortality in comparison to previous trials [31, 32], which focused on reducing the need for intubation. No difference was found between groups with regard to the primary endpoint, the mortality rate at 28 days after randomization (NIV 24.1% vs. oxygen 27.3%, $p = 0.47$). Secondary outcomes, such as the proportion of patients requiring endotracheal intubation, time to intubation, ICU-acquired infections, duration of mechanical ventilation, and length of stay in ICU and hospital, were also similar between the two groups. However, the lower mortality rate than expected in the control group reduced the power of this study to find a significant difference in the primary outcome. Furthermore, HFNC was used in almost 40% of overall patients, especially in the oxygen group, probably leading to a dilution of the NIV effect. Also, the median duration of NIV use has been considered inadequately low according to current practice in different centers. Finally, differences in patient populations may be one of the reasons for the different findings with respect to previous studies. Patients in this study showed lower degrees of tachypnea compared to previous studies [31, 32] suggesting a difference in severity of the acute condition.

Several reviews of RCTs, cohort studies and post hoc analysis have been made about the efficacy of NIV and oxygenation management in immunocompromised patients, including solid organ recipients.

Huang et al. [34] aimed to perform a systematic review and meta-analysis of five RCTs with 592 patients, comparing early use of NIV with oxygen therapy alone in immunocompromised patients, to determine if differences exist between these two strategies in overall mortality, rate of intubation, and length of ICU stay. Early NIV significantly reduced short-term mortality ($p = 0.04$) and intubation rate ($p = 0.01$) when compared with oxygen therapy alone, with significant heterogeneity in these two outcomes between the pooled studies. In addition, early NIV was associated with a shorter length of ICU stay ($p = 0.008$) but not long-term mortality ($p = 0.46$). This meta-analysis has provided evidence to support and expand the weak suggestion in the 2011 Canadian guidelines [35] to use NPPV in immunocompromised patients with ARF.

However, some studies did not show any benefit from NIV compared with HFNC or COT in these patients. The EFRAIM study [36] was a multinational prospective cohort study that enrolled 1611 immunocompromised patients from 68 ICUs. Patients

were affected by a non-AIDS related immune deficiency (hematologic or solid tumors, solid organ transplant, and steroids/immunosuppressive therapy) and hypoxemic ARF. Primary endpoints were the need for IMV for patients not intubated at ICU admission, and all-cause hospital mortality. Patients received standard oxygen (N = 496, 53.9%), HFNC therapy (N = 187, 20.3%), NIV (N = 153, 17.2%), and NIV + HFNC (N = 79, 8.6%). After propensity score matching, HFNC, but not NIV, had an effect on IMV rate (p = 0.05). ICU, hospital, and day-90 mortality rates were 32.4%, 44.1%, and 56.4%, respectively, but the authors did not identify any association between the adopted oxygenation strategy and mortality rate. These results are in line with those previously published by Lemiale et al. [33] and Azoulay et al. [37] showing that among immunocompromised patients admitted to the ICU with hypoxemic ARF, early NIV or HFNC compared with oxygen therapy alone did not improve ICU survival. Dumas et al. [38] also failed to show any evidence of difference between initial ventilation/oxygenation management (NIV/HFNC/COT/NIV + HFNC) and the need for intubation on the coming day within the first 3 days of ICU admission, based on the data of 847 immunocompromised patients with ARF, from three previously published studies [6, 33, 39]. Furthermore, Zayed et al. [40] tried to evaluate the efficacy of various oxygenation strategies, including NIV, HFNC and COT, in immunocompromised patients with ARF, based on data from nine RCTs comparing different modalities. NIV was associated with a significantly reduced intubation rate compared with standard oxygen therapy (OR 0.53; 95% CrI 0.26–0.91), but not compared with HFNC (OR 0.83; 95% CrI 0.35–2.11). There were no significant differences between all groups regarding short-term (28-day or ICU) mortality or long-term (90-day or hospital) mortality or ICU-acquired infections ($p > 0.05$).

In contrast, some studies show that NIV might be associated with an increased risk of intubation and mortality and should be used cautiously in immunocompromised patients with hypoxemic ARF. Frat et al. did a post-hoc subgroup analysis in the subset of immunocompromised patients from a multicenter RCT [41]. In this trial, patients from 23 ICUs in France and Belgium were randomly assigned (1:1:1) to receive either standard oxygen, HFNC alone, or NIV interspaced with HFNC between NIV sessions. The primary outcome was the proportion of patients who required endotracheal intubation within 28 days after randomization. Odds ratios for intubation were higher in patients treated with NIV than in those treated with HFNC. After multivariable logistic regression, the two factors independently associated with endotracheal intubation and mortality were age and use of NIV as first-line therapy. Coudroy et al. [42] compared outcomes of immunocompromised patients treated using HFNC alone or NIV as a first-line therapy for ARF in an observational cohort study over an 8-year period. The rates of intubation and 28-day mortality were higher in patients treated with NIV than with HFNC (55% vs. 35%, p = 0.04, and 40% vs. 20%, p = 0.02, respectively). The beneficial effects of HFNC could be largely due to tolerance. By contrast, NIV could be harmful due to potential ventilator-induced lung injury generated by pressure support that increases tidal volumes [43] and leads to high transpulmonary pressure [44], especially in patients with ARDS. Indeed, in this study, the majority of patients treated with NIV had clinical criteria for ARDS.

61.4 Risk Factors and Rates of Noninvasive Ventilation Failure

Corrêa et al. [45] tried to evaluate the rate of NIV failure, the predictors of NIV failure, the ICU and hospital length of stay, and 28-day mortality in hypoxemic patients who admitted to a mixed ICU during a 3-month period. NIV failure was associated with an increased risk of in-hospital death, ICU and hospital stay, and was not affected by baseline $PaCO_2$ levels. In this study, transplanted patients were comparatively younger than non-transplanted patients (45 ± 15 vs. 77 ± 13 years, respectively, $p < 0.001$). The younger age and higher failure rate in the transplanted patients may have contributed to the finding that comparatively younger age (67 ± 21 vs. 77 ± 14) was an independent predictor of NIV failure in this study.

Razlaf et al. [46] analyzed the data of 120 immunocompromised patients who had been admitted to ICU and were treated with NIV due to ARF, to examine failure rates and risk factors for NIV failure. Data included patients with hematological malignancies, patients with other kinds of bone marrow failure, after solid organ transplantation, as well as those who received immunosuppressive drugs due to auto-immune diseases. Regression analyses revealed a high APACHE II score ($p < 0.01$), need for catecholamines ($p < 0.05$), and low PaO_2/FiO_2 ratio ($p < 0.05$) as risk factors for NIV failure. Patients with ARF due to lung infiltrations had a longer stay in ICU and showed a trend toward longer NIV duration than those who had secondary ARF caused by sepsis of extrapulmonary origin. Almost 50% of the immunocompromised patients treated with NIV did not require intubation independent of the etiology of ARF.

Coudroy et al. [47] assessed the impact of immunosuppression status on NIV failure in a post hoc analysis pooling two studies including patients with de novo hypoxemic ARF treated with NIV. Immunocompromised patients of the studies had higher severity scores upon ICU admission, higher pressure-support levels, and minute ventilation under NIV, and were more likely to have bilateral lung infiltrates than nonimmunocompromised patients. After adjustment or using a propensity score-matched analysis, immunosuppression was not associated with intubation, whereas it remained independently associated with ICU mortality with an adjusted odds ratio of 2.64 (95% CI 1.24–5.67, $p = 0.01$). Immunosuppression status may directly influence mortality but does not seem to be associated with an increased risk of intubation in patients with de novo hypoxemic ARF treated with NIV.

Approximately half of patients with hypoxemia, especially those with ARDS, are not helped with face mask ventilation. When high levels of PEEP are needed, face mask intolerance and air leaks can impede effective oxygenation. Therefore, the face mask has limitations that may contribute to reduced efficacy during ARF. An alternative is to deliver NIV via a helmet interface, which confers several advantages over face masks, including improved tolerability and less air leakage due to the helmet's lack of contact with the face and improved seal integrity at the neck. Antonelli et al. [48] demonstrated that NIV by helmet successfully treats hypoxemic ARF, with better tolerance and fewer complications than facial mask NIV. The

helmet system is associated with a lower failure rate than the facial mask and allows the continuous application of NIV for a longer period of time, avoiding the 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.

61.5 Conclusion

SOT is one of the significant advances in the medical field that have improved the quality of life and survival rates of patients with end-organ dysfunction. SOT has become the standard of care for 1000s of patients with otherwise limited options and offers them a definitive long-term treatment. Transplantation programs should consider the inclusion of NIV for the treatment of transplant recipients with ARF. NIV can be used in an early phase of respiratory failure as a treatment for preventing endotracheal intubation and postoperative pulmonary complications and facilitating early extubation and shortening weaning time. NIV is also attractive in preventing posttransplant infectious diseases as it leaves the upper airways intact, reduces bacterial colonization and nosocomially acquired infections. Early administration of NIV in the treatment of eligible patients with ARF who have no contraindications and who can be monitored safely in the appropriate environment seems to be well tolerated and associated with a significant reduction in the rate of endotracheal intubation, fatal complications, and ICU mortality.

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Noninvasive Positive Pressure Ventilation in Patients Undergoing Lung Resection Surgery

62

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Abbreviations

ARF	Acute respiratory failure
BIPAP	Bi-level positive airway pressure
CPAP	Continuous positive airway pressure
ETMV	Endotracheal intubation and mechanical ventilation
FiO_2	Fraction of inspired oxygen
FRC	Functional residual capacity
HFNC	High-flow nasal cannula
NIV	Noninvasive ventilation
NSCLC	Non-small-cell lung carcinoma
PaO_2	Arterial oxygen partial

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_62

PaO_2/FiO_2 ratio	Ratio of arterial oxygen partial pressure (PaO_2 in mmHg) to fractional inspired oxygen (FiO_2 expressed as a fraction, not a percentage)
PEEP	Positive end-expiratory pressure
PPCs	Post-operative pulmonary complications
PS	Pressure support
$SatO_2/FiO_2$ ratio	Ratio of arterial oxygen saturation to fractional inspired oxygen
SCLC	Small-cell lung carcinoma

62.1 Introduction

Lung cancer is among the malignant tumors that cause the most deaths internationally, being the second most common cancer in men (after prostate cancer) and in women (after breast cancer) [1]. There are several different types of lung cancer, but it is usually classified into two major groups: non-small-cell lung carcinoma (NSCLC) and small-cell lung carcinoma (SCLC) [2]. Surgery is the recommended treatment for localized non-small cell lung cancer (NSCLC), achieving a 5-year survival >50% for stages I to II [2].

Despite a more accurate pre-operative patient assessment, advances in surgical techniques, anesthesia, and peri-operative care, patients undergoing lung resection surgery are still at high risk of developing post-operative pulmonary complications (PPCs), with an incidence that varies between 24% and 42% [1].

Clinically significant pulmonary complications include retention of secretion, atelectasis, pneumonia, pulmonary edema, prolonged air leaks, and acute respiratory failure [3]. Post-operative acute respiratory failure is observed in 2–30% of patients and is fatal in 40% to more than 60% [1] of patients. Such high mortality is also related to post-operative re-intubation and mechanical ventilation, which occurs in approximately 5% of patients [4].

The main risk factors for complications are pre-operative impaired respiratory function, comorbidity, general anesthesia, surgery-related diaphragmatic trauma, and surgery duration >80 min [2].

The respiratory function may be substantially modified during the post-operative period. Anesthesia, post-operative pain and surgery, particularly when the site of the surgery approaches the diaphragm, often induce respiratory modifications such as hypoxemia, decreased pulmonary volume (vital capacity, functional residual capacity, tidal volume), and atelectasis associated with a restrictive syndrome and a diaphragm dysfunction [5]. Moreover, minimally invasive thoracoscopic surgery requires a one-lung ventilation technique, which may result in inadequate lung expansion and remaining micro atelectasis post-operatively [6].

Atelectasis usually occurs in the most dependent parts of the lung near the diaphragm, which include approximately 10% of the total lung tissue [5]. These modifications of the respiratory function occur early after surgery and can persist for days following the surgery [5]. Dysfunction of the respiratory muscles, especially of the diaphragm may persist up to 1 or 2 weeks [5].

All these factors can cause respiratory failure because of respiratory muscle impairment, with an increase in carbon dioxide and/or disorders of lung parenchyma, ventilation perfusion mismatching with important deterioration in arterial oxygenation [5].

Respiratory support and oxygen therapy after tracheal extubation are of major importance to prevent hypoxemia and subsequent respiratory failure or re-intubation in surgical patients under general anesthesia [7, 8]. Although conventional oxygen therapy via nasal prongs or a face mask can supplement oxygen administration, in some of the patients (especially those who have undergone lobectomy), it is ineffective to compensate for loss in lung volume or to maintain gas exchange [9].

Endotracheal intubation and mechanical ventilation (ETMV) for acute respiratory failure (ARF) after major lung resections is associated with a very high mortality rate (60–80%) [10]. ETMV is clearly associated with many life-threatening complications such as pulmonary infection, persistent pleural air leaks, and bronchopleural fistula. Therefore, avoiding endotracheal intubation after lung resection appears to be a determinant goal of supportive therapy [10].

62.2 Discussion and Analysis Main Topic

62.2.1 Noninvasive Ventilation

The immediate post-operative period is key for the treatment or prophylaxis of atelectasis because the residual effects of anesthesia combined with reduced muscle strength prevent deep inspiration and expansion of collapsed alveolar units. The more commonly applied strategies to prevent post-operative pulmonary complications include good analgesia, physiotherapy, oxygen therapy, and early mobilization [11].

Lung recruitment maneuvers proposed to prevent or treat atelectasis include taking deep breaths (sighs), incentive spirometry, chest physiotherapy, and noninvasive ventilation (NIV) [1].

NIV for the acute phase of critical care management has been introduced as a therapeutic alternative to intubated mechanical ventilation in patients with poor pulmonary function [6].

There are two types of NIV: continuous positive airway pressure (CPAP) and bi-level positive airway pressure (BIPAP). The effectiveness of NIV, both BIPAP and CPAP, in the post-operative period (with both prophylactic and therapeutic purpose) has been investigated in different types of surgeries since the 1980s [4].

It has been suggested that there are two potential goals of NIV in the post-operative period [5]:

1. to treat acute respiratory failure (ARF) and avoid re-intubation (curative treatment)
2. to prevent acute respiratory failure (ARF) (preventive or prophylactic treatment)

Some studies have shown benefits from the use of NIV in the treatment of acute respiratory failure, and published clinical trials have suggested that the use of NIV can reduce the number of pulmonary complications and mortality in patients with ARF following lung resection surgery [1]. Imaging studies have shown that the use of NIV may increase lung aeration and decrease the amount of atelectasis during the post-operative period of patients undergoing major abdominal surgery [5].

A single prospective randomized study [12] found that in selected patients with ARF following lung cancer resection, NIV was effective in decreasing the need for tracheal intubation and in improving hospital mortality. Patients were enrolled if they presented at least three of the following criteria: respiratory rate higher than 25 breaths per min, active contraction of the accessory respiratory muscles, arterial oxygen ratio lower than 200 mmHg and chest radiographic abnormalities [1].

[13], in another observational prospective cohort survey, confirmed the feasibility and efficacy of NIV in both hypercapnic and hypoxic ARF following lung resection. Applying NIV through a mask, after lung resection surgery, could unload respiratory work of breathing, prevent diaphragmatic fatigue, induce a significant reduction in the magnitude of the post-operative pulmonary restrictive syndrome and improve gas exchange [10].

In a physiologic study [14], investigated the short-term effects of bi-level ventilation in patients extubated after lung surgery and able to maintain spontaneous breathing compared to conventional treatment. The NIV was maintained for 60 min: NIV significantly increased the arterial oxygenation, and this effect was still present 1 h after removing the ventilator support. The addition of NIV resulted in improved arterial oxygenation without changes in arterial carbon dioxide levels, dead space, and pleural leaks. However, only short-term data were recorded, and it is unclear whether the alveolar recruitment was kept after BIPAP suspension [1].

Okada et al. [6] demonstrated that for patients with lung cancer who underwent pulmonary lobectomy, NIV during the early post-operative phase, might improve oxygenation until post-operative day 1. NIV showed clinical benefits especially in patients with impaired oxygenation (PaO_2/FiO_2 ratio ≤ 300) immediately after surgery [6].

The use of CPAP has also been investigated by numerous authors: [15], showed that preventive application of CPAP during the immediate post-operative period after lung resection was safe and was effective in improving oxygenation without increasing air leaks [1].

[16] found that prophylactic post-operative CPAP administered to patients with a Boussignac mask (5–7 cmH_2O) during the first 6 h after thoracic surgery improved gas exchange at 24 h compared with patients receiving oxygen therapy via a Venturi mask. Continuous application of air pressure improves functional residual capacity (FRC) and prevents airway collapse, thus reducing respiratory effort. In patients in whom CPAP was not used, the PaO_2/FiO_2 ratio decreased with the increasing respiratory risk, whereas patients in the CPAP group had similar PaO_2/FiO_2 values, regardless of their respiratory risk score [1].

Barbagallo et al. [4] evaluated the prophylactic use of helmet CPAP after lung lobectomy, and they showed that the prophylactic use of helmet CPAP can

progressively improve the PaO_2/FiO_2 ratio, reaching a statistically significant higher value at the end of the second round of CPAP, compared to the control group [4]. However, the improvement in oxygenation was not lasting, and after conclusion of the treatment the values turned out to be similar to those in the control group after 24 h, 48 h, and 1 week after surgery [4].

As prophylaxis, NIV was found to improve functional lung parameters and arterial oxygenation [2]. Pre-operative NIV seems to improve functional parameters when realized during induction of anesthesia. The pathophysiology remains unclear, but improvement in bronchial drainage and respiratory flow and volume could explain these improved functional parameters. Pre-operative NIV could also acclimate the patient to this procedure if NIV is necessary after surgery, because pre-operative introduction, training, and familiarization with ventilator support makes patients confident when using the mask even in uncomfortable circumstances [2].

Danner et al. [17] conducted a randomized clinical trial to evaluate the potential beneficial effects of prophylactic pre- and post-operative use of NIV on overall clinical outcome, especially considering pulmonary complications. Although post-operative continuation of NIV had no strong effect on the rate of pulmonary complications, pre-operative application of NIV may have had a positive effect on post-operative outcome [1].

In a prospective clinical trial, Perrin et al. [18] tested the hypothesis of whether a peri-operative prophylactic use of NIV (pre- and post-operatively) produced a better gas exchange and pulmonary function after lung resection compared to oxygen therapy in patients presenting a forced expiratory volume lower than 70% of the predicted [18]. NIV was initiated 7 days before surgery and was continued post-operatively for 3 days. NIV was applied for at least five 1-h periods per day. Gas exchange and the spirometric values were significantly better in the NIV group compared to the control group from day 1 to day 3. The hospital length of stay was significantly lower in the NIV group (12 ± 1 days) than in the control group (19 ± 3 days).

However, the POPVNI trial assessed systematic post-operative prophylactic NIV on acute respiratory events after major lung resection in patients with COPD, showing no reduction of acute respiratory events [19]. The preOVNI randomized controlled open-label study investigated whether pre-operative NIV could reduce post-operative complications after lung cancer surgery and no benefit was evidenced for pre-operative NIV before lung cancer surgery [2].

62.2.2 Air Leaks

Some surgeons are skeptical about the early use of CPAP or BIPAP after thoracic surgery because of the theoretical risk that intra-bronchial pressure induced by NIV might increase pulmonary air leaks and broncho-pleural fistula [1, 4, 6].

Lefebvre found that only 1 of the 89 patients who received NIV after suffering post-operative respiratory failure subsequent to lung resection presented persistent

air leaks, and this result was attributed to application of low pressure [10]. Other studies have been consistent with these findings, such as the study by Perrin et al., in which no difference in the duration of chest tube drainage between groups with conventional treatment and NIV was shown, even with the use of higher inspiratory pressures during application of bi-level ventilation [1].

Okada et al. reported that only 1 of 112 patients receiving NIV had increased pulmonary air leaks and discontinued NIV [6]. Barbagallo reported no difference between the two groups; there was even a slightly higher number of air leaks in the control group [4].

Use of positive pressure exerts a force on the suture, increases the spring mechanism and further increases the tendency toward distancing from skin edges. However, studies have shown that prolonged air leaks after lung resection are related to a number of risk factors, including impairment of lung function, fragility of the lung parenchyma, steroid use, operative protocols for upper lobectomy and presence of pleural adhesions [1].

Thus, the negative outcome regarding air leaks seems clinically acceptable when NIV was applied to patients with no or minor air leaks after surgery, although attention should be paid to the worsening of air leaks [6].

62.2.3 High Flow Nasal Cannula

The routine use of NIV in clinical practice requires personnel expertise and technological resources that may not be available in all post-anesthesia care units and surgical wards [7]. In addition, NIV may be uncomfortable for patients because it is applied by a tight-fitting mask, and patients may complain of difficulty with communication, eating and drinking, and mobilization; consequently, compliance is often poor [3].

The use of nasal cannula to deliver high flow rates of heated and humidified gas at a predetermined fraction of inspired oxygen (FiO_2) is an attractive alternative to conventional oxygen therapy and possibly to NIV [3, 7, 9]. The beneficial effects of high-flow nasal cannula (HFNC) include [7]:

(a) delivery of high flows (with a maximum flow of 60 L/min) that better match patients' peak inspiratory flow, finally enabling administration of set FiO_2;
(b) provision of a small degree of positive pressure in the airways that increases end-expiratory lung volume;
(c) washout of nasopharyngeal dead space which enhances carbon dioxide (CO_2) removal;
(d) good tolerance and comfort.

HFNC delivers some level of continuous positive airway pressure via high-flow ventilation. However, the value of PEEP is unstable (from 1 to 7 cmH_2O) because of leaks around the nasal cannula and the fact that a closed mouth of the patients cannot always be guaranteed [9]. Due to the provision of distending pressure and

increase in end-expiratory lung volume, some researchers proposed that HFNC decreased airway resistance and flushed nasopharyngeal dead space, thereby contributing to the reduced work of breathing [9].

Favorable results on the preemptive use of HFNC, as compared to low-flow oxygen, have been reported in critically ill patients, while the evidence appears conflicting in the post-operative period. Pennisi et al. [7] conducted a randomized trial in patients undergoing thoracotomic lung lobectomy, and reported that preemptive use of HFNC after extubation, as compared to Venturi mask oxygen therapy, did not result in lower incidence of post-operative hypoxemia nor had any effect on other prespecified secondary outcomes (incidence of post-operative respiratory complications and respiratory failure requiring ventilatory support, persistent need for oxygen therapy on post-operative day 2, post-operative dyspnea) [7].

However, in a multicenter randomized interventional trial, Yu et al. [9] found that the application of HFNC oxygen therapy in patients with thoracoscopic lobectomy after extubation could reduce the risk of hypoxemia and reintubation as well as improve oxygenation represented by PaO_2, PaO_2/FiO_2 ratio, and $SatO_2/FiO_2$ ratio [9].

In their study, the patients enrolled were those who underwent lobectomy and the occurrence of hypoxemia in HFNC was relatively lower than that in conventional oxygen therapy, as well as the rate of needing NIV and the rate of reintubation, which reflected the advantage of HFNC.

In conclusion Zayed et al. [8] conducted a meta-analysis to compare the efficacy and safety of HFNC, NIV, and standard oxygen therapy in the treatment of patients who developed or were considered high risk for post-operative respiratory failure [8].

In this network meta-analysis, comparing various oxygenation strategies in patients at risk for hypoxemic respiratory failure or established respiratory failure within 7 days of surgery, they found that NIV and HFNC were associated with a significant reduction in intubation rates and ICU-acquired infections when compared to standard oxygen therapy. However, when compared to standard oxygen therapy, only NIV was found to have a mortality benefit in this patient population.

The use of HFNC has shown beneficial effects in patients who developed post-extubation respiratory failure or when used during intubation to prevent hypoxemia when compared to standard oxygen [8].

In addition, HFNC was associated with lower intubation rates in patients following cardiothoracic surgeries but not following abdominal surgeries when compared to standard oxygen therapy. This could be explained by the fact that in thoracic surgery, HFNC could minimize lung decruitment post-extubation by providing some level of continuous positive airway pressure through high-flow ventilation, though this positive pressure can be variable due to the leak around the nasal cannula and non-guaranteed closed mouth of the patients.

Furthermore, they found lower rates of infections with HFNC and NIV when compared to standard oxygen, probably attributed to lower intubation rates in both interventions, which avoided the need for mechanical ventilation.

Currently, NIV is recommended in the treatment of patients with post-operative respiratory failure according to the ERS/ATS guidelines [20].

62.2.4 Failure of NIV

However, approximately 20% of patients under NIV needed to be subsequently intubated after lung resection [21]. Delays in reintubation after the development of acute respiratory failure actually correlated with worsened survival rates [21]. Therefore, early identification and surveillance to determine which patients require reintubation appears essential. Such patients should be promptly intubated because a delay in reintubation entails the development of a respiratory crisis, requiring emergent intubations and increasing the likelihood of morbidity and mortality [21].

Failure rate of NIV ranged from 19% to 72% [21]. Population heterogeneity and causes of acute respiratory failure are probably the two major factors implied in explaining such a discrepancy [21]. Riviere et al. have identified three early risk factors of failure: severity of illness; respiratory rate and number of hours spent on NIV [21]; in a single prospective randomized study; Lefebvre et al. reported that patients experiencing failure of NIV were older, had more frequent cardiovascular co-morbidities, post-operative pneumonia, and admission in surgical ICU [10]. However, multivariate analysis identified only two independent factors were significantly associated with NIV failure: cardiac comorbidities and no initial response to NIV [10].

Modalities of NIV application could be of interest for the success or failure rate. Secretion management must also be considered when reporting success or failure of NIV: failing to maintain a clear airway results in increased airway resistance to NIV and patient fatigue, and is associated with atelectasis and pneumonia [21].

62.2.5 Setting

Ventilator settings should be adjusted to provide the lowest inspiratory pressures or volumes needed to produce improved patient comfort (a decrease in respiratory rate and respiratory muscle unloading) and gas exchange [5].

The choice of interface is a major determinant of the success of this technique because the patient cannot tolerate and accept NIV in the case of facial discomfort, skin injury, or significant air leaks. There are different types of interfaces: full face masks (enclose mouth and nose), nasal masks, nasal pillows or plugs (insert directly into the nostrils), and helmets. Today, none has proven to be superior to the other in terms of outcome [20].

Patient comfort and interface acceptance may be gained by starting with PEEP alone and then slowly increasing the pressure support (PS) level once the mask is applied. It is recommended to start with a PS of 3 to 5 cmH_2O and to proceed with increments of 2 cmH_2O to achieve a 6–8 mL/kg expiratory tidal volume, a decrease in the patient's respiratory rate, and a comfort improvement. The PEEP is started at 3 to 5 cmH_2O and increased as needed to improve oxygenation without adverse hemodynamic effects up to 10 cmH_2O. The applied insufflation pressure (PS + PEEP) should be less than 25 cmH_2O. However, before initiating NIV in the post-operative period in patients with acute respiratory failure, a surgical

complication (anastomoses leakage, intra-abdominal sepsis) should be excluded or treated. Then, if the patient is cooperative and able to protect his/her airway, NIV can be initiated regardless of the safety procedures and respect of contraindications.

62.3 Conclusions

In the post-operative period (in general but especially in thoracic surgery), it is sometimes difficult to clearly separate a "preventive" from "curative" application of NIV. Probably part of the patients received NIV for a "grey zone" indication (when starting NIV and also after), which may be considered as an intermediary state between both a "preventive" and "curative" application of NIV.

Both CPAP and BIPAP improve the physiological mechanisms of post-operative ARF, with partial compensation of the affected respiratory function by reducing the work of breathing, improving alveolar recruitment with better oxygenation and ventilation, and reducing the left ventricular afterload, thus increasing cardiac output and improving hemodynamics. The evidence suggests that CPAP, BIPAP, and HFNC are effective strategies to improve clinical outcomes in patients with post-operative acute respiratory failure, without increasing air losses. This results in reduction of intubation rates, nosocomial infections, length of stay, morbidity, and mortality.

Prophylactic use of NIV appears to be effective and safe and the prophylactic introduction with ventilator support makes patients confident when using the mask during an acute event.

Finally, NIV is a supportive symptomatic treatment, which will always be associated with the etiologic treatment of the disease leading to respiratory distress. A careful search for any possible surgical complication and the selection of the correct interface and type of NIV (CPAP/NIV/HFNC) combined with the individual characteristics of the patients is fundamental for increasing NIV success.

Key Major Recommendations

- NIV may represent the first step in the treatment of post-operative respiratory failure
- NIV is a supportive treatment, which will always be associated with the etiologic treatment of the disease leading to respiratory failure
- The success of the NIV depends on the correct choice of interface and type of NIV (CPAP/BIPAP/HFNC) combined with the individual characteristics of the patients
- Prophylactic use of NIV appears to be effective and safe, but further studies are needed
- Even if the evidence is still lacking, HFNC seems to be more tolerated by patients

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Part IX

NIMV Analgesia and Sedation

Sedation and Analgesia During Noninvasive Ventilation in Intensive Care

63

Catarina Mendes Silva

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Abbreviations

ARF	Acute respiratory failure
BPS	Behavioral Pain Scale
BPS-NI	Behavioral Pain Scale in nonintubated
CI	Confidence interval
CPOT	Critical-Care Pain Observation Tool
ERS/ATS	European Respiratory Society/American Thoracic Society
GABA	γ-aminobutyric acid
ICU	Intensive Care Unit
NIV	Noninvasive ventilation
NRS	Numeric Rating Scale
RR	Relative risk
TCI	Target-controlled infusion
VDS	Verbal Descriptor Scale

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_63

63.1 Introduction

The role of noninvasive ventilation (NIV) in intensive care units (ICU) has gained relevance in the past few decades in response to evidence of its benefits as a means of reducing dependence on endotracheal intubation and invasive mechanical ventilation and its associated complications. According to the European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines, published in 2017, in acute settings, NIV is highly recommended for acute exacerbations of chronic obstructive pulmonary disease and severe cardiogenic pulmonary edema. It should be considered in immunocompromised patients with acute respiratory failure (ARF), weaning of hypercapnic patients, prevention of post-extubation failure of high-risk patients, postoperative period, chest trauma patients, and as a palliative treatment [1]. The main purpose of NIV in these settings is to correct gas exchange and decrease work of breathing, but different goals according to severity and end-of-life choices can be applied. NIV can be used to prevent the occurrence of ARF, to prevent further clinical deterioration and the need for endotracheal intubation when ARF is already established, or as "ceiling treatment" or palliative care in do not intubate/do not resuscitate patients [2].

The success of NIV is dependent on patient's acceptance and compliance, which is affected by the severity of illness, claustrophobia, anxiety, patient–ventilator dyssynchronies, abdominal distension, dryness of upper airways, and interface related problems, such as air leaks, poor mask fitting, mask intolerance, and pain associated with skin lesions. The patient may refuse to continue with uncomfortable support, causing its discontinuation and subsequent requirement for endotracheal intubation. If the patient learns to breathe through the ventilator, and if the support overcomes the respiratory distress, then the need for help and reassurance decreases. The presence of healthcare staff at the bedside during the initial hours of application may help this process. Discomfort, anxiety, agitation, pain, dyspnea, and delirium may be associated with NIV failure and worst outcomes. Application of analgesia and sedation may increase patient comfort and NIV tolerance and success in specific situations, but expert teams and highly monitored settings are required, such as intensive care units. The goal is to achieve sedation to a point where the patients are comfortable and awake/arousable. There is limited data available to guide the development of best practice, prevailing local practice patterns [3].

Low-dose sedatives could be used during NIV in mildly agitated patients [2], but sedation may also delay a necessary intubation. Sedation could be of benefit in situations where NIV is clearly indicated and where careful evaluation identifies anxiety, dyspnea with a high affective dimension, or delirium as barriers to its successful implementation [3]. This rationale for sedation during NIV may be applied to the first hours of adaptation to ventilation, and later when prolonged ventilation is required [4]. The choice of NIV interface and assisted ventilation pattern may influence the need for sedation. Patient acceptance increases with less constricting interfaces (e.g., helmet). Moreover, bilevel positive airway pressure is more often related to need for anxiolytics or sedatives than continuous positive airway pressure [3].

Before considering sedation or analgesia, there are other measures that can be applied to improve tolerance of NIV. For example, an adequate choice of mask type and size, applying a rotation strategy, and using newer algorithms that enhance patient–ventilator synchrony may avoid intolerance. Also, the expertise of the NIV team contributing to appropriate adjustments in equipment and ventilator settings and to a feeling of confidence to the patient can improve the success of NIV [5]. If the patient remains intolerant and uncooperative despite these strategies, administration of analgesia and sedation may be considered to optimize the chances of success during NIV for minimizing the requirement for endotracheal intubation or when NIV is a "ceiling treatment."

63.2 Discussion

The goals of sedation for a conscious and cooperative patient in ICU are to provide a good control of anxiety, agitation and discomfort, assure analgesia, preserve day/night cycles, and provide good sleep quality. Sleep quality can be optimized by avoiding factors that cause sleep disturbance such as exposure to sound and light that may disrupt circadian rhythm and cause frequent arousals from sleep. Other goals for sedation include hemodynamic stability, preservation of metabolic homeostasis, muscular relaxation, preservation of diaphragmatic function, and attenuation of the stress/immune response [3]. An ideal drug should accomplish all these goals and additionally have short acting activity, no accumulation in case of renal or liver failure, and no rebound effects when discontinued.

For patients in ICU requiring endotracheal intubation and invasive mechanical ventilation, it has been described that outcomes improve with routine monitoring of the depth of sedation, presence of pain and delirium, prompt and effective pain treatment, and when administration of sedatives is kept to the minimum necessary for the comfort and safety of the patient [6]. However, information on the management of pain, agitation, and delirium in patients undergoing NIV is scarce and there are no guidelines focusing on this subject. The recently published Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption (PADIS) in Adult Patients in the ICU do not include recommendations for patients undergoing NIV [7]. The lack of evidence-based information results in heterogeneous practices in different centers guided by individual clinical experience.

In ICU patients undergoing NIV with a high risk of failure it is important, when using sedation and analgesia, to avoid respiratory drive depression and to guarantee easy arousal with alleviation of NIV-induced discomfort. This permits patients to discharge their secretions and avoid aspiration, ultimately leading to an increase in the rate of adherence to NIV and, hopefully, the chance of success in avoiding endotracheal intubation and invasive mechanical ventilation [4].

In a survey published in 2007 [8] on sedation practices during NIV in North America, Europe and Australia/Asia, physicians reported using sedation in less than 25% of patients. Sedation and analgesia were more commonly used by North

Americans than Europeans (41% vs. 24% for sedation, 48% vs. 35% for analgesia) and critical care versus noncritical care physicians (42% vs. 24% for sedation and 50% vs. 34% for analgesia). In North America, benzodiazepine alone was the preferred agent (33%), followed by an 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. The differences in prescribing patterns suggest that the choice of agent is determined more by familiarity than by evidence-based practice. These results are outdated and probably do not represent current practices.

Muriel et al. published a multicenter observational study, in 2015, based on data collected in 2010, including patients who received at least 2 h of NIV as first-line therapy at ICU admission. They concluded that nearly 20% of patients received sedation or analgesia during NIV. Midazolam and morphine were the most commonly used sedative and analgesic drugs. The use of analgesics or sedatives alone was not associated with outcome but their simultaneous use was associated with NIV failure, ICU mortality and 28-day mortality [9]. Another retrospective study using data from a tertiary referral hospital in Japan, published in 2015, showed that 3.4% of patients receiving NIV due to acute respiratory failure were given sedatives to control agitation [10]. Morphine, dexmedetomidine, propofol, midazolam, and fentanyl were used in 19%, 15%, 13%, 9%, and 9% of the cases, respectively.

Pilot studies have suggested that continuous infusion of a single sedative or analgesic agent may decrease patient discomfort, with no significant deleterious effects on respiratory drive, respiratory pattern or hemodynamics, and with improvement in gas exchanges [11]. There are no robust data to favor any one drug, class of drugs, or protocol over all others [3].

The most traditionally classes of drugs used in continuous infusion to provide analgesia and sedation in ICU patients include γ-aminobutyric acid (GABA) receptor agonists (i.e., propofol and midazolam) and opioids (i.e., morphine and fentanyl). However, both classes of drugs may blunt the output of the respiratory center [5]. Modern drugs with very short half-lives and favorable pharmacokinetic profiles (i.e., remifentanil) or that do not interfere with respiratory drive (i.e., dexmedetomidine) may be of help to start and keep a mild analgosedation level under NIV [2].

63.2.1 Drugs for Sedation and Analgesia During NIV

Several dugs have been used for analgesia and sedation of patients during NIV. They have distinct pharmacokinetic and pharmacodynamic properties, and different side-effects (Table 63.1) that must be accounted for when choosing the optimal sedation agent for a patient.

Propofol, a widely used drug for sedation in ICU, could have a role for sedation during NIV. It acts as a $GABA_A$ agonist, with other effects, including on glutamate and cannabinoid receptors, and has a short-acting activity with a half-life of 30–60 min. Propofol causes vasodilation and negative inotropy, inducing

Table 63.1 Comparison of properties of drugs used for analgesia and sedation

	Sedation	Analgesia	Hemodynamic effects	Respiratory depression	Delirium
Propofol	+ + +	0	+ + +	+ + +	+ +
Midazolam	+ + +	0	+	+ +	+ + +
Remifentanil	+	+ + +	+	+	0
Dexmedetomidine	+ +	+	+ +	0	+
Ketamine	+ +	+ +	+	0	0

+ + + = high; + + = moderate; + = low; 0 = none

hypotension and bradycardia [6]. 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 [12]. Clouzeau et al. published a small cohort study with 10 patients assessing the feasibility and safety of target-controlled infusion (TCI) of propofol for conscious sedation of patients with NIV failure due to low tolerance [12]. TCI allows rapid and precise adjustment of the propofol concentration according to the clinical response of the patient. This preliminary study showed that in a selected population, TCI of propofol could be safe and effective for the treatment of NIV failure due to low tolerance. However, no further studies have been published and there is still a lack of evidence on the safety and efficacy of propofol for NIV tolerance.

Benzodiazepines act as $GABA_A$ receptor agonists but have a high risk of delirium and tolerance, and continuous administration should be discouraged. Midazolam is a short-acting benzodiazepine with a half-life of 3–11 h, but active metabolite accumulates with prolonged infusion [6]. Anxiolytic properties may be attractive for patients under NIV, but single bolus administration of the lowest possible dose followed, or not, by another sedative drug should be preferable. Benzodiazepines have been strongly associated with higher incidence of delirium. Studies in mechanically ventilated patients have concluded that benzodiazepines have worst clinical outcomes than other sedatives, and guidelines suggest using either propofol or dexmedetomidine over benzodiazepines [7]. Although there is a lack of trials evaluating benzodiazepines use in NIV, similar results are expected.

Remifentanil is a μ-opioid receptor agonist with pharmacodynamic properties similar to those of other opioids, with potent analgesic and light sedative effect, but with a unique pharmacokinetic profile. It is a potent, short-acting opioid with a half-life of 3–4 min, and does not accumulate with prolonged infusion [6]. Its metabolism is unaffected by hepatic or renal dysfunction, since it is metabolized by plasma esterases into an inactive metabolite. Its main adverse effects include nausea, constipation, respiratory depression, and bradycardia. At low dose, remifentanil increases comfort without decreasing respiratory drive, and because it does not accumulate, there are no concerns about unpredictable or delayed recovery, making its use possible even in NIV. In a pilot study, Constantin et al. showed that remifentanil-based sedation as a continuous infusion in selected patients with NIV failure was effective in increasing NIV tolerance and safety [13]. However, in that

study, the required level of sedation was not achieved in 3 of the 13 patients with the maximum allowed dose of remifentanil. To avoid high doses of opioids, which decrease respiratory drive, a combination of propofol and remifentanil was used, but $PaCO_2$ increased.

Dexmedetomidine, a highly selective α2-adrenoreceptor agonist that stimulates receptors in the *locus ceruleus* to provide sedation and in the spinal cord to enhance analgesia. It also has sympatholytic effects via central and peripheral mechanisms [6]. It has mild sedative, anxiolytic, analgesic, and opioid-sparing effects without causing significant respiratory depression and is suitable for short-term sedation in an intensive care setting. Due to it pharmacologic profile, it has been used as a useful sedative in ICU patients. Also, it offers a qualitatively different type of sedation, when compared to propofol and benzodiazepines, since sedation is obtained when patients are undisturbed, but they can be easily aroused with minimal stimulation [4]. The use of dexmedetomidine is associated with hemodynamic adverse effects, causing hypotension and bradycardia. Other adverse effects include dry mouth and nausea [6].

Given the pathophysiology of NIV failure, dexmedetomidine appears to offer the range of qualities best configured to address these concerns, namely it does not interfere with the patency of the upper airway, does not cause respiratory depression, and improves the affective dimension of dyspnea [3]. In comparison, opioids, propofol, and benzodiazepines may decrease upper airway diameter with possible deleterious risk during NIV. Furthermore, dexmedetomidine produces analgesia, another advantage over propofol and benzodiazepines.

In a recent systematic review and meta-analysis [14], on the safety and efficacy of dexmedetomidine in acutely ill patients requiring NIV, 12 randomized controlled trials were included. The use of dexmedetomidine, compared to other sedation strategies or placebo, reduced the risk of endotracheal intubation and mechanical ventilation [relative risk (RR) 0.54, 95% confidence interval (CI) 0.41–0.71], delirium (RR 0.34, 95% CI 0.22–0.54), ICU length of stay [mean difference −2.40 days, 95% CI −3.51 to −1.29], and risk of developing pneumonia (RR 0.30, 95% CI 0.17–0.52), while increasing the risk of bradycardia (RR 2.80, 95% CI 1.92–4.07) and hypotension (RR 1.98, 95% CI 1.32–2.98). The majority of studies allowed dexmedetomidine dosing that ranged from 0.2–0.7 μg/kg/h. There was no difference in duration of NIV with dexmedetomidine compared to other strategies. The authors concluded that the benefits of dexmedetomidine should be weighed against the probable undesirable effects of hypotension and bradycardia.

Ketamine is a short-acting drug with sedative, analgesic, anti-inflammatory, and antidepressant effects properties that are mainly attributed to its activity as an inhibitor of the N-methyl-d-aspartate (NMDA) receptor [15]. It exhibits dissociative effects by perpetuating a dream-like detachment from the environment and has potential for abuse and adverse neuropsychiatric reactions. Ketamine typically exhibits a rapid onset of action; the elimination half-life is approximately 2–3 h and depends on hepatic and renal function. Ketamine does not cause respiratory depression at doses given for analgesia or procedural sedation [3], but has the capacity of causing bronchodilation by increasing circulating catecholamines, inhibiting vagal

outflow, and relaxing airway smooth muscle, which could be useful for some types of patients needing NIV. Complications associated with ketamine administration include fatigue, dizziness, nausea, feelings of unreality, hemodynamic effects (increases blood pressure and heart rate), arrhythmias, hypersalivation, emergence reactions, and laryngospasm [15]. There is a relatively abundant literature concerning the use of ketamine for procedural sedation, but experience for sedation during NIV is limited [3].

63.2.2 Monitoring Sedation and Pain During NIV

Although sedation can play a role in preventing intolerance to NIV, it is also potentially dangerous because of the risk of oversedation, need for intubation and undesired side effects. For that reason their use should be carefully considered. The depressant effects of sedation and analgesia on respiratory function vary between individuals depending on the choice and dose of the drug, its sedative or analgesic effects, and sensitivity and metabolic capabilities of the patient [5]. The incidence and severity of sedative-related complications in patients admitted in ICU are variable and depend on the dosage, type of drug, severity or ARF and expertise of the team [4]. Monitoring sedation during NIV is a key point of a successful procedure. Sedation and analgesia should be administered by experienced staff, with continuous monitoring of cardiorespiratory and ventilator parameters, and prompt capacity of endotracheal intubation if NIV fails. Several scales are available that may be helpful in ensuring a minimal level of sedation for NIV tolerance, which also requires trained staff to be applied [5].

As for all ICU patients, evaluation of sedation and pain should be performed by trained personnel according to a scale. Moreover, sedation for NIV should be included in a sedation protocol in each ICU that includes the recommended scales for evaluation and measures to be applied accordingly to the evaluation. Besides sedation and pain, delirium should also be assessed.

For sedation assessment, the most commonly used scores are Richmond Agitation-Sedation Scale (RASS) and Ramsay Sedation Score (RAS). There is a lack of data comparing the different scales. At least one clinical tool should be used to assess the neurological status of patients under NIV with the aim of obtaining the desired neurological sedative effect for the delivered dose of the chosen drug [4]. In the study of Matsumoto et al., patients were most often managed between −2 and 0 on the RASS during sedation [10].

A patient's self-report of pain is the reference standard for pain assessment in patients who can communicate reliably [7]. Among critically ill adults who are able to self-report pain, the 0–10 Numeric Rating Scale (NRS) administered either verbally or visually is a valid and feasible pain scale. A descriptive pain scale like the Verbal Descriptor Scale (VDS) should be considered for ICU patients unable to use a numerically formatted scale such as the 0–10 NRS. Among critically ill adults unable to self-report pain and in whom behaviors are observable, the Behavioral Pain Scale in intubated (BPS) and nonintubated (BPS-NI) patients and the

Critical-Care Pain Observation Tool (CPOT) demonstrate the greatest validity and reliability for monitoring pain [7]. The BPS-NI was developed for patients with delirium and/or an impaired vigilance status unable to communicate, contains three domains (i.e., facial expressions, movements of upper limbs, vocalization), and each domain contains four descriptors rated on a 1 to 4 scale [16]. Although it was not validated in patients under NIV, it may be useful for patients with this type of respiratory support and unable to self-report.

63.3 Conclusion

Sedation and analgesia can reduce NIV failure and so decrease morbidity in selected patients. This practice must be performed in an ICU setting with trained individuals and close monitoring. The ideal drug does not exist, but dexmedetomidine and ketamine may be interesting alternatives in experienced units due to their pharmacological profiles. Propofol and opioids (such as remifentanil) are in an intermediate position. The continuous administration of benzodiazepines should be discouraged, but the anxiolytic properties of these drugs may be used in a single-shot administration. A sedation protocol must be implemented in the ICU and scales should be used for assessment.

Key Major Recommendations

- Sedation and analgesia can reduce NIV failure to avoid endotracheal intubation or when NIV is a "ceiling treatment."
- Sedation and analgesia should be administered by experienced staff with close monitoring, and using the minimum doses to avoid oversedation and adverse side effects.
- Dexmedetomidine appears to offer the best range of qualities, but the benefits should be weighed against the probable undesirable effects of hypotension and bradycardia.
- Ketamine may be an interesting alternative, but there is a lack of information on efficacy and safety for sedation during NIV.
- A sedation protocol must be implemented in the ICU and scales should be used for assessment.

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Part X

Weaning from Conventional MV and Post-extubation Failure

Noninvasive Positive Pressure Ventilation in the Post-Extubation Period

64

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https://doi.org/10.1007/978-3-031-28963-7_64

Abbreviations

ARF	Acute respiratory failure
COPD	Chronic obstructive pulmonary disease
COT	Conventional oxygen therapy
ETT	Endotracheal tube
FRC	Functional residual capacity
HFNO	High flow nasal oxygen
ICU	Intensive care unit
IMV	Invasive mechanical ventilation
MV	Mechanical ventilation
NIV	Noninvasive ventilation
P_{alv}	Alveolar pressure
P_{aw}	Airway pressure
PEEP	Positive end-expiratory pressure
PSILI	Patient self-inflicted lung injury
RCT	Randomized controlled trial
T_e	Expiratory time
T_i	Inspiratory time
UAO	Upper airway obstruction
V/*Q*	Ventilation/perfusion
V_A	Alveolar ventilation
VAP	Ventilator associated pneumonia
V_E	Minute ventilation

64.1 Introduction

Invasive mechanical ventilation (IMV) is a crucial intervention in supporting critically ill patients. A protocolized approach with low tidal volume ventilation, daily awakening trials, and daily spontaneous breathing trials has substantially reduced the duration of IMV and improved outcomes for ICU patients.

Extubation is a critical period during a patient' s stay in ICU. Extubation failure has been defined as the need for reintubation due to a new episode of respiratory failure after a planned removal of the endotracheal tube (ETT). A number of studies have indicated that the specific time frame for the development of extubation failure is 48–72 h, which may be extended up to 7 days [1].

Many factors contribute to respiratory failure after extubation, including the inability to maintain airway patency, cough impairment, poor cardiorespiratory reserves, sepsis, critical illness polyneuromyopathy, poor nutrition, and surgical complications. The literature suggests that 10–20% of unselected patients will present acute respiratory failure (ARF) requiring reintubation within the first 4–5 days after planned extubation [1, 2]. Interestingly, extubation failure occurs in over 30% of patients at high risk of post-extubation

respiratory failure. It is also important to note that extubation failure is associated with increased mortality, increased ICU length of stay, increased duration of mechanical ventilation, and increased rates of ventilator associated pneumonia (VAP).

As the pathophysiology of extubation failure has yet to be satisfactorily explained, our understanding of how to prevent and manage this issue is limited. Consequently, the rates of reintubation have not changed significantly over the past 20 years.

NIV application in the post-extubation period has been suggested to reduce the rates of re-intubation. In this review, we will describe: the post-extubation pathophysiological changes, attributing them to the passage from assisted ventilation to spontaneous breathing, the physiological effects of NIV in this setting, and the implications of NIV as a facilitative, preventive, and therapeutic modality to support patients after removal of the endotracheal tube (ETT).

64.2 Pathophysiological Changes during the Post-Extubation Period: Causes of Extubation Failure

It is important to distinguish weaning failure (inability to tolerate spontaneous breathing without ventilatory support) from extubation failure (inability to sustain removal of the endotracheal tube). Nonetheless, certain pathophysiological changes including the loss of lung aeration, the capacity/load imbalance of respiratory muscles, and the hemodynamic derangements, alone or in combination, are involved in both weaning failure or extubation failure [1].

The transition from MV to spontaneous breathing may be associated with the marked reduction of aerated lung units resulting in decreased lung compliance, ventilation/perfusion (V/Q) mismatching, and intrapulmonary shunt. During unassisted breathing, the end-expiratory transpulmonary pressure can reduce the lung volume below the closing capacity, especially in elderly and obese patients, leading to the collapse of unstable alveoli and atelectasis. Atelectasis is the major pathophysiological change after removal of mechanical ventilation, as it may create large regional driving transpulmonary pressures exacerbating lung injury, pulmonary edema, and respiratory distress. To a lesser degree, transudative pulmonary edema might also occur because of the increased gradient between intracapillary and alveolar pressures [1, 2].

The discontinuation of MV requires an adequate capacity of respiratory muscles (especially of the diaphragm) to overcome the respiratory system impedance, to maintain adequate gas exchange and to meet metabolic demands. It has clearly been established that MV, even of a short duration, is associated with diaphragmatic weakness, atrophy, and injury. There are also other factors contributing to diaphragmatic dysfunction, such as critical illness poly-neuromyopathy, malnutrition, and hypoperfusion. Interestingly, it has been demonstrated that up to 50% of patients with extubation failure exhibit signs of respiratory muscle capacity/load imbalance suggesting that even a 2-hr spontaneous breathing trial (SBT) might be unable to detect signs of such an imbalance. Moreover, ventilatory over-assistance with CPAP and low level

pressure support ventilation during the weaning trials may contribute to extubation failure after a planned removal of the ETT in patients who meet the readiness criteria for extubation. These modes may over-assist the patient who is not yet ready to tolerate fully unassisted breathing [2]. After removal of MV, the respiratory muscle capacity/load imbalance can lead to clinical manifestations of respiratory distress characterized by rapid shallow breathing, use of accessory muscles, paradoxical breathing, and blood gas derangements. Consequently, work of breathing (WOB) increases, oxygenation and CO_2 elimination worsens, leading to further increase of respiratory muscle load and finally to diaphragmatic failure with development of ARF.

Similarly, hemodynamic impairment may contribute to both weaning and extubation failure. The transition from MV to spontaneous breathing has been compared to a cardiac stress test challenging the cardiovascular reserves of the patient. In short, without the ventilatory support, the left ventricular afterload increases because of the negative swings in intrathoracic pressure and the subsequent increase of transmural pressure of the left ventricle. In addition, on the right side of the heart, the variations in intrathoracic pressures together with the increase in transdiaphragmatic pressure (the difference between the intra-abdominal and the intra-thoracic pressures) promote the venous return of the blood and thus also the right ventricular preload resulting in increased output of the right ventricle. These changes, frequently combined with increased sympathetic activity (tachycardia, arrhythmias, hypertension) at extubation, secondary to irritation of airway receptors, may pave the way for pulmonary edema, especially in patients with either left ventricle systolic or diastolic dysfunction [1].

Another determinant of pulmonary edema formation during unassisted breathing is the gradient between the pressure in the airways (P_{aw}) and the pressure inside the alveolus (P_{alv}). Without the positive pressure ventilation, the difference ($P_{aw} - P_{alv}$) increases due to the diminution of $P_{alv,}$ promoting the increase in the gradient between the intra-capillary pressure and P_{alv} and thus augmenting fluid exudation towards diseased alveoli.

Extubation failure, distinct from weaning failure, can occur due to upper airway obstruction and the inability to manage the tracheobronchial secretions. The patency of the airway is a frequent concern in the post extubation period; 12–16% of critically ill patients present upper airway obstruction (UAO), requiring in some cases immediate reintubation. Of note, laryngeal edema is the most common cause of UAO deriving from mechanical trauma in the glottic and subglottic area and leading to increased resistance of flow and respiratory distress. The laryngotracheal lesion is characterized by inflammation, edema, granuloma, and ulceration and may be associated with difficult or prolonged intubation, multiple intubation attempts, excessive cuff pressure, and emergency reintubation after accidental extubation.

Moreover, post-extubation stridor, as a manifestation of laryngeal edema, is a feared adverse event that may lead to reintubation, often under unfavorable and precarious conditions. Occasionally, the involuntary muscle contraction of the vocal folds, triggered by reflexogenic stimuli after extubation, may result in laryngospasm and post-extubation stridor.

It is important to note that laryngeal injuries (granulations and vocal cord dysmotility) may often go unrecognized and may lead to augmented WOB and/or aspiration due to glottis dysfunction. .

The ability of the patient to clear the tracheobronchial secretions is also a major factor on which the success or failure of extubation hinges [1]. The efficient clearance of secretions depends on several factors, including adequate laryngeal function, expiratory muscle function, and effective cough. It is also of note that, after extubation, patients often exhibit swallowing dysfunction, which can result in aspiration.

64.3 Physiological Advantages Offered by NIV

The physiological advantages provided by NIV, are generally similar to those offered by IMV.

64.3.1 Improvement of Blood Gas Exchange through Augmentation of Minute Ventilation (V_E)

Changes in arterial PO_2 and PCO_2 depend on alveolar ventilation (V_A), alveolar–capillary membrane gas transfer and V/Q relationship. The distribution of V_E and V_A is determined by a number of factors, including regional lung compliance and resistance, functional residual capacity (FRC), the parameters set on the ventilator (PEEP, pressure/flow, etc.), and body position. There are substantial differences in the way blood gases respond to the increase in V_E and V_A during NIV. Oxygenation depends primarily on V/Q matching and secondarily on hemoglobin levels. Because the hemoglobin is fully saturated at arterial $PO_2 > 70–80$ mmHg, the arterial content of O_2 tends to plateau, as V_E and V_A are increased with NIV. In contrast, the arterial content of CO_2 decreases almost linearly as V_E and V_A are increased with NIV [2].

64.3.2 Improvement of Blood Gas Exchange through Alveolar Recruitment

In patients with lung injury, the tidal volume provided by NIV can recruit a large number of collapsed/atelectatic alveoli. Moreover, the application of PEEP can prevent de-recruitment of collapsed lung units. PEEP can also offer additional advantages: (i) it improves V/Q matching and gas exchange, (ii) it protects patent alveoli from the injury caused by shear stress of repeated opening and closing of alveoli, and (iii) it improves compliance by preventing surfactant disruption in collapsing alveoli. It should also be stressed that, by avoiding the repeated airway closure and reopening during the respiratory cycle, most notably for patients with a high respiratory drive, NIV with appropriate settings may prevent the development of patient self-inflicted lung injury (PSILI) [1, 2].

It should be pointed out that PEEP may also have serious disadvantages. The application of PEEP alongside tidal volume in patients with lung injury characterized by significant heterogeneity can expose healthy lung regions to the risk of overdistension. Finally, as PEEP increases mean intrathoracic pressure, it can compromise cardiac filling in patients with cardiac dysfunction.

64.3.3 Unloading of Respiratory Muscles

After extubation, respiratory muscles (primarily the diaphragm) may have diminished strength and endurance because of excessive loading, secondary to derangements in mechanical properties of the respiratory system (decreased compliance, increased resistance, increased elastic load due to auto-PEEP). Other factors contributing to muscle impairment include anemia, hypoperfusion, hypoxia, malnutrition, and metabolic derangements due to the systemic inflammatory response syndrome. The impending respiratory muscle failure results in hypoventilation, hypercapnia, and hypoxemia and is characterized by two factors: (i) muscle fatigue from muscle overloading and (ii) the augmented respiratory drive which does not protect the muscle from fatigue. NIV unloads the respiratory muscles by reducing the number of required patient inspiratory efforts and by diminishing the respiratory muscle load with assisted breathing.

64.3.4 Resetting the Respiratory Center

It is well known that the respiratory center in the medulla controls the ventilatory pattern [tidal volume, frequency, inspiratory time/expiratory time (T_i/T_e)]. Furthermore, the respiratory center receives stimuli not only from the central and peripheral chemoreceptors (sensitive to changes of PaO_2, $PaCO_2$, and pH), but also from mechanoreceptors (sensitive to stretching and irritation) in the thorax and respiratory muscles. While NIV offers adequate gas exchange (correcting hypoxemia and hypercapnia) and unloading of the respiratory muscles, the respiratory center output is reset by decreasing its intensity and frequency [2].

64.3.5 Reduction of Inspiratory Triggering Load Caused by Auto-PEEP

In obstructive patients (e.g., COPD) it is established that auto-PEEP imposes an elastic load on the respiratory muscles at the beginning of spontaneous breathing; during the inspiratory effort, the alveolar pressure must drop below the level of auto-PEEP before the beginning of airflow into the airways. In this setting, NIV combined with appropriately selected external PEEP (below the auto-PEEP level), can reduce the inspiratory triggering load by reducing the gradient between alveolar pressure and mask pressure [2].

64.3.6 Cardiac Interactions

The cardiovascular effects of NIV present both favorable and adverse characteristics. In patients with left ventricular systolic or diastolic dysfunction, the increased intrathoracic pressures on the one hand reduce left ventricular afterload while on the other reduce preload (venous return) and afterload in the right ventricle. Of note is the fact that as NIV provides more comfortable breathing conditions and prevents respiratory distress, it also reduces the stress-triggered sympathetic stimulation.

64.3.7 Maintenance of Upper-Airway Patency

PEEP combined with NIV may act as a splint that helps maintain the patency of the upper airway, a feature that is particularly helpful when the patient sleeps.

64.4 NIV Implications during Post-Extubation Period

NIV can potentially be used in three ways during the post-extubation period, these being:

- A facilitative technique—to permit early extubation in selected patients who fail to meet standard extubation criteria (failed spontaneous breathing trial, SBT)

Table 64.1 Techniques of post-extubation noninvasive ventilatory support: to facilitate weaning, to prevent and to treat respiratory failure in medical and post-operative patients

		To facilitate	To prevent	To treat
Medical patients	NIV[a]	– Hypercapnic RF	– Low risk: not suggested	Not suggested
		– No recommendation for Hypoxemic RF	– High risk: suggested	
	HFNO	No data	– Low risk: better than COT	No data
			– High risk: equal to NIV	
Post-operative patients	NIV[a]	No data	– Low risk: not suggested	Suggested
			– High risk: suggested	
	HFNO	No data	– High risk after cardiothoracic surgery: at least non-inferior to NIV	– After cardiothoracic surgery: Non-inferior to NIV

HFNO high flow nasal oxygen, *COT* conventional oxygen therapy, *RF* respiratory failure
[a]Based on ERS/ATS and ACCP/ATS clinical practice guidelines [3, 4]

- A preventive or prophylactic technique—to prevent extubation failure in selected or non-selected patients who passed the SBT
- A therapeutic technique—to avoid re-intubation in patients who fail extubation (Table 64.1).

64.5 To Facilitate Weaning from Invasive Mechanical Ventilation

During IMV, the ultimate goal is to wean and liberate the patient from the ventilator. Prolonged IMV is associated with increased morbidity and mortality. It has been established that chronically hypercapnic patients (e.g., COPD) who are intubated for ARF present high rates of weaning failure and prolonged IMV. As a consequence, strategies which facilitate the weaning process are expected to improve outcomes.

In their pioneering RCT study, Nava et al. [5] found that in selected patients who were intubated for acute hypercapnic respiratory failure, early extubation after a SBT and the immediate application of NIV as a bridge to weaning reduced the duration of IMV, the length of stay in ICU, and the 60 day mortality. A few years later, Girault et al. [6], in a larger cohort of difficult-to-wean patients with chronic hypercapnic RF, duplicated the results of the previous study, concluding that NIV as a weaning technique may shorten the intubation duration and reduce the risk of post-extubation ARF.

Since then, a number of RCTs have investigated the role of NIV as an instrument to facilitate liberation from the ventilator and shorten the duration of weaning. In a Cochrane systematic review by Burns et al. [7], which included 16 trials and 994 patients, mostly with COPD, NIV used as a strategy to facilitate weaning, was associated with more favorable outcomes regarding mortality, weaning failure, and length of stay (both in ICU and hospital). Additionally, a positive effect was observed with significantly reduced rates of tracheostomy and reintubation.

More recently, another meta-analysis [8] (25 RCT and quasi-RCT trials, 1609 patients) concluded that the use of NIV in weaning from IMV reduces hospital mortality and the rates of ventilator-associated pneumonia (VAP) and ICU length of stay. Furthermore, it was pointed out that NIV as a weaning strategy appears to be most beneficial in COPD patients.

Based on the previous evidence, using NIV to aid weaning from IMV is recommended by both the European Respiratory Society/American Thoracic Society (ERS/ATS) [3] (conditional recommendation, moderate certainty of evidence) and the British Thoracic Society and the Intensive Care Society (BTS/ICS) (grade B) [9] in patients with hypercapnic respiratory failure (e.g., COPD). As there is weak evidence for non-hypercapnic patients, no recommendation can be made for these patients. Nonetheless, BTS/ICS do advise a more cautious approach in patients with hypoxemic respiratory failure and underline the significance of expertise in using

NIV, which should be combined with physiotherapy and cough assist, to improve the likelihood of success.

Unfortunately, there is scarce clinical evidence concerning patients with tracheostomy in weaning from mechanical ventilation. Liang et al. investigated using NIV to assist the progress of weaning in 22 tracheostomized difficult-to-wean patients (at least one failed SBT) [10]. In the intervention group, after successfully completing an SBT, the tracheostomy was removed and closed and NIV was applied via a facial or nasal mask. According to their findings, this method shortened the duration of weaning and the ICU length of stay. A most recent narrative review of the literature [11] supports the potential role for NIV in weaning tracheostomized patients. NIV is usually delivered using a facial interface and the tracheostomy is capped. This technique appears to facilitate liberation from the ventilatory support and eventually decannulation.

It is well known that high flow nasal oxygen (HFNO) offers some physiological advantages, including the PEEP effect, reduced WOB, improvement in mucociliary clearance, a higher level of comfort and tolerance, constant fraction of inspired oxygen, reduction of pharyngeal dead space, and lower carbon dioxide rebreathing. Although there is at present a paucity of solid data, some evidence is emerging of the efficacy of HFNO as a weaning technique, at least for COPD patients after extubation. Jing et al. [12], investigated the effects of HFNO in comparison to NIV on vital signs and arterial blood gases in 42 COPD patients who had persistent hypercapnia after extubation. Interestingly, they showed that HFNO was not inferior to NIV regarding treatment failure, reintubation, and arterial blood gases. Furthermore, in the patients treated with HFNO, comfort scores were higher and clearance of airway secretions was more manageable (requiring fewer interventions such as bronchoscopy). Most recently, Tan et al. [13] found that the immediate application of HFNO after extubation was not inferior to NIV in terms of treatment failure in 96 COPD patients receiving IMV for severe hypercapnic respiratory failure. Moreover, HFNO performed better in terms of tolerance and comfort. Taken together, these findings suggest using HFNO as an alternative to NIV in COPD patients after extubation, especially for those who cannot tolerate NIV. Clearly, more and better powered trials are called for, before a definitive answer emerges on this subject.

64.6 To Prevent Acute Respiratory Failure and Reintubation

Several studies have addressed the question whether prophylactic use of NIV within 24–48 h after extubation could reduce the risk of post-extubation respiratory failure and the rate of reintubation in high-risk patients who have passed the SBT. Of these, only 2 single-center RCTs and one before–after study, all with a small number of patients, have found that reintubation rates were lower with NIV than with conventional oxygen therapy [14–16]. It has also been demonstrated that post-extubation support with NIV may be more effective in hypercapnic patients at the end of SBT

in reducing reintubation and improving 90-day mortality [17]. Interestingly, in the aforementioned studies, NIV was commenced immediately after extubation for ≤18 h/day or by sessions of 1–2 h for a total period of at least 8 h/day during the first 48 h.

Considering these findings, the application of NIV as a prophylactic modality to prevent respiratory failure in high-risk patients was a conditional recommendation (low certainty of evidence), in the recent ERS/ATS clinical practical guidelines [3]. Furthermore, in the clinical practice guidelines published by the American College of Chest Physicians and American Thoracic Society (ACCP/ATS) [4], it was pointed out that the desirable consequences of NIV (e.g., improved extubation success, lower rates of reintubation, reduced ICU length of stay) clearly outweigh any disadvantages (e.g., facial skin damage, conjunctivitis). It was also suggested that NIV should be applied immediately after extubation so that physicians could realize the outcome benefits.

Therefore, identifying these high-risk patients is an important first step in the successful management of the post-extubation hazards. The risk factors of post-extubation respiratory failure include prolonged duration of ventilation, multiple attempts at weaning before SBT success, age > 65 years, Acute Physiology and Chronic Health Evaluation (APACHE) II score exceeding 12 on the day of extubation, congestive heart failure, left ventricular dysfunction (ejection fraction < 45%), hypercapnia, weak cough, upper airway stridor, and pulmonary comorbidities [1]. In short, patients at high risk of post-extubation respiratory failure and reintubation include those older than 65 years or those with underlying respiratory and heart diseases. Interestingly, these patients exhibit reintubation rate > 30% if both co-morbidities are present and > 20% if one of the two is present.

Regarding the low-risk patients, the ERS/ATS practice guidelines, based on very low certainty of evidence, should not suggest the use of NIV as a tool to prevent respiratory failure and reintubation (conditional recommendation) [3].

Recent analyses suggest that HFNO has been considered as an alternative modality to standard oxygen therapy during the post-extubation period. More specifically, two RCT studies have demonstrated that the application of HFNO after planned extubation reduced the rate of reintubation compared with conventional oxygen therapy [18, 19]. More specifically, Hernadez et al. concluded that among patients at low risk of reintubation, HFNO compared to standard oxygen reduced the rate of reintubation at 72 h [20]. The same group of investigators found that HFNO was not inferior to NIV in preventing post extubation respiratory failure and reintubation in high-risk patients [19]. Taken together, these findings highlight that HFNO may be an alternative modality to conventional O_2 to support post extubated patients. Addressing the issue of a possible synergistic effect of NIV and HFNO, Thille et al. [21] studied 641 patients at high risk of extubation failure in a multicenter RCT. They found that the combined application of HFNO and NIV immediately after extubation compared to HFNO alone significantly decreased the rates of reintubation.

Nevertheless, a meta-analysis by Sang et al. [22], comparing the efficacy of HFNO, conventional oxygen therapy and NIV, concluded that NIV reduces reintubation rates in patients undergoing planned extubation, but that there was no statistically significant difference in comparison with HFNO and the conventional oxygen groups. Another meta-analysis published in 2020 concluded that after a planned extubation, NIV was the most effective modality of respiratory support not only for preventing extubation failure and reintubation but also for reducing short-term mortality, especially in high-risk medical patients [23].

64.7 To Treat Post-Extubation Acute Respiratory Failure

The ERS/ATS guidelines [3] conditionally recommend against using NIV as a therapeutic method to manage post-extubation ARF in patients at low and high risk who passed the SBT, but experienced ARF within 48 h after extubation. This was based on the findings of two prospective RCTs [24, 25] that provided no evidence of benefit from the use of NIV compared to conventional oxygen therapy on rates of reintubation and ICU length of stay. On the contrary, these findings suggested a detrimental effect on mortality, which was attributed to delayed intubation (12 h in the NIV group vs. 2.5 h in the standard care group).

Two meta-analyses published a few years ago [26, 27] included not only patients with established ARF after extubation, but also those at high risk for developing post-extubation ARF. They found that NIV compared to conventional O_2 does not provide any benefit in non-surgical patients who developed post-extubation ARF in terms of mortality and ICU length of stay. They also stressed that in these patients, post-extubation respiratory failure warrants cautious monitoring as well as readiness to reintubate immediately. It should be pointed out that the subject of insufficient experience in the application of NIV in the aforementioned trials has been discussed, raising skepticism regarding the credibility of the negative results observed in the NIV groups.

A more physiological explanation for the failure of the NIV in question was hypothesized to be the fact that, despite acceptable arterial blood gas in the NIV group, a longer period of excessive WOB, compared to the standard therapy, led to PSILI, caused by exaggerated swings in the transpulmonary pressure and the emergence of overdistended areas in the lung, as discussed in a review by Kacmarek [28]. Thus, it is advisable to pay more attention to the presence of signs and symptoms of respiratory distress, rather than on the assessment of the arterial blood gases alone, in patients with established post-extubation ARF. Procrastination and failure to intubate in a timely manner may result in seriously adverse outcomes.

Interestingly, in the subpopulation of hypercapnic patients with COPD, the BTS/ICS guidelines [9] state that a trial of NIV as a rescue therapy, after planned extubation, is justified where there is familiarity with this method of ventilatory support. This was supported by data from post hoc analysis from available studies, as well as

from the encouraging results obtained by the application of NIV in other situations for this specific subgroup.

64.8 NIV after Extubation in a Post-Operative Setting

Post-operative patients develop post-extubation failure less frequently (<10%) in comparison with medical critically ill patients (≤20%). The pathophysiological effects of surgery include diaphragmatic dysfunction, anesthesia and pain, which can cause loss of lung volume, atelectasis, inadequate cough, hypoxemia, and respiratory distress [1]. Post-operative patients at high risk for post-extubation failure include age > 65 years, obesity, previous pulmonary (i.e., COPD), heart disease (i.e., LVEF≤40%), and failure of previous extubation.

Many studies demonstrated the benefit of NIV and CPAP, used as preventive or therapeutic modalities, after various types of surgeries (cardiothoracic, vascular, abdominal) in reducing post-operative complications, rates of reintubation, and ICU length of stay by improving lung volumes and gas exchange. In a large multicenter RCT (298 patients who developed hypoxemic respiratory failure after abdominal surgery), Jaber et al. concluded that NIV was superior to conventional oxygen therapy (COT) in reducing reintubation rates within 7 days after surgery (46% vs. 33%, $p = 0.03$) and nosocomial infections (31% as opposed to 49%, $p = 0.003$) [29].

Taken together these findings suggest the usefulness of NIV in the postoperative setting after abdominal surgery. According to the ERS/ATS guidelines [3], the deployment of NIV for patients with post-operative ARF is conditionally recommended (with moderate certainty of evidence) without discriminating between its preventive and therapeutic use. It is worth noting that before applying NIV, a thorough clinical examination should be preceded to exclude serious surgical complications.

Recently, physiological pilot and controlled trials have drawn attention to the potential role of HFNO as a noninvasive technique to support post-operative patients who developed post-extubation ARF. Over the past decade, three studies have shown, although not powered to these outcomes, that HFNO compared to COT reduced the intubation rates and the escalation in respiratory support after extubation in post-operative patients (cardiac and thoracic surgery). However, the study by Stephan et al. [30] was the first large non-inferiority multicenter RCT that compared NIV with HFNO (according to facilitative, preventive, and therapeutic strategies) in 830 patients after cardio-thoracic surgery who developed hypoxemic respiratory failure during the SBT or after extubation. There was no difference in terms of treatment failure (reintubation), switch to other treatment, or discontinuation of therapy (21.9% for NIV and 21% for HFNO, for the three strategies combined). Moreover, a post-hoc analysis showed that treatment failure between NIV and HFNO was not different when these techniques were used as facilitative or therapeutic. On the contrary, applying them as a preventive strategy, treatment failure was lower in HFNO compared to NIV (6% as opposed to 13%, $p = 0.04$). In the OPERA trial, Futier et al. compared HFNO to COT, applied

directly after extubation, in 220 medium-high risk patients after major abdominal surgery. They found that early preventive use of HFNO did not result in improvement of oxygenation (at 1 h after extubation and at the discontinuation of treatment) compared with COT [31].

Given the available evidence in the post-operative setting, NIV is suggested as a preventive and therapeutic technique in high-risk patients after abdominal (including abdominal vascular surgery) and cardio-thoracic surgery (including thoracic vascular surgery). HFNO can be considered as an alternative to NIV (at least, not inferior) after cardio-thoracic surgery (Table 64.1). A significant advantage of HFNO over NIV is the increased comfort and cooperation of the patient. However, since PEEP is a major factor counteracting atelectasis and correcting hypoxemia, especially in obese patients, it should not be forgotten that the levels of PEEP achieved by HFNO are markedly lower than those achieved by NIV [2].

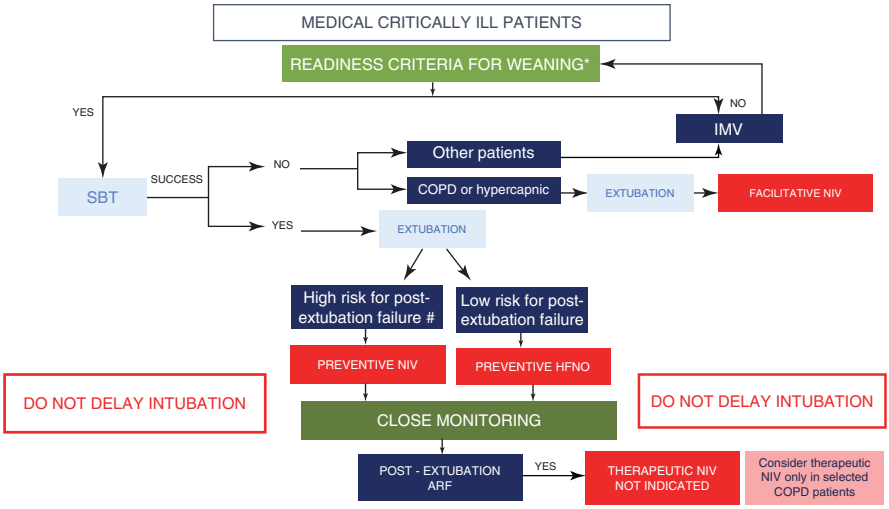

Fig. 64.1 Algorithmic approach for noninvasive ventilatory support in medical critically ill patients. ***Readiness criteria for weaning:** resolution of the reason why the patient was intubated, stable neurologic status with no or minimal sedation, stable hemodynamic status (i.e., HR ≤ 140 breaths/min, systolic BP 90–150 mmHg with no or minimal vasopressors, adequate oxygenation (i.e., $SpO_2 > 90\%$ on $FiO_2 \leq 50\%$ or $PaO_2/FiO_2 \geq 150$ on PEEP ≤ 8 mmHg), adequate pulmonary reserves (i.e., RR ≤ 35/min, $V_T > 5$ mL/kg, VC > 10 mL/kg, $RR/V_T \leq 105$ breaths/min, MIP ≤ −20 to −25 cmH_2O, no significant respiratory acidosis. **# High risk patients for post-extubation failure:** See text. IMV, invasive mechanical ventilation; NIV, noninvasive ventilation; HFNO, high flow nasal oxygen; ARF, acute respiratory failure; SBT, spontaneous breathing trial; COPD, chronic obstrcted plmonary disease; HR, heart rate; RR, respiratory rate; BP, blood pressure; V_T, tidal volume; VC, vital capacity; MIP, maximal inspiratory pressure

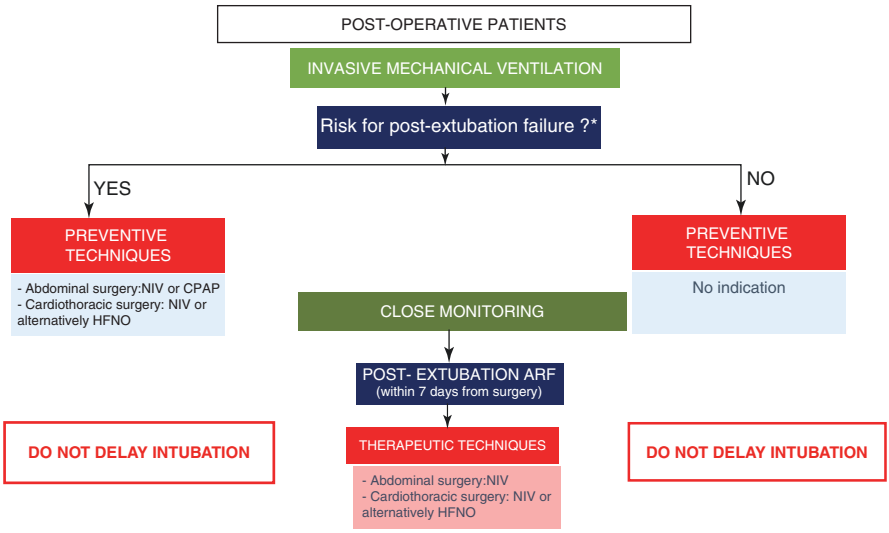

Fig. 64.2 Algorithmic approach for noninvasive ventilatory support after extubation in post-operative patients. ***Risk factors for post-extubation failure:** age > 65 years, obesity, known pulmonary (i.e., COPD) or heart disease (i.e., LVEF ≤ 40%), failure of previous extubation. NIV, noninvasive ventilation; CPAP, continuous positive airway pressure; HFNO, high flow nasal oxygen; ARF, acute respiratory failure; LVEF, left ventricular ejection fraction; COPD, chronic obstructed plmonary disease

64.9 Summary of Clinical Implications

The weaning process does not end with the discontinuation of IMV. Rather, it extends to the period after extubation when ARF might occur requiring appropriate interventions.

After extubation, these techniques could potentially facilitate weaning, as well as prevent and treat ARF. The selection of these techniques depends on the type of patients (medical or post-operative), the degree of risk for post-extubation ARF, and the etiology of ARF (Table 64.1, Figs. 64.1 and 64.2).

As soon as the medical critically ill patients meet the readiness criteria for weaning, a SBT should be performed on a daily basis. After a failed SBT a facilitative technique could be considered for selected patients (i.e., COPD or hypercapnic during SBT). Conversely, after a successful SBT, the risks of post-extubation failure should be evaluated. For low-risk patients, preventive HFNO is preferable over COT, whereas for high risk patients, preventive NIV is indicated especially for those with COPD exacerbation or heart failure. It is worth noting that preventive NIV should begin immediately after extubation and continue for the first 24 h. For high-risk patients, preventive HFNO, offering more comfort, can be used as an alternative to NIV. If ARF develops after extubation, therapeutic NIV is not indicated and intubation is the best option. Nevertheless, selected patients with COPD with

post-extubation ARF could be considered for a trial with NIV inside a safe environment (Fig. 64.1).

In post-operative patients, the use of noninvasive modalities differ according to the level of risk for post-extubation failure and the type of surgery. In high-risk patients after abdominal surgery, including vascular surgery, preventive NIV or CPAP is beneficial. After cardiothoracic surgery, including vascular surgery, NIV and HFNO, as an alternative to NIV, should be considered. Should ARF develop within 7 days following abdominal or cardiothoracic surgery, therapeutic NIV should be used. Additionally, HFNO can be used, as an alternative to NIV, in patients following cardiothoracic surgery who develop ARF (Fig. 64.2).

It is imperative to keep in mind that in either medical or post-operative patients, intubation should not be delayed when escalation to IMV is indicated. Any delay in intubation is associated with a worse outcome and increased mortality.

Key Messages

- Extubation failure is associated with worse outcomes (increased mortality, increased length of stay in ICU, increased rates of VAP).
- The pathophysiological mechanisms occurring during the passage from assisted ventilation to spontaneous breathing is of paramount importance to understand the physiological effects of noninvasive ventilation during the post-extubation period.
- NIV and/or HFNO applied in the post-extubation period improves outcomes of weaning from IMV.
- Identifying patients at high risk of post-extubation failure is the first step for selecting the appropriate strategy (facilitative, preventive, therapeutic) to avoid post-extubation failure and reintubation.
- Extreme caution should be used not to delay intubation in case there is a need for escalating therapy to IMV.

64.10 Conclusions

Noninvasive ventilatory support applied using NIV and/or HFNO improves outcomes of weaning from IMV. The rationale behind the implementation of these noninvasive techniques are the distinct pathophysiological mechanisms that characterize the transition from ventilatory support to unassisted breathing. NIV, unlike IMV, has beneficial physiological effects, averting weaning and extubation failure.

NIV can be used in different strategies to prevent or treat post-extubation respiratory failure and to facilitate extubation. The recently published guidelines should direct the every day clinical practice to avoid post-extubation failure and reintubation. Needless to say, clinical judgement and caution should always prevail; each

case should be assessed individually, taking into consideration all the relevant factors (comorbidities, local expertise, devices and interfaces, level of monitoring, patient's cooperation, etc.) and the application of NIV should be undertaken when the optimal standards of care are met.

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Extubation and Decannulation of Unweanable Patients with Neuromuscular Weakness Disorders

65

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65.1 Introduction

Neuromuscular diseases (NMDs) encompass several syndromes and diseases, which commonly determine neuromuscular weakness [1]. NMDs affect the peripheral nervous system, which includes the motor neurons and sensory neurons, the muscle itself, or the neuromuscular junction. Consequently, expiratory, inspiratory or upper airway muscles can be compromised, which can lead to chronic respiratory failure and the need to perform patient intubation and/or tracheotomy [2].

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_65

Respiratory muscle weakness is a major cause of morbidity and mortality in patients affected by NMDs. This muscular dysfunction may cause respiratory pump failure, upper airways instability with or without swallowing impairment and insufficient cough [3, 4].

Some NMDs, such as Guillain-Barré syndrome (GBS), myasthenia gravis (MG), polymyositis (PM) and multiple sclerosis (MS), often present with acute respiratory failure due to sudden respiratory muscle weakness that can resolve after specific treatment of the underlying disease. In such cases, ventilatory assistance may only be temporary [5, 6].

In contrast, other NMDs, such as amyotrophic lateral sclerosis (ALS) or Duchenne's muscular dystrophy (DMD), are progressive despite treatment and may require increasing degrees of respiratory support to sustain life. Moreover, patients affected by NMDs are prone to develop several other respiratory complications, such as infections, atelectasis due to mucus plugging and aspiration, that may precipitate acute respiratory failure in an already compromised ventilatory function [4, 7–11].

65.2 Noninvasive Respiratory Supports in NMDS

Progressive respiratory muscle weakness results in a step-by-step worsening of the respiratory pump function. Sleep breathing disorders are the first sign of pump failure, followed by diurnal hypoventilation in the later stages of the disease [4, 7].

All patients with NMDs should therefore be monitored and periodically evaluated for the need for chronic ventilatory support. Mechanical ventilation should be started in patients with symptoms of nocturnal hypoventilation (morning headache, fatigue, daytime sleepiness) plus abnormal findings in oximetry or capnography (long lasting desaturations and/or nocturnal hypercapnia). Other indications include a vital capacity (VC) <50%, decreased respiratory muscle pressure (sniff nasal inspiratory pressure/SNIP < 40 cmH_2O, maximum inspiratory pressure/MIP < 65 cmH_2O) or daytime $PaCO_2$ > 45 mmHg [5, 7].

The first approach to mechanical ventilation is usually with noninvasive positive pressure ventilation (NIV) strategies. NIV can be provided with nasal or oro-nasal masks or – especially during daytime – with mouthpieces that allow the patient to suck a relatively large amount of air (800–1500 mL) as needed. This intermittent support with variable tidal volumes facilitates daytime tolerability to NIV, as it allows changing speech volumes and lengths, cough flow and active lung volume recruitment maneuvers [7, 8, 12, 13].

Furthermore, adequacy of cough should be evaluated measuring cough peak flow (PCF). Cough results are ineffective when PCF drops below 160 L/min and may became insufficient even when PCF < 270 L/min when the patient is unwell. There are several techniques to improve the cough efficacy, but the most effective one is mechanical insufflation-exsufflation (MIE), a tool that can provide a quick switch from high positive pressures to very low negative pressures (usually +40 cmH_2O and −40 cmH_2O) to open the lung and then suck the secretions out [7].

65.3 Drifting to Invasive Ventilation: The Conventional Paradigm

Patients with NMDs may require invasive ventilation in two different settings.

The first scenario is the occurrence of an acute event, such as a severe acute respiratory failure (ARF) due to pneumonia or an episode of rapidly progressive muscular weakness during a myasthenic crisis or GBS. In these cases, a trial of NIV might be useful to avoid unnecessary endotracheal intubation (ETT). However, often invasive ventilation is required anyway, to stabilize the patient while other therapies (such as antibiotics, pulmonary toilette or specific drugs) are administered to maximize respiratory recovery.

Hopefully, ETT is successful in bridging the patient to independent respiratory function. If not, one option is to proceed to tracheostomy and hence chronic invasive ventilation, while the other alternative is compassionate extubation [5, 6, 14, 15].

Unfortunately, patients affected by NMDs do not often match the criteria for a safe extubation because of their already compromised respiratory muscle dysfunction.

In fact, extubation protocols in general intensive care units (ICU) generally require [15, 16]:

1. Patients awake and cooperative (Glasgow coma scale >8)
2. Good coughing and swallowing
3. Spontaneous breathing trial of at least 30 min with:
   (a) $PaO_2 > 60$ and increase $PaCO_2 < 15$ mmHg
   (b) Low respiratory rate (RR < 30/min)
   (c) Adequate tidal volume (Vt > 5 mL/kg)
   (d) Rapid shallow breathing index (RSBI): RR/Vt < 105
   (e) Minute volume (MVe ca. 10 L)
   (f) PaO_2/FiO_2 ratio 150–200

Rates of weaning failure in NMDs are high, ranging from 27% to 48%. Therefore, tracheostomy is commonly considered after 7 to 10 days of intubation for patients who fail weaning or extubation with no identifiable reversable cause, provided this is consistent with the patient's desire [17].

Tracheostomy reduces work of breathing, airway resistance, peak inspiratory pressure, intrinsic positive end-expiratory pressure (auto-PEEP) and patient–ventilator asynchronies. It also makes clearance of the secretion much easier and reduces the need of sedation [15, 17–19].

The second scenario where NMDs patients undergo tracheostomy is when non-invasive strategies become either ineffective, especially in patients with severe bulbar disfunction, or unbearable for the patient. This is a chronic setting that requires thoughtful consideration based on the goals of the patient and family [14].

Similar to other respiratory supports, tracheostomy may represent a bridge to recovery of pulmonary function, or a stabilizing action in the hope that novel therapies may prove beneficial. In other situations, tracheostomy is a definitive approach,

requiring weighing the implications of chronic mechanical ventilation. Tracheostomy offers practical benefits in terms of comfort and stability, but, at the same time, it is linked to an increase in the patient's level of dependence on medical technology and on the caregivers [14, 20, 21].

Also, tracheal mechanical ventilation (TMV) increases ventilator dependence by tube-triggered airway secretions and by further respiratory muscle deconditioning. It also makes speech and swallowing even more difficult [7].

65.4 Weaning of the Unweanable Patients: Changing the Paradigm?

Some authors, such as Bach J, and other colleagues who work in highly specialized centers, published several case series of successful weaning of NMDs patients, even if they were conventionally considered unweanable from ETT and TMV [7].

In their experience, full ventilator weaning and passing spontaneous breathing trials are not prerequisites for successful extubation or decannulation in NMDs if the patient can be switched to NIV (even continuous) and MIE [7, 22].

Bach J reported criteria for safe extubation and decannulation for ventilator unweanable patients [7].

These criteria are:

1. Patient fully alert and cooperative with any sedative medications discontinued
2. No other vital organ dysfunction apart from respiratory failure
3. Afebrile with normal white blood cell count, chest radiograph abnormalities cleared or clearing
4. No history of substance abuse or uncontrollable seizures
5. $PaCO_2 \leq 40$ mmHg at peak inspiratory pressures less than 35 cmH_2O on full ventilatory support settings with physiologic back-up rate as needed.
6. $SpO_2 \geq 95\%$ for ≥12 h with FiO_2 21% with all transient oxyhemoglobin desaturations below 95% reversed by MIE via ETT or tracheal cannula
7. Sufficient air leakage via upper airway for vocalization with ETT/tracheal cannula cuff deflated
8. No conditions that might interfere with the use of NIV interfaces (facial fractures, inadequate bite or neck rotation for mouthpiece entry, presence of a nasogastric tube or a beard that hampers airtight interface seal)

These criteria are met in NMDs patients with patent airways affected by respiratory pump failure alone (the lungs are normal, but the muscular pump does not work, i.e. a patient with $SpO_2 \geq 95\%$ with FiO_2 21% and insufficient cough and/or impaired bulbar function with mild aspirations that can be managed with frequent and aggressive usage of MIE.

Once these criteria are met, ETT can be removed and the patient is directly switched to NIV in assist-control with volume preset from 800–1500 mL and respiratory rate 10–14/min, always in ambient air. Once successfully ventilated via nasal

or oro-nasal interfaces, the patient is taught to use mouth-piece ventilation for daytime, as this technique requires a specific training to use the soft palate to block air from leaking out of the nose. After extubation, SpO_2 must be closely monitored, since desats could results from insufficient positive inspiratory pressure, air leakage from the mask or the tubes, or secretions that must be promptly treated with MIE [7].

A similar protocol has been proposed for transition from tracheotomy to noninvasive supports, once the patient meets the aforementioned criteria. However, in this situation the patient is already stabilized with the tracheostomy, so there is no hurry for decannulation.

First, the tracheostomy tube is changed to a cuffed fenestrated one, then the patient gets accustomed to speaking and maintaining ventilation by using TMV with the cuffs deflated. From the ventilator setting point of view, delivered air volume is increased (typically 1500 mL or more) to compensate for air leakage around the tube. This leaked air allows speech, while the other air enters the lungs, providing alveolar ventilation. Also, in this setting, no supplemental O_2 is used, and all desats are reversed by using MIE.

Subsequently, TMV is stopped and the cannula is capped so that the patients can practice mouthpiece ventilation during the daytime and nasal or oro-nasal NIV during sleep.

Once NIV and MIE are mastered, the tube is changed to a fenestrated and cuffless one, capped permanently, and the patient keeps using NIV as aforementioned for at least 1 week. After this, the tracheostomy tube is removed and a temporary ostomy button can be placed in site to let the patient continue practicing NIV without letting the ostomy close. After tube or button removal, a pressured dressing is placed over the ostomy to make it heal and to prevent excessive air leakage [7, 22].

In 2010, Bach et al. reported extubating 157 consecutive ‘unweanable’ patients: 25 with spinal muscular atrophy (SMA), 20 with DMD, 16 with ALS, 51 with other NMDs, 17 with spinal cord injury, and 11 post-polio syndromes (PPS), with an extubation success rate of 95%. Only two bulbar ALS patients underwent tracheotomy [23]. Moreover, in 2015 the author reported an additional 97 of 98 unweanable patients successfully extubated with 45 having been totally dependent on NIV and MIE before being intubated. In these cases, normal baseline SpO_2 was the primary criterion needed for extubation success. After extubation, VC increased significantly within 3 weeks following extubation, and weaning from continuous NIV to part-time ventilation was achieved by all 52 patients who had not been continuous NIV dependent before intubation [24].

65.5 When to Trach?

These results suggest that no extent of respiratory muscle failure or ventilator dependence is a strict indication for tracheotomy. Even total paralysis of bulbar-innervated muscles does not indicate need for tracheotomy, since patients can be positioned to drool rather than to aspirate. The only indication for tracheostomy is inability to cooperate with NIV or aspiration of airway secretions that cause a drop

in SpO_2 despite NIV and MIE. Generally, this only occurs in patients with advanced upper motor neuron bulbar amyotrophic ALS [7, 14].

65.6 Amyotrophic Lateral Sclerosis

ALS is a paralytic and progressive disorder caused by motor neurons degeneration in the brain and spinal cord. ALS begins insidiously with focal weakness, but it spreads progressively, involving most muscles and the diaphragm.

The corticospinal motor neurons compromission determines muscle stiffness and spasticity, whereas lower motor neurons involvement leads initially to an excessive electrical irritability (fasciculations) and, with the progression of degeneration and the losing of synaptic connectivity, to muscular atrophy.

The ALS diagnosis is achieved by clinical examination of characteristic symptoms (progressive difficulty chewing, dysphonia and dysphagia), the electromyography (extent of denervation), and laboratory testing [25, 26].

The current treatment options for patients affected by ALS are based on appropriately managing the progression of ALS symptoms, including use of nasogastric feeding, percutaneous endoscopic gastrostomy (PEG) tube, control of salivary secretions and use of cough-assist devices, ventilatory support with bilevel positive airway pressure, or performing a tracheostomy for full ventilation support [27, 28].

Respiratory system dysfunction is the terminal event for most patients with ALS. Despite variable presentations, respiratory system disfunction represents the most frequent complication in ALS patients, who experience progressively dysphonia, airway clearance, dysphagia with aspiration, dyspnea, orthopnea, and hypoventilation [28]. A Forced Vital Capacity (FVC) < 50% is considered indicative of respiratory failure. Noninvasive Ventilation (NIV) has become the standard of care for respiratory support in patients with ALS, demonstrating survival significant support with an improvement of quality of life [28]. The early NIV support (FVC ≥ 80%) seems to suggest a better survival support [28]. Furthermore, NIV can be applied as invasive ventilation for patients who choose to undergone permanent tracheostomy.

Permanent tracheostomy is carried out in 2% to 15% of ALS patients and represents the most critical issue in ALS disease, considering that tracheostomy does not modify the progression of the disease [25, 26].

In our institution, the permanent tracheostomy is usually performed by the skin-lined technique, first described by Mayer and Penta in the 1960s and proposed in conditions of chronic severe respiratory failure, such as severe grade of Miastenia Gravis and ALS [29, 30]. In this technique, two horizontal cutaneous flaps of 2 or 3 cm in length, and high 1.5–2 cm are saturated with the lateral opening of the tracheotomy. The median tracheotomy flaps (usually one tracheal cartilage superiorly and two tracheal cartilages inferiorly) are saturated with the median cervical skin. In this way, a skin-trachea anatomical funnel is created [30] (Fig. 65.1).

Skin-lined tracheostomy allows obtaining a greater tracheostoma stability, for the presence of an epithelialized inlet between the trachea and the anterior cervical

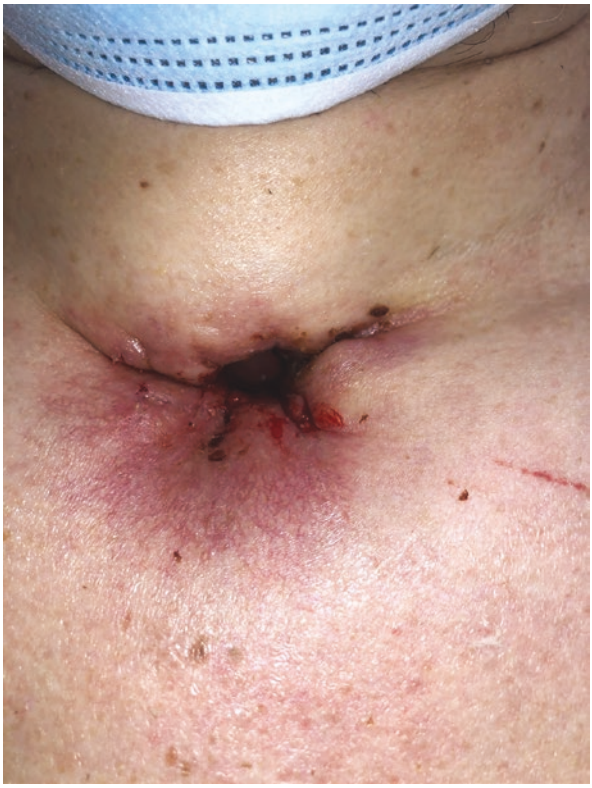

Fig. 65.1 Skin-lined tracheostomy final result

skin, which prevents retracting. Furthermore, skin-lined tracheostomy significantly reduces the risk of granulation tissue because of the lower tendency of peristomal connective tissue to penetrate into the tracheal lumen. Finally, a larger opening of tracheostomy allows an easier and safer home management of the cannula.

NIV and invasive mechanical ventilation (TMV) are more feasible by means of skin-lined tracheostomy, as well as airway clearance.

Performing the skin-lined tracheostomy in ALS early stages could allow maintaining the tracheostoma without the cannula, maybe during some daytime hours and without the risk of rapid stenosis of the tracheostoma. Applying customized obturator, also a residual phonation could be possible.

A limit of skin-lined tracheostomy is related to the complexity of the surgical procedure, which is not easily feasible under local anaesthesia.

In addition, the presence of a cannula represents a negative factor which can affect the swallowing.

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Chest Physiotherapy and Noninvasive Ventilation in Post-Extubation Respiratory Failure: Prevention and Indications

66

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_66

66.1 Weaning of Invasive Mechanical Ventilation (IMV)

Weaning from mechanical ventilation is the process of gradually reducing the ventilatory support that leads to the reestablishment of spontaneous ventilation. Planned extubation occurs in approximately 50–60% of patients in the intensive care unit (ICU), 30% die or undergoes tracheostomy while still intubated, and only about 5–15% are unplanned events (e.g., accidental or self-extubation). Some patients undergo terminal extubation at the end of life [1].

Guidance on the optimal strategies and timing of weaning vary in the literature, and potential complications overrun the process. The weaning strategies must be integrated with the daily sedation interruption to identify which patients are ready. In summary, patients potentially ready for weaning tests include those with the resolution of the primary cause that led to ventilation and additionally: adequate oxygenation $PaO_2/FiO_2 > 150$ mmHg with PEEP ≤ 6 cmH_2O; hemodynamic stability with good tissue perfusion; and an appropriate level of consciousness. Several other parameters must be optimized (e.g., ionic disturbances and transfusion support), and the maximal inspiratory airway pressure and the rapid shallow breathing index (RSBI) are helpful indicators to aid physicians in deciding when to begin weaning strategies.

Spontaneous Breathing Tests (SBT) are one of the most efficient weaning strategies, using a T-tube trial or low-level pressure support [2]. An integrated evaluation of respiratory rate and pattern, gas exchange, comfort, and hemodynamic changes during this period can help evaluate the patient's tolerance for extubation.

66.2 Extubation Failure and Acute Respiratory Failure

Extubation failure is the inability to sustain spontaneous breathing after removing the artificial airway and the need for reintubation within hours or days after planned extubation. The time interval for extubation failure varies from 48 to 72 h, or 1 week, depending on the literature consulted. Among patients who meet all weaning criteria, 10–20% require reintubation, mainly within the first 24 h. Over half of the patients who undergo unplanned extubation require immediate reintubation [1].

There are several reasons behind extubation failure: lack of improvement in autonomous breathing capacity; hypoxemia; respiratory acidosis in patients with chronic respiratory diseases or hypoventilation associated with ICU acquired weakness (ICU-AW) or diaphragmatic dysfunction; retained secretions; inappropriate levels of consciousness (e.g., delirium, neurocognitive disorders, neurosurgical patients, excess sedation).

A review published in the European Medical Journal (October 2017) stratified potential risk factors for post-extubation failure [3]. Risk factors with strong supporting evidence included positive fluid balance, upper airway obstruction, advanced age, pneumonia-causing IMV, and RSBI >105. The patient's conscious level, cough strength, secretion load, delirium, and ICU polyneuropathy were considered risk factors with weak supporting evidence [3].

Reintubation secondary to post-extubation acute respiratory failure (ARF) is associated with elevated ICU mortality. Therefore, the risks of possible post-extubation ARF must be balanced against the risks associated with prolonged mechanical ventilation [1].

66.3 Approach to Acute Respiratory Failure

It is important to differentiate patients into two main categories [4]:

1. Low risk of reintubation—patients that typically do well on low-flow oxygen and can be discharged from the ICU after 12–24 h, provided no other indications for ICU care are present.
2. High risk of reintubation—patients requiring careful monitoring and management with continued therapies, including airway clearance measures, oxygenation, and ventilation, to help prevent reintubation.

An interdisciplinary team model is highly advisable in the ICU environment, where the nursing staff, physiotherapists, and rehabilitation specialists, are crucial elements of this team. It is essential to elaborate an individualized plan for each patient to guarantee shorter weaning times and successful extubation.

66.3.1 Chest Physiotherapy in Weaning and Post-Extubation Respiratory Failure Prevention

Critically ill patients in an ICU can be confined to their beds for long periods, especially during endotracheal intubation, resulting in physical deconditioning, which can affect several body systems, including the respiratory system. Chest physiotherapy can use a variety of manual, instrument, or mechanical techniques to achieve the following aims:

1. Lung volume recruitment;
2. Airway secretion clearance;
3. Optimization of the ventilation/perfusion relation;
4. Strengthening of the inspiratory muscles.

Lung volume recruitment may be helpful in patients with restrictive syndromes or atelectasis as it increases the number of alveoli in the dependent part of the lungs, increases lung compliance, and reduces intrapulmonary shunt. Bag valve mask ventilation, volumetric ventilator, or mechanically in-exsufflation devices are helpful for this purpose, as they can re-open the collapsed field of the lungs by temporarily elevating intrapulmonary pressure to levels higher than those achieved during tidal ventilation. Data to support lung volume recruitment is limited to observational series, with limited data to support an effect on concrete clinical outcomes. The

efficacy likely varies between patients, but it is unclear which patients may benefit [5].

Manual techniques such as patient positioning (side-lying with the affected side uppermost), deep breathing exercises, and thoracic expansion exercises are encouraged, as they can optimize the ventilation/perfusion ratio by looking to ventilate lung areas that are better perfused without increasing lung volume.

Patients in ICU receiving mechanical ventilation may experience impaired clearance of airway secretions during intubation and, once extubated, due to ineffective cough and deficit bronchial hygiene, which may occur in restrictive syndromes (e.g., respiratory muscle weakness, ICU-AW, neuromuscular disorders, spinal cord injury). Spontaneous or provoked coughs are independent predictors of successful extubation procedures [6]. Extubation failure is more frequent when a combination of risk factors affecting airway patency are present, for example, patients with reduced cough peak expiratory flow rate (PEF $\leq$ 60 L/min), increased sputum volume (>2.5 mL/h), and impaired neurologic function (inability to follow commands) [7].

The Airway Care Score is a helpful tool to predict the capability of keeping an airway open safely (see Table 66.1). Neither the original Airway Care Score nor any modifications have been validated externally, but a score of $\leq$6 predicts successful extubations [6].

Several manual techniques can help with airway hygiene, such as postural drainage, manual chest percussion, vibration and shaking, active cycle of breathing technique, or forced expiratory maneuver (coughing or huffing). These manual bronchial hygiene techniques are time-consuming for the rehabilitation therapist, come at an added cost, and require a lot of collaboration from the patients. Since there is controversy about the effectiveness of manual techniques [8], the recommendation level of these techniques is conditional.

Instead, mechanically assisted cough is exceptionally efficient in the acute setting for patients with neuromuscular diseases and those with respiratory failure due to respiratory tract infections. The inclusion of mechanically-assisted cough in weaning and post-extubation of ICU patients reduces reintubation rates and consequently reduces post-extubation ICU length of stay [9].

Table 66.1 Airway Care Score. The Airway Care Score has a range of 0–18 points. An elevated score may indicate poor spontaneous airway protection

Grade	Cough during aspiration maneuver	Number of secretions (need for passes)	Color of secretions	Viscosity of secretions	Intervale of aspiration of secretions	Vomiting reflex
0	Vigorous	0	Clear	Aqueous	More than 3 h	Vigorous
1	Moderate	1	Clear brown	Frothy	Every 2–3 h	Moderate
2	Weak	2	Yellow	Dense	Every 1–2 h	Weak
3	Absent	≥3	Green	Sticky	<1 h	Absent

Other than evaluating the patient's capacity to cough efficiently, the patient's deglutition should also be evaluated and upper airway obstruction excluded to guarantee airway protection. Post-extubation stridor occurs in less than 10% of critically ill patients. Risk factors for post-extubation stridor include prolonged intubation, age >80 years, a larger endotracheal tube (>8 mm in men, >7 mm in women), elevated APACHE II score, GCS score < 8, traumatic intubation, history of asthma, and aspiration. Patients with ≥1 risk factor should undergo a "cuff leak" test. For those with a high risk of post-extubation stridor and a reduced or absent cuff leak, glucocorticoid may be considered to prevent extubation failure [10].

Critically ill patients with prolonged IMV duration with a complex weaning process with several trials are prone to develop ICU-AW with respiratory muscle weakness, which has an increased risk of infection, complications, and mortality. Inspiratory muscle training includes using threshold pressure devices or ventilator pressure trigger sensitivity adjudgments to strengthen inspiratory muscles by improving maximal inspiratory pressure. In selected patients, these techniques facilitate weaning, potentially reducing the length of stay and the duration of noninvasive ventilatory support after extubation [11].

66.3.2 Noninvasive Ventilation in Post-Extubation Respiratory Failure

It is vital to distinguish therapeutic NIV from prophylactic NIV. Therapeutic NIV is used in patients with post-extubation respiratory distress, whereas prophylactic NIV is the routine use of NIV to prevent respiratory distress post-extubation and avoid reintubation.

66.3.2.1 Prophylactic Noninvasive Ventilation

Low Risk of Post-Extubation Respiratory Failure

All patients submitted to IMV should be oxygenated after extubation [4]. Low-flow devices are sufficient for most patients (i.e., nasal prongs, simple or venturi face masks). A high-flow nasal cannula (HFNC) has better patient tolerance, which can improve oxygenation with fewer desaturations compared to low-flow devices [12]. HFNC allows for greater oxygen delivery and ventilation by the washout of dead space, provides small amounts of positive-end-expiratory pressure, and can assist in airway hygiene by delivering heated and humidified nasal flow.

In favor of using HFNC in this low-risk population, *Hernandez* et al. concluded that they had a lower reintubation rate within 72 h compared to conventional oxygen therapy [13]. However, the case-mix in this study included a high percentage of surgical and neurocritical patients, which could account for the high proportion of non–respiratory-related reintubations and the significant improvement in reintubation secondary to the inability to clear respiratory secretions [13].

Therefore, in light of the available information, the routine use of HFNC is not recommended in patients with a low risk of post-extubation respiratory failure.

High Risk of Post-Extubation Respiratory Failure

Prophylactic NIV or HFNC, or in combination, are possible options for patients at-risk of ARF in the post-extubation period. The available studies either included unselected patients (i.e., any patient with planned extubation) or selected patients at risk of post-extubation ARF. However, there is a notable inconsistency and a significant discrepancy between studies in selecting high-risk patients, which handicap the elaboration of clear orientations to support the routine use of NIV or HFNC in these situations. For this reason, although the Official European Respiratory Society and American Thoracic Society clinical practice guidelines on noninvasive ventilation for acute respiratory failure suggest that NIV can be used to prevent post-extubation respiratory failure in high-risk patients, the recommendation is conditional, with low certainty of evidence.

In daily clinical practice, due to this low certainty of the evidence, each center applies NIV or HFNC to their local criteria, according to the local expertise and at the discretion of the physician or respiratory therapist's judgment.

Some patients at higher risk of ARF may be selected to be extubated directly to NIV and/or HFNC, while others may endure a period of close observation in a *wait-and-see* approach. The decision must be individualized for each patient involving the interdisciplinary team and made upon the sum of several factors: capacity to protect the airway and efficient cough, with accumulating secretions, atelectasis, and consequent respiratory infections (a vicious cycle); type of respiratory failure (i.e., hypoxic, hypercapnic) according to the medical history, current condition and evolution ICU with possible ICU-AW; oxygenation and ventilation requirements with possible need for positive-end-expiratory-pressure; local availability of and expertise in NIV and HFNC.

Possible risk factors for post-extubation AFR have previously been highlighted in this chapter. According to the available studies, patients at highest risk are patients with neuromuscular disorders with an unproductive cough and poor muscular strength, patients with hypercapnic COPD or congestive heart failure, and early extubated patients with high oxygen requirements or patients with previous failed extubating.

Patients with hypercapnic respiratory failure due to hypoventilation, restrictive syndrome, poor respiratory muscle strength, or cardiac failure are a well-established high-risk group of patients for prophylactic NIV. Studies have proved the advantage of NIV over standard medical therapy in preventing post-extubation ARF in these patients [14–16]. The benefit of NIV in patients with hypoventilation was further supported in a trial with severely obese patients that showed that the application of NIV during the first 48 h after extubation reduced the rate of ARF and significantly reduced the length of ICU hospital stay when compared with the conventional therapy [17].

On the other hand, patients with severe hypoxemic respiratory failure or a high oxygen requirement, whether due to a previous respiratory dysfunction, pulmonary parenchyma destruction, or an acute respiratory infection, may benefit from HFNC, NIV, or both. The COVID-19 pandemic further increased our knowledge of prophylactic NIV, extending its use to patients recovering from hypoxemic

non-hypercapnic ARF. The application of NIV immediately after early extubation in COVID-19 patients still dependent on relatively high positive end-expiratory pressure and inspiratory assistance had lower rates of extubation failure and lower rates of reintubation when compared to the standard weaning group [18]. Previously, studies had also shown the benefits of NIV in early discontinuation of IMV in high-selected patients with non-hypercapnic hypoxemic ARF, resulting in a shorter duration of IMV and fewer complications [18].

HFNC is not routinely used following extubation as a preventative measure against reintubation but may be considered in patients with hypoxemic respiratory failure, in the peri-intubation period, and post-operatively for bedside clinicians [19]. Some studies have attempted to prove the benefit of HFNC in high-risk patients. Still, most lack standardization in patient selection and have several inconsistencies in the studies. In a large study involving 604 high-risk patients for post-extubation ARF, where HFNC was compared to NIV, the results showed a non-inferiority of HFNC, with a nonsignificant reduction in reintubation and rate of post-extubation respiratory failure. However, this study included a small proportion of patients with COPD; therefore, these results are insufficient to recommend HFNC over NIV in high-risk patients with hypercapnic respiratory failure [13].

The combined use of NIV with HFNC had encouraging results that showed a reduced reintubation rate in comparison to HFNC alone, although no impact on mortality was shown. In a posthoc analysis, the benefit of adding NIV to HFNC was evident in hypercapnic respiratory failure, as expected from that mentioned above [20]. This study also had several inconsistencies and confounding factors, for example, the use of HFNC as the control group and NIV as rescue therapy in one-third of patients in the HFNC group. Therefore, in light of the currently available literature, there is insufficient evidence to recommend using HFNC alone in high-risk hypercapnic patients.

66.3.2.2 Therapeutic Noninvasive Ventilation

Studies have consistently shown that NIV is ineffective in treating post-extubation ARF and may even increase patient morbidity and mortality when delaying reintubation once ARF has been installed [21]. The Official European Respiratory Society and American Thoracic Society clinical practice guidelines suggest against using NIV in established ARF pos-extubation, as a conditional recommendation, with low certainty of evidence. If the physician decides to initiate NIV, a short trial of approximately 1–2 h is warranted, and if a clear benefit is not achieved, the threshold to reintubate should be low.

66.4 Special Situations of Extubation Failure

66.4.1 Post-Operative Respiratory Failure

Post-operative respiratory failure requiring unplanned reintubation is associated with high morbidity, extended hospital stay, and increased 30-day mortality. The

incidence of unplanned reintubation in the first 72 h is low but slightly higher in older patients [22]. The most common reasons for reintubation within the first 6 h of extubation were pulmonary edema, atelectasis, pneumonia, impaired brain function, aspiration, and airway obstruction. NIV was shown to be superior to standard oxygen therapy in preventing reintubation among patients that develop hypoxemic respiratory failure following abdominal surgery [23]. HFNC appears to be a valid option in patients submitted to cardiac surgery, as HFNC non-inferiority was shown when compared with intermittent NIV in preventing ARF [24].

66.4.2 Patients with Unplanned Extubation

Unplanned extubation is more commonly due to deliberate maneuvers of the patients (i.e., agitated patients with a poorly fixed endotracheal tube, orotracheal intubation, low levels of intravenous sedation, or physical restraint). Reintubation is more often after unplanned extubation than planned extubation [25]. These patients should be promptly assessed with a low threshold to reintubate. Reintubation in these patients is associated with an increased mortality rate for several reasons: technical difficulty reintubating in this setting and a longer duration of mechanical ventilation, ICU stay, and hospitalization duration.

Five Main Learning Points

- Approximately 10% to 20% of patients that successfully meet all weaning criteria will undergo post-extubation respiratory failure.
- The rehabilitation team is a crucial element of the ICU team to guarantee shorter weaning times and successful extubation.
- Prophylactic NIV helps reduce the rate of post-extubation acute respiratory failure and reintubation in patients at high-risk.
- Most studies have considered high-risk hypercapnic patients, but recent studies show benefits in early extubation of hypoxemic patients. Further studies are required to validate risk-factors for post-extubation acute respiratory failure.
- NIV is ineffective in treating post-extubation acute respiratory failure.

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Part XI

Rehabilitation Applications

Noninvasive Ventilation During Rehabilitation

67

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Abbreviations

6MWD	6 minute walk distance
CF	Cystic fibrosis
CI	Confidence interval

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_67

CO	Cardiac output
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CWR	Chest wall restriction
EPAP	Expiratory positive airway pressure
$FEV_1\%$	Percent predicted forced expiratory volume in 1 s
FVC	Forced vital capacity
HRQL	Health-related quality of life
ILD	Interstitial lung disease
IPS	Inspiratory pressure support
NIV	Noninvasive ventilation
$PaCO_2$	Partial pressure of arterial carbon dioxide
PAV	Proportional assist ventilation
PS	Pressure support
PVA	Patient–ventilator asynchrony
RCT	Randomised controlled trial
TLC	Total lung capacity
V_S	Stroke volume

67.1 Introduction

Exercise training as a component of pulmonary rehabilitation is a standard of care for people with chronic obstructive pulmonary disease (COPD) and is associated with improvements in exercise capacity, health-related quality of life (HRQL), symptoms and healthcare utilisation [1]. Growing evidence also supports using exercise training in other patient groups with chronic respiratory disease, including those with chronic respiratory failure [1]. Physiological changes in response to exercise training, including improved skeletal muscle oxidative capacity and capillary density, and a reduction in exercise induced lactate production, are important to achieve a number of benefits post pulmonary rehabilitation. However, some individuals with severe disease have difficulty performing exercise at an adequate intensity or duration to derive physiological training effects. A number of adjuncts to exercise have been proposed, including supplemental oxygen, Heliox and noninvasive ventilation (NIV), with the aim of reducing ventilatory load or improving ventilatory capacity during exercise to facilitate exercise training at a higher intensity.

Investigation of the role of NIV as an adjunct to rehabilitation began over 30 years ago. Initial studies examined the acute effects of continuous positive airway pressure (CPAP) during exercise in people with severe COPD. Since then, assessment of true modes of ventilatory support during rehabilitation, including inspiratory pressure support (IPS), proportional assist ventilation (PAV) and bilevel NIV, have formed the majority of the evidence base and have been performed predominantly in patients with COPD. However, studies including people with chest wall restrictive (CWR) disorders, chronic heart failure, obesity, cystic fibrosis (CF),

interstitial lung disease (ILD) and spinal cord injury have also been conducted. Noninvasive ventilation can be used nocturnally in conjunction with daytime exercise rehabilitation, directly during exercise rehabilitation or a combination of nocturnal NIV and NIV during exercise rehabilitation. This chapter will review the effects of NIV as an adjunct to exercise rehabilitation in each of these situations, including the proposed mechanisms of benefit. Practical considerations regarding NIV use during rehabilitation will also be discussed.

67.2 Noninvasive Ventilation and Rehabilitation

67.2.1 Nocturnal Noninvasive Ventilation and Rehabilitation

Nocturnal NIV is a first line treatment for many patients with nocturnal hypoventilation and daytime chronic hypercapnic respiratory failure secondary to conditions including neuromuscular disease, obesity hypoventilation syndrome and CWR disorders. Historically, the use of long-term nocturnal NIV in patients with stable COPD has been controversial. However, recent large multi-centre randomised controlled trials (RCT) have demonstrated benefits to mortality, HRQL [2] and hospital readmission rates [3] with long-term NIV in individuals with persistent daytime hypercapnia ($PaCO_2 \geq 52$ mmHg) when stable or within 2–4 weeks after an episode of acute hypercapnic respiratory failure compared to standard care. Importantly, high inspiratory pressures with or without a high back-up rate were used with the aim of normalising daytime $PaCO_2$. Recent international guidelines now support using long-term NIV to treat chronic hypercapnic respiratory failure in people with stable COPD, although this is a conditional recommendation [4]. While nocturnal NIV alone may improve exercise tolerance in some patient groups, exercise capacity remains below that of healthy people and consequently these individuals may benefit from rehabilitation.

Several RCTs have assessed the effect of nocturnal NIV in combination with daytime exercise training in people with severe COPD, most of whom also had chronic hypercapnic respiratory failure (Table 67.1). Sample size ranged from 45 to 88 participants in individual trials. Exercise training programs were 8–12 weeks duration and were typically performed in the outpatient setting. One long-term study was also performed over 2 years [5]. Nocturnal NIV and exercise training were compared to exercise training alone or nocturnal NIV alone. Overall, the addition of nocturnal NIV to exercise training improved exercise capacity and arterial blood gases above that of exercise training or nocturnal NIV alone. HRQL was also enhanced with nocturnal NIV and exercise training compared with exercise training alone. The magnitude of improvements in exercise capacity and HRQL appear to be clinically important. In addition to these benefits, the long-term study by Duiverman and co-workers [5] found an improvement in dyspnoea and stabilisation of percent predicted forced expiratory volume in 1 s (FEV_1%) in the nocturnal NIV and exercise training group, whereas FEV_1% significantly declined in the group that performed exercise training alone. Despite these benefits, no differences were found in

Table 67.1 Nocturnal noninvasive ventilation and daytime exercise training: Summary of randomised controlled trials

	Garrod 2000	Duivermann 2008	Duivermann 2011	Marquez-Martin 2014	Cui 2019
	AJRCCM	Thorax	Respir Research	Respir Med	Pak J Med Sci
Population	$n = 45$ (37 completed), stable severe COPD ($PaCO_2$ NIV + ET gp 44 (7) mmHg; ET gp 46 (9) mmHg)	$n = 72$ (56 completed), stable severe COPD + CHRF ($PaCO_2$ NIV + ET gp 52 (5) mmHg; ET gp 51 (6) mmHg)	$n = 56$ (35 completed), stable severe COPD with CHRF (2 year follow-up from Duiverman 2008 Thorax)	$n = 45$ (43 completed), stable severe COPD with CHRF (median $PaCO_2$ NIV + ET gp 50 mmHg, NIV gp 51 mmHg, ET gp 48 mmHg)	$n = 88$, stable severe COPD ($PaCO_2$ control 53 (5) mmHg; NIV 53 (5); NIV + ET gp 52 (5) mmHg; ET gp 54 (4) mmHg)
Rehabilitation program	Outpatient, 8 week, ×2/week, 60 min upper and lower limb exercise, education, walking intensity 80% VO_2 peak from ISWT	Inpatient, 12 week, ×3/week, 60 min strength training, cycling, walking, IMT, education, psychological and nutritional support	Outpatient, from the end of a 12 week inpatient program to 2 years, ×1–2/week, 30 min interval cycling intensity 140% PWC, strength training, IMT 30–70% MIP	Outpatient, 12 week, ×3/week, resistance and strength training	Outpatient, 12 week, ×3/week, 30 min cycling 30–40% W_{max}, 15 min breathing exercises
Intervention	Nocturnal NIV + ET ($n = 17$)	Nocturnal NIV + ET ($n = 24$)	Nocturnal NIV + ET ($n = 15$)	Nocturnal NIV + ET ($n = 14$)	Nocturnal NIV + ET ($n = 29$)
	Bilevel, S mode, IPAP median 16 (13–24) cmH_2O, EPAP median 4 (4–6) cmH_2O	Bilevel, ST mode, IPAP 20 (4) cmH_2O, EPAP 6 (2) cmH_2O	Bilevel, ST mode, rate 18 (3) bpm, IPAP 23 (4) cmH_2O, EPAP 6 (2) cmH_2O	Bilevel, ST mode, IPAP median 16 cmH_2O, EPAP median 4 cmH_2O	CPAP 6cmH_2O for hypoxia, Bilevel for CHRF, ST mode, rate 15 bpm, IPAP 8–12 cmH_2O, EPAP 4cmH_2O
	NIV adherence median 2.08 (0–11.4) h/day	NIV adherence median 7.7 (5.8–8.5) h/day	NIV adherence median 6.9 (0.7–11.4) h/day	NIV adherence median 7 (6.5–9) h/day	NIV adherence >6 h/day
Comparison	ET alone ($n = 20$)	ET alone ($n = 32$)	ET alone ($n = 20$)	ET alone ($n = 14$) or Nocturnal NIV alone ($n = 15$)	Standard care ($n = 29$)
					Nocturnal NIV alone ($n = 30$)

	Garrod 2000	Duivermann 2008	Duivermann 2011	Marquez-Martin 2014	Cui 2019
	AJRCCM	Thorax	Respir Research	Respir Med	Pak J Med Sci
Outcomes	*Nocturnal NIV + ET > ET alone:* ↑ ISWT distance; ↑ CRDQ total score and fatigue component	*Nocturnal NIV + ET > ET alone:* ↑ CRDQ fatigue domain; ↑ MRF-28 total and cognition domain scores; ↓ $PaCO_2$; ↑ daily step count	*Nocturnal NIV + ET > ET alone:* ↑ MRF-28 total score and daily activities and invalidity domains; ↑ SRI physical functioning; ↓ HADS; ↓ MRC dyspnoea; ↑ 6MWD (prevented decline); ↑ PaO_2; ↓ $PaCO_2$; ↑ FEV_1 (prevented decline)	*Nocturnal NIV + ET* vs. *ET alone:* no differences	*Nocturnal NIV + ET and Nocturnal NIV alone > Standard care:* ↑W_{max}; ↑ peak VO_2; ↑6MWD; ↓ MRC dyspnoea; improved BODE index; ↑HRQL; ↓ $PaCO_2$;↑ PaO_2
	No between gp differences: $PaCO_2$; spirometry	*No between gp differences:* CRDQ total score; 6MWD; ESWT; incremental cycle test (VO_{2max}), HADS, MRC dyspnoea; PaO_2	*No between gp differences:* CRDQ total score; VC; RV/%TLC; MIP; exacerbation frequency	*Nocturnal NIV + ET > Nocturnal NIV alone*: ↑ peak VO_2	*Nocturnal NIV + ET > Nocturnal NIV alone:* ↑6MWD; ↓ MRC dyspnoea, ↑HRQL; ↓ $PaCO_2$;↑ PaO_2
	Nocturnal NIV + ET gp only: ↑ PaO_2; ↑ MIP	*Nocturnal NIV + ET gp only:* ↑ SRI summary score and five subscales		*Nocturnal NIV + ET and ET alone > Nocturnal NIV alone:* ↑ peak and endurance cycle tests, ↑ PaO_2	
				No between gp differences: CRDQ total score; 6MWD; CRP, TNF-α, IL-6, IL-8, SP-D; BODE index; dyspnoea; peripheral mm strength	

(continued)

Table 67.1 (continued)

	Garrod 2000	Duivermann 2008	Duivermann 2011	Marquez-Martin 2014	Cui 2019
	AJRCCM	Thorax	Respir Research	Respir Med	Pak J Med Sci
PEDro score	6/10	4/10	7/10	5/10	Not available

Data presented as mean (standard deviation) unless otherwise indicated
AJRCCM American Journal of Respiratory & Critical Care Medicine, *Pak J Med Sci* Pakistan Journal of Medical Sciences, *COPD* chronic obstructive pulmonary disease, $PaCO_2$ partial pressure of arterial carbon dioxide, *NIV* noninvasive ventilation, *ET* exercise training, *CHRF* chronic hypercapnic respiratory failure, VO_2 oxygen consumption, *ISWT* incremental shuttle walk test, *IMT* inspiratory muscle training, *PWC* peak work capacity, *S mode* spontaneous mode, *IPAP* inspiratory positive airway pressure, *EPAP* expiratory positive airway pressure, *ST mode* spontaneous timed mode, *CPAP* continuous positive airway pressure, *CRDQ* Chronic Respiratory Disease Questionnaire, PaO_2 partial pressure of arterial oxygen, *MIP* maximum inspiratory pressure, *MRF-28* Maugeri Respiratory Failure questionnaire, *6MWD* 6 minute walk distance, *ESWT* endurance shuttle walk test, VO_{2max} maximum oxygen consumption, *HADS* Hospital Anxiety and Depression Score, *MRC* Medical Research Council dyspnoea scale, *SRI* Severe Respiratory Insufficiency questionnaire, FEV_1 forced expiratory volume in 1 s, *VC* vital capacity, *RV/%TLC* ratio of residual volume and total lung capacity expressed as a percentage, *CRP* C-reactive protein, *TNF-α* tumour necrosis factor α, *IL-6* interleukin 6, *IL-8* interleukin 8, *SP-D* surfactant protein-D, *PEDro* Physiotherapy Evidence Database

the frequency of exacerbations. Similarly, an RCT in 27 individuals with chronic hypercapnic respiratory failure secondary to severe kyphoscoliosis on long-term nocturnal NIV demonstrated benefits from the addition of exercise training, with clinically relevant improvements in HRQL and dyspnoea, increased peripheral muscle strength and a trend for greater distance walked in the incremental shuttle walk test compared to nocturnal NIV alone [6].

Possible mechanisms of benefit associated with the addition of nocturnal NIV to exercise training include respiratory muscle rest, improvements in gas exchange and lung mechanics, and increased sleep quality. However, careful titration of NIV settings to ensure adequate management of nocturnal hypoventilation, along with sufficient adherence to long-term nocturnal NIV are likely to be important to derive benefits. In summary, the combination of nocturnal NIV and exercise training appears to produce benefits to exercise capacity and HRQL above either exercise training or nocturnal NIV alone in people with chronic hypercapnic respiratory failure secondary to COPD or severe CWR. Consequently, individuals with these disorders using long-term nocturnal NIV should be offered pulmonary rehabilitation.

67.2.2 Noninvasive Ventilation During Exercise

67.2.2.1 Effects of Noninvasive Ventilation During a Single Session of Exercise

Some individuals with severe chronic respiratory disorders experience symptoms such as severe exertional dyspnoea, which can serve as a barrier to exercise. In this situation, using NIV during exercise may be beneficial (Fig. 67.1). Numerous studies have assessed the acute effects of NIV during a single exercise session compared to exercise without NIV or exercise with sham NIV. Studies were predominantly performed in stable people with severe COPD, both with and without chronic hypercapnia. Endurance cycling or treadmill exercise tests were almost exclusively used to evaluate exercise performance, with few studies assessing ground walking, quadriceps strength or unsupported arm exercise capacity. There is significant heterogeneity in the modes and settings used to deliver NIV during exercise. Modes including CPAP, IPS, PAV ± CPAP, bilevel and assist pressure control ventilation have been applied. While there are few direct comparisons between modes, it appears that the delivery of both pressure support (PS) or PAV with expiratory positive airway pressure (EPAP) is superior to CPAP or the delivery of PS or PAV alone. Pressure support levels during exercise were typically low to moderate (e.g., PS 6–16 cmH_2O) with a small number of studies using high pressures (PS > 20 cmH_2O). Oronasal, nasal masks and mouthpiece interfaces have all been used successfully during exercise.

A systematic review and meta-analysis found that NIV during exercise in stable patients with severe COPD was associated with clinically important improvements in exercise endurance time (30–55% increase) and exertional dyspnoea (two-point reduction on the Borg scale) [7]. Similar benefits have been reported in stable patients with CWR, CF, obesity and ILD. While overall group responses to NIV

Fig. 67.1 Patient with severe chest wall restriction using NIV during treadmill exercise

during exercise often show improvements in exercise capacity, individual variability is frequently observed and some individuals do not benefit or perform worse with NIV during exercise. Understanding the mechanisms of action of NIV during exercise may assist in the selection of individuals who could benefit from using NIV during exercise, and guide clinicians and researchers in the selection of NIV settings to optimise outcomes.

67.2.2.2 Mechanisms

Arguably the most important mechanism associated with using NIV during exercise is respiratory muscle unloading and the related reduction in exertional dyspnoea [8]. The degree of respiratory muscle unloading is proportional to the level of PS provided. A change in pattern of breathing also often occurs, with a reduction in respiratory rate and increase in tidal volume [9]. This improves the efficiency of breathing, reduces dead space ventilation and improves arterial blood gases [9], which may be particularly beneficial in patients with hypercapnia. In addition, a reduction in respiratory rate prolongs expiratory time which may reduce dynamic hyperinflation in patients with severe airflow obstruction [10]. In people with severe COPD, the addition of EPAP during exercise may further reduce work of breathing by splinting open small airways to prevent dynamic

collapse during exhalation, offsetting intrinsic positive end expiratory pressure and reducing the inspiratory threshold load.

In addition to benefits within the respiratory system, extra-pulmonary effects have also been reported with NIV during exercise. Borghi-Silva and colleagues [11] found that NIV during high intensity cycling exercise improved locomotor muscle oxygenation and perfusion compared to exercise with sham NIV. This most likely reflects a redirection of a portion of cardiac output (CO) away from respiratory muscles to exercising peripheral muscles as a direct result of respiratory muscle unloading with NIV. A reduction in exercise-induced blood lactate and a decrease in perception of leg effort was also found with NIV [11]. Furthermore, NIV during cycling exercise improved post exercise quadriceps endurance compared to exercise without NIV, suggestive of a reduction in quadriceps fatigue [12]. A summary of pulmonary and extra-pulmonary mechanisms is presented in Fig. 67.2.

67.2.2.3 Noninvasive Ventilation During Exercise Training

Improvements in exercise tolerance and symptoms during a single bout of exercise with NIV are promising. However, the effect of NIV across multiple exercise sessions, i.e. during exercise training, has the potential to allow physiological and other benefits above that of exercise training alone. Over the past two decades, a number of RCTs have assessed the effects of NIV during exercise training compared to

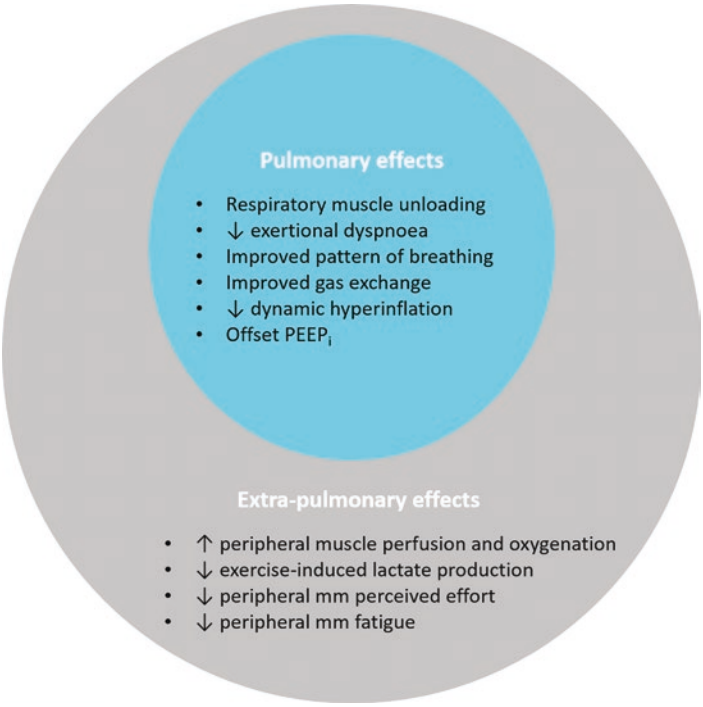

Fig. 67.2 Mechanisms of benefit associated with NIV during exercise

exercise training alone, or exercise training with either sham NIV or supplemental oxygen. Studies primarily recruited patients with severe to very severe COPD. Sample sizes were generally small, ranging from 14 to 43 participants in individual trials. Exercise training programs were performed in the outpatient setting, often for 6–8 weeks with 2–3 sessions per week. Rehabilitation programs consisted of moderate to high intensity endurance treadmill or cycling training. NIV was primarily provided using bilevel and the level of PS used during training was low at approximately 8–10 cmH_2O. All RCTs reported exercise capacity outcomes post training. However, less than half reported on HRQL. A summary of NIV during exercise training RCTs in people with COPD is presented in Table 67.2.

A systematic review and meta-analysis [13] that included data from 6 RCTs (total of 126 participants) and examined the effects of NIV during exercise training in people with COPD found that NIV during exercise training allowed patients to exercise at a higher intensity (mean difference 13%, 95% confidence interval (CI) 1 to 27) and achieve a greater physiological training response (isoload lactate mean difference −0.97 mmol/L, 95% CI −1.58 to −0.36) compared to exercise training alone or exercise training with sham NIV. However, despite these benefits, a consistent improvement in exercise capacity was not found with NIV during exercise training. Percentage change in peak and endurance exercise capacity was higher with NIV during exercise training (mean difference 17%, 95% CI 7 to 27; mean difference 59%, 95% CI 4 to 114, respectively), and while the mean change for endurance time may be clinically important, the 95% CI was very wide. In contrast, all other exercise capacity outcomes showed no difference between training with or without NIV. Furthermore, NIV during exercise training did not improve or worsen HRQL compared to exercise training alone or exercise training with sham NIV. Of note, outcomes were assessed post training, off NIV.

More recently, the effects of NIV during a 12 week endurance cycling training program were assessed in 53 stable obese individuals (body mass index 35–45 kg/m^2) with obstructive sleep apnoea who were treated with nocturnal CPAP [14]. Compared to exercise training alone or exercise training in combination with respiratory muscle training, NIV during exercise training significantly reduced self-measured blood pressure and decreased waist and neck circumference. No between-group differences were found for the primary outcome, 6-min walk distance (6MWD). Peak oxygen consumption during an incremental cycle test was greater with NIV and respiratory muscle training groups compared to exercise training alone. While the effect of NIV during exercise training on exercise capacity outcomes was variable, the reduction in cardiometabolic risk factors in this group of obese individuals may be important.

The majority of NIV during exercise training studies has been conducted in stable patients. However, the role of NIV during exercise training in the acute care setting has also been investigated. As NIV during exercise can reduce dyspnoea [8] and improve gas exchange [9], it has the potential to improve safety and tolerance of early exercise rehabilitation in hospitalised patients with severe breathlessness and exercise-induced oxygen desaturation. Oliveira and colleagues [15] assessed the effects of NIV during endurance cycling training compared with standard care

Table 67.2 Noninvasive ventilation during exercise training in COPD: Summary of randomised controlled trials

	Bianchi 2002	Hawkins 2002	Johnson 2002	Costes 2003	Reuveny 2005	van 't Hul 2006	Toledo 2007	Borghi-Silva 2010	Marrara 2018
	Respir Med	Thorax	Chest	J Cardiopulm Rehab	IMAJ	ERJ	Clinics	Respiration	Respir Care
Study design	RCT	RCT	RCT	Quasi-RCT*	RCT	RCT	RCT	RCT	RCT
Population	*n* = 19, moderate—severe COPD	*n* = 19, very severe COPD	*n* = 22, severe—very severe COPD	*n* = 14, moderate—severe COPD	*n* = 19, severe—very severe COPD	*n* = 29, severe COPD	*n* = 18, severe—very severe COPD	*n* = 28, severe COPD	*n* = 43 moderate—very severe COPD
Rehabilitation program	Outpatient, 6 week, ×3/week, 30 min cycling, 50–70% PWC	Outpatient, 6 week, ×3/week, 30 min cycling, 70% PWC	Outpatient, 6 week, ×2/week, 20 min treadmill, 50–60% max METs	Outpatient, 8 week, ×3/week, 30 min cycling, 60% VO_2 peak	Outpatient, 8 week, ×2/week, 45 min treadmill, 65–70% max speed	Outpatient, 8 week, ×3/week, 45 min cycling, 65% PWC	Outpatient, 12 week, ×3/week, 30 min treadmill, 70% max speed	Outpatient, 6 week, ×3/week, 60 min treadmill, 70% max speed	Outpatient, 6 week, ×3/week, 60 min treadmill, 80% max velocity
Intervention	ET + NIV: PAV	ET + NIV: PAV	ET + NIV: Bilevel	ET + NIV: Bilevel	ET + NIV: Bilevel	ET + NIV: IPS	ET + NIV: Bilevel	ET + NIV: Bilevel	ET + NIV: Bilevel
	FA 3.5 (1.6) cmH_2O/L/s	FA 3.6 (0.7) cmH_2O/L/s	IPAP 8–12 cmH_2O	IPAP maximum tolerated during exercise	IPAP 7–10 cmH_2O	IPS 10 cmH_2O	IPAP 10–15 cmH_2O	IPAP 12 (1) cmH_2O	IPAP 12 (2) cmH_2O
	VA 6.6 (2.2) cmH_2O/L	VA 12.7 (1.5) cmH_2O/L	EPAP 2 cmH_2O	EPAP 4–8 cmH_2O	EPAP 2 cmH_2O		EPAP 4–6 cmH_2O	EPAP 4 (2) cmH_2O	EPAP 5 (1) cmH_2O
	CPAP 2 cmH_2O	CPAP 0 cmH_2O							
Comparison	ET alone	ET alone	ET alone or ET + Heliox	ET alone	ET alone	ET + Sham NIV: IPS 5 cmH_2O	ET alone	ET + Supp O_2: (1.5 ± 0.8 L/min)	ET alone

(continued)

Table 67.2 (continued)

	Bianchi 2002	Hawkins 2002	Johnson 2002	Costes 2003	Reuveny 2005	van 't Hul 2006	Toledo 2007	Borghi-Silva 2010	Marrara 2018
	Respir Med	Thorax	Chest	J Cardiopulm Rehab	IMAJ	ERJ	Clinics	Respiration	Respir Care
Outcomes	*No between gp differences:* exercise capacity; HRQL; dyspnoea; leg fatigue, PFTs; training intensity	*ET + NIV > ET:* ↑ PWR; ↑ training intensity	*ET + NIV > ET:* ↑ % change exercise endurance time	*ET + NIV > ET:* ↑ peak VO_2; ↓ isoload V_E; ↓ isoload V_D/V_T; ↓ V_E/VO_2 ratio	*ET + NIV > ET:* ↑ training intensity; ↑ V_T peak exercise	*ET + NIV > sham NIV + ET:* ↑ SWT distance; ↑ cycle endurance time (%); ↑ training intensity; ↓ isoload V_E	*ET + NIV > ET:* ↓ isoload La	*ET + NIV > ET + O_2:* ↑ 6MWD; ↑ VO_2 max; ↓ La/speed; ↓ dyspnoea; ↓ SpO_2/speed; ↓ leg fatigue; ↑ MIP	*No between gp differences:* 6MWD, MIP, BODE index, HRQL
		No between gp differences: CWR endurance time; isoload La (trend lower with NIV); dyspnoea	*No between gp differences:* PWR, exercise endurance time	*No between gp differences:* CWR endurance time; isotime La; PWR; isotime and end exercise SpO_2	*No between gp differences:* PFTs	*No between gp differences:* cycle endurance time (mins); HRQL	*No between gp differences:* peak exercise capacity; SpO_2; dyspnoea; respiratory muscle strength	*No between gp differences:* HRQL; training intensity	*ET + NIV gp only:* ↑ VO_2 max, ↑ MEP, ↑ max METs, ↑ circulatory power, ↑ max SpO_2
					NIV + ET gp only: ↑ VO_{2max}; ↑ O_2 pulse; ↑ V_E peak exercise		*NIV + ET gp only:* improvement in VO_2, HR and SBP	*NIV + ET gp only:* ↑ MEP; ↑ periph muscle strength; ↓ activity and total score SGRQ	
PEDro score	5/10	5/10	4/10	N/A*	6/10	8/10	3/10	7/10	7/10

Data presented as mean (standard deviation) unless otherwise indicated
RCT randomised controlled trial, *COPD* chronic obstructive pulmonary disease, *PWC* peak work capacity, *MET*: metabolic equivalent, VO_2 oxygen consumption, *ET* exercise training, *NIV* noninvasive ventilation, *PAV* proportional assist ventilation, *FA* flow assist, *VA* volume assist, *CPAP* continuous positive airway pressure, *IPAP* inspiratory positive airway pressure, *EPAP* expiratory positive airway pressure, *IPS* inspiratory pressure support, O_2 oxygen, *HRQL* health related quality of life, *PFT* pulmonary function tests, *CWR* constant work rate, *PWR* peak work rate, *La* lactate, V_E minute ventilation, V_D dead space ventilation, V_T tidal volume, SpO_2 oxygen saturation, *PFT* pulmonary function tests, *SWT* shuttle walk test, *HR* heart rate, *SBP* systolic blood pressure, *6MWD* 6-minute walk distance, *MIP* maximum inspiratory pressure, *MEP* maximum expiratory pressure, *SGRQ* St George's Respiratory Questionnaire, *N/A* not applicable

or sham NIV during exercise training in 29 hospitalised patients with acute decompensated heart failure. Participants performed a 6-min walk test on day 1 and day 10 of the hospital admission and performed eight daily sessions of unloaded endurance cycling training between assessments. No adverse events were reported. Compared to standard care and exercise training with sham NIV, NIV during exercise training significantly improved 6MWD, increased total exercise time, reduced dyspnoea and decreased length of stay. Of note, length of hospital stay was long in this study (standard care group 39 ± 15 days, sham NIV group 23 ± 8 days; NIV group 17 ± 10 days). The ability to conduct NIV during exercise training studies or to use NIV during exercise training in clinical practice in the acute care setting may be impacted by early discharge programs and limited by length of stay in some patient groups, e.g. in non-hypercapnic acute exacerbations of COPD. However, NIV could be considered as an adjunct to exercise in select cases and further research in this setting is warranted.

In summary, current evidence does not support the routine use of NIV during exercise training in stable people with COPD. Evidence is limited in other patient groups and in the acute care setting. However, both patient selection and the NIV settings used during exercise are likely to impact the efficacy of NIV during exercise training. Exercise training is a highly effective treatment for people with COPD [1]. In order for NIV to produce clinically relevant benefits above exercise training alone, individuals who are unlikely to benefit from exercise training alone should be selected. This may include individuals with greater disease severity, such as those with chronic hypercapnic respiratory failure on long-term NIV.

67.2.3 Nocturnal NIV and NIV During Exercise Training

Two RCTs have assessed the effect of NIV during exercise training in stable people with chronic hypercapnic respiratory failure on long-term NIV. Vitacca and colleagues [16] performed a multi-centre RCT in 42 patients with chronic hypercapnic respiratory failure secondary to severe COPD or severe CWR who were established on long-term NIV and supplemental oxygen. The 3 week inpatient training program consisted of 20 sessions of endurance cycle training either with or without NIV during exercise training. Participants who trained with NIV used their own home NIV device and mask during exercise. Home NIV pressures were adjusted as needed during exercise for comfort. While the primary outcome, 6MWD, improved post training, there was no difference between groups. In contrast, cycle endurance time was significantly greater with NIV during exercise training. Training intensity and HRQL did not differ between groups. As participants performed cycle training, not walking training, specificity of training may explain in part the lack of difference between groups in 6MWD. In addition, it is unclear whether 3 weeks was a sufficient timeframe for significant changes to occur in some outcomes. As with many studies that have used NIV during exercise training, it is not known whether NIV settings were adequate to unload respiratory muscles and reduce work of breathing during exercise training sessions, or if the home NIV devices used were able to meet

the increased ventilatory demands associated with exercise. As exercise training intensity was not higher in the NIV during exercise training group, NIV settings or NIV device performance may not have been optimal for exercise and could have impacted the results.

In an earlier RCT by Borel and co-workers [17], 16 patients with chronic hypercapnic respiratory failure secondary to CWR disorders on long-term NIV performed a home-based endurance cycling training program. Exercise training was conducted over 8 weeks with three to five exercise sessions per week. Participants were randomised to perform exercise either with or without NIV. Both groups significantly increased constant workload cycling endurance time and HRQL, and small improvements were also found in incremental cycle peak work rate and 6MWD. However, no between group differences were found. While the sample size was small and a type II error cannot be excluded, patient selection may have influenced the results. Post-hoc, the authors classified participants as either NIV responders (n = 10) or non-responders (n = 6) based on their initial response to NIV during an endurance cycle test. Responders were defined as a >50% improvement in endurance time with NIV during exercise compared with unassisted exercise. Responders had a greater severity of pulmonary restriction (lower total lung capacity (TLC), forced vital capacity (FVC) and FEV_1) and a higher resting $PaCO_2$ compared with non-responders. Despite very low numbers, phenotyping participants in this way revealed a trend towards improved 6MWD and HRQL in the sub-group of NIV responders who used NIV during exercise training (n = 6) compared with NIV responders who did not train with NIV (n = 4).

There are a number of potential benefits associated with the combination of nocturnal NIV and NIV during exercise training in people on long-term NIV. Firstly, individuals are already acclimatised to NIV and may better tolerate NIV during exercise. For example, a drop-out rate of 1/26 (4%) due to intolerance of NIV during exercise training was reported by Vitacca and colleagues [16] in patients with chronic hypercapnic respiratory failure secondary to severe COPD or severe CWR on long-term NIV. In contrast, a higher drop-out rate of 5/18 (28%) due to intolerance of NIV during exercise training was reported in an earlier study [18] that recruited a milder cohort of patients with moderate to severe COPD who were naïve to NIV. However, patient attitudes towards using NIV during exercise are unknown and it is unclear whether there are differences between those with and without prior experience with NIV. Secondly, patients on long-term NIV are more likely to be independent with NIV equipment and may require less assistance from rehabilitation staff during exercise training. Little is documented regarding the time and extra costs associated with using NIV during exercise. One study that assessed NIV during exercise training in COPD patients who were naïve to NIV [18] reported that staff spent an average of 11 ± 3 min to set the ventilator and adjust settings during exercise. Demands on clinician time to alter ventilator settings are likely to decrease over the course of an exercise training program but there is limited data in this area. Finally, patients on long-term NIV have ready access to an NIV device, mask and circuit that could potentially be used during exercise. This could improve the feasibility of using NIV during exercise training and reduce costs associated with

accessing equipment. However, some home NIV devices may not have a sufficient flow generator to adequately pressurise and deliver pre-set pressures during exercise. Furthermore, settings used for sleep may be inappropriate for exercise (e.g. high EPAP to treat upper airway obstruction during sleep) and may need to be altered during training sessions.

Another consideration for research and clinical applications of NIV during exercise training in patients with chronic hypercapnic respiratory failure on long-term NIV is the physical setting. Studies by Vitacca [16] and Borel [17] were performed in inpatient rehabilitation facilities [16] or in the patient's home [17]. Inpatient rehabilitation facilities with prolonged stays for exercise rehabilitation, while accessible in some countries, are not universally available worldwide. The feasibility of very severe patients with chronic hypercapnic respiratory failure on long-term NIV (with or without long term supplemental oxygen) attending an outpatient rehabilitation program 2–3 times per week for 6–8 weeks is unclear. Home exercise training programs with the assistance of telehealth and remote ventilator monitoring may be easier for patients, but further studies regarding the efficacy of this option are required. In addition, issues regarding safety (e.g. exercise-induced hypoxia, trip hazards), the modes of exercise training that can be performed at home and access to exercise equipment need to be considered.

In summary, there is limited evidence supporting NIV use during exercise training in people with chronic hypercapnic respiratory failure secondary to severe COPD or severe CWR on long-term NIV. It is unclear whether NIV during exercise training is associated with clinically worthwhile improvements in exercise capacity and HRQL or if it is cost effective in this population. Further studies are required to clarify the role of NIV during exercise training in people on long-term NIV.

67.2.4 Practical Considerations

While beneficial effects have been described with the acute use of NIV during exercise, variability in individual responses are often reported. In addition, it is unclear whether NIV during exercise training can produce worthwhile improvements in exercise capacity and other outcomes above exercise training alone. However, the following factors may impact the efficacy of NIV during exercise and should be considered in future trials and in clinical practice.

67.2.4.1 Patient Selection

Patients with COPD are the most commonly studied diagnostic group in the literature on NIV during rehabilitation. NIV during exercise has been trialled in moderate to very severe disease, although no individual studies have reported the effects of NIV during exercise across the disease spectrum. Of the RCTs that assessed the effects of NIV during exercise training in people with COPD (Table 67.2), only one RCT did not show any benefits associated with NIV during exercise training [18]. Bianchi and co-workers [18] recruited a milder cohort of COPD patients compared with other studies, suggesting that disease severity is important [13]. However, even

within groups of similar disease severity, or in highly selected sub-groups with either a ventilatory limitation to exercise, chronic hypercapnia or severe resting lung hyperinflation, variability in the response to NIV during exercise has been reported, indicating that other factors play a role in determining an individual's response to NIV during exercise. One of these factors may be the haemodynamic response to NIV during exercise. In a study on 21 people with severe COPD, Oliveira and colleagues [19] found that 11 participants improved endurance time with bilevel NIV (PS 16, EPAP 5) during a constant work rate cycling test, whereas 10 participants did not. Individuals without an improvement in endurance time with NIV during exercise had greater levels of resting lung hyperinflation and experienced a decrease in stroke volume (V_S) and CO during exercise with NIV. Whereas the sub-group that improved endurance time did not experience a fall in V_S or CO with NIV during exercise.

In contrast, disease severity appears to have a significant effect on the response to NIV during exercise in people with CWR. Based on the initial acute change in exercise endurance time with NIV during exercise compared to exercise without NIV, NIV responders (>50% improvement in endurance time) had significantly lower TLC, FVC and FEV_1 compared to non-responders [17]. In addition, NIV responders may derive benefits from NIV during an exercise training program above that of exercise training alone [17]. Consequently, individuals with CWR and severely restricted lung volumes (e.g., FVC ≤1.0 L) could be considered for a trial of NIV during exercise.

Disease severity is likely to impact the effectiveness of NIV during exercise in a number of patient groups. However, further research is required to better define phenotypes who are likely to benefit from NIV during rehabilitation.

67.2.4.2 Noninvasive Ventilation Settings for Exercise

Few studies have examined the effects of varying PS during exercise within a patient group. However, the effect of altering EPAP or rise time (pressurisation) during exercise has not been investigated. In people with severe COPD, IPS 10 cmH_2O increased cycle endurance time compared to exercise with IPS 5 cmH_2O and exercise without NIV, and no differences were found between exercise with IPS 5 cmH_2O and exercise without NIV [20]. High levels of PS (>20 cmH_2O) have been used successfully during ground walking and cycling exercise in individuals with severe COPD and chronic hypercapnic respiratory failure. However, it is unclear if high level PS is superior to low-moderate levels of PS during exercise in COPD. Similarly, in patients with CWR secondary to severe kyphoscoliosis, high level PS (20 cmH_2O) during endurance treadmill exercise produced greater improvements in endurance time compared with low level PS (10 cmH_2O), sham NIV (CPAP 4 cmH_2O) and exercise without NIV [21].

As severe exertional dyspnoea is a common symptom limiting exercise in people with severe chronic respiratory disease, it is important to use sufficiently high levels of PS during exercise to unload respiratory muscles, decrease work of breathing and reduce exercise-induced dyspnoea relative to exercise without NIV. Of note, different modes of exercise may require higher levels of PS within an individual to

adequately unload respiratory muscles, e.g. higher PS may be required during ground walking compared with cycling as weight is not supported and a larger muscle mass is used.

67.2.4.3 Device Capacity

The minimum device specifications required for NIV during exercise are unknown. Home NIV devices are designed for use during sleep and it is not clear which devices can also be used during exercise where ventilatory demand is significantly higher. If the flow generator cannot meet the inspiratory demands of the exercising patient, as was observed in 21 patients with severe COPD using a home life support ventilator during constant work rate cycling exercise [22], pre-set pressures will not be delivered and exercise performance will be impaired. If the ventilator flow generator is inadequate, respiratory muscle unloading is unlikely to be achieved and work of breathing may increase due to the added dead space and resistance of the mask and circuit. Inadequate device capacity should be excluded prior to classifying an individual as a non-responder to NIV during exercise.

67.2.4.4 Interfaces

Oronasal masks, nasal masks and mouthpieces have all been used with NIV during exercise with success. However, in a recent randomised crossover study [22], NIV during exercise using a nasal mask was associated with greater patient–ventilator asynchronies (PVA) compared to exercise with an oronasal mask. Ineffective efforts secondary to mouth leak was the predominant issue and endurance time was significantly reduced due to PVAs. As oronasal breathing during exercise is almost universal, an oronasal mask may be preferable. Although, due to the increased dead space in oronasal masks compared with nasal masks, the expiratory port should ideally be located within the mask to reduce the risk of carbon dioxide rebreathing.

67.3 Conclusion

Noninvasive ventilation is increasingly used as an adjunct to rehabilitation in a number of patient groups. The combination of nocturnal NIV and exercise training appears to produce benefits to exercise capacity and HRQL above either exercise training or nocturnal NIV alone in people with chronic hypercapnic respiratory failure secondary to COPD or severe CWR. Consequently, individuals with these disorders using long-term nocturnal NIV should be offered pulmonary rehabilitation. Using NIV during exercise can unload respiratory muscles, improve pattern of breathing and gas exchange, and reduce exercise-induced dyspnoea and peripheral muscle effort. However, individual responses to NIV during exercise do vary. While NIV during exercise training can assist individuals with COPD to exercise at a higher intensity and may allow greater physiological training effects post training, it is unclear whether NIV during exercise training is associated with clinically important improvements in exercise capacity. Furthermore, NIV during exercise training does not appear to provide additional benefits to HRQL compared to

exercise training alone. Current evidence does not support the routine use of NIV during exercise training in people with COPD or other diagnostic groups. Pulmonary rehabilitation guidelines recommend that NIV could be considered as an adjunct to exercise training in selected individuals with severe disease who have a suboptimal response to exercise in order to facilitate exercise training at an adequate intensity [1]. In addition, selection of individuals who demonstrate an acute benefit from NIV during exercise (i.e. NIV responders) may be worthwhile. Finally, NIV settings, the capacity of the ventilator and the interaction between the patient and the ventilator can impact the effectiveness of NIV during exercise.

Key Major Recommendations

- Individuals with chronic hypercapnic respiratory failure secondary to COPD or severe CWR on long-term NIV should be offered pulmonary rehabilitation
- NIV should not be used routinely as an adjunct to exercise training in pulmonary rehabilitation, although it may be considered in selected individuals with severe disease and a sub-optimal response to exercise
- Further studies are needed to define phenotypes who are likely to benefit from NIV during exercise training
- Investigation of the optimal method of selecting NIV settings for exercise and the minimum NIV device specifications for exercise is warranted

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Combination of Noninvasive Mechanical Ventilation and Complementary Therapies to Clear Airway Secretions

68

Rosana Mara da Silva and Thales Cantelle Baggio

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68.1 Introduction

Invasive and noninvasive artificial ventilatory support for critically ill patients has evolved and a multitude of evidence has emerged that may have an impact on improving the survival rates and the quality of care offered in the hospital environment [1].

Using noninvasive ventilation (NIV) in respiratory therapy optimizes pulmonary reexpansion, aids in the removal of secretion, and reduces respiratory work during respiratory muscle training [2]. In addition, the use of NIV during respiratory physiotherapy has been shown to increase the patient's tolerance to treatment, reducing the sensation of dyspnea, and increasing their adherence to treatment [3].

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_68

Normal airway clearance is based on two basic mechanisms: mucociliary clearance and effective coughing [4]. When these mechanisms are altered, they promote an excessive increase in secretion in the lungs and respiratory airways, impairing the transport of the mucociliary system, which can result in complete or partial airway obstruction [5]. Complete obstruction can lead to atelectasis and worsen ventilation due to shunt. Partial obstruction can increase respiratory work and lead to air trapping, hyperdistension, and imbalance in the ventilation/perfusion ratio [6].

Respiratory physiotherapy contributes to prevent and treat various aspects of respiratory disorders, such as airflow obstruction, secretion retention, changes in ventilatory function, dyspnea, improved performance of physical exercises, and quality of life. Thus, the combination of the use of noninvasive ventilation (NIV) with the bronchial hygiene techniques of respiratory physiotherapy demonstrates the effectiveness of this therapy [2].

68.2 Discussion and Analysis

Pulmonary collapse frequently occurs in patients with respiratory and neuromuscular diseases, patients bedridden for long periods, under mechanical ventilation, and in the postoperative period, mainly in abdominal and cardiac surgery [2, 7]. This loss of pulmonary volume causes a reduction in the residual functional capacity and a decrease in pulmonary compliance, especially in severity-dependent pulmonary regions. As a result, there is an imbalance in the ventilation/perfusion ratio with functional repercussions, such as hypoxemia and hypercapnia, increased pulmonary vascular resistance, excessive distension of adjacent alveolar units, risk of infections and lung injury [2, 7, 8].

The physiotherapist must know the pathophysiological process that causes pulmonary collapse to decide which type of positive pressure is the most appropriate in each case and which are the appropriate parameters for pulmonary reexpansion [2].

The application of NIV in the airway facilitates the air flow to regions with accumulation of secretion and greater resistance, generating a pressure gradient through the mucus plug that moves the secretions toward the larger and central airways from where they can be expectorated. In addition, the positive expiratory pressure (PEP) improves collateral ventilation, allowing a better movement of secretions toward the central airway. The improvement in gas exchange and peripheral oxygen saturation supports this reasoning [2, 9, 10].

Respiratory physiotherapy contributes to prevent and treat various aspects of respiratory disorders, such as airflow obstruction, secretion retention, changes in ventilatory function, dyspnea, improvement in physical exercise performance, and quality of life. The main objectives of Bronchial Hygiene techniques—a set of noninvasive physiotherapeutic techniques—are the detachment and mobilization of secretions. These maneuvers favor the release of secretions from the distal bronchopulmonary segments to the large bronchi, for a better expulsion, promoting the cleaning of the respiratory airways and improving gas exchange, in addition to

preventing and minimizing the complications resulting from pneumopathies. A wide variety of airway clearance techniques have been developed, all with the same objective: reducing the progression of respiratory disease, optimizing mucociliary clearance mechanisms, and facilitating expectoration [6]. Since they are associated with NIV, the final objective is to prevent the exacerbation of pulmonary hypersecretion and obstruction, avoiding the worsening of the patient and possible intubation and the need of invasive mechanical ventilation (IMV).

Wang et al. [11] conducted a prospective cohort study, evaluating patients with acute exacerbations of chronic obstructive pulmonary disease, where they compared the use of NIV and IMV combined with a noninvasive strategy to clear secretions from the respiratory tract, between October 2013 and August 2015, in an intensive care unit of a large university hospital in China. Of the patients evaluated, 74 received NIV and 90 received IMV. It was concluded that noninvasive ventilation may be superior to conventional mechanical ventilation in patients with acute exacerbations of chronic obstructive pulmonary disease. The combination of NIV with bronchial hygiene techniques of respiratory physiotherapy promoted the efficient elimination of respiratory secretions, and this innovative strategy reduced the risks of nosocomial infection, the need for intubation and hospital mortality, and presented superior results in terms of weaning ventilation [11].

Scala et al. [12] determined that NIV (without specific interventions to clear respiratory secretions) was associated with a lower rate of complications, mainly due to fewer cases of nosocomial infection or sepsis, and a shorter ventilation time than VMI [12].

Liu et al. [13] performed a meta-analysis and found that, compared to VMI, noninvasive ventilation significantly reduced the mortality rate, the intubation rate, the rate of ventilation-related complications, and the duration of ventilation [13], proving to be highly effective in association with bronchial hygiene techniques of respiratory physiotherapy.

68.3 Conclusion

Using NIV associated with bronchial hygiene techniques as a resource for respiratory physiotherapy is feasible, safe, and effective for adult and pediatric patients. Regarding pulmonary reexpansion therapy, there is evidence to support the use of NIV associated with bronchial hygiene techniques in the prevention and reversal of atelectasis, pneumonia, and bronchial hypersecretion. The effectiveness of NIV in airway clearance therapy is well reported in the literature, especially in patients with cystic fibrosis and with hypersecretory conditions.

Studies show that NIV associated with respiratory physiotherapy techniques reduced the risks of nosocomial infection, the need for intubation and hospital mortality, and presented superior results in terms of weaning from invasive mechanical ventilation.

Key Major Recommendations

- The airway clearance techniques applied by respiratory physiotherapy are indicated for patients with the aim of preventing or removing mucus accumulation in the airways, thus optimizing the relationship between ventilation and perfusion [2].
- The application of NIV in the airway facilitates the air flow to regions with secretion accumulation and greater resistance, generating a greater pressure gradient through the mucus plug, moving secretions toward larger and central airways, where they can be expectorated or aspirated [2, 9, 10].
- In clinical practice, NIV has been used in association with airway clearance techniques applied by respiratory physiotherapy [2, 12].

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Part XII

Training and Education NIMV

Skills and Training in Noninvasive Mechanical Ventilation

69

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Abbreviations

BTS British Thorasic Society
NIV Noninvasive ventilation
SBT Simulation-based training

69.1 Introduction

Noninvasive ventilation is a standard therapy in the management of both hypoxemic and hypercapnic respiratory failure in special situations. If properly administered, NIV can save patients' lives and improve long-term prognosis. In patients with life-threatening respiratory failure such as acute exacerbation of COPD or acute pulmonary edema, proper use of NIV allows avoiding and delaying invasive ventilation.

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_69

The training and skills of medical staff in noninvasive ventilation administration is quite important for increasing the success of treatment of respiratory failure [1]. This chapter analyzes the role of medical personnel education and skills in the outcome of NIV.

69.2 Importance and Influence of Staff Training on the Outcome with NIV

It is a known fact that some of the patients who undergo NIV will fail and will eventually require intubation and invasive mechanical ventilation. Therefore, providing safe and effective NIV therapy depends on the experience and skills of physicians, nurses and respiratory therapists, as well as careful patient selection.

Factors at the time of initiating NIV, or soon after, have been described to be able to predict the likelihood of its success or failure. The pH value measured a few hours after NIV application is the most important parameter in this matter [2]. An improvement in respiratory rate, heart rate, pCO_2, state of consciousness, and pH is an indicator of successful NIV in hypercapnic respiratory failure [3].

A prospective observational study identified a number of factors associated with unsuccessful NIV therapy in a group of patients with acute hypercapnic respiratory failure (AHRF) requiring NIV in wards. Despite the small number of patients included, the authors determined that NIV could be used suboptimally due to the lack of training of healthcare professionals in all patients who failed NIV therapy [4]. As a result, NIV could not be applied in some shifts, as the current health personnel were not familiar with NIV.

The application of NIV by experienced and trained staff can reduce the cost and duration of hospitalization of patients and it can prevent disease exacerbations [5]. This is also important for detecting the failure of NIV application. Successful NIV administration requires training and experience as well as evaluating the treatment response in an appropriate time and moving to the next step without delay.

In one study, it was stated that the time required by a respiratory therapist to initiate NIV varies significantly with the level of education [6]. Another study showed that doctors and nurses often felt unprepared to administer NIV safely in accordance with guidelines [7]. This may clarify why NIV remains underutilized despite that the technology has dramatically improved and most NIV ventilators are user-friendly and easily available in many areas of different hospitals, including the emergency department and ward. [7] With the introduction of user-friendly devices into practice, it is necessary to follow the developments in the technical features of these devices and to closely monitor the reflection of these developments in clinical practice. It is also important that team leaders convey these changes to practitioners in a timely manner.

A study demonstrated that optimized ventilation using flow and pressure waveforms analysis led to a more rapid normalization of pH at 2 h. The patient's tolerance was better and a faster pCO_2 reduction was achieved with this method [8]. The

authors concluded that NIV should be administered by a team with experience in analyzing waveforms.

69.3 Educational Programs

Comprehensive reviews and recommendations are currently available that include information about NIV indications, ventilator modes, settings, and interfaces. These publications are intended to provide guidance for the use of NIV by clinicians, but they offer few recommendations on how to train the NIV team. The BTS (British Thorasic Society) guidelines contain a few suggestions on education and skills.

In most countries, training is mostly limited to physicians and is provided through practical training during conferences. This type of training has been evaluated to have a weak effect on changing clinical practice [9]. In recent years, simulation-based training (SBT) has been used in medical education. Simulation is considered as a training method, not a technology. Simulation-based medical teaching can be defined as an educational activity that uses a set of tools to imitate clinical practice [10]. In the online SBT program on NIV, which included 762 participants, it was determined that simulation-based training developed four important topics such as physiology, indications, settings, and failure [11].

69.4 Content of Educational Programs

Educational programs should deliver knowledge in increments to ensure understanding of the various NIV-related issues. Table 69.1 summarizes the main issues that should be included in NIV education. This program should be mandatory for all healthcare professionals (nurses, respiratory therapist, and physiotherapists) involved in NIV treatment, not just physicians. The training time required for healthcare professionals varies greatly in different studies. Some authors have suggested that 2-h training, three times a month, can give enough foundation to start using NIV safely [1]. These periods can be shorter with the increasing experience of the staff.

Ideal management of NIV requires that all members of the team are experienced and skillful. Doctors need to select the right patients and quickly identify the patients who experience NIV failure. They must be able to choose the most appropriate mask to optimize patient comfort, reduce air leakage, prevent the occurrence of skin lesions, and significantly reduce respiratory distress. Nurses should have the knowledge of both monitoring the patient and preventing, detecting, and solving equipment problems. In-service training and updates will help to maintain healthcare staff skills and keep them informed of new developments [12]. An optimal NIV course should consist of 30% theoretical courses, 20% specific questions of participants, and 50% practical training. The total duration of the course and the ratio of theoretical–practical lesson duration should be determined according to the characteristics of the participants (profession, number, background, and experience),

Table 69.1 Minimum content of a training program for healthcare professionals using NIV

1. Approach to respiratory failure
• Physiology and pathophysiology of respiratory failure
• Symptoms and signs of respiratory failure
• Hypoxic versus hypercapnic respiratory failure
• Common respiratory diseases requiring NIV
2. Principles of NIV technology
• Types of ventilators
• Ventilator circuit
• Selection of interfaces
• Definition and selection of the ventilator mode
• Initial operation of the equipment
3. Goals and strategies of NIV
• Prescribing of NIV application according to patient
• Analysis of flow and pressure curve
• Monitoring of NIV application
• Noninvasive and invasive cardiorespiratory monitoring in different set-ups
4. Evaluation of NIV success
• Recognition of treatment failure of NIV
• Recognition of complications during NIV application
• Recognition of patient–ventilator synchronization/desynchronization
• Recognition/management of secretion
5. Treatment support in NIV application
• Patient sedation during NIV
• Enteral feeding during NIV
• Aerosol delivering during NIV
6. Special procedures during NIV application
• Nasogastric tube insertion during NIV treatment
• Optimal gas humidification during NIV treatment
• Air stacking, assisted cough, cough assist devices
• Bronchoscopy during NIV
• Management of oxygen therapy during pauses between NIV cycles
• NIV in pulmonary rehabilitation programs, aerobic exercise training

equipment types and complexity of NIV modalities (e.g., high flow CPAP, helmet/mask CPAP). Using highly accurate simulation training can be useful for gaining NIV experience [13–15]. Hands-on training sessions should also give participants the opportunity to play the "patient" role. Wearing a mask or helmet, having an experience with PEEP, and pressure support ventilation help participants understand the NIV working process and its side effects on patients. After the course, participants should continue to practice NIV regularly. The number of patients receiving NIV and the recording of their results weekly or monthly should be considered as part of the training. In this way, problems or malfunctions in the application can be easily detected with the self-evaluations of the followed patients.

Another important point in education is the regular repetition of these trainings and their integration into developing and changing technologies in NIV application. In this respect, team leaders should pay attention to the frequency, content, efficiency, and updating of the trainings according to the developing technologies and take the necessary steps in this direction. The adaptation of new personnel added to the team can also be achieved in this way.

Key Major Recommendations

- Training of healthcare professionals on the use of NIV is associated with patient survival and length of hospital stay.
- Adequate and regular training should be provided for staff who frequently encounter patients in need of NIV.
- Staff training should be adapted to local and individual needs (method, content, duration, and frequency).
- The ideal training protocol should be established with future studies.

69.5 Conclusion

The succes of NIV therapy, the staff applying the therapy and following the patients needs to have many different skills. The team leader must ensure that all aspects of NIV therapy are addressed and gained to the staff with appropirate educational programme. The content and duration of the training should be adapted to the proffesion of the staff and updated according to developing techonolgy.

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Part XIII

NIV Practice and Trends. Epidemiology Perspectives

Trends of Noninvasive Ventilation: Epidemiology Insights

70

Alvaro Alonso and Alejandro Ubeda

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70.1 Introduction

The first described uses of NIV were 100 years ago, but modern NIV did not begin until 1987 when Delaubier and Rideau described its use in patients with Duchenne's disease for the treatment of hypoventilation [1].

NIV proved to be so successful that it has become widely accepted as the standard method of ventilation in patients with chronic hypercapnic respiratory failure. Over time, it has also become an established approach in the management of patients with acute respiratory failure (ARF), acute exacerbations of chronic obstructive pulmonary disease (COPD), and acute cardiogenic pulmonary edema (ACPE) [2]. Currently, it is an alternative to endotracheal intubation in intensive care units (ICU), especially in immunocompromised patients or patients with many

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_70

comorbidities. In the past few years, it has also been used in ICUs patients with difficulty weaning in prevention of post-extubation failure.

70.2 Current Main Indications

NIV is now a first-line therapy in emergency departments, regular hospital wards, palliative and pediatric care units, and even in out-of-hospital patients. The appropriate selection of patients and the capacity of the team and the patients to achieve a proper adaptation to the technique is a key aspect of NIV [2]. Despite no significant technological discoveries in the area of ARF in recent years, new ventilatory modes and interfaces have recently been introduced to optimize hospital care, further expanding the role of NIV in the health system.

Since 2000, several trials have shown that the use of NIV in Acute Cardiogenic Pulmonary Edema (ACPE) has increased in detriment to IMV. Miller et al. analyzed the National Impatient Sample database in 2019 (data from 2002 to 2014), and noted an improvement of the symptoms, and a decreased requirement of intubation, the length of stay in ICU or hospital and hospital charges [3].

A multicenter prospective observational study in 54 French and Belgian ICUs concluded that NIV use and success rate have increased. The authors observed that the highest failure rates were seen in patients with de novo ARF, without associating an excess in mortality, which probably reflected better patient selection (Fig. 70.1) [4].

A recent survey carried out in the US showed that the use of NIV to treat acute exacerbations of COPD increased more than 400% in one decade (from 1% in 1998 to 4.5% in 2008) and was associated with a 42% reduction in invasive mechanical ventilation (IMV) [5]. Another study, performed in Spain by Miguel-Diez et al. from 2001 to 2015, showed similar conclusions (Fig. 70.2) [6].

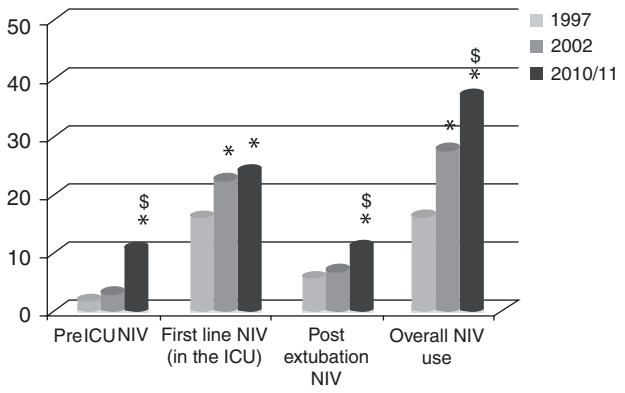

Fig. 70.1 Changes in the use of noninvasive ventilation across the three study periods. *ICU* intensive care units, *NIV* noninvasive ventilation. Extracted from: Demoule et al. [4]

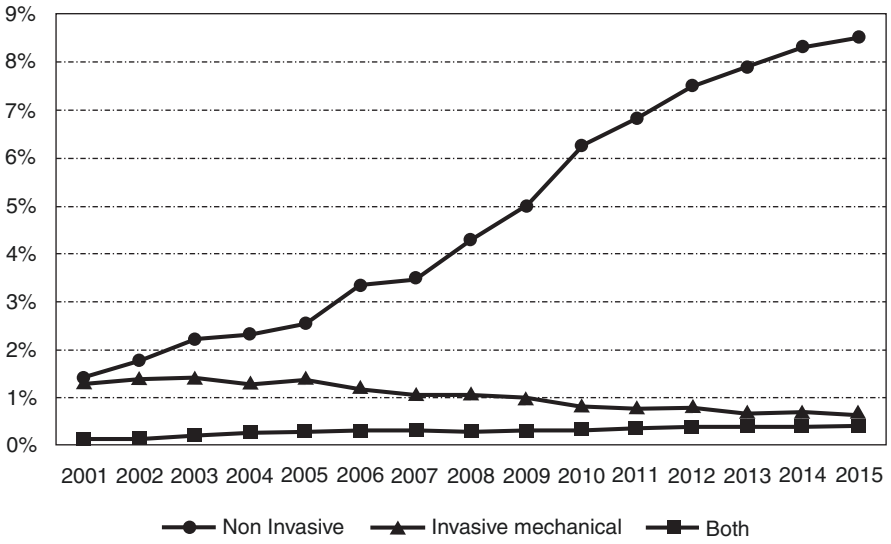

Fig. 70.2 Trends in mechanical ventilation among patients hospitalized with acute exacerbations of chronic obstructive pulmonary disease (COPD) in Spain, 2001 to 2015. Extracted from: de Miguel-Diez et al. [6]

Pneumonia is another situation in which NIV could be indicated; in 2021, Harshil Shah et al. published an article comparing the use of NIV versus IMV in community-acquired pneumonia (CAP). The authors extracted the data from a cohort from the National Inpatient Sample from US hospitals from 2008 to 2017. They concluded that there was an increase of NIV use in CAP while the trend of IMV use had decreased [7].

In the past few years, the use of NIV has been implemented in pediatric critically ill patients to prevent or replace invasive procedures, like in adult patients, in certain circumstances such as asthma exacerbations, bronchiolitis, or tracheomalacia [8].

70.3 Home NIV

Ease of use at home, feasibility, and benefits of NIV to improve nocturnal gas exchange in patients with obstructive sleep apnea or neuromuscular and chest wall disorders (diseases with increased life expectancy in recent years due to alternatives in their managements and complications) have increased the use of home NIV, improving the quality of life in these patients. The main advance has been the possibility of varying the ventilation mode and improving the patient's adaptation. In this field is where Jolly et al. [9] reviewed the initiation and efficiency of using home NIV, showing that there is still much to do in this area to identify and improve

effective strategies for home NIV. In the next years, software will be developed for remote control and assessment of the effectiveness and daily adaptation of the patient to NIV, which will lead to a greater therapeutic adherence, and therefore, naturally, better use of NIV at home [10].

70.4 NIV in ARDS

Initially, NIV was not uncommonly used in acute respiratory distress syndrome (ARDS), although IMV continues to be the main respiratory support in these patients. NIV may be useful in selected patients with mild ARDS as the initial support, but it can be used with great caution in moderate to severe ARDS [2]. The principal problem in ARDS is that lung injury carries the risk that vigorous inspiratory effort combined with mechanical increases in inspiratory airway pressure produce high transpulmonary pressure with potential important lung damage. HFNC and helmet interface-NIV reduce the inspiratory effort, representing the most promising techniques for first-line treatment of severe patients. Personalized treatments based on patients' phenotypes, clinicians' expertise, optimized interfaces, control of respiratory drive, and strict physiological monitoring represent the wisest approach [11].

In 2016, the LUNG SAFE Study [12], a clinical trial performed with ICU's patients, showed that NIV failure in ARDS occurred in more than one-third of patients, and the mortality rate in those patients was high. Finally, NIV was associated with worse adjusted ICU mortality than IMV in patients with a PaO_2/FiO_2 lower than 150 mmHg.

This situation changed with the arrival of the novel coronavirus disease 2019 (COVID-19) pandemic, because of the high hospital pressure in the ICUs, NIV became, with HFNC, the main option in the initial management of patients with moderate to severe ARDS, especially in those patients who would not benefit from admission in the ICU due to their comorbidities. Diverse studies compared the use of NIV versus HFNC in patients with COVID-19 and ARDS without immediate intubation criteria. The results of these studies were mixed; therefore, the decision of the best management strategy requires randomized clinical trials [13].

70.5 Chronic NIV for COPD

Regardless of the timing of initiation, chronic NIV improves daytime hypercapnia. In addition, in stable COPD, survival seems to be improved and there might be a short-term health-related quality of life benefit. In people with persistent hypercapnia after a COPD exacerbation, chronic NIV might prolong admission-free survival without a beneficial effect on health-related quality of life.

In stable COPD, future randomized controlled trials comparing NIV to a control group receiving standard care might no longer be warranted, but research should focus on identifying participant characteristics that would define treatment success. Furthermore, the optimal timing for initiation of NIV after a severe COPD exacerbation is still unknown [14].

70.6 NIV and HFNC

Since its inception in the 1980s, the application of NIV in patients with ARF has progressively increased as an alternative to endotracheal intubation in ICU, even doubling its rate of use in a period of 7 years. NIV use occurs in 11–23% of all ventilated patients, which represents a use of 8–13% among all patients admitted in ICU [15]. In the past few years, the appearance of HFNC has led to a decrease in the initial use of NIV as a noninvasive ventilation method, due to its tolerance and ability to provide high doses of oxygen.

Cortegiani et al. published a clinical trial comparing the initial use of NIV versus HFNC in mild–moderate hypercapnia exacerbation of COPD, concluding that HFNC was not statistically non-inferior to NIV in this situation, but 32% of patients receiving HFNC required NIV in 6 h [16].

The recent European Respiratory Journal (ERJ) guidelines suggest either NIV or HFNC in post- operative patients at high risk of respiratory complications after extubation. Moreover, the ERJ guidelines suggest the use of NIV over HFNC after extubation in nonsurgical patients; HFNC appears to result in a small, but probably clinically important, increased risk of reintubation (~4%) compared to NIV. In patients with COPD and acute hypercapnic respiratory failure, the ERJ expert panel suggests a trial of NIV prior to use of HFNC [17].

70.7 Future Research

Telemanagement and telemedicine applications have a wide range of implementations, and there has been robust evidence about their clinical benefits, cost-effectiveness, simplicity, and positive impact on critical care safety and quality. The telemanagement decision support option provides many potential benefits by reducing the specialist's workload caused by regular revision of all the results; this option allows patients' measurement patterns to indicate health status deteriorations and the identification of patients with higher priorities for revision.

Deep learning has also been used as a recognized candidate to predict the probability that a future patient would experience therapeutic failure; this was due to its ability to exploit the intramodality correlations efficiently allowing for extraction of the hierarchical representations of the data, as well as its ability to perform feature extractions [18].

70.8 Conclusions

NIV use has increased in all healthcare areas because it is a good alternative in the initial management in most ARF. There has been a further increase in its use since the arrival of COVID-19. This increase is mainly due to its efficacy in patients with respiratory failure (chronic or acute), the best adaptation to the NIV, and the reduction in the rate of intubation. In the coming years, recent studies indicate there will be a reduction in the use of NIV in favor of HFNC, which shows similar results with better tolerance.

The future of NIV will depend on technological advances, both in remote home control and in the development of new interfaces that improve the tolerance and ventilatory mechanics in certain patients, and obviously in new areas of use defined by doctors in future [19].

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Part XIV

NIMV Do Not Endotracheal Intubation Order, Palliative and Quality of Life Influence

Palliative Use of Noninvasive Ventilation

71

Pasquale Buonanno, Maria Vargas, and Giuseppe Servillo

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71.1 Introduction

Noninvasive ventilation (NIV) has been extensively investigated for its use in both hypoxemic and hypercapnic respiratory failure of different causes and as respiratory support after extubation [1]. Only a few studies have been conducted so far to elucidate its role in the palliative care setting and many questions remain unsolved. End of life is, in fact, a general definition which includes different conditions and the outcome of NIV cannot be measured only by clinical parameters but ethical and psychological aspects also have to be considered. Furthermore, even if the patient has to be the center of care efforts, relatives' perspective have to be taken into account because, as the birth, the death too is a fundamental moment of family and community life [2].

Another pivotal question is to assess if NIV can improve quality of life in these patients or if it simply prolongs an inescapable death without a significant improvement of symptoms [3].

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_71

NIV could be considered to improve respiratory symptoms in two clinical scenarios, i.e., patients affected by solid or hematological cancers and patients suffering from end-stage chronic respiratory diseases [4].

In both cases, patients and relatives have to be adequately informed at the right time to ensure a reasoned choice.

End-of-life condition can be managed in many ways according to the patient's desire and legislation:

- Withholding: the decision not to start life-sustaining therapies (e.g., vasoactive drugs, continuous renal replacement therapy, intubation)
- Withdrawal: the decision to suspend treatments in course in order to not prolong life anymore.
- Euthanasia: it refers to an active and deliberate administration of lethal substances by a physician to relieve unbearable symptoms upon patient's request.
- Physician-assisted suicide: it occurs when the physician provides all the means and/or the information to a patient in order to facilitate his death (e.g., prescribing drugs and giving information about the lethal dose, route of administration, etc.)

End-of-life decision is one of the thorniest ethical problems for physicians who have to manage critical patients daily and many factors concur to the approach of this kind of scenario: religious beliefs of patients and health care providers, physician skills and experience, national laws and guidelines, which are dramatically different among the states [5, 6].

A short life expectancy and a worse prognosis along with an unlikely prevision to get through the acute exacerbation of the disease are all elements that can influence end-of-life decisions particularly in end stage chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, amyotrophic lateral sclerosis, and cancer [7].

Patients who potentially would benefit from NIV can be grouped into three categories: patients who desire all the possible life supporting treatment; patients who set boundaries to intervention (e.g., do not intubate (DNI) order), and patients who wants to receive comfort measures only (CMO).

71.2 End-Stage Chronic Respiratory Disease

Patient and relatives' education and information about the evolution and prognosis of the underlying disease is fundamental to achieve a decision about ventilation in the end stage respiratory diseases and to decide an advance care plan. Dales et al. showed that in COPD patients that informative material such as an audiocassette and booklet explaining the technique, advantages and risks of mechanical ventilation can effectively help the patient to make a decision [8].

Unfortunately, communication is widely lacking and the decision about end-of-life management is often taken by the medical staff [7, 9, 10].

COPD patients as well as those affected by cancer or cardiogenic pulmonary oedema (CPO) tend to accept low-burden treatment but not a highly invasive procedure to restore the previous health and functional condition; the majority of patients refuse even low-burden treatments if they implicate a subsequent significant reduction of functional or cognitive status [11].

NIV can be an optimal choice for patients who set limitations to the treatments or for those choosing CMO. In this case, NIV represents a life support treatment that combines the instances of both patients with DNI orders because of its low invasiveness and CMO patients who want only to achieve relief from dyspnea [3]. The consideration of NIV utility varies among physicians; pulmonologists are generally more confident in NIV effectiveness to reduce respiratory symptoms in end-of-life patients compared to intensive care physicians; this could be explained because pulmonologists generally follow the entire evolution of the disease from its beginning till the fatal end, whereas intensive care professionals are focused on the acute episode and do not take into account the previous condition [12].

Some limitations of NIV use is also due to definitions: NIV, in fact is a type of mechanical ventilation and its role to prolong life has not yet been established so physicians could deny this treatment to CMO patients and conversely CMO patients could be afraid to extend their sufferance. Some authors suggested to add the term "do not noninvasively ventilate order" thus implicitly pointing out the need for correct information about this treatment option just as for intubation.

Some doubts and uncertainty about the targets to achieve when NIV is used in the end-of-life scenario are also responsible for its scant application and they can lead to negative consequences as undesired life prolongation, psychological and physical stress of patients and relatives, and delusion of patients and family expectations [13, 14]. The fundamental statement of NIV use in end-of-life is that it is a mean to control symptoms (i.e., dyspnea) and sometimes to give patients additional time to talk with their loved ones and to settle their affairs [15].

The goals of NIV vary among the three abovementioned groups of patients classified according to the Task Force on the "Palliation Use of NIV" from the Society of Critical Care Medicine. Patients who desire all the support to prolong their life have to be encouraged to tolerate potential discomfort because the target is to ameliorate gas exchange. In contrast, in CMO patients, the goal of NIV is to improve dyspnea and to maintain the possibility to communicate with friends and family; consequently, the patient does not need to be encouraged to tolerate any discomfort, and other forms of CMO have to be potentiated in these cases [16]. Similarly, while a consciousness impairment is not an absolute contraindication to NIV, patients not responsive to the surroundings could not take advantage of NIV as they are probably not aware of their symptoms and consequently not aware of the potential benefits of the respiratory support [17]. Palliative use of NIV includes its use to lead patients to their own home to spend their last hours in a more pleasant place with family and friends.

The goals of NIV in palliative care has to be regularly reassessed as the patients might pass from one category to another, changing their mind about the level and type of care they desire to receive.

A European survey highlighted NIV is poorly considered in palliative care, and its use is more frequently proposed to DNI patients than to CMO ones [7].

No RCTs have so far been conducted to elucidate the role of NIV not only in CMO but also in DNI patients because of the exclusion of these categories from trials; this make physicians' choice to start NIV with palliative purposes quite difficult even if it has been demonstrated to be effective in reducing dyspnea in acute respiratory failure in COPD and solid cancer patients [18, 19]. The decision about NIV utilization has to take into account a detailed information not only about benefits but also about the possible risks, e.g., gastrointestinal distension, eye irritation, hemodynamic instability, pneumothorax, and patient–ventilator asynchronies [20].

COPD is the main disease that has been investigated for the palliative use of NIV as it represents the most common chronic respiratory condition; NIV has become the first-line therapy for COPD exacerbation [3]. Neuromuscular and neurological degenerative diseases (e.g., Duchenne dystrophy, amyotrophic lateral sclerosis) can also be considered for palliative use of NIV even if the ethical issue is more compelling in these cases because of the irreversible nature of these syndromes; the use of NIV in the early stages of these disorders has dramatically improved the survival and in the last phase patients become fully dependent on NIV. Most patients decide to continue NIV even in the latest stages of the disease even if tracheostomy remains a fundamental indication in this kind of patients not only for the respiratory support but also to effectively remove secretions [21–23]. Pulmonary fibrosis is another unexplored field of application of NIV; acute respiratory failure often occurs as a terminal event and the advantage of NIV compared to oxygen and medical therapy has not yet been elucidated [24, 25].

71.3 Neoplastic Disease

An episode of acute respiratory failure is one of the most common causes of admission of patients with cancer to intensive care units; new pharmacological and radiological therapies along with hematopoietic stem cells and bone marrow transplantation for hematological malignancies have dramatically changed the prognosis of these patients but not without risks. In fact, patients undergoing these treatments can be more prone to immunosuppression and consequently at higher risk of infections, and drug-related toxicity can impair organ function, thus making patients more fragile [26–28]. Patients with cancer are often not admitted to ICU because of the poor chances for most of them to get through the acute event. ICU mortality significantly decreased in the past few years, in particular for those requiring mechanical ventilation, settling below 50%; for mechanical ventilated patients, mortality remains high ~75–80% [27, 29]. The improvement of cancer patients' survival in ICU has a multifactorial explanation: denied admission for patients who cannot benefit from intensive therapy treatments, early ICU admission of patients eligible for potential effective therapy, and a better knowledge of complications and pathophysiology of this subgroup of patients [30, 31]. The high mortality of patients

undergoing mechanical ventilation raises the question of ICU admission suitability and the issue to alleviate symptoms.

NIV seems to have an important role in the ICU survival improvement and its application to treat acute episodes of respiratory failure is dramatically spreading. Tracheal intubation, in fact, may contribute to the development of respiratory infection and ventilator-acquired pneumonia, which can be particularly dangerous for immunosuppressed patients; NIV could avoid such an invasive procedure and it showed to reduce ICU mortality and improve arterial blood gases [32–34]. There is a paucity of studies investigating the outcome differences between the type of interface used for NIV. Helmet has a lower incidence of skin injury compared to face mask, but it can be harmful for CO_2 rebreathing, especially for hypercapnic patients [35, 36].

Patients with cancer, in particular those who decided not to be intubated in any circumstances, are often excluded from ventilatory support despite that many episodes of acute respiratory failure could be reversible or effectively treated with NIV. Even if end-of life related dyspnea could not be reversible, some authors showed that NIV may decrease respiratory fatigue and reduce the need for opioids [37].

The most appropriate location for NIV in end-of-life depends on the severity of symptoms, which influences the experience of health care providers needed to manage them; the more severe the symptoms are, the more experienced the team has to be [38]. Another important factor is the decision of patients to undergo invasive ventilation or not: in the former case, the chance to be promptly intubated has been ensured and the intensive care unit represents the best setting for this kind of patient.

DNI and CMO patients could benefit from a more open environment such as hospice or respiratory unit in which sudden decline of respiratory function can be quickly recognized to give the appropriate care and where relatives might be present at the bed side to assist the patient in the last days.

It is important to underline that NIV is a powerful tool to manage end-of-life respiratory symptoms if physicians and nurses are adequately trained; otherwise, NIV can only increase discomfort.

Key Message

- NIV can effectively alleviate symptoms in the palliative setting of both end-stage chronic respiratory disease and neoplastic disease.
- NIV has to be managed by appropriately trained physicians and nurses.
- The targets of NIV treatment have to be individualized according to the patient's expectations and wishes.
- Patient and relatives' psychological condition has to be taken into account.
- The location of palliative NIV depends on severity of symptoms and the decision of the patient to be intubated or not.

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Do Not Endotracheal Intubate Order, Use of Noninvasive Ventilation

72

Brigitte Mathias Leal Dias Pereira

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72.1 Do Not Intubate (DNI) Order, What Is It?

Acute respiratory failure (ARF) is a common criteria for admission in an Intensive Care Unit (ICU) [1], and often needs supportive treatment (while treating the underlying etiology) such as oxygenation, noninvasive ventilation, endotracheal

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_72

intubation and invasive ventilation, high-flow nasal cannula oxygenation (HFNC), and extracorporeal membrane oxygenation (ECMO).

Not all patients with ARF will benefit from an invasive ventilation, and the aim of a clinician is to restore pre-admission health status, maintain patient's quality of life and his/her dignity.

The Do Not Endotracheal Intubate order (DNI) is mostly used in end-of-life illnesses.

This is often a physician's decision, and is based on the severity of the illness, patient's daily life activities, and cognitive, functional, and respiratory status. The other factors reported to contribute to making DNI decisions were the patient's and family's wishes, the lack of resource availability which resulted in triaging ICU beds and ventilators, and the social/cultural/religious beliefs [2–5].

There are countries where life support withdrawal is illegal, or unacceptable [6].

Asia and Europe, occurring more frequently in Northern Europe compared with Southern Europe, have a higher rate of DNI orders compared to North America. Some authors believe that it is due to the fact that physicians in these countries anticipate end-of-life, and they often discuss forgoing life-sustaining treatments with patients [2, 3, 7].

There is not only a variability in DNI orders according to geographical location (internationally and nationally), but also in the same hospital [3].

In the United Kingdom (UK), the Emergency Medicine physicians feel "frustrated" that the decision not to intubate is often influenced by non-clinical factors, most often by ICU bed availability [8].

It has been observed that the physicians' characteristics, the country of medical education, the time since graduation (young clinicians), and those who have obtained their training and experience on decisions making, had a significant effect on end-of-life decisions. This has an implication in deciding and registering DNI orders [2, 9, 10]. Similarly, in a European Pulmonologist survey, the indications for withdrawing and withholding treatment, as well as DNI/DNR decisions, were highly related to the judgment of the involved physician. Once again, this highlights that these decisions could be influenced by the physician's age, religion, skill, and experience [11].

The DNI decision and order can be made at any time during the patient's medical course: in an outpatient setting, in the emergency room, in the medical ward, and when the patient develops an acute respiratory failure in the ICU ward [12–15].

The rate of DNI orders in patients with ARF have increased over time, according to the authors Wilson and colleagues [3]. These researchers were surprised to find that factors such as the illness severity did not significantly affect the rates of DNI decisions, thus suggesting that other factors could play a larger role in how such decisions are made.

Decisions about pursuing mechanical ventilation are often matters of life and death. Wilson warns "If there is suboptimal decision-making, then there can be devastating consequences for patients" [3]. Therefore, various authors are of the opinion that there should be a specific postgraduate-education program involving end-of-life care, and that this program should be undertaken by all physicians

leading with end-of-life decisions. They also emphasize that when dealing with DNI there should be supervision by older and more experienced colleagues, as it is an ethically complex decision [2, 12, 16].

The decision for DNI should be based on the patient's best interest, respect his/her rights, and provide the necessary and effective treatments aiming to restore the pre-admission health status [17].

DNI is different from a DNR (Do Not Reanimate) order, as DNI may use chest compressions and cardiac drugs, but no endotracheal tube is placed in the patient [18]. There is also a Do-Not-Operate (DNO) order: the goal is reducing suffering from non-beneficial surgical interventions in patients with severe illness at the end of life [19].

The goals for noninvasive ventilation (NIV) when used with DNI orders is reversing ARF, alleviating symptoms (dyspnea), avoiding death from ARF (as intubation is not an option), and allowing the patient to be discharged from the hospital.

72.2 Questions Like WHO, WHEN, WHERE, and WHY Have NIV with DNI Order?

72.2.1 Who and When Will Benefit from NIV?

There are three categories for indications for NIV:

Those patients who are to have all possible treatments and life-support; those who have been elected to have specific limits on life-support and treatment (DNI orders); and those patients at the very near end of life who will receive comfort measures only (CMO) [17].

The table below elaborated by Robert M Kacmarek [17], shows the three indications for noninvasive ventilation in chronic obstructive pulmonary disease.

Care Category	Goals and Comments	Example Patient
Life support without pre-set limits	Restore pre-admission health status. Intubate only if necessary to improve oxygenation and ventilation. Discomfort of intubation outweighed by potential benefits.	Patient with an exacerbation of COPD, who has never been hospitalized and wants all possible treatments and life-support.
Life support with limits (DNI)	Restore pre-admission health status without using treatments and techniques the patient has elected against (eg, intubation).	Patient with an exacerbation of COPD, who was previously hospitalized, intubated, and ventilated. The patient does not want to be intubated again, but wants all other treatments and life-support.
Comfort measures only	Maximize comfort and minimize pain and other discomforts, including adverse effects of treatments.	Patient with an exacerbation of COPD and terminal-stage lung cancer, who does not want to be intubated but wants to be as comfortable as possible.

COPD = chronic obstructive pulmonary disease
DNI = do not intubate

Examples of patients in the three categories of indications for noninvasive ventilation

In this chapter, we will only discuss: **Life support with limits (DNI).**

The International Consensus Conference on *challenges in end-of-life care in the ICU,* published in 2004, defines DNI as "*Withholding*" as it is a planned decision not to introduce therapies that are otherwise warranted. While the end-of-life care is defined as the care (comfort, supportive, or symptom care) provided to a person in their final stages of life [20].

The "palliative use" of NIV in patients who have decided not to forego endotracheal intubation (ETI) remains controversial [21, 22].

Some authors suggest that NIV alleviates the respiratory distress and/or to allows communication with family/staff members, and/or provides additional time to organize their personal affairs, and to be able to come to the acceptance of death [17, 23]. It is also known that NIV can be noisy, uncomfortable, and frightening. It may also interfere with sleep. It is not free of complications such as gastro-distension, eye irritation, pneumothorax, agitation, patient–ventilator asynchrony, and hemodynamic instability. Therefore, some authors suggest that it may further reduce the poor quality of life and increase discomfort in DNI patients [24, 25].

Other authors concluded in their study that mechanical ventilation via face mask offers an effective, comfortable, and dignified method of supporting patients with end-stage disease and ARF, and who refused endotracheal intubation [26].

In Denmark, 15% of patients with DNI instructions, and who received NIV during 2002 and 2003, survived at least a year with COPD and congestive heart failure [27].

From 2000 to 2017, Sullivan et al. [28] observed that there was a rapid increase in NIV use, especially among patients with evidence-based indications, such as CHF or COPD, but there was also an increased use in persons with cancer and dementia. The authors concluded similar to other studies, NIV can be indicated for CHF and COPD as it had favorable outcomes, and therefore in this group it can be justified [23]. While the increased use of NIV among patients with cancer and dementia suggests possible over-treatment [28].

As the experience and use of NIV grows, so does the technical and personnel resources (nursing and respiratory therapy), and also the staff's skill and experience.

The BTS/ICS Guidelines for the Ventilatory Management of Acute Hypercapnic Respiratory Failure in Adults states: *"Health professionals experienced in NIV delivery have a more positive view of the benefit of NIV and perceive patient treatment wishes more positively than do clinicians with less experience of NIV"* [29].

In end-of-life care, it is essential to avoid physical or psychological harm, while providing active and ongoing communication strategies. Chakrabarti reported [30] that in the interviews with 50 patients with stable COPD, the discussion and the demonstration of NIV equipment altered future treatment perceptions and willingness. Also Dr. Nava emphasized that patient selection for NIV should not only be based on specific disease factors but also, and most importantly, on the patient's willingness to accept the mask; the patient should decide and accept which treatment to receive, have autonomy [31].

Perhaps the outcomes are dependent on patient selection, professional experience, and an effective timely communication.

The following pathologies are often discussed and considered for DNI orders.

72.2.1.1 Advanced Physiological Age (>85 Years/Old) with Instability

The elderly comprise an increasing proportion of the population and represent a progressively increasing number of patients admitted to the ICU.

Studies suggest that the comorbid factors associated with age rather than just age itself contribute to the worse outcomes of these elderly patients when invasive ventilation is used [32–34]. Comorbid illness increases from approximately 17% at age 40–65% by the age of 75 [34].

Owing to the loss of muscle mass, the underlying pulmonary disease and other comorbid conditions, the incidence of acute respiratory failure (ARF) also increases exponentially with age [32, 35, 36].

Patients with a good nutritional status, who are independently able to perform their daily living activities, and have minimum comorbidities have a more favorable prognosis when invasive ventilation is applied regardless of their age. Nevertheless, complications exist, resulting from the use of heavy sedation, prolonged ventilation, immobilization, and insufficient/inadequate nutrition, which are often seen in this very old population with invasive ventilation and the associated ICU environment [34]. Elderly patients in the ICU suffer a functional decline, cognitive impairment, functional disability, and poor quality-adjusted survival. It has also been referred that this cognitive impairment, the psychological symptoms, the alterations in the sleep cycle, and the delirium that are common complications of critical illness are associated with an increased prescription of specific medications, such as antipsychotics or benzodiazepines in this geriatric population [37].

Another aspect is airway management in this group. There are four aspects of airway management: performing intubation, providing effective ventilation and oxygenation to prevent a desaturation event, and decreasing the risk of aspiration. Because in these octogenarians there are changes in the anatomic, physiopathologic, and cognitive states, these patients are vulnerable during airway management and there are risks of complications associated with intubation. For these reasons, the North American Anesthesiologists created a protocol combining each aspect of airway management with specific techniques specifically for these geriatric patients to decrease the incidence of complications in Airway Management, by using conventional devices, supralaryngeal devices, and specialized airway devices [38].

Another concern in the critically ill elderly patients who have been intubated and ventilated is the extubation failure, which increases with the duration of mechanical ventilation, length in ICU stay/hospital stay, and also carries a higher morbidity and mortality [39]. Poor nutrition indices (e.g., severe hypoalbuminemia) were one of the causes of this unsuccessful event, and it is probably due to weakness of inspiratory muscles, decrease in ventilatory drive, and the alteration of immune lung defenses.

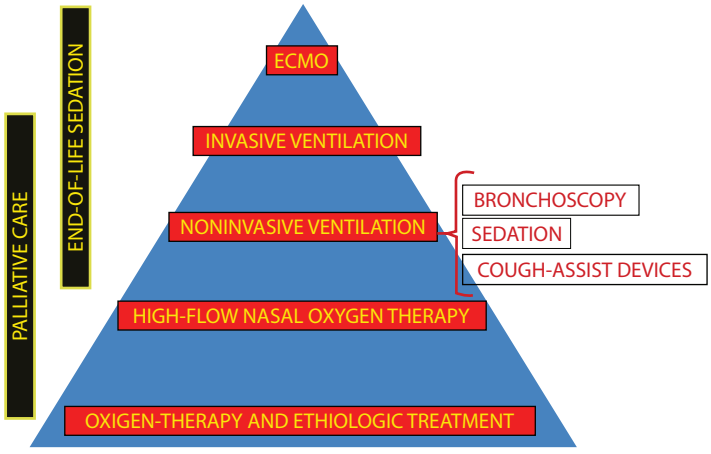
Other factors that were also identified as common etiologies for this failure, were the COPD related hypercapnic respiratory failure that were unable to clear secretions, and the need for mechanical ventilation for more than 4 days in elderly patients who had underlying pulmonary disease [39]. Another study revealed that some physiological parameters (lower body temperature, higher Faces Anxiety

Scale/FAS) and metabolic parameters (urea, sodium, calcium, and anion gap) were associated with the increased rate of extubation failure in these patients [40].

Therefore, it is essential to identify the elderly patients who may be at increased risk of developing these complications and are least likely to benefit from this invasive treatment and from the aggressive ICU environment. Therefore, limited endotracheal intubation and invasive ventilation (DNI) is often carried out in elderly patients who have multiple morbidity, chronic advanced cardio-respiratory disease, and neurological end-stage diseases.

The advantages of NIV is to offer similar physiological effects of invasive mechanical ventilation without the need of placing an endotracheal tube, and by unloading respiratory muscles, improvement gas exchange, augment alveolar ventilation, avoiding ventilator-associated pneumonia. Most patients receiving NIV are managed without/little sedation, avoiding sedative drug-related complications [41, 42].

NIV is commonly used as a first-choice ventilatory technique (and often successful) in diseases such as chronic obstructive pulmonary disease (COPD), cardiogenic pulmonary edema, immunosuppression of different origin, neuromuscular disease without severe bulbar impairment, obesity hypoventilation syndrome, and chest wall deformity. As all of these have a high prevalence in the elderly, this NIV strategy has been applied in elderly with DNI.



Therapeutic Options in Elderly with Acute Respiratory Failure [35, 43]

Studies have shown that in this elderly population the use of noninvasive ventilation is associated with less discomfort, fewer complications, and better short-term results than is endotracheal ventilation [33]. Particularly for elderly patients, NIV is effective and well tolerated, and it has become a "key ventilatory technique in the management of ARF" [44].

The table below shows the likelihood of success of NIV in elderly patients according to the different types of ARF [43]:

Clinical condition with Acute Respiratory Failure	Avoidance of intubation Reduction of Mortality
COPD exacerbations	+++
Cardiogenic pulmonary edema	+++
Immuno-compromised status	+++
Obesity-hypoventilation	+++
Chest wall deformities	+++
Weaning/Extubation in COPD	++–
Mild-moderate Encephalopathy	++–
Neuromuscular diseases[a]	++–
Community Acquired Pneumonia	+––
Mild ARDS	+––
Agitation/Delirium[b]	+––
Interstitial fibrotic lung diseases	–––
Multi-organ failure/Comorbidities	–––

[a] with cough augmentation techniques
[b] with low doses of sedatives

A DNI order can therefore be used to avoid intubation and invasive ventilation complications particularly in these fragile patients. By applying NIV while concomitantly treating the underlying (reversible) etiology these patients may return to their base-line health [21].

72.2.1.2 Dementia

Advanced dementia is characterized by profound *memory deficits, reduced verbal abilities, and severely diminished cognition* [45].

Factors that may be present in these patients, such as agitation or lack of cooperation, copious airway secretions, or being unable to protect their airway, are relative contraindications to initiate NIV, and probably are the basis of NIV failure in these patients. The absence of psychomotor skills and reflexes, and the generalized rigidity may exacerbate the patient–ventilator asynchrony, often characterized by air leaks, causing NIV failure. Pneumonia is common in dementia; therefore, the use of NIV can present difficulties with clearing of the secretions, which increases NIV failure and increases its associated mortality [45, 46].

In Sullivan et al.'s study [28], there is an increase in use of NIV among patients with dementia and cancer, without a concomitant decrease in invasive mechanical ventilation. NIV failure may be associated with agitation and distress for patients at the end of life, and also prolonging their death. This suggests the *possible over-treatment or low-quality care* as the risks outweigh the benefit in these patients.

Emanuele et al. showed that 22 elderly patients with dementia submitted to NIV with hypercapnic respiratory failure (cardiogenic pulmonary edema or acute-on-chronic respiratory failure from COPD) had a high mortality [46].

To date, various studies have shown that NIV in patients with dementia at the end of life had no demonstrable benefit, and may even have the potential to introduce harm. Therefore, NIV in this population should be considered very carefully.

72.2.1.3 Advanced Lung Disease: Terminal Respiratory Disease (Malignant/Nonmalignant Severe Respiratory Disease)

1. **COPD** has an unpredictable trajectory and has an uncertain prognosis [47]. It has been documented that NIV use in acute exacerbations of COPD reduced the need for ICU admission and intubation, and reduced mortality and nosocomial pneumonia associated with intubation [48]. Most patients with NIV failure that are intubated are more likely to be "sicker" and therefore have a poor prognosis [18, 49]. While patients on long-term oxygen therapy did not have worse outcomes compared to COPD patients who were not using oxygen before admission [49].

   All these factors and the potential for the patient's poor understanding of COPD as a life-limiting disease make it challenging to implement appropriate and timely DNI orders.
2. **Interstitial lung diseases (ILDs)** "*are a heterogeneous group of diseases characterized by widespread fibrotic and inflammatory abnormalities of the lung*" [50].

   ARF is a common complication in advanced stages or following acute exacerbation of the underlying disease. Neither NIV nor Invasive Mechanical Ventilation (IMV) change the poor outcomes associated with advanced stages of ILDs. Idiopathic Pulmonary Fibrosis has a median survival of 2–5 years at the time of diagnosis [50, 51].

   Faverio et al. [50] state that more invasive techniques (IMV and Extracorporeal Membrane Oxygenation) should be limited to patients listed for lung transplant or with reversible causes of ARF. In carefully selected patients, such as those with less severe ARF, an *NIV trial* might help early recognition of NIV-responder patients, who may have a better short-term prognosis.
3. **Advanced Lung Cancer**

   In the United States, lung cancer is the second most common malignancy, after prostate cancer in males and breast cancer in females [52].

   DNI in these patients can be offered in advanced refractory disease or in patients with poor performance status. The best management and decision-making in such patients is engaging in a multidisciplinary team approach, which includes the intensivist, the medical oncologist, and the palliative care specialist [31, 53].

   In a study presented by Dr. Stefano Nava (the Istituto Scientifico di Pavia in Italy) at the American Thoracic Society's International Conference in Toronto in 2008, he compared two therapies to relieve the respiratory distress in 92 end-stage cancer patients (solid tumors), either by delivery of oxygen or NIV. The NIV therapy showed an effective and more rapid treatment in improving dyspnea than standard oxygen therapy in end-stage cancer patients, and the patients who received NIV had a lower use of morphine in the first 24 h [54].

   Patients with end-stage lung cancer, who need comfort-measures for their hospital stay, while a therapeutic plan is executed to reverse the ARF, can benefit from NIV as it is more effective in reducing dyspnea than standard oxygen

therapy, and also reducing patients' reliance on morphine, thus improving lucidity in their final days and permitting communication with family and staff.

Advanced Cancers

Cancer patients with ARF might benefit from NIV use because they may have underlying COPD, be immunosuppressed, and/or have cardiogenic pulmonary edema related to the cardiac toxicity of the anticancer agents and the hyper-hydration during chemotherapy. These are the three major indications for NIV. An example is ARF in breast cancer patients that is associated with severe atelectasis, fluid in the lungs, or a compression of a bronchi or the trachea [31].

Cancer patients are often frail and anemic because of their underlying disease and the subsequent treatment (chemotherapy/radiotherapy/surgery), and when there is a need to increase the work of breathing to maintain oxygenation, the demand of the respiratory muscles can become excessive, causing fatigue and carbon dioxide retention. NIV has been shown to be effective in improving oxygenation, recruiting under-ventilated alveoli, preventing alveolar collapse, and reducing the work of breathing. As previously described before, NIV is more effective than standard oxygen therapy in reducing the respiratory rate, dyspnea, and patients' reliance on morphine, allowing and preserving normal swallowing, speech, and cough mechanisms in these cancer patients [54].

Dr. John E. Hefner, MD, Medical Director of Medical University of South Carolina, Division of Pulmonary and Critical Care Medicine (a past president of the American Thoracic Society) did not agree totally with Dr. Nava's statement about the similarities between the etiology for dyspnea in patients with COPD and patients with cancer, and their likelihood to respond to NIV near the end of life. He added that patients with COPD may become short of breath at the end of life because of the underlying COPD and attendant airway obstruction. NIV has been shown to improve breathing in these circumstances as it decreases the labored breathing efforts during end-of-life care.

On the other hand, cancer patients without COPD will most likely not have airway obstruction as a source of dyspnea at the end of life, and so will not receive benefit from NIV through its specific positive value for "supporting" airways that are obstructed. But both COPD and non-COPD patients near the end of life may have shared causes of dyspnea, such as fluid overload in the lung, cardiac failure, pleural effusions, or infiltrations of cancer through the lung tissue [31].

In the ICU of the *Institut Jules Bordet*, Belgium, a study was done from January 2000 to April 2004; it involved 87 patients with cancer requiring NIV, of these only 18 (20.6%) had "life-support techniques limitation." They showed that 77.7% and 55.5% of these 18 patients were discharged from ICU and from the hospital, respectively [55]. They, therefore, concluded that NIV is an *effective and comfortable method of supporting cancer patients with "life-support techniques limitations"* who still have a therapeutic plan and a reversible cause of acute respiratory failure [56].

We can then assume that NIV is generally well tolerated, and can prolong life, allowing other anti-cancer therapy or eventually permit life closure tasks to be

completed. However, in patients whose death is inevitable, physicians should be careful in prolonging survival in a futile manner [56].

72.2.1.4 Advanced Heart Disease (End Stage Cardiac Failure)

In the past decade, there has been an increased consciousness that heart failure (itself the final common pathway of several etiologies such as hypertension, ischemic and valvular heart disease, and cardiomyopathy) is a terminal illness, but these patients are more likely to have a less clear understanding of their own illness compared to patients with malignant diseases [57].

The main symptoms in heart failure (HF) are dyspnea and fatigue during exercise and/or during daily life activities. A decreased level of activity will lead to reduced physical fitness, which will further worsen the symptoms, limiting daily life activities, and thus the quality of life [58].

These patients may suffer a sudden death due to arrhythmia or myocardial infarction, or may have a slow decline with episodes of decompensation, precipitated by infection or further ischemic events limiting exercise tolerance, and progressively leading to dyspnea at rest [57].

NIV can improve cardiac function in patients with congestive heart failure (CHF) through hemodynamic, ventilatory, and peripheral muscle effects.

72.2.1.5 Progressive Neuromyopathies/Motor Neuron Disease

Duchenne muscular dystrophy (DMD), motor neuron disease/amyotrophic lateral sclerosis (MND/ALS), and children with severe spinal muscular atrophy are examples of neuromuscular diseases (NMD) or neurological disorders that impair respiratory function [59].

Simons states that without ventilatory support, the average age of death in patients with DMD is 18–20 years, and the prognosis is less than 1 year if these patients become hypercapnic. Almost all children with type 1 SMA die by the age of 2 years [60].

Using NIV with new modes in selected patients (muscular dystrophies and ALS without severe bulbar dysfunction) improves symptoms, gas exchange, has prolonged survival rates with good self-reported quality of life [60], and most of the neuro-muscular patients treated with NIV opt to continue until their terminal phase.

In patients with severe bulbar muscle weakness (facial, oropharyngeal and laryngeal muscles) that have difficulties in swallowing who are often drooling, have difficulty in the clearing of secretions and difficultly speaking, often have NIV-intolerance and also gained no survival benefit from this treatment [61, 62].

In patients with serious illness at the end of life, NIV is often the only way to sustain NMD patients who decline endotracheal intubation and invasive mechanical ventilation.

72.2.1.6 Patient's Will (Who Refuses Intubation)

Does a physician need the patient's consent for NIV and DNI orders?

It is the medical doctor's responsibility to make decisions in the patient's best interests and to respect the patient's rights. The physician after gathering all the

information on the patient's co-morbidities, functional, cognitive, and nutritional status, and having a medical judgment of futility, should discuss with the patient and family the decision of DNI. This discussion should be based on resolving symptoms, restoring health, maintaining the patient's quality of life, dignity, and allowing the individual to leave the hospital and return home. This process of shared decision making between the clinicians, the patient and the family, should consider the patient's perception of quality of life, respecting his individual hierarchy of values, beliefs, and cultures [63].

The medical community and society need to acknowledge that a "*consent for do-not-intubate*" order should exist so that it respects not only the interest of the patient but also those of health care providers.

72.2.1.7 Other Diseases

ARF and Self-Prone-Position (in Acute Viral Pneumonias)

An example is the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), sweeping through much of the world, causing the coronavirus disease 2019 (COVID-19) pandemic, and consequently resulting in a significant surge of critically ill patients and a high demand on intensive care services. This imposes challenges on healthcare systems and professionals worldwide [64].

"In a context of grave shortage of health resources," *the guidelines say, intensive care should be given to "patients with the best chance of success"* and those with the "best hope of life" should be prioritized [65]. Physicians have ethically demanding situations when confronted with triaging when the number of critically ill patients exceeds the healthcare infrastructure's capacity in a given location (namely ventilators).

The medical doctors' decision not to intubate (DNI) should utilize objective clinical indicators so that the patients benefits from the treatment, avoiding *a treatment that is deemed futile, burdensome, or disproportionate*.

Should there be a NON-INTUBATION CHECKLIST?

Since in some countries the decision not to intubate is often executed by the physician in the emergency or intensive care unit, it is often influenced by non-clinical factors such as ICU bed availability. Inviting the opinion of another critical care specialists or having the most senior available physicians participating in the discussion could help in the decision-making of DNI [11]. Another option is the creation of a hospital-check-list to help decide on a DNI patient [8, 12, 13].

In the United States, a triage committee was created to decide who to intubate or not to intubate to avoid the stressful decision being imposed solely on the physician.

The triage team (or committee) is composed of volunteers who are respected clinicians and leaders among their peers and the medical community. Their purpose is to evaluate COVID-19 patients, utilize objective clinical indicators to prioritize which patients will receive critical care treatments (most notably a ventilator). They create protocols that help ensure objectivity in decision making, minimize conflicts of interests, and mitigate moral distress for the care team [66–68].

Should we PRONE these patients?

Some physicians have placed patients in prone position to prevent the need for intubation and invasive mechanical ventilation, as it is known that pronation can recruit dorsal lung regions and drain airway secretions, thus improving gas exchange and survival in acute respiratory distress syndrome (ARDS) [6].

In an emergency department in New York, 50 patients with COVID-19 were place in self-prone position to avoid intubation and were supplemented with oxygen (either non-rebreather mask or nasal cannula). Only 13 patients (24%) failed and needed endotracheal intubation within 24 h in the emergency ward. The investigators concluded that an early awake self-proning improved the oxygen saturation in these patients [69].

In another academic medical center in the USA, a study was done from March 2020 to April 2020, where nine COVID-19 hypoxemic adults were eligible for self-proning (every 2 h alternated from supine to prone position), to avoid intubation. Patients required oxygen therapy with nasal cannula or high-flow nasal cannula (HFNC). Two patients required intubation.

Although a "very small" study, it revealed that oxygenation rapidly improved after prone position and reduced the respiratory rate. At 28 days, all patients were discharged from the hospital to their homes.

In April 2020, at the San Raffaele Scientific Institute, Milan, Italy, a small number of patients (15), received a short duration of NIV in the prone position outside the ICU [70].

It was observed that the respiratory rate was lower and the oxygenation was higher during and after pronation. The 11 patients (73.3%) had an improvement in comfort during pronation. At 14-day follow-up, nine patients were discharged home, one improved and stopped pronation, three continued pronation, one patient was intubated and admitted to ICU, and one patient died.

This study, although involving also a small number of patients, demonstrated that it is feasible to provide NIV in the prone position to patients with COVID-19 and ARDS in the general wards [71].

Given the physiological benefits of self-prone positioning, and being easily implemented and low-cost, this could be a strategy together with NIV in DNI patients with ARF.

ARF and Acute Renal Failure (Acute Kidney Injury)

In a study done in an Italian Respiratory Care Unit, of seven patients with DNI orders that were admitted with ARF and developed acute kidney injury, 71% died receiving both NIV and renal replacement therapy. This high mortality is not surprising as NIV failure increases with the increase of organ dysfunction (SOFA scores) caused by sepsis [72–74].

Therefore, this study only confirms the probable futility in initiating NIV in DNI patients with ARF and multi-organ dysfunction.

End-Stage Liver Disease

Patients with advanced liver disease, liver failure, and decompensated cirrhosis, given the general irreversibility of these conditions (Child-Pugh score $\geq$ 12 or a

MELD score ≥ 21), particularly if they are not candidates for transplantation are also not candidates for invasive ventilation [75]. NIV is not a standard practice in these cirrhotic patients with altered mental status from encephalopathy [46].

72.2.2 Where Should the Patients Be Monitored?

Choosing the appropriate environment for NIV requires understanding what level of monitoring is needed for these patients. The clinician should be familiar with the capabilities of the units in their facility, including both technical and personnel resources (nursing and respiratory therapy), and also the staff's skill and experience, and try to match these with the patient's need for monitoring [76].

It has been discussed previously that the successful implementation of programs for noninvasive ventilation requires 24-h availability of an experienced team and appropriate selection of patients [77]. *Placing a patient that is not to be intubated in an ICU bed to be monitored (SpO_2, arterial blood gases, vital signs, patient comfort, mask leaks, and the patient's ability to expectorate) raises financial and ethical concerns* [78].

The precious, costly, and limited ICU resources should be allocated for patients who will benefit from invasive procedures, namely invasive ventilation. Occupying these beds with DNI patients who need a lower level of care, placing them in this aggressive environment while managing ARF, and distancing them from the contact with their friends and family is very questionable. Clinicians should be reminded of the two basic ethical principles of the beneficence and nonmaleficence; "above all do not harm, or primum non nocere"! [79]. The ethical obligation of a medical doctor is to restore the patient's health and relief suffering, so the ideal care for 'DNI patients' is most likely to be more appropriate outside the ICU!

Choosing an adequate surgical/medical ward with experienced, trained staff and patient monitoring, or having an expert pulmonology unit/Step-Down unit, is an option to achieve economic and ethical benefits that surpass those of the ICU [80, 81].

72.2.3 WHY Use NIV in DNI Order?

The primary goal of the NIV-treatment is to restore or maintain health, but if this treatment fails or provides no net benefit, i.e., it is futile, it is ethically and morally correct to withhold or withdraw the treatment. So, who in the end will benefit from this treatment?

As explained before, there is a group of patients with ARF who are poor candidates for endotracheal intubation, and there are patients who do not want intubation (DNI) but accept NIV.

The increase in severity of illness and comorbidities of the patients seen in more economically developed countries, and the increased perception and understanding

of the medical society of the bad prognosis in these patients when intubated, reflects the increase in DNI orders.

The provision of NIV in a well-equipped hospital ward may be a viable alternative to the ICU for selected patients [82] providing an effective, comfortable, and dignified method of supporting patients with end-stage disease with acute respiratory failure [82, 83].

In a published meta-analysis by Wilson et al. [82]. DNI patients receiving NIV had a 56% survival rate at hospital discharge and 32% survival at 1-year. The higher survival was seen in patients with COPD and pulmonary edema as the cause of their respiratory failure, as opposed to pneumonia or malignancy. In surviving patients, there was no decrease in quality of life at 3 months, but quality of life was not assessed in the time before death in the non-survivors. The better survival with NIV for DNI patients with underlying chronic obstructive pulmonary disease (COPD) and congestive heart failure (CHF) were seen in patients who were awake and with a good cough [84–86]. DNI survivors receiving NIV showed no decrease in health-related quality of life or post-ICU psychological burden such as symptoms of post-traumatic stress disorder, anxiety, or depression [86].

Because NIV reverses the hypoxemic respiratory distress and improves breathlessness, it is a useful technique in the DNI population as a "therapeutic ceiling," but with careful case selection as observed with CODP and chronic heart failure as these seem to have a reasonable outcome [87].

72.3 High-Flow Nasal Cannula Oxygen (HFNC) as an Alternative to NIV?

High flow nasal cannula (HFNC) has emerged as an increasingly common support modality for acute hypoxemic failure and may be used as a substitute or adjunct to NIV. HFNC delivers oxygen with flows of 30–60 L/min, a high fraction of heated and humidified inspired oxygen, flushes anatomic dead space, and provides mild continuous positive airway pressure, especially with the mouth closed. HFNC may be as effective as and better tolerated than face mask techniques of NIV [88, 89]. Humidification may benefit mucociliary clearance, mobilization of respiratory secretions, and patient comfort [90, 91]. Also, HFNC requires less training than NIV, this modality may be more acceptable to the hospital staff, and could be broadly applied, allowing many patients to be treated outside the ICU environment [92].

HFNC in DNI status, has been poorly studied. The paucity of data, and the inadequate evidence in the primary outcomes (mortality, dyspnea, work of breathing, quality of life) today limits the formal indication of HFCN in DNI orders.

In a relatively small sample study of 50 DNI patients with hypoxemic respiratory distress admitted to an ICU in a single institute who received HFNC [93], it was well tolerated and only 18% of these patients progressed to NIV. There was an increase in oxygenation and a reduced respiratory rate from the base line. The

hospital mortality was 60% (30/50), probably due to the underlying pathology and severity of the disease (a high fraction had end-stage pulmonary fibrosis). As seen with NIV treatment in DNI patients, patient selection is essential to have an optimal treatment and outcome when using HFNC.

We need more studies to understand the risks and potential benefits.

72.4 In Conclusion, Remember…

In most Intensive Care Units, the most common reason for a patient to be admitted is acute respiratory failure (ARF). Invasive and noninvasive ventilation (NIV) is commonly applied to support this respiratory dysfunction, while treating the underlying etiology.

Some patients do not receive intubation and invasive ventilation. This is due to factors such as patient wishes, physician belief that this would not offer any therapeutic benefit, and also when there is a lack of resource availability and the physicians are forced to select (triage) ICU beds and ventilators to other patients.

In the Do Not Intubate order (DNI), other options such proning with supplemental oxygen therapy, high-flow nasal cannula oxygen, or NIV can be used while treating the etiology and providing comfort.

Studies have shown that in patients with DNI order and in ARF, who are awake, and have pathologies such as congestive heart failure and/or chronic obstructive pulmonary disease (with effective cough), NIV use may often permit the patient to be discharged from the hospital.

It is important to remember that there should be balance between the patient's autonomy and the physician's non-maleficence approach when deciding DNI.

Hippocratic oath: *"I will use treatment to help the sick according to my ability and judgement (beneficence), but I will never use it to injure or wrong them (nonmalevolence)".*

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Influence of Noninvasive Mechanical Ventilation and Implications of Quality of Life

73

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Abbreviations

AVAPS	Average volume assured pressure support
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
EDS	Excessive daytime sleepiness
HRQoL	Health related quality of life
IVAPS	Intelligent volume assured pressure support
MRF	Maugeri respiratory failure questionnaire
NIV	Noninvasive ventilation
NMD	Neuromuscular disease
OHS	Obesity hypoventilation syndrome
OSA	Obstructive sleep apnea
PCV	Pressure control ventilation

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_73

PSV	Pressure support ventilation
RTD	Restrictive thoracic disorders
SF36	Short-form health survey
SGRQ	San George respiratory questionnaire
SRI	Severe respiratory insufficiency

73.1 Introduction

Noninvasive mechanical ventilation (NIV) provides ventilatory support through the patient's upper airway using a ventilator–patient interface that includes nasal, oronasal, facial masks, helmet [1], and uses different modalities (Table 73.1).

NIV is increasingly characterized as an essential support in the treatment of respiratory failure: it is recognized as an essential therapy, especially in acute exacerbations and in the long-term treatment of chronic obstructive and restrictive diseases [2] (Table 73.2).

Although long-term NIV patients are a very heterogeneous population, they share a number of characteristics: they often have different comorbidities (most often cardiovascular, cerebrovascular, or neurological disorders), they are increasingly overweight or obese [3], and the average age of this population is increasing [4]. Mild or moderate cognitive impairment can coexist with the underlying pathology such as severe COPD, neuromuscular disease (NMD), and chronic brain injury. The follow-up of NIV patients must therefore address all of these conditions. The most common side effects of NIV are nasal bridge or face ulceration, gastric distension, ocular irritation, dryness, and oronasal congestion, risk of aspiration pneumonia, and barotrauma with pneumothorax [5]. Proper mask identification, good educational approach, and patient comfort are key factors for patient fit and success of NIV [6]. Claustrophobia, poor patient cooperation, patient discomfort defined as a sensation associated with excessive air pressure, interface air leaks, and asynchrony can lead the patient to frequently remove the mask and refuse NIV treatment [7–9]. Healthcare professionals should seek to optimize proper mask use to optimize patient comfort by promoting successful NIV treatment, choosing an appropriate interface, and motivating the patient [10]. Adaptation and tolerability to ventilation are in fact closely related with the ability of the medical–nursing staff to

Table 73.1 Ventilator modes available on most devices used for home noninvasive ventilation

Abbreviation	Mode
CPAP	Continuous positive airway pressure
PSV-S	Pressure support ventilation, spontaneous mode
PSV-T	Pressure support ventilation, spontaneous/timed mode
PSV-T	Pressure support ventilation timed mode
(a) PCV	(assisted) Pressure control ventilation
Automated modes	Intelligent and Average volume-assured pressure support ventilation
IVAPS, AVAPS	

Table 73.2 Most frequent indications for long-term ventilation

1. Obstructive lung disorders
• Chronic obstructive pulmonary disease
• Overlap syndrome
• Bronchiolitis obliterans
• Cystic fibrosis
• Diffuse bronchiectasis
2. Sleep-related breathing disorders
• Obstructive sleep apnea
• Central sleep apnea
• Obesity hypoventilation syndrome
3. Restrictive chest wall and parenchymal disorders other than obesity hypoventilation
• Restrictive pleural diseases
• Sequalae of tuberculosis and/or thoracoplasty and/or thoracic surgery for cancer
• Chest trauma
• Ankylosing spondylitis
• Kyphoscoliosis and other chest wall deformities
4. Neuromuscular disorders
• Muscular dystrophies
• Amyotrophic lateral sclerosis
• Myasthenia gravis
• Spinal muscular atrophy

guide, motivate, and "accompany" the patient's treatment. As with any medical intervention, the skill and competence of the operator is the key to a successful outcome. NIV is also applied during sleep and therefore a good knowledge of the physiology of sleep by the medical staff is important [11]. Chronic respiratory failure causes reduced health-related quality of life (HRQoL) and adverse outcomes. HRQoL is defined as "the functional effect of a disease and subsequent therapy on a patient, as perceived by the patient himself". It is an important outcome measure in patients with chronic respiratory failure. These patients indeed suffer from physical, psychological, and social limitations in daily life [12].

Long-term mechanical ventilation, in addition to improving respiratory failure, optimizes the use of medical care and, most importantly for patients, improves HRQoL [13]. For this reason, HRQoL measurements are important tools for quality control, therapy optimization, and even prediction of NIV results.

Questionnaires are the most common form of HRQoL assessment in clinical trials of NIV. Disease- or condition-specific questionnaires are hypothesized to be more sensitive to changes than general quality-of-life questionnaires and, therefore, are more appropriate for clinical trials where specific therapeutic interventions are evaluated [14]. Indeed, general health quality surveys may be inaccurate in specific disease groups [12]. One of the most efficient questionnaires designed for this purpose, to date, is the SRI Questionnaire (Severe Respiratory Insufficiency), a multimode instrument with high psychometric properties, specifically designed to

evaluate the HRQoL in patients who fight chronic respiratory conditions. The SRI comprises 7 subscales with 49 items covering the following aspects: respiratory disorders, physical functioning, sleep related symptoms, social relationships, anxiety, psychological well-being, and social functioning. SRI is available in many languages and is widely validated for various disorders such as chronic obstructive pulmonary disease, restrictive chest disorders, neuromuscular disorders, and obesity hypoventilation syndrome [15]. Studies have also shown that HRQoL differs markedly in patients with chronic respiratory failure from a variety of causes [16]. In a multicenter study [17], the benefits and burdens associated with home mechanical ventilation in various conditions at 1 month and 1 year after the start of NIV were compared using the Medical Outcome Study 36-Item Short-form Health Survey (SF-36; general HRQoL) and the SRI (condition-specific HRQoL). Overall improvements in HRQoL, and changes in individual HRQoL specific domains regarding the SRI subscales differed significantly depending on the underlying disease. Despite the improvement in respiratory disorder scores in all patients, improvements in physical functioning and social functioning scores were observed only in patients with chronic obstructive pulmonary disease (COPD) and restrictive thoracic disorders (RTD); less clearly, in patients with obesity hypoventilation syndrome (OHS), while no improvement was observed in neuromuscular disease (NMD), probably due to the detriment that accompanies this respiratory dysfunction. Conversely, improvements in sleep-associated symptom scores were more impressive in patients with NMD and OHS, while improvements in psychological well-being scores were more pronounced in patients with COPD and RTD. Additionally, all patients showed significant improvements in anxiety scores. This clearly indicates that the disease responsible for the development of respiratory failure has a major impact on changes in specific aspects of HRQoL after the establishment of NIV. A recent study [18] described the effect of home mechanical ventilation on HRQoL in a group of patients with chronic respiratory diseases using the SRI questionnaire. HRQoL was assessed at baseline and 6 months after initiation of home mechanical ventilation. The results of this study show that the HRQL subscales that were most noticeably improved were those related to breathing disorders and sleep-associated symptoms, which are in fact the primary goals of long-term mechanical ventilation. The anxiety subscales also showed significant improvement, probably because of the improvement of the previous two scales. Social relationships and social functioning did not show any changes, suggesting that these subscales are influenced by more complex disease attributes and are not exclusively related to respiratory symptoms. The change in physical functioning also showed no significant overall improvement, which is understandable since several patient groups had stable or progressive neuromuscular impairment. These results suggest that the improvement in HRQoL is independent of classic markers of chronic respiratory failure severity (i.e., baseline lung function, arterial blood gas value, and hours of need for ventilation) or of the interface used for ventilation. It mainly depends on the type of disease causing chronic respiratory failure, the timing of onset of NIV. In acute versus elective, from the initial HRQoL (low initial HRQoL) values, one can expect the maximum benefit; neuromuscular patients can expect to

preserve overall HRQoL despite ongoing neurological deterioration [19]. A recent study tested and clinically evaluated the psychometric properties of an SRI App designed and developed for mobile electronic devices. The time taken to fill in the SRI was compared to both the classic paper SRI and the SRI App groups. The main results are the SRI app is a practical tool, well accepted by patients with severe chronic respiratory failure; the usage of the SRI app completely prevents the occurrence of missing values [19]. Other specific questionnaires are the Maugeri Respiratory Failure Questionnaire (MRF), the San George Respiratory Questionnaire (SGRQ), and the Chronic Respiratory Disease Questionnaire (CRQ) [13]. The St. George's Respiratory Questionnaire (SGRQ) is the most widely applied respiratory disease-specific HRQoL assessment questionnaire, and its use has been validated in various respiratory disorders, including COPD, idiopathic pulmonary fibrosis, and pulmonary tuberculosis [20]. Compared to existing generic quality-of-life questionnaires such as (SF-36) and disease-specific questionnaires such as the SGRQ respiratory questionnaire and CRQ, both MRF and SRI have proven to be valid and reliable and have discriminatory characteristics, better evaluative and predictive than other questionnaires [18]. The MRF questionnaire was designed to identify a primary set of elements that can characterize the impairment of health in chronic respiratory failure. Main component analysis identified three specific factors: "daily activities," "cognitive function," and "disability." One study characterized two areas of health damage in chronic respiratory failure: effects of impaired cognitive function on daily life and a sense of disability. A sense of general disability appears to be a specific component of ill health in severe respiratory failure. The invalidity component reflected impaired mood very strongly and correlated with PaO_2. This latter correlation appears too strong to have occurred by chance and may be due to an effect of hypoxia on activity, leading to social isolation and dependency upon others [21].

Among the indications of NIV, a wide chapter is occupied by sleep-disordered breathing. Obstructive sleep apnea (OSA) is a respiratory disorder characterized by intermittent, partial, or complete obstruction of the upper airways during sleep, associated with recurrent arousals, intermittent hypoxemia, increased sympathetic tone, systemic changes such as inflammation and oxidative stress that are the basis of clinical phenomena and a greater risk for various diseases, including cardiovascular, neurological, metabolic, and oncological ones. OSA patients may present with several typical symptoms, including habitual and intermittent snoring, nocturia, excessive night sweating, unrefreshing sleep, waking headache, fatigue, excessive daytime sleepiness (EDS), and neuro-cognitive impairment. These symptoms often have a negative impact on mood and HRQoL [22].

There are several options for OSA treatment such as lifestyle recommendations, mandibular advancement devices, and surgical procedures. However, continuous positive airway pressure (CPAP) is the most effective and commonly used treatment for moderate-to-severe OSA or mild OSA with comorbidities [23]. It is well established that CPAP use improves sleep quality, oxygen saturation, daytime sleepiness, blood pressure, cardiovascular risk, mood, and HRQoL. For most OSA patients, a reduction in their HRQoL is due to symptoms such as EDS, fatigue, poor sleep

quality, and problems sharing a bedroom with the bed partner [24]. Indeed, untreated patients with OSA, regardless of severity, have a worse quality of life than the general population [25]. The consequences of sleep-related breathing disorders on HRQoL may be considered as a multifactorial phenomenon, including not only sleep disruption, sleepiness and obesity, but also mood and psychosocial factors, which are all implicated in different aspects of physical and mental health perception. The beneficial effect of CPAP on parameters such as sleepiness, fatigue, irritability, impaired memory and concentration partly explained the improvement in HRQoL. The expectation of improved HRQoL may motivate patients to undergo tests and treatments for sleep apnea [26]. The impact of CPAP treatment on many aspects related to perceived HRQoL, such as mood, psychological well-being, self-control, energy, and mental and physical health, has been investigated by numerous studies and still needs further investigation. In one study, the relationship between gender, somnolence, and CPAP adherence was explored by analyzing HRQoL in OSA patients at the first visit and after CPAP treatment [27]. Patients' HRQoL was assessed at the first visit and at the first follow-up after 2–9 months of CPAP therapy. This study, in agreement with previous studies, shows the improvement of HRQoL in OSA patients as an effect of CPAP treatment. Gender comparison showed higher HRQoL scores in males at first visit and follow-up, despite more significant improvement with CPAP in females. At the first visit, patients with EDS had worse HRQoL than those without, regardless of the severity of OSA. At the time of follow-up, the EDS group improved their perceived well-being reaching similar values to the non-EDS group who had a satisfactory HRQoL level at the first visit. This study shows that CPAP treatment can lead to an overall increase in perceived well-being. Patients with perceived sleepiness report a worse perceived HRQoL than patients without EDS, but after CPAP treatment, the HRQoL scores of both groups are similar. Furthermore, these results confirm that CPAP use $\geq$4 h/night provides a more significant improvement in overall HRQoL and in all specific dimensions analyzed (mood, anxiety, psychological well-being, self-control, mental and physical health, energy, EDS). Other studies have analyzed the effect of CPAP therapy on HRQoL by pointing out significant improvement with CPAP treatment in domains such as vitality, social functioning, mental health, and daily functioning or depressive symptoms [27]. CPAP therapy, therefore, improves symptoms and perceived HRQoL. However, patients have variable responses and adaptations to treatment: some patients find immediate improvement in symptoms and a renewed dynamism that makes acceptance of treatment relatively easy, others suffer side effects such as skin abrasions or dry nose and mouth, or do not experience any noticeable improvement in health or HRQoL, which can make adaptation to therapy more difficult [28].

A previous prospective observational study [29] has reported the immediate effect of CPAP titration on perceived health related quality of life. Patients' HRQoL was assessed at the first visit, and after CPAP titration performed using auto-adjusting CPAP units. The results of this study showed that HRQoL was impaired at first visit and CPAP titration was followed by a further improvement in HRQoL irrespective of age, BMI, OSA severity, nocturnal hypoxia, and EDS.

Symptoms of reduced sleepiness and improvement in HRQoL following CPAP treatment were predominantly assessed in the middle-aged population. The efficacy of CPAP therapy in the elderly population and its relationship with sleepiness, HRQoL, mood, and neuro-cognitive function is less well known and investigated. The elderly population (≥65 years old) reported different clinical characteristics compared to middle-aged patients with OSA. Elderly patients have more comorbidities and have differences in sleepiness and cognitive function, both of which are relevant findings. The main findings of a meta-analysis of randomized controlled trials that included elderly patients with OSA [30] are as follows: in elderly patients with OSA, CPAP therapy leads to a clinically significant improvement in sleepiness, measured as changes in EDS, improves HRQoL in domains such as hypersomnolence, daytime symptoms, nocturnal symptoms, emotions and social interaction, and results in an improvement in the domain of depression, but not of anxiety. Furthermore, CPAP therapy is associated with a slight improvement in neurocognitive function in the cognitive domains of memory, less on vigilance and executive function. In general, the lack of normalization of neurobehavioral function after CPAP treatment is due to milder disease, inadequate CPAP use, or irreversible damage to specific brain regions. This dissociation in improvement in different cognitive domains may reflect the temporal difference in the restoration of cognitive function with treatment, which may correspond to improvements in the structure or function of brain regions associated with performance in these tasks. It is also likely that these residual impairments are the result of comorbidities [31]. The aspect of adherence to CPAP therapy represents the key point in the management of the OSA patient. Epidemiological data show that on average 25% of patients with OSA do not accept CPAP treatment and, of those who undertake the therapy, only 30–60% can be considered adherent [32]. The experiences and perceptions on one's own health, on the impact of OSA, and the perceived effectiveness of the treatment fix the coping strategies, those cognitive and behavioral efforts that the patient will adopt to cope with stressful events, real or perceived as such [28].

73.2 Conclusions

NIV is increasingly characterized as an essential support in the treatment of respiratory failure and its use is expanding. The availability of a wide range of fans and interfaces allows the effective application of NIV with different modalities that can be managed in a very flexible manner in multiple pathological conditions. NIV appears to be free from serious complications or adverse reactions. Key factors for the success of NIV are the careful selection of patients and the presence of well-defined application protocols. Improving the health-related quality of life is an important goal in the management of patients with chronic respiratory failure on noninvasive home ventilation, and HRQoL measurements are important tools for quality control, therapy optimization, and prediction of results of the therapy. If correctly applied, it can improve the long-term prognosis, leading to a progressive improvement. Furthermore, its advantages such as ease of application and removal,

intermittent application with the possibility of suspension at any time, the preservation of the defense mechanisms of the airways, and the reduction of the need for sedation are all factors that lead to an objective improvement in quality of life of the treated patients.

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Use of Noninvasive Mechanical Ventilation in Older Patients

74

Sven Stieglitz

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Abbreviations

ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
BMI	Body mass index
COPD	Chronic obstructive pulmonary disease
DRM	Disease-related malnutrition
FEV1	Forced expiratory volume in 1 s
ICU	Intensive care unit
IPF	Idiopathic lung fibrosis
NIV	Noninvasive ventilation
VC	Vital capacity

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_74

74.1 Introduction

The population worldwide is expected to increase by approximately 40% by the year 2050. This will lead to a global population of 10 billion persons. By 2050, 1.5 billion persons will be aged 65 or older which is a common definition of the elderly. Even now, nearly 50% of patients admitted to intensive care units (ICU) are aged 65 older.

Common issues in the treatment of the elderly are multimorbidity with polypharmacy and frailty. Additionally, activities of daily life are impaired often by cognitive and gait disturbances, hearing loss, visual impairment, edentulism and incontinence [1]. Frailty is characterized by sarcopenia which leads to muscle weakness, exhaustion and slowing of voluntary muscle functions. This reduces physical activity of aged persons which further aggravates the loss of muscle mass. Decreased gait velocity is associated with limited mobility, community participation, cognitive decline and increased risk of falls [2]. Often, frailty is accompanied by fatigue. Another feature of frailty is the reduction of resilience which, in turn, increases the susceptibility for stressors such as infections [3]. Though there is in general a trend towards deterioration, frailty may be improved by exercise and supportive measures. Sarcopenia should not be confused with malnutrition, which is also common in aged people. Disease-related malnutrition (DRM) in people older than 65 years is defined by a body mass index BMI <20 kg/m^2 and a weight loss >5% within 3 months. An albumin serum concentration <30 g/L is a marker for malnutrition. Sarcopenia may be assessed by measurement of hand grip. Additionally, the SARC-F symptom score may predict persons at risk for sarcopenia [4].

Symptoms may be different in the elderly. Therefore, pneumonia may be presented without fever. Furthermore, another important point is the changing perception of symptoms with age. For example, symptoms may be complained about with delay or even be misinterpreted (e.g., complaining of pain instead of dyspnoea). Additionally, the threshold for pain and dyspnoea may be increased in the elderly. Notably, regarding dyspnoea a severely impaired agility (e.g. wheelchair dependent mobility) disguises the severity of dyspnoea because of the lack of physical exertion.

Also, a neurological deterioration is typical for older patients in acute illness. Older patients with pneumonia may present with delirium as a leading symptom [5]. The CRB-65 index (confusion, respiratory rate, blood pressure, age above 65 years) for ambulant acquired pneumonia takes this into account.

74.2 Gerontopneumology

In pulmonology, three main factors characterize aged patients. Firstly, there is a regular decline of lung function by age consisting of a reduced vital capacity VC, FEV1, diffusion capacity and respiratory drive. Weakness of respiratory muscles result not only in a reduced inspiratory strength, which make the elder patients susceptible for respiratory failure, but also in expiratory muscle weakness, which

reduces the cough effectivity. This is one explanation for the increasing incidence of pneumonia in the aged.

Secondly, some changes are typical for the elderly but not always evident. These factors include dysphagia and slow down gait. Immunosenescence is another characteristic which describes age-related changes of the immune system resulting in an increased susceptibility to infections. The main factors are thymus involution as well as functional and structural loss of bone marrow, resulting in a loss of T-cells while B-cells are reduced in men only. These changes may be summarized as the twilight of immunity [6].

Thirdly, there is a typical increase of pulmonary diseases by age with frequently poor outcome. Examples for diseases are pneumonia, COPD and sleep apnoea. Acute and chronic lung diseases often are more severe in the aged [7]. End stage lung diseases are not exclusively seen in geriatric patients but most of the patients show geriatric characteristics (e.g. nursing home, care level). Some diseases such as idiopathic pulmonary fibrosis (IPF) only occur in aged persons. Moreover, frailty and sarcopenia are not only hallmarks of geriatric patients but also are common in pulmonary diseases such as COPD, IPF and tuberculosis. In lung disease, frailty has been realized to be an independent risk factor of poor outcome. Many patients listed for lung transplantation [8] show frailty which may be fully reversible after transplantation. Sarcopenia also represents an overlap between pneumology and gerontology. Examples for pulmonary diseases with common sarcopenia are tuberculosis, chronic obstructive pulmonary disease COPD [9] and IPF [10]. Finally, gait speed is not only a functional measurement in geriatric patients but may also assess the functional status of COPD patients [11].

Dyspnoea is the leading symptom in many pulmonary diseases. Owing to multimorbidity in the aged, other diseases with dyspnoea as a leading cause contribute to respiratory failure. Common examples are heart failure, pleural effusions, anaemia and lunge artery embolism (Fig. 74.1).

74.3 Acute Respiratory Failure in Older Patients

There has been an increasing demand for emergency department ED services in the western world. In England, the number of ED visits by older patients increased nearly by 50% in the past decade. In the Netherlands, 25% of the patients in contact with an ED were aged 65 years or older [12]. The need for hospitalization and an unfavourable outcome is high in this cohort, where do-not-intubate/do-not resuscitate status is common and led to concepts for developing specialized geriatric ED.

Acute respiratory failure is common in elderly patients. In emergency departments, the main causes of ARF in the elderly are cardiogenic pulmonary oedema (43%), community-acquired pneumonia (35%), acute exacerbation of chronic respiratory disease (32%), pulmonary embolism (18%) and acute asthma (3%). Typically for the aged, approximately 50% had more than two diagnoses [13]. Elderly patients can recover from an acute respiratory failure completely if adequate support is provided, although some may require long-term ventilatory assistance.

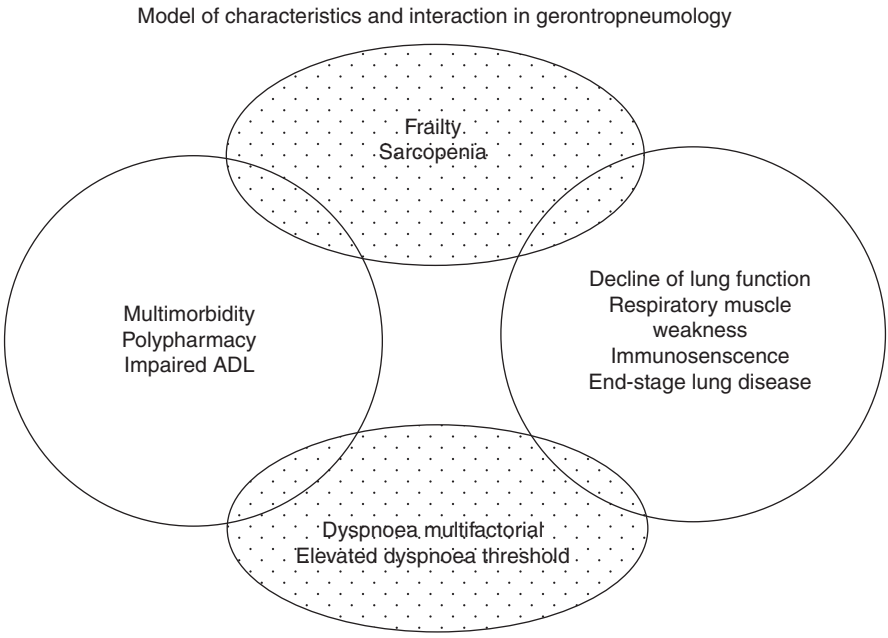

Fig. 74.1 Summarizes the interaction between gerontology and pneumology

Noninvasive ventilation may be a good alternative to intubation and analgesia since the complications (delirium, critical illness polyneuropathy, swallowing disorder, ventilator-associated pneumonia) of invasive ventilation in the elderly may be dramatic and depends on geriatric factors (plasma albumin) as well as on pulmonary factors and level of multiorgan failure. Diaphragm atrophy during invasive mechanical ventilation has recently been recognized to have an important impact on clinical outcome [14]. This will probably be more pronounced in elderly patients suffering from sarcopenia.

Risk factors for adverse ICU outcome include multimorbidity and frailty. Depending on the specialization of ICU, short-term hospital survival rates are approximately 70%. The severity of illness at ICU admission as measured by scoring systems such as the Acute and Chronic Health Evaluation II (APACHE II) has a higher impact on mortality than the age of the patients.

Key factors for respiratory failure and sepsis in elderly are dementia/delirium, decreased gag and cough reflex, malnutrition, immunosenescence, reduced organ function, reduced cardiopulmonary reserve and polypharmacy.

Nearly two thirds of all sepsis cases occur in the elderly, and 80% of the deaths by sepsis are in this cohort. This makes sepsis a major disease in geriatric patients. Sepsis, in turn, is a major cause for developing acute respiratory distress ARDS in the elderly, and the mortality of ARDS is doubled compared to younger patients. Weaning from the respirator and discharge from the ICU is more difficult and takes more time for elderly patients.

74.4 Chronic Respiratory Failure in Older Patients

Common diseases leading to *chronic respiratory failure* in the elderly are COPD, obesity hypoventilation syndrome, scoliosis, end-stage lung fibrosis, and neuromuscular disorders such as amyotrophic lateral sclerosis ALS. Often acute diseases such as pulmonary oedema, pleural effusions and pneumonia lead to an acute deterioration of the chronic respiratory failure.

The acute failure may be distinguished from chronic respiratory failure by the elevated bicarbonate in the blood gas analysis. In the elderly, the common prescription of diuretics due to heart failure also causes an elevated serum bicarbonate leading to a metabolic alkalosis. Both, chronic heart failure as well as metabolic alkalosis cause central sleep apnoea.

74.5 Discussion and Analysis: Noninvasive Ventilation of Elderly Patients

Turbine-driven portable ventilators are superior to classical ICU ventilators regarding NIV. The reasons are higher flow delivery and optimized trigger algorithm. Furthermore, the miniaturization of turbine-driven ventilators led to liberalization from the central gas supply which is provided at an ICU only. As a result, also the treatment of respiratory organ failure was no longer restricted to the environment of an ICU. In fact, the success of NIV was also achieved by the ability to ventilate in different areas and different situations all over the hospital: emergency room, recovery room after surgery, endoscopic unit with bronchoscopy, ICU, sleep laboratory and pulmonology ward.

Nevertheless, the ICU is a well-defined ward with staff that is experienced in ventilation and airway management, but the situation outside the ICU is entirely different. Therefore, a specialized NIV team is strongly recommended to ensure the correct management of NIV all over the hospital.

Remarkably, the acceptance for positive pressure therapies such as CPAP in sleep apnoea is higher in older patients compared to younger patients. Furthermore, a reduction of mortality due to CPAP treatment in sleep apnoea has been demonstrated only in elderly patients. NIV is the ventilatory support of first choice for aged patients when physicians consider the correct indication. NIV may also be helpful to avoid ICU admittance of the elderly, which may be inadequate regarding their needs.

Some age-related remarks must be considered:

Firstly, starting NIV in the elderly requires a quiet setting without activity. The NIV specialized doctor or therapist plays a key role in initiating NIV, setting not only the ventilator parameters but also creating an atmosphere of trust and providing support. Elderly patients will need more time to understand detailed explanations of NIV. One should be aware that hearing loss is common and that correct understanding and interpretation of the words listened to will take more time in the aged.

Secondly, edentulousness is common in aged patients. This aggravates cachexia, sarcopenia, leads to mandibular atrophy and sunken cheeks. Successful NIV requires a good mask seal and airway patency. The presence of dentures helps maintain the shape of the facial soft tissues, and thus improves the mask seal. Additionally, reduction in muscle tone by sedation reduces the air space in the oropharynx, and leads to a posterior displacement of the tongue, soft palate and epiglottis which tends to close the airway. Resorption of alveolar bone and elevation of the tongue in the oral cavity in edentulous patients leads to a relative tongue enlargement. When dentures are removed, the tongue spreads laterally, compromising the patency of the airways. In fact, dentures-in improves the effectivity of NIV in edentulousness patients [15].

Thirdly, the management of delirium (inattention, memory impairment, disorientation, disorganized thinking, sleep changes, hyperactive or hypoactive motor activity changes) and dementia (cognitive impairment) is essential for NIV success. Dementia is the fifth leading cause of death in patients over the age of 65. Urinary tract infections and (aspiration) pneumonia are major causes of death of patients with dementia. The differential diagnosis between delirium and dementia may be difficult in the acute setting. A simple clinical estimation can be done: Patients with dementia still will be able to count backwards while patients with delirium will not. Delirium usually is fully reversible but also the symptoms of dementia may present with fluctuation. Delirium is extremely common in hospitalized older adults. One third of general medical patients who are 70 years of age or older have delirium; the condition is present in half of these patients on admission and develops during hospitalization in the other half [16]. Delirium is a strong factor for NIV failure [17].

Finally, the clinical decision for NIV should not solely be made on capillary blood gas analysis. Capillary blood gas analysis shows values for PO_2 that are approximately 6 mmHg lower compared to arterial blood gas analysis. This may be much more pronounced in heart failure because of increased peripheral oxygen extraction. Since heart failure is common (up to 10% systolic heart failure above 80 years), low capillary PO_2 is a common finding in the elderly. This must be considered to avoid making the wrong decision.

Though the number of clinical trials in aged patients is limited, the evidence for beneficial NIV use in the elderly is striking. In hypercapnic respiratory failure, in patients >75 years, NIV avoids the need for endotracheal intubation significantly. Furthermore, the mortality is lower with NIV compared to standard medical care or intubation [18]. Even in very old patients (>80 years) with a heterogenous type of respiratory failure (COPD, cardiac oedema, hypoxemic failure) NIV may be performed successfully. In a recent study, 75% of these patients could be discharged home [19]. NIV failure should be managed carefully depending on the will of the patients to undergo either the escalating therapy or the palliative care [20].

74.6 Conclusion

Noninvasive mechanical ventilation constitutes a successful therapeutic tool in the elderly because, similar to in younger patients, it is able to prevent endotracheal intubation in a wide range of acute conditions; moreover, this ventilator technique is largely applied in the elderly in whom invasive mechanical ventilation is considered inappropriate.

Domiciliary noninvasive ventilation (NIV) in chronic respiratory failure patients has been largely used; however, data from older people is scarce.

Key Major Recommendations

- NIV is the ventilatory strategy of first choice in a wide spectrum of indications in elderly patients.
- A dedicated NIV team should determine the correct NIV equipment as well as starting the therapy together with the patient.
- Treating elderly patients requires more time and more patience for therapists and doctors.
- Delirium and dementia are important obstacles for a successful NIV treatment.
- Comorbidities must be considered when treating respiratory failure in elderly.

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

75

Aksu Funda, Aksu Kurtuluş, and A. M. Esquinas

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Abbreviations

6-MWD	6-minute walking distance
BE	Base excess
BMI	Body mass index
CHRF	Chronic hypercapnic respiratory failure
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
FEV1	Forced expiratory volume in 1 s
Hb	Hemoglobin
HI-NIV	High-intensity NIV
IPAP	Inspiratory positive airway pressure

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_75

LI-NIV	Low-intensity NIV
NIV	Noninvasive ventilation
OHS	Obesity hypoventilation syndrome
P0.1	Mouth occlusion pressure at 100 ms during quiet breathing
$PaCO_2$	Arterial carbon dioxide tension
PaO_2	Arterial oxygen tension
PI_{max}	Maximal inspiratory mouth pressure
RTD	Restrictive thoracic disorders
RV	Residual volume
SRI	Severe respiratory insufficiency questionnaire
SRI-SS	SRI summary score
TLC	Total lung capacity
VC	Vital capacity

75.1 Introduction

Noninvasive ventilation (NIV) use has increased significantly over the past two decades, and it has become an integral part of ventilator support in the management of patients with either acute or chronic respiratory failure. NIV provides ventilation support without the need for an invasive artificial airway (endotracheal tube or tracheostomy tube) and supports the respiratory muscle pump by both reducing the work of breathing and improving tidal volume. With its flexibility, NIV is a valuable complement to patient management [1].

The availability of NIV techniques has led to a large increase in the number of patients treated with mechanical ventilation at home for chronic hypercapnic respiratory failure (CHRF). NIV is an established therapy for severe chronic obstructive pulmonary disease (COPD) and restrictive thoracic disorders (RTD) with CHRF. A wide variety of RTD, including chest wall deformities, kyphoscoliosis, spinal cord injury, in addition to progressive neuromuscular conditions such as amyotrophic lateral sclerosis and myopathic/neuropathic disorders, and obesity hypoventilation syndrome (OHS) have been successfully treated with NIV [2]. Prognostic parameters in patients with CHRF receiving NIV therapy will be discussed in this chapter.

75.2 Chronic Obstructive Pulmonary Disease

Patients with severe COPD often develop CHRF with disabling symptoms and poor survival. COPD with concomitant CHRF is one of the leading indications for long-term NIV. Patients suffering from COPD who present with exacerbation and hypercapnic respiratory failure are the group most likely to be successfully treated with NIV supported by a strong evidence base. In the case of COPD exacerbations, work

of breathing increases, and it may exceed the capacity of patient to ventilate adequately. NIV offloads respiratory muscles, reduces rate of respiration and work of the diaphragm, and increases tidal volume. This assistance provided by NIV effectively improves oxygenation, reduces hypercapnia, and ameliorates dyspnea [3]. However, available data are still not fully conclusive regarding the long-term benefits of NIV in severe COPD. Although there is consensus that patients with CHRF are at high risk of recurrent hospitalization and death, the role of NIV in long-term survival in these patients remains controversial [4].

With the demonstration of the relationship of hypercapnia with mortality in patients with severe COPD and hypoxemia, research has intensified on the question of whether NIV is beneficial in patients with severe COPD other than exacerbations [5]. Evidence did not support any difference in the rate of acute exacerbations, hospitalization, intubations, and mortality in patients with stable severe COPD when comparing treatment with NIV and long-term supplemental oxygen therapy [6]. The addition of NIV (with back-up rate) to long-term oxygen therapy in patients with stable COPD and chronic hypercapnia showed a reduction in arterial carbon dioxide tension ($PaCO_2$) as the follow-up time of NIV is prolonged, compared to supplemental oxygen treatment alone. However, no difference in hospital or intensive care unit admissions was noted between the two treatment modalities in these patients [7].

Using long-term nocturnal NIV to treat CHRF in COPD has also been controversial due to conflicting evidence. Nocturnal NIV use in severe COPD patients has been observed to improve sleep quality and sleep-related hypercapnia compared to supplemental oxygen alone, but lead to no change in daytime CO_2 levels or forced expiratory volume in 1 s (FEV_1). A decrease was observed in the quality of life in patients who were administered nocturnal NIV plus supplemental oxygen. A significant survival advantage in favor of nocturnal NIV was not recorded in unadjusted analysis [8]. When the role of high levels of pressure support was examined in stable severe COPD patients, it was seen that higher inspiratory pressures were associated with larger tidal volumes and decreased respiratory rates unloading the respiratory muscles. Accordingly, higher inspiratory pressures in NIV were associated with improvements in both arterial oxygen tension (PaO_2) and $PaCO_2$ levels, FEV_1 values, 6-min walking distance (6-MWD), and dyspnea scores in severe COPD patients [9, 10].

Although the role of NIV on long-term survival in CHRF remains a matter of debate, CHRF and COPD have become an important indication for NIV at home, as these patients are at high risk for recurrent hospitalization and death. In a study conducted in patients with COPD discharged from the hospital receiving NIV, overall mortality was reported to be 44.7% with 1-year, 2-year, and 5-year survival rates of 84.0% (95% confidence interval [CI], 69.3 to 96.3%), 65.3% (95% CI, 49.5% to 82.8%); and 26.4% (95% CI, 16.5% to 42.2%), respectively. According to univariate analyses in the long-term follow-up of COPD patients with CHRF receiving NIV, the parameters reported to be associated with prognosis are age, nutritional

status as assessed by body mass index (BMI), hemoglobin (Hb), FEV_1, specific airway resistance, hyperinflation assessed by residual volume (RV)/total lung capacity (TLC) ratio, pH, and base excess (BE). On the contrary, mean daily ventilator use (hours per day), the levels of inspiratory positive airway pressure (IPAP), expiratory positive airway pressure, or respiratory frequency, comorbidities, and medical treatment were not associated with prognosis. However, according to multivariate analysis, only increased age, lower BMI, increased RV/TLC, and increased BE are independent predictors of prognosis. Favorable alteration in these predictors in patients at risk (increase in BMI in patients with BMI <25 kg/m^2, 4% reduction in RV/TLC ratio in patients with RV/TLC ratio ≥73%, and ≥50% reduction in BE in patients with baseline BE ≥9 mmol/L) were associated with improved survival [11].

The IPAP levels used in the studies were thought to be too low to successfully reduce the increased $PaCO_2$ and therefore failed to improve outcome in patients. Based on this idea, the superiority of high-intensity NIV (HI-NIV) over low-intensity NIV (LI-NIV) was investigated. It was reported that HI-NIV (using controlled ventilation with mean inspiratory pressures of 28.6 ± 1.9 mbar) resulted in significant improvements in exercise-related dyspnea, daytime $PaCO_2$, FEV_1, vital capacity (VC), and the severe respiratory insufficiency questionnaire (SRI) summary score (SRI-SS) compared to LI-NIV (using assisted ventilation with mean inspiratory pressures of 14.6 ± 0.8 mbar) [12]. Another report again noted that adding long-term NIV to standard therapy improves survival of patients with hypercapnic, stable COPD when NIV is targeted to reduce hypercapnia [13].

Regarding laboratory parameters, elevated Hb levels were associated with long-term survival in patients with COPD and CHRF treated with NIV and long-term oxygen therapy. Hb levels greater than 14.3 g/dL in females and 15.1 g/dL in males yielded the highest discriminative value for survival prediction [14]. A prospective observational study conducted in patients with severe persistent hypercapnic COPD revealed that patients receiving NIV at high inspiratory pressure levels and showing high adherence to this therapy had better long-term survival compared to non-ventilated patients. Moreover, patients displaying more severe disease based on known risk factors seemed to benefit most from long-term NIV. According to this report, NIV is more effective independent of BMI but particularly in patients with lower age, $PaCO_2$, pH (<7.41), FEV_1 (<27.5%), and Hb (<13.8 g/dL) and higher BE (BE; > 8.9 mmol/L), leucocytes, and excessive hyperinflation (RV/TLC > 189.7% predicted) [15].

The relationship between functional parameters and prognosis in patients with CHRF receiving NIV has also been a subject of research. The 6-MWD is a strong predictor of long-term survival in the presence of CHRF and NIV in patients with COPD. Using 280 meters as cutoff, the hazard ratio was found to be 3.75 (95% confidence interval 2.24–6.38) and increasing 6-MWD was associated with stepwise improved survival [16].

Results of a meta-analysis evaluating the efficacy of long-term NIV revealed that $PaCO_2$ decreased significantly in patients receiving long-term NIV, but there was no

significant difference in mortality, PaO_2, acute exacerbation frequency, lung function, respiratory muscle functions, and exercise capacity. Subgroup analysis showed that NIV significantly improved survival in patients who received NIV mainly aimed at decreasing $PaCO_2$ [17].

75.3 Restrictive Thoracic Disorders

Patients with CHRF other than COPD are characterized by a restrictive ventilation pattern predominantly caused by decreased lung volumes either due to pathologies in lung parenchyma, pleura or chest wall deformities or due to neuromuscular disorders, decreased chest wall compliance, and impaired respiratory mechanics. In these patients, mechanisms such as impairment in lung mechanics or airway function, ventilation–perfusion mismatch, corruption of central ventilatory drive, or respiratory muscle fatigue may lead to hypercapnic respiratory failure. These patients are at high risk of death and hospitalization and NIV is a therapeutic option in them [2, 16].

Nocturnal $PaCO_2$ is the most important independent predictor of long-term survival in patients with RTD. Nocturnal $PaCO_2$ < 65.0 mmHg (75th percentile) is associated with higher overall survival, while daytime $PaCO_2$ is not an important prognostic factor. Therefore, nocturnal hypercapnia should be considered in evaluating patients with RTD and NIV and making decisions to initiate treatment. Although Hb levels < 131 g/L (25th percentile) and daily BE >11.0 mmol/L (75th percentile) are associated with worse prognosis, they are not independent predictors of reduced long-term survival in patients with RTD and NIV. Small differences in daily duration of NIV use and ventilator settings are not significantly associated with survival [18].

In a cohort of stable patients with CHRF diagnosed with COPD and non-COPD (OHS, restrictive disorders and neuromuscular disorders) and receiving home mechanical ventilation, survival rates (standard error) at 1, 2, and 3 years were 93.1 (1.7), 84.3 (2.4), and 78.4 (3.0)%, respectively. Survival rates were significantly lower in patients with COPD. In univariate analyses, BMI, leukocyte count, BE, FEV_1, and FEV_1/inspiratory vital capacity ratio were significantly associated with overall survival. In that study, the specific health-related quality of life was also assessed by the SRI questionnaire. In patients with CHRF treated with home mechanical ventilation, SRI scores was an independent predictor of long-term survival. Most of the SRI-SS and sub-scores were associated with prognosis, especially in patients without COPD who showed a favorable survival compared to COPD. In COPD, the predictive power of SRI for survival was lower compared to biological measures. Leukocyte count, FEV_1, and SRI-SS emerged as independent predictors of survival in the stepwise multivariate Cox regression analysis [19].

Meanwhile, the respiratory muscle function of the patients with CHRF receiving NIV, as assessed by mouth occlusion pressure, and their functional states, as assessed according to 6-MWD, were revealed to predict survival. In patients with CHRF due to various underlying disorders (COPD and restrictive disorders

including OHS, chest wall diseases, neuromuscular disorders, or interstitial lung disease) and current NIV therapy, survival was associated with age, BMI, lung function, leukocytes, Hb, maximal inspiratory mouth pressure (PI_{max}), mouth occlusion pressure at 100 ms during quiet breathing ($P_{0.1}$), and the ratio $P_{0.1}/PI_{max}$. Using multivariate Cox regression age, lower BMI and FEV_1, increased leukocytes and high $P_{0.1}/PI_{max}$ were identified as independent predictors of poor long-term survival. Furthermore, a reduction in $P_{0.1}/PI_{max}$ after initiation of NIV was associated with improved survival in patients with high baseline $P_{0.1}/PI_{max}$ [20]. In another study conducted in stable patients with CHRF and NIV comprising COPD, restrictive diseases and OHS overall mortality during 24.9 months was reported to be 22.9%. In univariate analyses, it was seen that 6-MWD, age, BMI, leukocytes, specific airway resistance, RV/TLC ratio, FEV_1, VC, and $P_{0.1}$ predicted long-term survival. In a stepwise multivariate Cox regression analysis, only 6-MWD, BMI, leukocyte count, and FEV_1 remained independent predictors of mortality. In COPD, 6-MWD was a strong predictor of long-term survival, using 280 m (or 58.6% previously) as cut-off and an increase in 6-MWD was associated with progressively improved survival. However, in patients with restrictive diseases, 6-MWD was only significantly associated with impaired survival when it was reduced to 204 m or less, while 6-MWD in OHS had no prognostic value [16].

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Part XV

NIMV in Neonates and Children

Noninvasive Ventilation in Children with Hypoxemic RF

76

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Abbreviations

ALI	Acute lung injury
ARDS	Acute respiratory distress syndrome
BIPAP	Bi-level positive airway pressure
CPAP	Continuous positive airway pressure
EPAP	Expiratory positive airway pressure
HFNC	High-flow nasal cannula
ICU	Intensive care unit
IMV	Invasive mechanical ventilation

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_76

IPAP	Inspiratory positive airway pressure
NIV	Noninvasive ventilation
$PaCO_2$	Arterial partial pressure of carbon dioxide
PaO_2	Arterial partial pressure of oxygen
PARDS	Pediatric acute respiratory distress syndrome
PEEP	Positive end-expiratory pressure
RF	Respiratory failure
WOB	Work of breathing

76.1 Introduction

Respiratory failure (RF) is defined as the non-functioning of the respiratory system in the processes of oxygenation, ventilation, or both. Gas exchange impairment can occur in two forms: hypoxemic RF and hypercapnic RF. The underlying mechanism of hypoxemic RF is gas diffusion impairment or a ventilation/perfusion mismatch in regional lung units. The blood gas assessment of a patient with hypoxemic RF will show an arterial partial pressure of oxygen (PaO_2) less than 60 mmHg and an arterial partial pressure of carbon dioxide ($PaCO_2$) that is either normal or a low value. By contrast, the $PaCO_2$ in hypercapnic RF is greater than 50 mmHg and the pH value is compatible with respiratory acidosis (<7.35) [1]. Hypoxemic or hypercarbic RF can develop acutely or chronically. The developmental periods of acute and chronic RF differ in terms of time. While acute RF develops within hours, chronic RF develops within days. Similarly, acute and chronic hypoxemic RF can also be difficult to distinguish with blood gas determinations alone. In this case, the patient's clinical characteristics and laboratory findings should be considered [2].

RF can be seen frequently in infants and small children due to their differences from adults in their anatomy and physiology. Lung and airway disease and neuromuscular disorders are typically responsible for the etiology of RF in children. Evaluation of the clinical features of children with RF includes many parameters, ranging from clinical signs and arterial blood gas evaluations to radiological findings [1, 2]. Hypoxemia can be analyzed in three categories (mild, moderate, and severe) according to clinical signs and blood gas assessments. The clinical signs in moderate hypoxemia (PaO_2 < 60 mmHg) include dyspnea, headaches, dizziness, fatigue, pallor, tachycardia, cardiac arrhythmias, hypertension, mood changes, ataxia, and tingling, whereas mild hypoxemia (PaO_2 < 80 mmHg) is characterized by no signs or a weakly depressed efficiency. By contrast, patients with severe hypoxemia (PaO_2 < 40 mmHg) exhibit cyanosis, hypotension, bradycardia, visual impairment, and neurologic symptoms (loss of consciousness, seizures, and coma) [2, 3]. Assessments of these parameters are used for planning of the most appropriate respiratory support treatment for the patient [1, 2].

RF is the most common reason for cardiopulmonary arrest in children; therefore, early recognition, monitoring, and respiratory management are of vital importance for patients with RF. Respiratory support is the mainstay of treatment and can be

Table 76.1 Indications for using noninvasive ventilation in children

Acute respiratory failure
Acute respiratory distress syndrome
Respiratory failure associated with chronic lung disease
Pulmonary edema secondary to renal or cardiac failure
Asthma
Bronchiolitis
Cystic fibrosis
Chest wall disorders
Neuromuscular and neurologic disorders
Respiratory tract obstructions (obstructive sleep apnea, tracheomalacia, and laryngomalacia)
Post-operative and post-extubation respiratory support

provided as three major types: supplemental oxygen, noninvasive ventilation (NIV), and invasive mechanical ventilation (IMV) [2]. IMV is applied through an endotracheal tube or tracheostomy, and IMV use has some disadvantages, such as the need for heavy sedation, the potential for laryngeal–tracheal injury, increased incidence of ventilator-associated pneumonia, and longer hospital and intensive care unit (ICU) stays [4, 5]. By contrast, NIV administration has better effects in eligible patients.

Negative or positive systems can be used in NIV application, but positive pressure NIV is more frequently used today. Therefore, this chapter will focus on positive pressure NIV application. In general, NIV is respiratory support applied with nasal prongs, nasal or face masks, or helmets; therefore, it avoids the implementation of endotracheal tubes or tracheostomies. NIV is generally used in pediatric emergency departments, in pediatric ICUs, or at home [6, 7]. Indications for NIV use are presented in Table 76.1.

The positive effects of NIV on the pulmonary system include a reduction in the work of breathing (WOB) and improvements in oxygenation and ventilation parameters. Furthermore, NIV allows for spontaneous breathing, protection of airway reflexes, speech, and enteral nutrition in appropriate cases [7]. In infants and children, NIV can be applied with three basic modes: continuous positive airway pressure (CPAP), bi-level positive airway pressure (BIPAP; also known as noninvasive positive pressure ventilation), and high-flow nasal cannula (HFNC) therapy [8, 9]. In this chapter, NIV use, including CPAP, BIPAP, and HFNC, in hypoxemic children will be discussed.

76.2 Discussion and Analysis of the Main Topic

CPAP, which was first applied in the neonatal population due to respiratory distress syndrome, has been included in treatment protocols since the 1970s. The goal of CPAP application in spontaneously breathing patients is to provide a constant distending pressure throughout the respiratory cycle to keep the airways open. The pulmonary mechanics of CPAP are as follows: prevention of alveolar collapse,

increase in the functional residual capacity, improvement in oxygenation, and reduction of the WOB [7, 10]. Generally, CPAP is used in small children with hypoxemic RF.

Intensive care and portable ventilators can be used to perform CPAP; however, an intensive care ventilator is also suitable in the follow-up of acute events or acute exacerbations of diseases in patients in ICUs or emergency departments. Currently, intensive care ventilators have a high degree of leak compensation and can be easily applied to children in conjunction with non-leak masks. Portable ventilators are also suitable for home use [7, 9]. CPAP is applied by continuous or variable flow. Examples of continuous-flow CPAPs are the bubble CPAP and the ventilator-derived CPAP (conventional CPAP), while variable-flow CPAPs include the infant flow drive and Benveniste gas-jet valve CPAPs [11]. All these CPAPs have advantages and disadvantages compared to each other. The user's experience is therefore important in this regard.

The interfaces used with CPAP are another important consideration with respect to both successful ventilation and to prevent possible adverse effects. An interface compatible with the patient's facial morphology reduces air leaks, thereby positively affecting the efficiency of CPAP. Currently, CPAP is performed with several interface types, such as nasal prongs, nasal cannulas, nasal masks, full-face (oronasal) masks, total-face masks, helmets, and mouthpieces. The nasal prong, nasal mask, and nasal cannula are mostly used in infants. For children, full-face masks, total-face masks, helmets, and mouthpieces can be preferred. Full-face masks and nasal masks may be good interface options in the acute cases, as the nasal mask does not cover the mouth. This can offer some comfort to those patients, as they can easily perform the actions of eating, speaking, and coughing. A nasal mask also causes less air swallowing. However, if the patient's mouth is open, this reduces the ventilation performance due to air leakage. For this reason, a total full-face mask is preferred, especially in patients with wounds around the nose and mouth [9].

No clear consensus exists among practitioners regarding the initial CPAP settings in children. Generally, pressure values from 4 to 8 cmH_2O in CPAP are regarded as safe because those values produce no serious side effects [4]. However, a point to remember is that the pressure levels used may vary depending on the indications and the severity of the disease. In children with low lung compliance, the pressure required may be in excess of 10 cmH_2O, so CPAP can only manage children who have sufficient central respiratory drive. If necessary, CPAP can be gradually increased to 10–12 cmH_2O to achieve the desired oxygen saturation values. When a sufficient CPAP level is reached, the respiratory parameters will begin to improve. The termination of CPAP use depends on the course of the disease and the improvement in the patient's clinical status. The weaning process can begin if the patient has a stable condition and the fraction of inspired oxygen is 0.4 and the CPAP level is 4–5 cmH_2O [10].

Compared to CPAP, BIPAP is a NIV method that applies higher pressure in inspiration (IPAP, inspiratory positive airway pressure) and lower pressure in expiration (EPAP, expiratory positive airway pressure). The IPAP and EPAP serve different purposes during the respiratory cycle: IPAP reduces the WOB, respiratory

rate, and $PaCO_2$, whereas EPAP decreases the intrinsic positive end-expiratory pressure (PEEP) and ameliorates oxygenation. The IPAP supporting the inspiratory phase is a value that can be set during the application. Conversely, the EPAP is a constant distending pressure that can be effective in both the inspiratory phase and the expiratory phase. The recommended pressure levels for the IPAP and EPAP are 4–30 cmH_2O and 4–20 cmH_2O, respectively [6].

Generally, BIPAP is used in children with hypoxic, hypercarbic RF; in cases where CPAP is not tolerated by the patient; or in patients who show no improvement in upper airway obstruction with CPAP. The two types of BIPAP that are effective on inspiration are the volume- and pressure-targeted BIPAPs. Pressure support promotes inspiration regardless of the patient's inspiratory effort, thereby increasing the patient's tidal volume and minute ventilation. By contrast, volume support may be achieved by the patient's inspiration effort. Poor interaction between the patient and the ventilator during mechanical ventilation may negatively affect the healing process [6, 9]. The interfaces used in BIPAP are the same as those used in CPAP.

Generally, BIPAP is used in four modes: spontaneous, spontaneous/timed, pressure control, and timed modes. The selection of an appropriate mode is made according to the patient's effort and underlying disease. The spontaneous mode, which is not preferred in children, is mostly used in adolescents with obesity hypoventilation and in children with sleep-disordered breathing where CPAP cannot be applied effectively. Similarly, the timed mode is not frequently used in children. In the spontaneous mode, the patient starts every breath; if the patient's breathing rate is below the back-up rate, the mode is activated [6].

In recent years, HFNC use has become increasingly common in both adult and pediatric patients. With HFNC, the patient receives warm, humidified high-flow oxygen. HFNC can be applied with a nasal cannula, thereby providing comfort to the patient. The HFNC functioning mechanism consists of three components: oxygenation, creation of a PEEP effect with high flow, and elimination of carbon dioxide from anatomical dead space. The positive effects of HFNC include improved mucociliary clearance, decreased inflammatory reactions and bronchoconstriction, and decreased airway resistance. The contribution to the patient is a reduction in tachypnea and the WOB [7, 10].

In children, the maximal HFNC flow rate is a controversial issue. Generally, the recommended flow rate is between 2 and 8 L/min, depending on the child's age. To be considered as high flow, the flow rates by age may be classified as follows: flow rate $\geq$1 L/min for the neonatal patients, flow rate $\geq$3 L/min for toddlers, and flow rate $\geq$5 L/min for older children [10, 11].

HFNC creates a positive distending pressure on the lungs; however, it is difficult to measure. Various methods have been attempted for measurement (e.g., pressure detection in the nasopharynx, pharynx, and esophagus; electrical impedance tomography; and electrical activity of the diaphragm). The consensus regarding the positive distending pressure provided by HFNC is that this pressure can vary depending on the patient's weight, the diameter of the nasal prongs, the flow rate, and the patient's mouth being closed during the procedure [11].

Adherence in child NIV application is an important issue, as noncompliance can necessitate a mandatory transition from NIV methods to invasive mechanical ventilation. In this process, the patient's monitoring occupies an important place, and pulse oximeter is a good guide for oxygenation. Conversely, blood gas sampling and transcutaneous carbon dioxide measurements can be used to evaluate ventilation. The patient's carbon dioxide values should be disease specific in terms of the compensated acid–base balance. Apart from the pulse oximeter and carbon dioxide values, the patient's clinical condition, especially the WOB and level of consciousness, and chest radiography play an important role in the follow-up of the disease process [10].

76.3 NIV Use in Specific Conditions

76.3.1 Acute Respiratory Failure

In children, acute hypoxemic RF is one of the most common indications for pediatric intensive care unit admission. Different terms, including acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), have been used for acute hypoxemic RF in the literature, and these have finally been based on the new Berlin definition as mild, moderate, and severe ARDS, instead of ALI [12].

In 2015, the Pediatric Acute Lung Injury Consensus Conference made recommendations on NIV use, including CPAP and BIPAP, for pediatric ARDS (PARDS). A weak recommendation was made for NIV use in the early stage of risk situations for PARDS, as well as in selected populations, such as children with impaired immunity. Conversely, NIV use was not recommended in children with severe PARDS [12]. Examination of the literature of recent years still reveals very few prospective studies, and the results of the research conducted with children with impaired immunity and ARF show a greater need for endotracheal intubation in the early CPAP group [13–16].

Essouri et al. reported that the effectiveness of NIV depends on a good patient–ventilator relationship based on the interfaces used. They also emphasized that facial and oronasal masks are more effective than nasal and helmet interfaces [12].

Mode selection during NIV usage is another controversial issue for children with PARDS. Physiological and clinical indicators in PARDS show that BIPAP is more effective than CPAP because BIPAP improves both oxygenation and ventilation [12]. Today, HFNC is used in addition to CPAP and BIPAP in PARDS cases, but the number of studies on children is limited. A prospective observational study comparing helmet CPAP and HFNC in children with mild to moderate PARDS showed that both strategies were effective in the recovery process of the patient; however, the clinical response was more effective with helmet CPAP than with HFNC [14]. Similarly, Milesi et al. compared HFNC and nasal CPAP in young infants with moderate to severe acute viral bronchiolitis and found that nasal CPAP may be more effective than HFNC [15].

Consequently, NIV therapy in children with mild and moderate PARDS seems effective in reducing the intubation rate, improving oxygenation and ventilation, and decreasing the WOB. However, an appropriate interface should be used during this treatment, and the clinical condition and laboratory parameters of the patients should be closely monitored during this process.

76.3.2 Asthma

Asthma is a chronic disease of the respiratory system and is characterized by bronchial smooth muscle spasms, airway obstruction created by inflammation, and mucus plugging [17]. Acute or subacute episodes with progressive worsening of symptoms are described as asthma exacerbation or asthma attack. In children, viral respiratory infections are the most common cause of asthma exacerbation. In addition, allergens or atopy, pollution, environment, and comorbidities are other reasons for asthma exacerbation in children [18].

Treatment of status asthmaticus includes corticosteroids, short-acting β agonists, ipratropium bromide, and magnesium sulfate. However, some children with status asthmaticus may need respiratory support, including IMV or NIV. The positive effects of NIV usage on status asthmaticus include resting of the respiratory muscle, alveolar recruitment, decreased air-trapping, and reduced airflow resistance [7]. However, the data available in the literature are insufficient on this topic. One prospective, randomized, controlled study that included 20 children with status asthmaticus compared BIPAP plus standard therapy and standard therapy alone and concluded that NIV may be effective in reducing the WOB despite the small study sample size [19]. A similar result was highlighted in another study conducted by Thill et al. [20].

In the literature, two different opinions have emerged regarding HFNC use in children with status asthmaticus. Two retrospective studies point out that HFNC may be well tolerated by children with severe asthma [21, 22]. However, another retrospective study comparing HFNC and BIPAP or CPAP indicated that some patients who have HFNC may need higher respiratory support [23].

76.3.3 Bronchiolitis

Bronchiolitis is more common in children under 2 years of age and is often caused by acute viral infections. HFNC, CPAP, and BIPAP can all be used in the management of bronchiolitis [7]. A recent systematic review concluded that NIV application in the treatment of bronchiolitis in children is encouraging, although more studies are needed [24]. Similarly, a narrative review reported that early NIV use, including HFNC, BIPAP, and CPAP, may decrease health care costs, admission rates to ICUs, and intubation rates [25].

76.4 Conclusion

NIV application reduces respiratory distress in children with RF. The important point here is to use an interface and NIV method that is most appropriate for the eligible patient. In addition, the clinical condition and laboratory values of these patients should be followed closely and fully evaluated in terms of recovery from the disease.

Key Major Recommendations

- NIV administration has positive effects in eligible patients.
- To increase effectiveness, an interface suitable for each patient should be used.
- Patients should be closely monitored by blood gas analysis, pulse oximeter, and clinical examinations.

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The Ethics of Noninvasive Ventilation in Palliative Care

77

Joana Pacheco and Sara Freitas

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Abbreviations

6MWT	6-minute walking test
CAT	COPD assessment test
EOL	End of life
FEV1	Forced expiratory flow in first second
FVC	Forced vital capacity
mMRC	Modified Medical Research Council
NIMV	Noninvasive mechanical ventilation
TLC	Total lung capacity

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_77

77.1 Introduction

Dyspnea is a common symptom in many respiratory diseases and is often worse in the terminal stage of the illness. It is associated with decreased quality of life and increased suffering for the patient and family. Noninvasive mechanical ventilation (NIMV) can be offered to relieve dyspnea in advanced stages of respiratory disease or for the treatment of acute respiratory failure, especially in cases of "do not intubate" orders [1].

The initiation of NIMV in the context of palliative care can be challenging, due to the difficulty in recognizing when a patient has entered the final stage of life [2]. Palliative care is often considered late in the patient's journey and is likely due to the lack of knowledge or communication barriers [3].

Numerous studies support NIMV use, mainly in advanced COPD, in neuromuscular diseases and cancer. In addition to improving symptoms, it allows patients to say goodbye to their families. Obviously, there are a number of ethical issues that need to be considered and the topic remains controversial [4].

77.2 Goals of Palliative Care and Palliative Ventilation

Palliative Medicine focuses on the care of advanced illness and the relief of suffering, including psychosocial and spiritual needs [5]. It addresses therapeutic options at the end of life with the aim to improve quality of life and not prognosis [6].

NIMV can be considered a form of palliation given its applicability in relieving the suffering inherent to dyspnea. A discussion with the patient and family about the concept of NIMV, as well as the pros and cons of it, is fundamental as part of shared decision-making. NIMV should not result in greater patient discomfort. In patients with no indication for invasive ventilation, NIMV has a beneficial impact on patient outcomes, but no effect on long-term survival [1].

Another important aspect is the physician's role in the decision making process regarding withdrawal of therapy, particularly in conditions that inevitably will progress to death. NIMV should be seen as respiratory support for patients with chronic respiratory failure. NIMV may lead to an unpleasant experience in some patients which, in turn, may negatively affect the clinician's view of NIMV and its use in the end stage of disease, i.e., prolonging the suffering of the patients unnecessarily.

This is a controversial topic-V. Guastella et al. conducted a prospective survey among French pulmonologists and palliative care physicians. They were asked, based on their own experience, if they were in favor of withdrawing or maintaining NIMV at end of life. This survey showed that, in most cases, the opinion was to withdraw, particularly in those who have palliative care training. Personal ethics were associated with the opinion of maintaining NIMV [7].

Conditions, such as cancer, traditionally have had greater access to palliative care than others, e.g., COPD, which may be due to the uncertainty of prognosis [1]. It is therefore important to be aware of its use in other chronic diseases.

77.3 NIMV in Advanced Chronic Obstructive Pulmonary Disease

Despite its increased mortality due to the persistence of symptoms and recurrent hospitalizations, many COPD patients die without access to palliative care [8]. Few patients are aware of their prognosis, and therefore end-of-life (EOL) care is not discussed, as well as therapeutic options for refractory dyspnea. Furthermore, EOL care is mainly discussed during the exacerbation of disease rather than in a stable phase, thus negatively affecting the decision-making process [9].

Palliative NIMV should be considered in COPD patients with frequent exacerbations, very severe airflow limitation (FEV1 < 30%), and marked decline in quality of life. Persistent hypercapnia after exacerbation is associated with higher mortality and readmission rates [4]. Numerous studies have been conducted to establish the benefit of NIMV and oxygen therapy. Murphy et al. carried out a multicenter trial of 116 patients who were either randomized to receive home oxygen plus home NIMV or oxygen alone. An improvement in time to readmission or death within 12 months was observed in the group of patients who did the combined therapy. However, there was only a modest effect on quality of life due to the severity of disease of the selected patients [10]. Zikyri et al. performed another study that evaluated the effect of domiciliary NIMV in CAT, BODE index, and acute exacerbations in COPD. They found that there was a significant progress of FEV1, blood gas changes, mMRC, and 6-minute walking test (6MWT) in the first 6 months. The modified Medical Research Council (mMRC) dyspnea scale improvement can probably be explained because of the reduction of hyperinflation, relieving fatigue of respiratory muscles, and allowing acquiring some exercise capacity. It also helps to mobilize secretions and thus prevent infectious complications [11]. Although there is still no consensus, home level NIMV may delay disease progression and provide symptomatic relief.

77.4 NIMV in Neuromuscular Diseases

Neuromuscular disease can develop at any age, is often hereditary, and is characterized by progressive muscle weakness. These patients benefit from palliative treatment as there is no cure for most of them.

The main disease is amyotrophic lateral sclerosis (ALS) which most commonly presents with limb-onset muscle weakness and bulbar onset in 25–30% of cases. Patients often complain of swallowing difficulty and speech impairment at some point in the course of their disease. In ALS, 50% of patients die within 36 months after symptom onset, usually due to respiratory failure [12].

Communication is essential to convey the importance of early initiation of NIMV. Patient's acceptance depends on the level of education, culture, religion, as well as endogenous factors such as anxiety or depression. As described by Danel-Brunaud et al., we must recognize the opportunity to discuss the EOL issues: when the family asks for EOL information and interventions; when there's severe psychological and/or social or spiritual distress or suffering; when pain requires a high

dose of analgesic medication and dysphagia requires a feeding, besides dyspnea or symptoms of hypoventilation [13].

Ventilatory support in association with cough-assist is routinely used in neuromuscular patients. The criteria for initiation of NIMV are based on both clinical and respiratory function, with a tendency to start at earlier stages of the disease. These measures have allowed a significant improvement in quality of care and life expectancy in these patients.

Neuromuscular patients often exhibit a restrictive defect at spirometry with reduced forced vital capacity (FVC) and total lung capacity (TLC) related to the weakness of the respiratory muscles. NIMV use is indicated in patients who present symptoms such as orthopnea, associated with respiratory dysfunction proven by the effects on the FVC (<50%) and/or maximum inspiratory pressures (MIP), as well as symptoms of hypoventilation in the presence of hypercapnia and nocturnal desaturation. Ventilators must be able to provide life support and all ventilation modes. For patients requiring ventilation 24-h per day, it is imperative to have two ventilators and extra batteries, as well as mouthpieces or masks without nasal support to prevent ulcers [14].

It is also important to plan ventilation withdrawal. According to Runacres et al., some patients make an informed decision to electively withdraw ventilation when they perceive it has become burdensome rather than beneficial. The wishes regarding the time of withdrawal must be respected, and we should review the decision over the course of the disease as the patient's opinion may change [15].

77.5 NIMV in Cancer

Palliative care has been increasingly recognized by Oncology, which has worked to raise awareness among different clinicians for the early referral of these patients. According to Aragon, patients who are referred at time of diagnosis had improved quality of life, mood, and increased survival with less use of aggressive medical treatment at EOL [6].

Patients with solid tumors often present with respiratory symptoms, including dyspnea. NIMV might be used as a method option to relieve dyspnea in these cases. In a multicenter randomized study conducted by Nava et al., patients who had end-stage cancer and solid tumors admitted to hospital because of acute respiratory failure and who had chosen to receive only palliative care support were randomly assigned to receive either NIMV or oxygen therapy. The aim was to compare the effectiveness of NIMV in reducing dyspnea compared to oxygen therapy and its acceptability as a palliative measure. This study showed that NIMV is more effective compared with oxygen in reducing dyspnea and decreasing the doses of morphine needed in patients with solid tumors. According to the authors, this measure is generally well accepted when properly explained, when a trial period is allowed, and when it is mentioned that withdrawal is possible when desired [16].

NIMV is also widely used in intensive care units, especially as an option for patients with no indication for invasive support measure, for example, in those with

respiratory failure and whose cancer has reached an advanced stage. Meert et al. developed a study to assess the efficacy of NIMV in cancer patients who were provided bi-level ventilatory mode with positive end expiratory pressure (PEEP) between 4 and 8 cmH_2O, pressure support between 10 and 18 cmH_2O, and FiO_2 adjusted to maintain a saturation of at least 90%. They concluded that NIMV is beneficial when introduced in these cases; however, it should be considered in patients who maintain a therapeutic plan and with a reversible cause for the acute respiratory failure, otherwise we run the risk of prolonging the suffering of someone whose death is an inevitable outcome [17].

77.6 NIMV Role as Supporting Chronic Respiratory Failure in Interstitial Lung Disease

Interstitial lung disease often evolves, especially in the terminal phase of the disease, to chronic respiratory failure, mostly after episodes of acute exacerbation. The absence of symptom control, such as dyspnea, coughing, and fatigue, leads to an important decrease in the patient's quality of life and degree of autonomy.

Palliative care may provide some improvement in quality of life and comfort at advanced stages of the disease for some patients. The great difficulty for the clinician is to understand when the barrier of benefit with more interventionist attitudes has been overcome, and planning of palliation should be started. In a review from Faverio et al., the palliation concept of "simultaneous care" is described, which is interesting because it consists of targeted treatments with palliative care until the EOL, when palliative care replaces effective treatments [18]. This way, the patient is progressively integrated, providing the best care throughout the entire disease, thus preparing for the terminal phase.

However, the timing for referral is not officially established and therefore several authors have suggested different criteria. In a review written by Faverio et al., the prescription of oxygen therapy, age over 70 years, previous exacerbations of the disease, honeycomb pattern on chest CT, and UIP histological pattern are described as possible criteria, as these are recognized factors that give a bad prognosis [18].

There are some peculiarities when applying NIMV in patients with interstitial lung disease. In another review by Faverio et al., patients with interstitial lung disease require higher pressures to receive the indicated tidal volume, and this has implications, such as the increased risk of iatrogenic pneumothorax. Low to moderate PEEP values should be used to prevent that event. They will adapt to the low tidal volumes with the reactive response of increasing respiratory rate [19].

77.7 Final Considerations

There remains a long way to go for NIMV to be unequivocally accepted as a fundamental pillar of palliative care.

However, several studies have already pointed out benefits in different clinical scenarios, from COPD to cancer patients, with improvement in quality of life. It is important, as members of society, to work toward informing and raising awareness of the need to provide palliative care in time.

More studies are needed to clarify the role of palliative NIMV in different groups of patients.

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Part XVI

NIMV and Health Care Organizations Models

78 New Models of Hospital Organization of Noninvasive Mechanical Ventilation: Step-Down Unit, Respiratory Intensive Care Units

Dušanka Obradović

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78.1 Introduction

Intensive care medicine has a history of almost 70 years. The concept of specially dedicated wards for threating critically ill patients was introduced during the well-known poliomyelitis epidemic in the 1950s of the past century when the first unit was established to treat the patients with respiratory failure. The "father" of the intensive care unit was the famous anesthesiologist Dr Bjorn Ibsen from Copenhagen, Denmark [1]. Since then, intensive care medicine has become one of the fastest growing branches of medicine.

After the establishment of general intensive care units in many hospitals in Europe and the United States, the specialized respiratory intensive care units (RICUs) were introduced in hospital organizations in the 1960s in the United States run by the respiratory specialists [2]. During the 1980s, in this country, the noninvasive respiratory care units (NRCUs) and high dependency units (HDUs) were developed [3].

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A. M. Esquinas (ed.), *Noninvasive Mechanical Ventilation*,
https://doi.org/10.1007/978-3-031-28963-7_78

The main indications for RICUs admission were acute respiratory failure (ARF) or acute-on-chronic respiratory failure (RF). The RICUs were the solution for lower costs, as according to the survey in many countries, the exacerbation of chronic RF (due to chronic obstructive pulmonary disease–COPD) was the main reason for the ICU treatment [4]. Patients with acute exacerbations of COPD (AECOPD) treated in ICUs had numerous complications connected with mechanical ventilation use. The guidelines that introduced noninvasive positive pressure ventilation (NPPV) as a first line of treatment for AECOPD contributed to the RICUs establishment in many countries [5]. In Europe, the introduction of the RICUs was started at the end of the twentieth century, admitting patients with acute RF and acute-on-chronic RF, mainly in Italy, the country with the largest experience in this field of respiratory medicine. The results of the national prospective cohort study by Confalonieri and colleagues [6] indicated two types of units according to the nurse–patient ratio among 26 units included in the study. More than half of the units had a nurse–patient ratio of 1:2 or 1:3, and according to the Italian Association of Hospital Pulmonologists (AIPO), these units can be defined as RICUs, while the rest of the units (nurse–patient ratio of 1:4) should be considered as NRCUs or noninvasive respiratory units. In NRCUSs, patients are usually not invasively ventilated; if intubation is required, those patients are transferred to the adjacent ICU. This study also pointed that the survival of 85% for patients treated in RICUs in Italy showed the importance of NIPPV use and close monitoring regarding the outcomes.

78.2 Step-Down Units: Outcomes and Costs

The role of RICUs was also apostrophized in other studies, especially for the patients with acute respiratory failure or those with the acute exacerbation of chronic respiratory failure (e.g., exacerbation of COPD) and indications for NIPPV. The presence of RICUs in hospital can contribute to avoiding a lower level of care on general wards, and on the other hand, increase the availability of ICU beds. Furthermore, this type of organization in general hospitals can save costs [7].

Another study by Confalonieri and colleagues in 2015 [8] showed a significantly lower in-hospital mortality rate in RICUs versus internal medicine units (IMUs) for the patients with ARF, AECOPD, and community acquired pneumonia (CAP), with reduced transfer to the ICU, shorter hospital stay and time for NIV application. These results are very important for better understanding the importance of RICUs as dedicated units in the light of managing patients with ARF as a one of the most frequent reason for hospitalization. In a retrospective cohort study from the USA [9], in two academic tertiary care hospitals, the authors investigated the association between opening the four bed Step-Down Unit (SDU) and outcomes (hospital mortality, hospital and ICU length of stay (LOS), and time to transfer to the ICU) in the interventional hospital versus control hospital without the SDU. The results of this study revealed no association of lowering the in-hospital mortality or hospital LOS after SDU opening in the interventional hospital, but the ICU LOS and time to transfer to the ICU were significantly reduced ($p = 0.019$ and $p = 0.014$, respectively).

In a multicenter European cohort study [10], the aim of the investigation was the in-hospital mortality in hospitals with so called Intermediate Care Units (IMCU), defined as independent units with the level of care lower than in the ICU but higher than at the general ward. In this study, which included 167 units from 17 European countries with more than 6000 admissions to the ICUs, the authors concluded that the higher risk of hospital death was associated with severity of illness at ICU admission, infection, hospital stay longer than 7 days before ICU admission, and unplanned admission to the ICU. The mortality was significantly lower in hospitals with IMCU (odds ratio of mortality 0.63 (95% CI 0.45 to 0.88, $p = 0.007$) except in cases where the reason for admission was just the observation of the patients (e.g., after surgery).

Some studies reported unfavorable results regarding the step-down unit outcomes. A study from Scotland [11], which was conducted over 10 years and with more than 6000 admissions to the single mixed medical-surgery ICU, concluded that a higher APACHE II score and discharge to a step-down unit were the independent risk factors for early ICU re-admission, and therefore higher mortality. In a retrospective cohort study of data from 28 ICUs in the Netherlands and patients admitted because of the severe sepsis [12], the results revealed that the presence of an IMCU in hospital was associated with higher in-hospital mortality.

Vincent and Rubenfeld [13] wrote a viewpoint about the intermediate care units and their advantages and disadvantages, with the analysis of the effects of intermediate care on outcomes and costs through the results of several studies and from the experts' perspectives. They concluded there is a lack of studies about cost savings and better outcomes for patients hospitalized in the IMCUs and who never need ICU care.

78.3 Noninvasive Mechanical Ventilation and New Models of Hospital Organization

Noninvasive positive pressure ventilation (NPPV) was initially established as a therapy of choice for patients with chronic RF, e.g., neuromuscular disorders. The indications for NIPPV were extended to other causes of RF such as the acute exacerbation of chronic obstructive pulmonary diseases (AECOPD). Today, NIPPV is a routine therapy for patients with different causes of RF outside ICUs – in the step-down units, IMCUs or RICUs – which is a great contribution to liberate the ICU capacities and free up ICU beds [14].

Invasive mechanical ventilation is connected with complications such as ventilator induced pneumonia (VAP), barotrauma or volutrauma of the lungs, with weaning problems and long-term tracheostomy. On the other hand, NIPPV is a mode of ventilation that avoids almost all these complications; therefore, it has become one of the most used ventilatory supports for numerous indications, including acute RF and acute-on-chronic RF. Together with progress using NIPPV, the question of where to perform it arises. According to the results of several studies, NIPPV should be performed in locations of care that can provide adequate monitoring of the

patients and should be close to the ICU [15, 16]. Several factors influence the NIPPV outcomes. One is the results of gas analysis regarding the degree of hypoxemia and respiratory acidosis, where the pH < 7.25 is a very powerful prognostic factor for NIPPV failure in patients with AECOPD [17]. The other very important factor is sufficient staff with experience [18]. The review about the implementation and delivery of NIPPV in patients with AECOPD from the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) in the UK [19] concluded that patient selection is very important. Mortality was higher in patients with pneumonia who were ventilated in the general wards and 91% of patients with pH < 7.25 were not treated in the High Dependency Unit, with the highest mortality (59%) for patients who started the NIPPV in general wards. Similar results were published in the study from our hospital [20], which is a tertiary teaching pulmonary hospital with a six-bed HDU. The study included 138 patients, with mainly AECOPD as an indication for NIPPV (85%). NIPPV was applied in 86 patients in the HDU. NIPPV failure was associated with the presence of consolidation in two or more quadrants and application of NIPPV in the general ward.

While expanding the indications for NIPPV, the need for defining the settings for noninvasive ventilation opened as a new frontier. It is clear that patients with acute RF or acute-on-chronic RF have to be ventilated in the units with adequate equipment, trained staff, and availability to properly monitor the vital parameters. Regarding the ventilators and modes of ventilation, enormous progress has been made in the past 30 years [21].

The COVID-19 pandemic had a big impact on use of NIPPV in patients with COVID-19 pneumonia and acute RF. At the beginning of the pandemic, NIPPV was not advocated for the patients with severe acute respiratory syndrome owing to generating aerosols and relying on the experience from previous pandemics. In a study from Wuhan [22], the authors reported significantly higher mortality in patients invasively ventilated than in patients with NIPPV (98% vs. 40.8%). As the pandemic was ongoing, using noninvasive respiratory treatment modalities for acute RF increased, especially the use of NIPPV and high-flow nasal oxygen. It changed the organization of the hospitals, and most of the units became units for treating patients with acute RF due to COVID-19 pneumonia. The hospitals' administration faced the need to reorganize the hospital settings, especially the respiratory intermediate units or step-down units, which served as units for treating severe RF due to COVID-19 [23].

Key Messages

- Expanded indications for NIPPV changed the everyday practice in hospitals
- NIPPV has to be applied in adequately equipped units with trained staff
- Understanding the respiratory failure physiology is very important for implementing NIPPV in various indications, which has become apparent during the COVID-19 pandemic
- The new models of hospital organization regarding the implementation of noninvasive ventilation become mandatory

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