Non-invasive ventilation in the treatment of sleep-related breathing disorders: A review and update

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Abstract Non-invasive mechanical ventilation (NIV) was originally used in patients with acute respiratory compromises or exacerbations of chronic respiratory diseases as an alternative to intubation. Over the last thirty years NIV has been used during the night in patients with stable chronic lung diseases such as obstructive sleep apnea, the overlap syndrome (COPD and obstructive sleep apnea), neuromuscular disorders, obesity-hypoventilation syndrome and in other conditions such as sleep disorders associated with congestive heart failure.

In this review we discuss the different types of NIV, the specific conditions in which they can be used as well as the indications, recommendations, and evidence supporting the efficacy of NIV.

Keywords Sleep-related respiratory disorders; Non-invasive ventilation; Continuous positive airway pressure; Bi-level positive airway pressure

Palavras-chave Distúrbios respiratórios do sono; Ventilação não invasiva; Pressão positiva contínua das vias
Background

Noninvasive mechanical ventilation (NIV) is any form of ventilatory support without an endotracheal tube. NIV was originally used in patients with acute respiratory compromises or exacerbations of chronic respiratory diseases, as an alternative to the endotracheal tube. Over the last thirty years NIV has been also used during the night in patients with stable chronic lung disease such as obstructive sleep apnea (OSA), chronic obstructive pulmonary disease (COPD), the overlap syndrome (COPD and obstructive sleep apnea), neuromuscular disorders, obesity-hypoventilation syndrome (OHS), and sleep disorders associated with congestive heart failure (Cheyne-Stokes respiration).1,2 In this review we discuss the different types of NIV, the specific conditions in which they can be used as well as the indications, recommendations and evidence supporting the efficacy of NIV.

Clinical conditions for NIV

Alveolar hypoventilation is a result of an imbalance between the capability of respiratory muscles to maintain ventilation and gas exchange and is characterized by hypercapnia assessed by blood gas analysis. If pathologies related to either peripheral and/or central nervous system dysfunction are excluded, the other conditions associated with developing alveolar hypoventilation are listed in Table 1.1-3 Of note, alveolar hypoventilation primarily develops during sleep; moreover, in all these entities daytime breathing abnormalities must be considered. These respiratory “daylight” deteriorations (particularly in patients with neuromuscular disorders) require an appreciation of the diagnosis, the progression of the disease, and the particular circumstances of the patient.1-3

Obstructive sleep apnea–hypoapnea syndrome (OSA)

OSA has an incidence of 2% in women and 4% in men.5,6 It is characterized by recurrent episodes of partial (hypoapnea) or complete (apnea), obstruction of the upper airway during sleep, and is associated with episodes of arousal and/or oxyhemoglobin desaturation.7-8 Symptoms of the syndrome include excessive daytime sleepiness, choking episodes during sleep, frequent awakenings, unrefreshing and unstructured sleep, daytime fatigue, difficulty concentrating and short-term memory loss1 (Table 2). The pathophysiology of OSA remains controversial. Obesity, the classic hallmark in OSA, is associated with obstruction of the upper airways.9 Possible hypotheses include adipose tissue infarction of the tongue and/or the dilator muscles of the pharynx.2 The upper airway becomes less efficient, reducing oropharyngeal space especially at the end of exhalation. As a result, at the beginning of the next inspiration the dilator

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Table 1 Main diseases which can benefit from NIV classified according the cause and progressiveness of the respiratory impairment.1,2

<table>
<thead>
<tr>
<th>Parietal disorders</th>
<th>Lung diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chest wall</strong></td>
<td><strong>Continuous worsening</strong></td>
</tr>
<tr>
<td>Kyphoscoliosis</td>
<td>Continuous worsening</td>
</tr>
<tr>
<td>Sequelae of tuberculosis</td>
<td>Continuous worsening</td>
</tr>
<tr>
<td>Obesity hypoventilation syndrome (OHS)</td>
<td>Continuous worsening</td>
</tr>
<tr>
<td>Neuromuscular</td>
<td>Continuous worsening</td>
</tr>
<tr>
<td>Spinal muscular atrophy</td>
<td>Continuous worsening</td>
</tr>
<tr>
<td>Acid maltase deficit</td>
<td>Continuous worsening</td>
</tr>
<tr>
<td>Duchene dystrophy</td>
<td>Continuous worsening</td>
</tr>
<tr>
<td>Myotonic myopathy</td>
<td>Continuous worsening</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td>Continuous worsening</td>
</tr>
</tbody>
</table>

**Table 2 Typical symptoms of OSA.1,2**

- Snoring
- Nocturia
- Unrefreshing sleep
- Choking
- Daytime sleepiness
- Decreased libido
- Morning headache
- Enuresis
muscles of the pharynx must produce a greater contraction to overcome the tendency of the pharyngeal wall to collapse (due to the negative pressure inside the cavity and pharynx). The supine position is potentially dangerous in some circumstances because the tongue tends to occlude the rear wall of the oropharynx which can increase the oropharynx occlusion. This syndrome has been associated with the development of hypertension, coronary artery disease, bleeding disorders, stroke and increased risk of sudden death during sleep. It is also associated with a higher rate and greater severity of traffic accidents, increased use of health care facilities and reduced capacity for work. Strong evidence exists that non-invasive ventilation, usually continuous airway positive pressure (CPAP), has significant advantages in this type of disease, improving sleep quality, daytime wakefulness, and cognitive function and so the quality of life improves. These improvements are wide-ranging: reduction of traffic accidents, lower arterial blood pressure and reduction in the morbidity and mortality rates of myocardial infarction and stroke demonstrate the wide spectrum of CPAP’s benefits.

Complex sleep apnea

We use the term "Complex Sleep Apnea" (CompSAS) to indicate a condition initially diagnosed as OSA. This syndrome is characterized while CPAP is being used) by the frequent occurrence of central apnea after elimination of obstructive events. CompSAS is diagnosed based on minimal apnea–hypopnea index (AHI) of five events per hour of sleep with a majority of obstructive events. If during titration there is a reduction in the number of obstructive events to <5 events per hour of sleep, while the central apnea index (CAI) is >5 events per hour sleep, the diagnosis is established. Rather than starting further treatments it is useful to consider whether CPAP pressure is too high and is provoking CompSAS (pressure toxicity). Patients with CompSAS most often respond to positive airway pressure, but the obstruction cannot be eliminated without producing central apnea. A possible preventive measure is the so-called permissive flow-limitation: the pressure is set at a level that permits a mild degree of airway obstruction, without disturbing ventilator control mechanisms. Also oxygen administration may lead to a decrease in the hypoxic ventilatory response. Also BiPAP in the spontaneous-timed (ST) mode or adaptive servo-ventilation (ASV) can be useful in the treatment of CompSAS.

Sleep-disturbances associated with cardiac dysfunction

The prevalence of obstructive sleep apnea in patients with impaired left ventricular ejection fraction is estimated to be about 11–53%. It is also known that the sleep obstructive apnea–hypopnea syndrome can worsen a state of congestive heart failure, by causing a periodic increase in negative intrathoracic pressure, by raising arterial blood pressure, and causing tachycardia from sympathetic nervous system stimulation from hypoxia, hypercapnia and arousals. CPAP treatment produces a reduction in blood pressure and improves left ventricular systolic function in patients with chronic heart failure and obstructive sleep apnea. Recent studies in patients with chronic heart failure associated with obstructive sleep apnea have shown a further improvement in cardiac function in patients treated with bilevel positive airway pressure ventilation (BIPAP). This may be due to the lower respiratory muscle work due to BIPAP. Moreover, reduced work of breathing, a lower positive intrathoracic pressure gives a greater ejection fraction.

Central sleep apnea (CSA) is associated with periodic breathing. Periodic breathing, Cheyne-Stokes respiration, is a particular variety of central sleep apnea which is frequently associated with congestive heart failure. CSA with its characteristic desaturation (apnea-related) and sympathetic hyperactivity tends to worsen the prognosis of heart failure. CSA is characterized by cessation of respiratory drive during sleep, which causes impaired gas exchange. Unlike the OSA in which there is a respiratory effort to overcome the resistance of the upper airway, CSA is characterized by the absence of respiratory movement due to the cessation of ventilation. In the heart failure patients, the onset of apnea occurs through a redistribution of blood volume from the lower limbs to pulmonary circulation that is primarily triggered by the supine position. Stimulation of pulmonary vagal receptors causes hyperventilation which results in hypocapnia. When the value decreases below the hypocapnic apnoeic threshold, stimulation of the bulbar center ceases, inspiratory drive stops, and apnea occurs. In patients with chronic heart failure, the prolonged circulation time due to the reduction in cardiac output leads to a delay of feedback between chemoreceptors and bulbar centers resulting in hyperventilation and respiratory instability. The main risk factors for CSA are male sex, hypoxemia, atrial fibrillation and advanced age. CPAP and BIPAP are often unable to correct this category of apneas; therefore, a servo-assisted mode (ASV or adaptive servo ventilation) is recommended.

The ASV device determinate automatically the extent of ventilatory support based on a continuous analysis of the breathing pattern and in more advanced machines also the expiratory pressure adjustment. Some studies have shown it to be most effective in controlling this type of apnea; it remains unclear whether ASV increases survival in these patients.

Obesity-hypoventilation syndrome

Obesity hypoventilation refers to a syndrome including daytime hypercapnia (PCO₂ > 45 mmHg) in obese people in which no other cause of hypoventilation is present. Its prevalence among patients with obstructive sleep apnea is 20–30% and is greater in extremely obese patients (BMI > 40). Approximately 10% of patients with obesity-hypoventilation syndrome do not have obstructive sleep apnea syndrome. Additionally, nocturnal hypoxemia and diurnal hypercapnia persist in about 40% of these patients after the treatment when CPAP eliminated apnea. Other factors contribute to the development of obesity-hypoventilation syndrome associated with the persistence of daytime hypercapnia: these include body mass index and apnea–hypopnea index, mean overnight oxygen saturation, and the severity of restrictive ventilatory syndrome. CPAP treatment is most
effective when there are certain predictive values: better spirometry results, and a higher apnea–hypoapnea index. BIPAP therapy may be useful in those patients for whom CPAP has failed or given unsatisfactory results. Titration of non-invasive ventilation pressure should follow the recommendations of pressure titration in obstructive sleep apnea with the goal of eliminating (hypo)apneas, snoring, respiratory effort-related arousals and lowering PCO2 levels to at least daytime values. No recommendations exist regarding the ventilation mode to favor in OHS. Trials exist providing evidence that a high backup respiratory rate leads to superior nighttime control of respiratory events.

The average volume-assured pressure support ventilation seems to be able to lower PCO2, but data regarding effect on oxygenation and long-term outcome are conflicting.

Neuromuscular and chest wall disorders

NIV has been used in patients with progressive neuromuscular disease or serious abnormalities of the thoracic cage, with recognized benefits, which include an improved survival rate and an improved quality of life. The benefits of NIV in this type of patient includes improvements of daytime levels of blood gas (including hypercapnia), a reduction in the oxygen cost of breathing, an increase in the ventilatory response to increased carbon dioxide, and improved lung compliance.

Chronic obstructive pulmonary disease and sleep apnea (overlap syndrome)

COPD is a challenging and ever increasing chronic pulmonary disease, affecting health care systems worldwide. It is projected to be fourth leading cause of mortality by 2030. COPD severely impacts quality of life. In severe COPD acute exacerbations often lead to acute hypoxemic and/or hypercapnic respiratory failure, resulting in further disease progression and possible chronic respiratory failure.

NIV is considered first-line treatment in acute exacerbations of COPD requiring ventilatory support, but recommendations regarding establishment of domiciliary long-term non-invasive ventilation in chronic hypercapnic failure due to COPD are conflicting. Sleep-disordered breathing (mainly obstructive sleep apnea) and chronic obstructive pulmonary disease (COPD) are the most common lung diseases: a large number of patients have both disorders, hence the term “overlap syndrome.”

The COPD overlap syndrome was first described by Flenley in 1985 as a combination of COPD and obstructive apnea–hypoapnea syndrome. Epidemiological studies have not shown a consistently higher incidence of sleep apnea–hypoapnea syndrome in patients with COPD compared to common OSA. Nevertheless, the coexistence of these conditions can lead to severe episodes of desaturation during sleep (particularly during rapid eye movement – REM-sleep), thus increasing the risk of hypoxemia, daytime hypercapnia and pulmonary hypertension. This results in a substantially greater morbidity and mortality, compared to those with COPD or OSA alone as well as more hospitalizations and higher mortality. Many questions remain about the definition of the disease, the prognosis and the optimal treatment which currently consists of CPAP and oxygen. Non-invasive ventilation may be useful in patients with overlap syndrome, but there are no controlled studies.

Clinical criteria for starting non-invasive ventilation

The presence of symptoms and physiological markers of hypoventilation are useful in identifying the clinical severity; moreover, these factors relate to therapeutic decision-making, especially initiating nocturnal non-invasive ventilation. In a typical "progressive disease" two consecutive steps occur:

1. Initial phase of nocturnal hypoventilation reversible during waking hours, associated with few or no clinical symptoms.
2. Nocturnal and daylight hypoventilation associated with clinical symptoms (see Table 3) which shows a reduced respiratory reserve.

Continuous sleep monitoring of PCO2 and O2 saturation values is necessary to document the presence of nocturnal hypoventilation which may be present in all the stages of sleep (in some cases only during REM sleep). Daytime hypoventilation is defined by reduced values of arterial oxygen tension (PaO2 <55 mmHg), high levels of arterial carbon dioxide tension (PaCO2 46–50 mmHg) and/or high serum bicarbonate levels with a relatively normal pH. Chronic daytime hypoventilation is an important indicator always associated with nocturnal hypoventilation (PaCO2 ≥55 mmHg or a rise in PtcCO2 to ≥10 mmHg). In the presence of daytime hypoventilation, polysomnography is recommended to exclude sleep apnea. Clinical symptoms, although modest, should be evaluated carefully, because they are very important determining disease severity and prognosis as well defining the need for NIV. Pulmonary function tests may be helpful in defining the reduction of lung function, but they have a low predictive value for patients with sleep-related hypoventilation. However, in patients with neuromuscular disease, there is a good correlation between lung function and nocturnal hypoventilation: it has

<table>
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<th>Table 3</th>
<th>Clinical features frequently associated with alveolar hypoventilation</th>
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<tr>
<td>Shortness of breath during activities of daily in the absence of paralysis</td>
<td>Orthopnea in patients with disordered diaphragmatic dysfunction</td>
</tr>
<tr>
<td>Poor sleep quality: insomnia, nightmares and frequent arousals</td>
<td>Nocturnal or early morning headaches</td>
</tr>
<tr>
<td>Daytime fatigue, drowsiness, loss of energy</td>
<td>Decrease in intellectual performance</td>
</tr>
<tr>
<td>Appearance of recurrent complications: respiratory infections</td>
<td>Clinical signs of cor pulmonale</td>
</tr>
</tbody>
</table>

Clinical signs of cor pulmonale:

- Appearance of recurrent complications: respiratory infections
- Decrease in intellectual performance
been shown that hypoventilation during REM only or during all sleep stages or in the daytime, appears respectively with supine inspiratory vital capacities of less than 40%, 25% or 12% of predicted values.\(^1,58\)

**Types of NIV and their use**

We now consider the main types of ventilation used to treat sleep-disordered breathing and respiratory conditions associated with hypoventilation and hypercapnia.

**CPAP (continuous positive airway pressure)**

CPAP is currently the most widely used mode of NIV in the treatment of obstructive sleep-disordered breathing\(^59\) and acute hypoxemic failure associated with chronic heart failure.\(^59,60\) It consists in the application of a constant level of positive pressure during spontaneous breathing. However, it has to be noted that CPAP should be only applied in sufficiently spontaneous breathing patients. It is not considered as a mode of mechanical ventilation.\(^61\) The mechanism of action of CPAP includes a series of actions on pathophysiological mechanisms:

(a) It prevents intermittent narrowing and collapse of the airways in patients with obstructive sleep apnea–hypopnea syndrome (by acting a virtual splint during sleep).

(b) It counteracts auto-positive end-expiratory pressure, which reduces respiratory muscles load, the work of breathing and daytime PaCO\(_2\) in patients with overlap syndrome.

(c) It improves lung function, particularly the functional residual capacity, daytime gas exchange in patients with obstructive sleep apnea–hypopnea syndrome.

(d) It improves systolic function of the left ventricle in patients with heart failure coexisting with obstructive sleep apnea–hypopnea syndrome.\(^3\)

**Auto-CPAP (automatic adjustment of continuous positive airway pressure)**

Auto-CPAP (APAP) is delivered via a self-titrating CPAP device, which uses algorithms to detect variations in the degree of obstruction and adjusts the pressure level to restore normal breathing. Auto-CPAP compensates for factors that modify the upper airway collapsibility, such as body position during sleep, stage of sleep, use of alcohol, and drugs that affect upper airway muscle tone.\(^2,3\) The auto-CPAP can be used during polysomnography or cardiorespiratory monitoring to titrate a single pressure value to be used later with fixed CPAP for treatment of OSA in patients without comorbid conditions (chronic heart failure, COPD, central apnea syndrome or hypventilation). The use of auto-CPAP is reserved only for those patients with sleep apnea syndrome only present during REM or respiratory events related to position, in whom constraining positional maneuvers are poorly tolerated.\(^59\)

**Adaptive servo-ventilation (ASV)**

The adaptive servo-ventilation (ASV) has been developed for the treatment of Cheyne-Stokes respiration-central apnea syndrome in patients with chronic heart failure who have a breathing pattern characterized by periods of crescendo–decrescendo change in tidal volume. This more complex device can use patient inspiratory positive airway pressure (EPAP) level sufficient to control the obstructive apnea. The device then automatically adjusts the inspiratory pressure support for each inspiration within a pre-specified range, to maintain a moving-target ventilation set at 90% of the patient’s recent average ventilation. The aim is the stabilization of breathing patterns and to reduce the respiratory alkalosis which can trigger apnea re-entry cycles.\(^29,30,63,64\)

**BIPAP (bilevel positive airway pressure)**

Bilevel positive airway pressure (BIPAP) is also used for sleep-related disorders, but its main indication is in pathological conditions associated with hypoventilation. The BIPAP devices deliver a higher pressure during inspiration (IPAP – inspiratory positive airway pressure) and a lower pressure during expiration (EPAP – expiratory positive airway pressure). The gradient between IPAP and EPAP (pressure support ventilation) is crucial in maintaining adequate alveolar ventilation and reducing PaCO\(_2\).\(^2,3\) The IPAP acts also in reducing the work of breathing and fatigue, reducing the workload of respiratory muscles; EPAP has the function of maintaining the patency of the upper airway, to control obstructive apnea and to improve the functional residual capacity.\(^3,65\) BIPAP is now proposed for the type of patients who require high expiratory pressures to control obstructive sleep apnea–hypopnea, but who cannot tolerate exhaling against a high-fixed CPAP pressure.\(^65\) Other indications of BIPAP are the treatment of coexisting central apnea or hypoventilation, the obesity-hypoventilation syndrome, the overlap syndrome and neuromuscular disorders. Although the patient should be able to maintain spontaneous breathing, it is used to set a back-up rate option for those patients whose ventilation during sleep may be particularly impaired (neuromuscular disorders, complex sleep apnea, central apnea in chronic heart failure, obesity-hypoventilation syndrome).\(^3,65\) Recently a new device has been introduced: an auto-adjusting bi-level positive airway pressure (auto-BIPAP) to provide greater flexibility in pressure changes for bi-level therapy. This treatment results in AHI (apnea–hypopnea index) reduction equivalent to that provided by a conventional BIPAP.\(^66\)

**Average volume-assured pressure support ventilation (AVAPS)**

Average volume-assured pressure support ventilation (AVAPS) is used in patients with chronic hypoventilation and in particular with obesity hypoventilation syndrome,\(^65\) neuromuscular diseases, and sometimes, in chronic obstructive pulmonary disease. In this mode a target tidal volume is set; the device adjusts the pressure support which to reach the selected tidal volume. It guarantees a delivered tidal...
Table 4  Types of non invasive positive pressure ventilation.\textsuperscript{3,49,50,59}

<table>
<thead>
<tr>
<th>Method</th>
<th>Applications</th>
<th>Setup requirements</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Continuous positive airway pressure (CPAP)</strong></td>
<td>obstructive sleep apnea; congestive heart failure with coexisting obstructive sleep apnea; obesity-hypoventilation syndrome with coexisting obstructive sleep apnea</td>
<td>CPAP level</td>
<td>simple to use; relatively inexpensive</td>
<td>minimal or no ventilation support; preset pressures may not address variability in obstructive sleep apnea or severity with sleep stages and positional stages</td>
</tr>
<tr>
<td><strong>AUTO-CPAP</strong></td>
<td>obstructive sleep apnea; congestive heart failure with coexisting obstructive sleep apnea; obesity-hypoventilation syndrome with coexisting obstructive sleep apnea</td>
<td>range of allowable CPAP levels</td>
<td>reduces number of titration studies; self-adjusting to adapt to variability in obstructive sleep apnea with sleep stages and positional changes; maybe useful for patients with ongoing weight loss such as after bariatric surgery</td>
<td>more expensive than fixed CPAP; may not be effective for patients with cardiopulmonary disorders or other conditions in which desaturation may be unrelated to obstructive events</td>
</tr>
<tr>
<td><strong>Adaptive servo-ventilation (ASV)</strong></td>
<td>congestive heart failure; central sleep apnea; complex sleep apnea syndrome</td>
<td>maximum and minimum inspiratory pressures; end-expiratory pressure</td>
<td>adapts pressure to maintain more consistency of respiration over time</td>
<td>more expensive than other modes; may worsen ventilation in disease with chronic ventilator insufficiency such as COPD or restrictive thoracic disorders</td>
</tr>
<tr>
<td><strong>Bilevel positive airway pressure (BIPAP)</strong></td>
<td>obstructive sleep apnea with CPAP intolerance; obstructive sleep apnea with central sleep apnea; restrictive thoracic disorders; severe chronic obstructive pulmonary disease; obesity hypoventilation syndrome with coexisting obstructive sleep apnea and residual hypoventilation despite CPAP</td>
<td>inspiratory and expiratory positive airway pressures</td>
<td>promotes alveolar ventilation; unloads respiratory muscles; decreases the work of breathing; controls obstructive hypopnea</td>
<td>more expensive than CPAP; may generate central apnea</td>
</tr>
<tr>
<td></td>
<td>Without backup rate</td>
<td>backup rate</td>
<td>more expensive than other modes; may generate central apnea</td>
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</tr>
<tr>
<td></td>
<td>central sleep apnea; complex sleep apnea syndrome; worsening restrictive disorder</td>
<td>backup rate; ratio of inspiratory time to expiratory time</td>
<td>provides mandatory respiratory support during central or pseudo-central apneas</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Setup requirements: inspiratory and expiratory positive airway pressure; backup rate; ratio of inspiratory time to expiratory time</td>
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<tr>
<td></td>
<td><strong>Average volume-assured pressure support (AVAPS)</strong></td>
<td>target tidal volume (8 ml/kg of ideal weight); Inspiratory positive airway pressure limits; respiratory rate</td>
<td>ensures a delivered tidal volume; compensates for diseases progression</td>
<td>more expensive than other modes</td>
</tr>
<tr>
<td></td>
<td>Applications: obesity-hypoventilation syndrome; neuromuscular disease; chronic obstructive pulmonary disease</td>
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</table>

volume adjusted despite variability in the patient effort, airway resistance, and lung or chest wall compliance. A particular benefit of this mode is that it may be modified as the disease progresses (as it occurs in neuromuscular disorders such as amyotrophic lateral sclerosis).\textsuperscript{1} Yet, this system remains controversial. It is not known if and to what extent hybrid ventilation modes (i.e. pressure-targeted ventilation with assured volume support) are beneficial in the management of chronic hypercapnic failure. Further large-scaled studies are needed.\textsuperscript{18} The various types of non-invasive positive pressure ventilation and their indications for the non-invasive ventilation for the various disorders are shown in Tables 4 and 5.

**Application and management of NIV**

**Nocturnal CPAP titration**

The titration of the therapeutic value of CPAP (value of positive pressure necessary to eliminate the sleep apnea) can be made with one of the following methods:

1. Sleep study with complete laboratory staff dedicated to monitoring and manual CPAP titration performed during polysomnography (the pressure is gradually increased to normalize the breathing pattern during sleep).\textsuperscript{52}

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volume adjusted despite variability in the patient effort, airway resistance, and lung or chest wall compliance. A particular benefit of this mode is that it may be modified as the disease progresses (as it occurs in neuromuscular disorders such as amyotrophic lateral sclerosis).\textsuperscript{1} Yet, this system remains controversial. It is not known if and to what extent hybrid ventilation modes (i.e. pressure-targeted ventilation with assured volume support) are beneficial in the management of chronic hypercapnic failure. Further large-scaled studies are needed.\textsuperscript{18} The various types of non-invasive positive pressure ventilation and their indications for the non-invasive ventilation for the various disorders are shown in Tables 4 and 5.
Table 5  Non-invasive ventilation indication.3,49,50,59

<table>
<thead>
<tr>
<th>Chronic obstructive pulmonary disease (COPD)</th>
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<tbody>
<tr>
<td><strong>NIV without backup rate</strong></td>
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<tr>
<td>PaCO\textsubscript{2} ≥ 50 mmHg when the patient is awake and O\textsubscript{2} saturation ≤ 88% (≥ 2 h of recording on nocturnal oximetry) while on the higher of 2 L per minute of O\textsubscript{2} and obstructive sleep apnea and CPAP treatment have been considered and ruled out by facility-based nocturnal polysomnography.</td>
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<tr>
<td><strong>NIV with backup rate, anytime after use without backup rate</strong></td>
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<tr>
<td>PaCO\textsubscript{2} ≥ 7 mmHg greater than the original qualifying result and O\textsubscript{2} saturation ≤ 88% for ≥ 5 min (2 h of recording on facility-based nocturnal polysomnography) while on NIV without backup rate and apnea–hypopnea index &lt; 5</td>
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<thead>
<tr>
<th>Restrictive thoracic disorders: progressive neuromuscular disease or thoracic cage abnormalities</th>
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<tr>
<td><strong>NIV with or without backup rate</strong></td>
<td></td>
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<tr>
<td>PaCO\textsubscript{2} ≥ 45 mmHg or O\textsubscript{2} saturation ≤ 88% for %minutes (≥ 2 h of recording on nocturnal oximetry) or (for neuromuscular diseases only) maximal inspiratory pressure (MIP) ≤ 60 cm H\textsubscript{2}O or FVC ≤ 50% of predicted</td>
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<tr>
<th>Central sleep apnea or complex sleep apnea syndrome</th>
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<tr>
<td><strong>NIV with or without backup rate</strong></td>
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<tr>
<td>All the following on facility-based on nocturnal polysomnography: apnea–hypopnea index &gt; 5, central events &gt; 50% of total, central events ≥ 5 per hour, excessive daytime sleepiness or disrupted sleep and significant improvement on NIV and FiO\textsubscript{2}</td>
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<table>
<thead>
<tr>
<th>Obstructive sleep apnea</th>
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<tr>
<td><strong>Continuous positive airway pressure (CPAP)</strong></td>
<td></td>
</tr>
<tr>
<td>Apnea–hypopnea syndrome index/respiratory disturbance index ≥ 15 (minimum 30 events) or apnea–hypopnea index/inspiratory disturbance index 5–14 with symptoms or cardiovascular risks (excessive daytime sleepiness, impaired cognition, mood disorders, insomnia, hypertension, ischemic heart disease, history of stroke)</td>
<td></td>
</tr>
<tr>
<td><strong>NIV without backup rate</strong></td>
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<td>All the following on facility-based on nocturnal polysomnography: apnea–hypopnea index &gt; 5, central events &gt; 50% of total, central events ≥ 5 per hour, excessive daytime sleepiness or disrupted sleep and significant improvement on NIV and FiO\textsubscript{2}</td>
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<table>
<thead>
<tr>
<th>Hypoventilation syndrome</th>
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<tbody>
<tr>
<td><strong>NIV without backup rate</strong></td>
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<tr>
<td>Awake PaCO\textsubscript{2} ≥ 45 mmHg and PaCO\textsubscript{2} ≥ 7 mmHg greater during sleep or upon awakening or O\textsubscript{2} saturation ≤ 88% for ≥ 5 min (≥ 2 h of recording on facility-based nocturnal polysomnography) with an apnea–hypopnea index &lt; 5</td>
<td></td>
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<tr>
<td><strong>NIV with backup rate</strong></td>
<td></td>
</tr>
<tr>
<td>Awake PaCO\textsubscript{2} up ≥ 7 mmHg from initial qualifying PaCO\textsubscript{2} despite using NIV without backup rate or O\textsubscript{2} saturation ≤ 88% for ≥ 5 min (≥ 2 h of recording on facility-based nocturnal polysomnography) while on NIV without backup and apnea–hypopnea index &lt; 5</td>
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</table>

(2) Complete polysomnographic study (with or without the continued presence of dedicated staff) with titration performed with auto-CPAP (usually the value of the 90th percentile).

(3) Polysomnographic full study or complete cardiorespiratory monitoring performed during nocturnal CPAP therapy whose value has been obtained on the basis of data extracted from the device auto-CPAP in the previous nocturnal recording (usually the value of the 90th percentile).

(4) Sleep study with complete laboratory staff dedicated to monitoring and titration of CPAP polysomnography performed in the course of using the split-night in which the patient is evaluated for 50% of the night in spontaneously breathing and the other 50% in incremental CPAP.1,69,70

Titration of PAP obtained by auto-CPAP therapy should be derived from visual analysis of a large recording period free of artifacts. The optimum pressure value of CPAP is the value which eliminates (in the course of a complete polysomnographic investigation) each apnea, hypoapnea, arterial desaturation, snoring, respiratory effort-related arousal (RERA) in each stage of sleep and body position. The same applies in the course of a complete cardiorespiratory monitoring.1,12 An acceptable level of CPAP leads to a low number of events residues during the titration procedures. The final value of pressure (PAP) is always a compromise between the function of patient adherence, the absolute value of PAP reached, and the clinical benefits derived.

It is also recommended that the procedures for titration of CPAP in points 2, 3 and 4 are made exclusively in patients with OSA in the absence of comorbidities such as COPD, chronic heart failure, and neuromuscular disorders.1,69–71

Management of non-invasive ventilation

Initiation and settings in case of nocturnal ventilation

The main objective of NIV use is the correction of blood gas values to near “normal” with the least possible discomfort or sleep disturbance. It is good practice to proceed in three successive steps. The first step is to choose and adjust the ventilator settings while the patient is awake,
Further and improves blood gases, lung function, hematocrit, and decrease COPD exacerbations rates. However, high-intensive NIV does not negatively influence sleep quality, compared to conventional ventilation strategies. Follow-up

Clinical follow-up and daytime arterial blood gases should be performed at least twice a year. The recordings during sleep (possibly identical to those performed for the adaptation to non-invasive ventilation), are useful. At any time, when there are indications of unsatisfactory results such as the recurrence of clinical symptoms and/or signs of hypoventilation on arterial blood gases, inadequate non-invasive ventilation should be suspected, and a complete objective assessment of ventilation during sleep with polysomnography must be undertaken.

Management of complications

Air leaks during ventilation The major potential adverse effect is the loss of effectiveness of the ventilation and therefore the potential fragmentation of sleep. A variety of more or less effective measures have been suggested to tackle the problem of leaks during NIV. These include the prevention of neck flexion, the semi-recumbent positioning of the patient, the use of a chin rest or a cervical collar to prevent opening of the...
Table 6  Management of complications and side effects of NIV.1,2

<table>
<thead>
<tr>
<th>Complication and/or side effect</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air leaks</td>
<td>Prevention of neck flexion</td>
</tr>
<tr>
<td></td>
<td>Semi-recumbent positioning</td>
</tr>
<tr>
<td></td>
<td>Use of chin rest</td>
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<tr>
<td></td>
<td>Use of cervical collar</td>
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<tr>
<td></td>
<td>Switch to controlled pressure mode</td>
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<tr>
<td></td>
<td>Decrease peak inspiratory pressure and increase volume</td>
</tr>
<tr>
<td></td>
<td>Optimize the interfaces (using oro-nasal mask)</td>
</tr>
<tr>
<td></td>
<td>Cold pass over</td>
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<tr>
<td>Nasal dryness, congestion</td>
<td>Heated humidifier</td>
</tr>
<tr>
<td>Aerofagia, eructation, flatulence, abdominal discomfort</td>
<td>Decrease peak inspiratory pressure below 25 cm H2O</td>
</tr>
</tbody>
</table>

Humidification of delivered gas may improve these symptoms. Sleep specialists should review the results of objective testing with the patient. Education of the patient is mandatory.

The choice of ventilator, its setting, the choice of interface between patient and ventilator are crucial for the success of NIV. A variety of masks are now available and manufacturers continue to improve mask design. Oronasal mask should be considered if the patient is mouth breather to avoid leaks through open mouth. In the past there were ventilators which had only pressure or volume controlled modes. Today most ventilators can work in either mode and the choice of the equipment should be considered by the patient’s point of view. The patient’s point of view is clinically relevant because better patient well-being is related to a better treatment adherence. This is a critical issue especially in patients chronically treated with non-invasive ventilation.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflicts of interest

The authors have no conflicts of interest to declare.

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