Non-Invasive Ventilation in Stable Chronic Obstructive Pulmonary Disease

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Abstract: The benefit of non-invasive ventilation (NIV) in stable chronic obstructive pulmonary disease (COPD) remains controversial. However, there is increasingly more evidence of NIV efficiency, especially high-flow NIV. This review presents the old and the new evidence of NIV effectiveness in stable COPD, considering pathophysiological arguments for NIV in COPD. Guidelines, randomized controlled trials (RCTs) and crossover studies included in review and metaanalysis based on patient-reported outcomes (PROs) have been analyzed. The role of NIV in rehabilitation and in palliative care and the role of telemedicine in relation with NIV are still up for debate. Challenges in choosing the right device and the optimal mode of ventilation still exist. There are also discussions on the criteria for patient inclusion and on how to meet them. More studies are needed to determine the ideal candidate for chronic NIV and to explain all the benefits of using NIV.

Keywords: COPD, NIV, pulmonary rehabilitation, telemedicine, ventilation, chronic treatment.

1. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive public health problem that affects an increasing number of patients due to population aging and is expected to be the third leading cause of mortality worldwide by 2020 [1]. Patients with advanced-stage COPD frequently develop nocturnal alterations in gas exchanges with pronounced respiratory failure, sometimes with both severe hypoxia and hypercapnia. They also experience waking symptoms such as dyspnea, leading to more frequent acute exacerbations or to severely impaired health-related quality of life (HRQoL) [2]. At this stage of the disease, pharmacological treatment options remain controversial and until now, only long-term oxygen therapy has been shown to improve hypoxemia, dyspnea and survival rates [3, 4]. Non-invasive ventilation (NIV) stands out among non-pharmacological treatments as a possible effective therapy in patients with chronic and stable hypercapnic COPD (Evidence B) [5]. Convincing evidence has demonstrated the benefits of NIV in acute respiratory failure [6]. Predictors, such as severe hypercapnia or acidosis, have been defined [7]. However, the benefits of chronic use of NIV in the context of stable hypercapnic COPD have been unclear due to the conflicting results obtained by various studies. This has led to a great variety in applying long-term NIV to COPD patients throughout Europe [8]. Nevertheless, increased experience and technological advances - the introduction of high-intensity (HI)-NIV - have proven great benefits [9-12] and the discussion about NIV in chronic COPD was revived. Moreover, NIV seems to be widely used even without clear evidence of its effectiveness [8, 13].

The benefits of NIV in the chronic treatment of COPD patients have long been debated. The pathophysiological effects induced by NIV in these patients must be understood if we want to make progress in this field. The initial interest in using (intermittent) NIV for patients with severe COPD came from physiological studies on the respiratory muscle function. Regional changes in airway caliber, perfusion and ventilation-perfusion ratio are some of the relevant pathophysiological parameters [14]. (Positive) NIV could improve the gas exchange function by increasing the Tidal volume and by producing positive airway pressure [11] which relaxes and relieves respiratory muscle fatigue and improves the sensitivity of the respiratory center to carbon dioxide (CO₂) [15].

Thus, to address the controversies regarding long-term NIV when used in stable hypercapnic COPD patients, we are reviewing and summarizing whether the most important recent evidence indicates indeed that long-term NIV plays a role in chronic hypercapnic COPD patients.

2. HISTORY OF NIV IN COPD

Since the 1980s, there has been an increased interest in using long-term NIV in patients with stable severe COPD. These first studies (Celli B 1989; Gigliotti F 1991; Gigliotti F 1994; Goti P 1995; Gutierrez M 1988; Scano G 1990,
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Shapiro SH 1992; Zibrik JD 1988) [16-23] focused on negative pressure ventilation, which served as a rest therapy for patients with stable severe COPD because their respiratory muscles were in a state of chronic fatigue. Thus, the use of assisted ventilation during the night would allow the muscles to rest and the patient’s function would improve, making them feel better the following day. However, the results varied across the studies and the majority concluded the tolerance was rather poor for long-term use [16-23].

With more widely available positive pressure ventilation in COPD in the 1990s, the benefits of this easier and tolerable ventilation mode in stable severe COPD patients [4, 24-29] were still not clearly demonstrated. Studies returned better results, but still showed suboptimal tolerance with inadequate ventilation [27].

Currently, high-pressure NIV is preferred in stable severe COPD. The concept is not new, it was introduced by Windisch in 2002 [10]. Further studies showed improvements in nocturnal and diurnal gas exchange due to efficient ventilation [10, 11, 30, 31]. Windisch et al. started to use ventilation with high inspiratory pressures and defined that higher inspiratory positive airway pressure (IPAP) levels aimed for maximal partial arterial carbon dioxide (PaCO2) reduction [31], with some impressive outcomes. A randomized cross-over trial showed that HI-NIV improved gas exchange and HRQoL versus a beforehand low-intensity (LI)-NIV settings [11, 32]. Nonetheless, the settings used for these studies were extremely high and, although compliance and sleep quality were not worse with HI-NIV [32, 33], in real life, patients often have difficulties tolerating HI-NIV [34].

Today, invasive and non-invasive home ventilation has become a well-established treatment option. In the past two decades, a large amount of research work on this topic has been published, with a focus on the question of whether long-term, mostly intermittent NIV therapy in a home setting can improve the outcomes in patients with chronic respiratory failure, such as:

- Functional parameters: lung function (forced expiratory volume in one second (FEV1), forced vital capacity (FVC), ventilator or breathing pattern), respiratory muscle function and gas exchange (arterial blood gases, arterial oxygen saturation and transcutaneous carbon dioxide tension);
- Clinical signs: symptoms (dyspnea), exercise tolerance, sleep efficiency;
- Morbidity (hospital or intensive care unit (ICU) admissions, number or severity of the acute exacerbations, quality of life);
- Mortality/ survival;
- Comfort.

3. PATHOPHYSIOLOGIC ARGUMENTS FOR NIV IN COPD (ACUTE AND CHRONIC)

Respiratory failure is an important complication of COPD. The classical theory regarding the pathophysiology of respiratory failure in COPD talks of disturbance in the ventilation/perfusion ratio and relative hypoventilation [35]. The use of multiple inert gas elimination techniques has confirmed the extent of these changes. Patients with COPD who develop respiratory failure present greater dead space and ventilation are predominant in this region, which will lead to an increase in the ventilation-perfusion ratio [36]. Another finding is the increased perfusion in not so well ventilated areas (low ventilation/perfusion ratio), which induces hypoxemia. Even though these aspects are known, their cause is still under debate.

The changes in pulmonary mechanics in case of hypercapnic respiratory failure seem to be central [37]. Patients with COPD and respiratory failure should greatly increase ventilation to offset the increased ventilation/ perfusion ratio. However, this does not happen, due to both severe limitations of the flow seen in severe COPD and a decrease in the respiratory functional reserve due to the inability of the respiratory muscles to shorten because of hyperinflation. Fatigue of the respiratory muscles may appear due to their elevated stimulation to develop the pressure required to counterbalance the increased ventilation/ perfusion ratio [38], thus further reducing muscle contraction force.

On the other hand, inflammation, bronchial wall edema and bronchoconstriction result in increased airway collapse pressure. Thus, the tele-expiratory volume increases over the normal functional residual capacity, causing the occurrence of pulmonary dynamic hyperinflation and intrapulmonary tele-expiratory pressure (intrinsic positive and expiratory pressure PEEP), which will have important consequences on pulmonary mechanics [39].

The respiratory drive, which causes respiratory muscle contraction, is also low, influenced by pulses from mechanical receptors and chemoreceptors. This change is most important initially during the night (Calverley 1982). However, the quality of sleep in patients with COPD and respiratory failure is poor, therefore hypventilation during sleep plays a less important role than in other chronic respiratory diseases [40, 41].

Even though patients with COPD and chronic respiratory failure have a change in respiratory drive, there is a difference in breathing patterns between patients who become hypercapnic and those who remain normocapnic. Normocapnic patients tend to adopt a rapid breathing pattern so that PaCO2 is inversely proportional to the current volume (low inspiratory time) and directly proportional to the maximum pleural pressure it can develop [42]. This type of breathing, if adopted on a long-term basis, increases the work of breathing and lead to respiratory muscle fatigue, thus generating a vicious circle [43].

Exacerbation of COPD causes a temporary worsening of these mechanisms, with increased severity of respiratory failure which, in the absence of rapid interventions, can put the patient's life at risk. NIV is a method of reversing these mechanisms and providing the ventilator support needed to improve gas exchange (GOLD 2018, 41). Moreover, there is a direct correlation between the rapid use of NIV in patients admitted for COPD exacerbation with hypercapnic respiratory failure and the favorable outcome (improved blood gas and shorter length of stay) [7].
It has been shown that NIV in patients with COPD can reduce hyperinflation, resulting in improved ventilation/perfusion ratio and, implicitly, gaseous changes. During an exacerbation of COPD, there is an increase in resistance in distal airways; the use of NIV, and in particular HI-NIV, can counterbalance these changes by decreasing the airway resistance and reducing the hyperinflation [14].

The role of mechanical ventilation in patients with COPD and hypercapnic respiratory failure can be seen as a support for respiratory muscles. Pressure support reduces respiratory mechanical work and electrical activity ( electromyographic study) of the diaphragm [44]. Thus, pressure support helps generate an appropriate current volume. Addition of PEEP to pressure support will counterbalance the intrinsic PEEP and increased airway resistance, specific to severe COPD, which will improve respiratory mechanics [45].

4. THE ROLE OF NIV IN COPD EXACERBATION

The use of NIV in COPD exacerbation is well known and the initiation indications are well established. Before NIV, one-fifth to one-third of COPD patients hospitalized with secondary respiratory failure of COPD exacerbation died in hospital despite the invasive mechanical ventilation [46]. The procedure of tracheal intubation and assisted ventilation is associated with high mortality and morbidity, and once invasive ventilation is initiated, ventilation weaning may be difficult [47]. NIV comes as a treatment alternative for patients with hypercapnic respiratory failure secondary to an acute exacerbation of COPD.

Current studies assess the effectiveness of NIV in patients with COPD exacerbation based on decreasing respiratory rates [48, 49], respiratory mechanical work [49, 50] and dyspnea severity [48, 49, 51].

A meta-analysis from 2003 [52] shows that the use of NIV, in addition to standard therapy, results in a significant reduction in mortality, complications, length of stay, and improvement in blood gas parameters (oxygenation, increased pH, decreased pCO2). Moreover, the use of NIV reduces the complications associated with invasive ventilation, ensuring a similar efficiency [52].

In patients with mild to moderate respiratory failure (pH 7.25-7.35), NIV may be administered several hours a day [<12h] with 15-20% failure rates [52, 53]. In patients with severe respiratory failure (pH <7.25), the risk of NIV failure increases considerably to 52-62% [54, 55]. However, current studies do not show an increase in mortality if these patients are initially on NIV; taking into account the high mortality rate of invasive ventilation, a clinical trial of NIV for these patients is justified [54, 55].

There are also contraindications of NIV in patients with respiratory failure secondary to COPD exacerbation. Among the absolute contraindications are [56-58]:

- Cardiac and/or respiratory arrest;
- Severe encephalopathy (Glasgow Coma Scale/Score <10);
- Hemodynamic instability (+/- angina pectoris);
- Severe gastrointestinal hemorrhage;
- Upper airways obstruction;
- Increased risk of aspiration;
- Inability to maintain secretion clearance.

5. CLINICAL GUIDELINES IN RELATION TO NIV IN STABLE COPD

The guidelines were updated over the decades according to the current literature, technical advances and healthcare developments [33]. Although the guidelines indications vary, the severe COPD patients most commonly subject to NIV are those with persistent hypercapnia and oxygen desaturation during sleep despite additional oxygen therapy and/or those with an acute exacerbation that requires sustained use of NIV during hospitalization [59] (Table 1).

From a historical point of view, one of the first reports, the International Association of clinical pharmacists (ACCP 1999) [60] encouraged physicians to prescribe positive pressure ventilation devices to COPD patients if the physiological criteria below were fulfilled. Later on, the French Society of Pneumology (latest update in 2014) [61] and the German Society of Pneumology (latest update in 2017) [59] recommend different criteria for using NIV in severe COPD patients.

Starting 2004, the British Thoracic Society [27] recommends that adequately treated patients with chronic respiratory failure who have required assisted ventilation (whether invasive or non-invasive) during an exacerbation or who are hypercapnic or acidic on long-term oxygen therapy (LTOT) be referred to a specialist center for considering long-term NIV.

The 2014 GOLD guide [62] recommends the use of NIV in patients with respiratory acidosis or severe dyspnea with suggestive clinical signs. In the updated 2018 GOLD document [5], there are no criteria for initiating VNI at home (except for patients with both COPD and obstructive sleep apnea), while the indication concerns those with daytime persistent hypercapnia (PaCO2 ≥52 mmHg).

6. RANDOMIZED CONTROLLED TRIALS (RCTS) AND CROSSOVER STUDIES INCLUDED IN REVIEW AND META-ANALYSIS: PATIENT-REPORTED OUTCOMES (PROS)

In the 2000s, studies and systematic reviews [63, 64] on the effects of chronic NIV in stable hypercapnic COPD patients have provided contradictory results due to small number of patients (between 7 and 47 patients) [63], uncontrolled designs and different bi-levels of PAP pressures delivered by the ventilator (IPAP between 10-18 cmH2O and expiratory PAP (EPAP) between 2-4 cmH2O [63]. Only recently, several new large RCTs have evaluated the potential efficacy of long-term high-level NIV on stable hypercapnic COPD patients with chronic RF.

In 2003, Wijkstra et al. [63] analyzed data from 4 RCTs (Casanova et al, 2000; Gay et al, 1996; Meecham Jones, 1995; Strumpf et al, 1991) [24, 28, 30, 65] that compared NIV with conventional management of patients with COPD and stable respiratory failure for minimum 5h per night and
non-invasive ventilation in stable chronic obstructive pulmonary disease

Table 1. NIV indications over time in guidelines.

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Symptoms</th>
<th>Hypercapnia</th>
<th>Hypoxemia</th>
<th>Hospitalization</th>
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<tr>
<td>ACCP 1999 [60]</td>
<td>YES</td>
<td>PaCO2 ≥ 55 mm Hg or PaCO2 50 - 54 mm Hg and nocturnal desaturation or PaCO2 50 - 54 mm Hg and hospitalization related to hypercapnic respiratory failure (RF)</td>
<td>Nocturnal SpO2 ≤ 88% (pulse oximeter) for 5 minutes under oxygen therapy 2 ≥ L/min</td>
<td>Recurrent (≥ 2 in a 12-month period) episodes of hypercapnic RF</td>
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<tr>
<td>French Society of Pneumology, 2014 [61]</td>
<td>-</td>
<td>PaCO2 &gt; 55 mm Hg</td>
<td>Clinical signs of nocturnal alveolar hypoventilation</td>
<td>High frequency of hospitalizations</td>
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<tr>
<td>German Respiratory Society (DGP) 2017 (Wolfram Windisch 2017) - update of 2010 recommendation [59]</td>
<td>YES</td>
<td>Chronic diurnal PaCO2 ≥50 mmHg; Nocturnal PaCO2 ≥55 mmHg; Mild diurnal hypercapnia (PaCO2 46–50 mmHg) and an increase in PtcCO2 ≥10 mm Hg during sleep; Persistent PaCO2 &gt; 53 mm Hg present at least 14 days after finishing acute ventilation therapy for acute respiratory acidosis;</td>
<td>NO</td>
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Abbreviations: PaO2: partial pressure of arterial oxygen; PaCO2: Partial pressure of arterial carbon dioxide; RF: respiratory failure; SpO2: peripheral capillary oxygen saturation; PtcCO2: Partial pressure of transcutaneous carbon dioxide.

minimum 3 weeks (an average of 3 months) follow-up, centered on gas exchange, pulmonary function, functional exercise capacity and HRQoL. The 3-week duration was set, as the authors [63] considered this period to be optimal for adjustment and familiarization to ventilatory support. Later on, a comprehensive meta-analysis of Kolodziej MA et al. [64] included 6 RCTs [5 days to 2 years] and 9 non RCTs [1-3 days to 6 months] with 466 chronically dyspneic COPD patients, with a baseline FEV1 < 1 L and FEV1/FVC < 50% predicted, the majority with PaCO2 > 50 mmHg. Bilevel Positive Airway Pressure (BiPAP) Spontaneous (ST) mode was used in up to half of the studies included in this meta-analysis, while the other studies used the spontaneous (S) mode, with IPAP delivered from 10 to 26 cmH2O and EPAP ≤ 5 cmH2O [64]. The authors analyzed the evidence to support the use of bilevel NIV in chronic RF in COPD patients via health-related outcomes, morbidity (hospital admissions, intensive care unit admissions and hospital length of stay) and mortality [survival estimates].

The recent publication [27, 66, 67] has also provided new evidence on routine long-term NIV in stable COPD patients, centered on patient-reported outcomes (PROs). For example, Struikes FM et al. [68] generated subgroup analyses based on results from previous studies [27, 30, 60, 68] and assumed that higher IPAP levels [≥ 18 cmH2O], more ventilation hours [≥ 5 h per night at least 3 consecutive weeks] and higher baseline PaCO2 [≥ 55 mmHg] improve PaCO2 when patients were followed up between 3 months to 1 year with NIV. Two more recent meta-analyses [66, 76] provided new evidence from updated new RCTs regarding NIV in the setting of stable COPD. All studies included in the above meta-analyses are detailed in the tables below (Tables 2 and 3).

7. OUTCOMES

7.1. Gas Exchange

Gas exchange was obtained in almost all studies across the literature. In recent RCTs (Gay et al., 1996; McEvoy et al., 2009; Struij et al., 2014; Köhnlein et al., 2014; Clini et al., 2002; Casanova et al., 2000; Zhou et al., 2017; Meecham Jones, 1995; Strumpf et al., 1991; Diaz el al 2002; Renston 1994; Garrod 2000) [2, 4, 24, 25, 27, 30, 65, 69-72], a significant decrease in PaCO2 was seen across NIV-treated groups (and a greater reduction in the RCTs with longer hours of bilevel NIV use), with no improvement in PaO2. When subgroup analysis of RCTs was compared [≤ 8 weeks or > 8 weeks], no evidence of improved gas exchange was found [64]. Jones et al. [30] reported a consequent decrease of hypercapnia via nocturnal monitoring of end-tidal carbon dioxide tension and partial pressure of transcutaneous carbon dioxide (PtcCO2).

7.2. Lung Function

There were no demonstrated benefits regarding the improvement of FEV1, FEV1/FVC in the NIV groups [4, 24, 25, 27, 28, 30, 65, 69-72]. One RCT [69] that included residual volume (RV) as dynamic hyperinflation reported a reduction in RV after 3 weeks of bi-level NIV. No benefits were demonstrated when RCTs analysed the respiratory muscle function in the NIV groups [24, 25, 69].

7.3. Exercise Tolerance

A number of studies [2, 25, 66, 69] did not show significant improvement in the 6-minute walk distance test (6MWD) in
Table 2. Studies included in the meta-analysis or reviews.

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<tr>
<td>Strumpf et al, 1991 [28]</td>
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<td>Renston et al, 1994 [69]</td>
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<td>Meecham Jones, 1995 [30]</td>
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<td>Gay et al, 1996 [65]</td>
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<td>Casanova et al, 2000 [24]</td>
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<td>Garrod et al, 2000 [70]</td>
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<td>Diaz et al, 2002 [72]</td>
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<td>Clini et al, 2002 [25]</td>
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<td>Chiang et al, 2004 [73]</td>
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<td>Sin et al, 2007 [74]</td>
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<td>Xiang et al, 2007 [75]</td>
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<tr>
<td>Duverman et al, 2011 [76]</td>
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<td>Funk et al, 2011 [77]</td>
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<td>Bhatt et al, 2013 [78]</td>
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<td>Köhnlein et al, 2014 [79]</td>
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<td>Struik et al, 2014 [27]</td>
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<td>Zhou et al, 2017 [71]</td>
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Notes: √ study included in meta-analyses and/or reviews.

Table 3. Inclusion criteria and outcomes reviewed in the meta-analysis or reviews.

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<tbody>
<tr>
<td>Studies Included</td>
<td>RCTs all languages, up to 2000</td>
<td>RCTs and non-RCTs (within subject crossover design) English, all languages, up to 2003</td>
<td>RCTs, up to August 2012</td>
<td>RCTs and randomized crossover studies, up to March 2015</td>
<td>RCTs, Up to May 2017</td>
</tr>
<tr>
<td>Subgroup Analyses</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>NIV groups</td>
<td>Nocturnal NIV via nasal or facemask for at least 5 h/day for at least 3 weeks</td>
<td>NIV via nasal, oronasal and/or total face mask interfaces</td>
<td>NIV applied through nasal or face mask, for at least 5 hours during the night, for at least 3 consecutives weeks.</td>
<td>NIV via nasal cannula or facemask for more than 3 weeks.</td>
<td>NIV at least 5 hours per day for at least 3 months in PaCO2 &gt; 50 mmHg</td>
</tr>
<tr>
<td>Control groups</td>
<td>usual management for COPD but not NIV</td>
<td>LTOT, shame ventilation, exercise</td>
<td>LTOT, bronchodilators, theophylline and inhaled and/or oral steroid</td>
<td>usual management for COPD but not NIV</td>
<td>usual management for COPD but not NIV</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Gas exchange</td>
<td>PaCO2, PaO2</td>
<td>PaCO2, PaO2, SaO2, PtcCO2</td>
<td>PaCO2, PatO2</td>
<td>PaCO2, PaO2</td>
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<tr>
<td>Symptom relief</td>
<td>dyspnea</td>
<td>dyspnea</td>
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<tbody>
<tr>
<td><strong>Functional status</strong></td>
<td>different dyspnea measurement scales</td>
<td>health-related quality-of-life measurements</td>
<td>health-related quality-of-life measurements</td>
<td>health-related quality-of-life measurements (HRQoL)</td>
<td></td>
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<tr>
<td><strong>Exercise tolerance</strong></td>
<td>6MWD</td>
<td>6MWD and shuttle walking test</td>
<td>6MWD</td>
<td>6MWD</td>
<td>6MWD</td>
</tr>
<tr>
<td><strong>Lung function</strong></td>
<td>FEV1, FVC</td>
<td>FEV1, V'E, VT, VT/inspiratory time (tI) ratio</td>
<td>FEV1, FVC</td>
<td>FEV1, FVC, PImax, PEmax,</td>
<td>FEV1, FVC, PImax</td>
</tr>
<tr>
<td><strong>Respiratory muscle function</strong></td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td><strong>Morbidity</strong></td>
<td>no</td>
<td>hospital admissions, ICU admissions and hospital length of stay</td>
<td>no</td>
<td>hospitalization and/or ICU admission</td>
<td></td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>survival</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
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<tr>
<td><strong>Comfort/compliance</strong></td>
<td>sleep efficiency</td>
<td>yes (sleep, asynchrony)</td>
<td>sleep efficiency</td>
<td>sleep efficiency</td>
<td>-</td>
</tr>
</tbody>
</table>

**Abbreviations:** RCTs: Randomized controlled trials; NIV: Noninvasive ventilation; COPD: chronic obstructive pulmonary disease; LTOT: Long-term oxygen therapy; PaO2: partial pressure of arterial oxygen; PaCO2: Partial pressure of arterial carbon dioxide; SaO2: arterial oxygen saturation; PtCO2: Partial pressure of transcutaneous carbon dioxide; 6MWD: 6-min walking distance; ICU: intensive care unit; HRQoL: health-related quality of life; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; PImax: maximal inspiratory pressure, PEmax: maximal expiratory pressure, V'E: minute ventilation, VT: tidal volume.

the NIV group, in terms of assessing the exercise capacity. One RCT [70] showed an increase of 100 m on the shuttle walking test (SWT) after 8 weeks of NIV, in the NIV and exercise group vs control group (exercise alone). It is not clear whether NIV alone or the combined interventions (bilevel NIV and exercise) contributed to this improvement [64].

### 7.4. Dyspnea

Dyspnea was measured in different, but comparable scales across studies (e.g., Casanova et al. used Medical Research Council (MRC) dyspnea and BORG scale, Clini et al. scale subjective dyspnea), [24, 25], Garrod et al. chronic respiratory disease questionnaire (CRDQ) [70], Strumpf used Dyspnea scale of Mahler [28]. Almost all above-mentioned RCTs reported significant improvement and flat evolution (up to 2 years) in dyspnea in the bilevel NIV group [24, 25, 65, 69, 70, 72]. Other studies [27, 71] did not show a significant difference in dyspnea. One explanation is that nocturnal NIV, which improves alveolar ventilation and reduces hyperinflation, in addition to exercise rehabilitation, has the potential to improve dyspnea, by the added effect.

### 7.5. Quality of Life

Different scales were used across studies. Meecham Jones [30] was one of the first non-RCT that studied quality of life in NIV groups and showed improvement in St. George's Respiratory Questionnaire (SGRQ) scores. Other studies [25, 30, 72] demonstrated significant improvement in the quality of life, from baseline to 2 years follow-up in NIV groups, on at least one validated measurement scale. Significant improvement in various validated measurement scales [30, 70] was found to be largely due to either symptom improvement (CRDQ total score and the fatigue component), or addition of exercise in the NIV group.

### 7.6. Mortality and Morbidity

Mortality was not significantly reduced in most RCTs [2, 4, 24, 25, 27, 71] in patients treated with NIV. Moreover, in the meta-analysis by Hao Liao [66], the 310-patient subgroup on NIV treatment (which seems to decrease PaCO2) had a lower risk of mortality than those in the control group (LTOT only).

Morbidity was measured differently across studies. Because the methods and frequency of acute COPD exacerbation evaluation were not similar, some literature did not provide sufficient data. Few studies evaluated the frequency of COPD exacerbations, including the hospitalization and/or intensive care unit admission [4, 27 24, 25, 71], and concluded that there was no significant difference in hospitalization rate and/or ICU admission rate between the treatment group (NIV and LTOT) and the control group (LTOT). Moreover, NIV decreases total hospital admission rates at 3 months in the treatment group, compared with the control group [24, 25, 27]. This decrease in total hospital admission rates was maintained after one year of follow-up in the Köhnlein study [27].

Sleep efficiency, defined as time asleep as a percentage of total time in bed, did not improve after 3 months of NIV treatment [24, 28, 30, 65].

### 7.7. Compliance/Tolerance

Studies that reported the above-mentioned outcomes were performed on a short period of time [24, 80] with short accommodation periods and high or low bilevel ventilator
pressure, which may have contributed to intolerance. In the studies (longer than 3 months), the most reported complaints were related to asynchrony [26] and sleep [28, 71, 70].

7.8. Cardiac Outcomes

Long-term home NIV (after 6 weeks) with adequate pressure to improve gas exchange and HRQoL has differential effects on cardiac output, depending on the patient and on ventilator settings [81].

7.9. Anemia

Anemia is reported as an independent negative predictor of exacerbations and mortality in severe COPD patients, as previously suggested, namely that low hemoglobin levels may impair gas exchange and cardio-respiratory clinical parameters in COPD patients [82, 83].

Despite some positive results, RCT is yet to reach an agreement regarding long-term NIV in stable COPD patients with respiratory failure. Thus, the indication should be carefully considered; concerns regarding patient selection (stable vs. after exacerbation COPD patients; diagnostic criteria of chronic hypercapnic respiratory failure), the optimal place to initiate NIV (home vs. hospitalization) and the optimal ventilatory settings (NIV hours per day using, high level vs. low-level NIV) still exist.

8. NON-INVASIVE VENTILATION AND PULMONARY REHABILITATION

Pulmonary rehabilitation is a complex intervention, based on a detailed assessment of the patient, followed by indications of therapies to induce the improvement of the physical and psychosocial condition of patients with chronic lung disease [84]. Pulmonary rehabilitation is recommended by GOLD 2018 [5] as an integrated part of COPD patient care, as it improves effort capacity and quality of life, improves dyspnea and decreases the number of exacerbations, regardless of COPD severity [85].

Sometimes, these goals can be difficult to achieve. The patients with severe COPD, especially those with hypercapnia, have an extremely limited tolerance to exercise, due to both dyspnea and low energy reserve [86]. The RECOVER clinical trial published in 2011 that followed patients with severe, stable COPD, evaluated the effects of NIV in addition to a rehabilitation program compared to rehabilitation program only [76, 87]. The ventilation settings were designed to maintain the patient daytime normocapnia using high IPAP pressures and increased backup respiratory rates. The patients were hospitalized for 7 days, during which two blood samples were collected to test for blood gases, then the patients were followed-up for 2 years. The mean ventilation values were 24 cmH2O for IPAP and a backup respiratory rate of 18 breaths/min. The results were satisfying; only 3 out of 31 patients in the combined NIV/rehabilitation group withdrew from the study. There was also a significant improvement in the quality of life and dyspnea in this group. Another important aspect observed in patients in the combined NIV/ rehabilitation group was the stabilization or even improvement of the FEV1 over the entire follow-up period of 2 years.

Another study followed 40 patients with COPD GOLD IV, with an indication for NIV and pulmonary rehabilitation [79]. The results were compared with a control lot, to which only pulmonary rehabilitation was applied. The average pressure selected for IPAP was 17.5 +/- 4.4 cmH2O and for EPAP, 4.5 +/- 0.9 cmH2O. In the group with NIV added to pulmonary rehabilitation, an improvement in the 6MWD test was observed, by 82m (vs. 50m in the rehabilitation-only group, p <0.04). Also, the combined NIV/rehabilitation group has seen an improvement in FEV1, pulmonary hyperinflation, and quality of life, which were not observed in the group with pulmonary rehabilitation only.

The physical effort in patients with COPD can cause an increase in inflammatory systemic markers [88], which may aggravate COPD comorbidities. NIV can prevent Interleukin 6 growth, as a response to a physical effort in patients with COPD and reduced muscle reserve [89].

Some authors have even confirmed the utility of NIV during pulmonary rehabilitation sessions [90, 91]. However, in this context, there are some issues that are worth mentioning, especially those related to the interface. During physical exercise, most patients prefer predominantly oral respiration, so a facial mask should be indicated. But its use may induce more discomfort than the nasal mask. Another important aspect is that reduced compliance was seen in patients receiving NIV during rehabilitation [92]. Moreover, initiating the session under NIV requires extra time (on average 17 minutes) to set up and mount the ventilator [93].

However, there are many questions that have not been answered yet. These include identifying the ideal candidate, establishing a protocol (night time NIV and/or NIV during exercises) and what are the best parameters that can be established in such patients.

9. NIV AND PALLIATIVE CARE OF PATIENTS WITH SEVERE COPD

The American Thoracic Society recommends that palliative care be available for all patients, regardless of the degree of dyspnea [94]. NIV is used in up to 1/3 of COPD cases with a very low life expectancy [87]. The use of NIV in this context is not well supported by clinical trials, but the improvement of dyspnea and oxygenation, and the increase in quality of life can be sufficient arguments [76]. One aspect to be considered is the patient's decision. Some patients regard NIV as an "obstacle" in letting them die, prolonging their suffering, especially through the mask, which may be uncomfortable, induce claustrophobia and prevent communication with the close ones [76].

Thus, their needs must be established through a clear dialogue between the medical team and the patient, regarding the diagnosis of COPD, implications, complications and a plan to anticipate the evolution of symptoms and their approach.

10. INITIATION OF NON-INVASIVE VENTILATION. IN-HOSPITAL OR AT HOME? THE ROLE OF TELEMEDICINE

Initiating of NIV at home can be an attractive aspect for both the patient and the healthcare system. However, this
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Prior to initiating long-term NIV, patients should be properly evaluated for the choice of the ideal candidate. Clinical history, diurnal symptoms (dyspnea, exacerbations, HRQoL) and nocturnal symptoms (including suspicion of obstructive sleep apnea syndrome), gas exchange (by arterial blood pressure), and pulmonary function must be assessed [2, 76].

Currently, there are no guidelines recommendations for optimal settings. Older studies used lower IPAP pressures, and probably this is the cause for inconsistency between their findings. In fact, it is recommended to use what is called HI-NIV, defined as "using higher IPAP levels than used in most of the older RCTs in addition to controlled ventilation aiming for maximum PaCO2 reduction" [31].

The benefits of HI-NIV are certain, reducing PaCO2 to an optimal level, improving dyspnea and increasing quality of life without a significant change in sleep quality [103].

Another study comparing the effects of HI-NIV vs. LI-NIV observed a significant increase in expiratory volumes (measured with a pneumotachograph), an increase in compliance with a significantly higher number of hours/day and a significant increase in FEV1, effort tolerance and reduction of diurnal PaCO2 in the HI-NIV group [32].

Windisch et al. showed that the use of HI-NIV improves the respiratory pattern, with increasing current volumes, decreasing the respiratory rate, obtaining better ventilation (expressed by increased minute-volume ventilation) [12]. Another observation made by the authors is a stable daytime PaCO2, explained by resetting the respiratory drive and reducing pulmonary hyperinflation (which determine pulmonary mechanics to improve).

Few studies have assessed the effects of HI-NIV on the respiratory drive, the likely explanation being the improvement in respiratory center chemosensitivity and in lung gas exchange, by improving ventilation [15, 104].

However, there are patients with severe COPD with a reduced respiratory reserve, which breath close to the threshold of respiratory exhaustion. In these patients, the benefits of HI-NIV were observed, probably by the second proposed mechanism - the reduction of hyperinflation (improvement of RV) [72]. In these patients, there was an increase in FEV1 under HI-NIV, which was maintained over time [2, 11, 76]. One of the explanations could be the counterbalance bronchoconstriction by increasing intra-bronchial pressure [105-107]. Another mechanism likely involved is an amelioration of respiratory muscle fatigue [108]. Unfortunately, there are no studies to fully explain this hypothesis.

There are also negative aspects to HI-NIV, such as longer time needed for patients to adapt to this mode [32, 81]. It underlines once again the importance of carefully following the HI-NIV initiation, which may increase patient compliance and allow for optimal ventilation parameters.

The patient with severe COPD is a complex patient with multiple comorbidities, the cardiovascular ones being the most important [5]. HI-VNI may negatively influence the cardiac function, an IPAP pressure of 28 cmH2O may decrease left ventricular ejection fraction (LVEF) [109]; however, this study followed patients for a short period of
time and did not assess the clinical impact. Another study did not show alterations of cardiac output or NT-proBNP [81]. This aspect should be clarified by studies on larger patient populations, followed over a longer period.

Some patients with severe COPD under HI-NIV manifest an exacerbation of dyspnea when NIV is discontinued (deventilation dyspnea). Respiratory muscles have been involved, which must resume their activity without the ventilator support or sudden change in intrabronchial pressure when the ventilator stops [110, 111].

The following parameters can predict the NIV success in patients with acute respiratory failure secondary to COPD exacerbation [112]:

- Low leaks;
- Low severity of the disease;
- Respiratory acidosis with PaCO2 > 45 mmHg but <92 mmHg;
- pH <7.25 but> 7.22;
- Improvement of gasometrical parameters in 2h after initiation of NIV;
- Improvement of respiratory frequency and heart rate.

### 12. DISADVANTAGES AND COMPLICATIONS OF THE NIV

The type of interface used is a determinant factor. Nasal masks have the advantage of adding less dead space and are generally well tolerated. Among the disadvantages of this type of mask are the large leaks in those who prefer oral respiration and a slower improvement of blood gas parameters. The full-face mask is the most effective, but less tolerated, does not allow for verbal communication, and in some patients, it can induce a degree of claustrophobia. The "helmet" interface is usually well tolerated, it is easy to mount, but less effective in correcting hypercapnia and reducing the respiratory effort, comes with a high level of noise and can induce internal ear injuries and is not currently recommended in patients with respiratory failure [75, 77, 99].

The most important complication of NIV is the failure to identify the ideal patient. At the initiation of NIV, especially in acute patients, careful monitoring of arterial blood gases is mandatory, and patients who do not get relief after 4-6 hours of use should be evaluated for invasive mechanical ventilation. Other complications are due to the interface being used, which can induce discomfort, facial erythema,

<table>
<thead>
<tr>
<th>Study (Author, Year)</th>
<th>Study Design</th>
<th>Length</th>
<th>IPAP (mmHg)</th>
<th>EPAP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strumpf et al, 1991 [28]</td>
<td>cross-over</td>
<td>3 months</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Renston et al, 1994 [69]</td>
<td>parallel</td>
<td>&lt; 1 week</td>
<td>15-20</td>
<td>2</td>
</tr>
<tr>
<td>Meecham Jones, 1995 [30]</td>
<td>cross-over</td>
<td>3 months</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Gay et al, 1996 [65]</td>
<td>parallel</td>
<td>3 months</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Garrod et al, 2000 [70]</td>
<td>parallel</td>
<td>8 weeks</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>Diaz et al, 2002 [72]</td>
<td>parallel</td>
<td>3 weeks</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Clini et al, 2002 [25]</td>
<td>parallel</td>
<td>2 years</td>
<td>14.6</td>
<td>3.8</td>
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<tr>
<td>Chiang et al, 2004 [73]</td>
<td>parallel</td>
<td>6 months</td>
<td>11.8</td>
<td>4.5</td>
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<tr>
<td>Sin et al, 2007 [74]</td>
<td>parallel</td>
<td>3 months</td>
<td>15.5</td>
<td>4</td>
</tr>
<tr>
<td>Xiang et al, 2007 [75]</td>
<td>parallel</td>
<td>2 years</td>
<td>16-20</td>
<td>2-4</td>
</tr>
<tr>
<td>McEvoy et al, 2009 [4]</td>
<td>parallel</td>
<td>2.21 years</td>
<td>12.8</td>
<td>5.1</td>
</tr>
<tr>
<td>Duiverman et al, 2011 [76]</td>
<td>parallel</td>
<td>2 years</td>
<td>23</td>
<td>6</td>
</tr>
<tr>
<td>Funk et al, 2011 [77]</td>
<td>parallel</td>
<td>1 year</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Bhatt et al, 2013 [78]</td>
<td>parallel</td>
<td>6 months</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Köhnlein et al, 2014 [79]</td>
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<td>1 year</td>
<td>21.6</td>
<td>4.8</td>
</tr>
<tr>
<td>Struijk et al, 2014 [27]</td>
<td>parallel</td>
<td>1 year</td>
<td>19.2</td>
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<tr>
<td>Zhou et al, 2017 [71]</td>
<td>parallel</td>
<td>3 months</td>
<td>17.8</td>
<td>4.2</td>
</tr>
</tbody>
</table>

**Abbreviations:** IPAP: intermittent positive airway pressure; EPAP: expiratory positive airway pressure; NS: not specified.
nasal ulceration, nasal congestion, eye irritation, aerophagia, aspiration pneumonia [113]. Another complication/disadvantage reported by some studies is patient-ventilator asynchrony [26, 114].

CONVIV

NIV has been increasingly used to treat COPD. In patients with COPD exacerbation, the use of NIV has a clear role. Observing the indications and contraindications to initiation of NIV in these patients leads to improved gas exchange, improved quality of life and reduced length of stay. Regarding stable COPD with chronic respiratory failure and hypercapnia, there is more and more evidence of NIV utility, especially of HI-NIV. In these patients, the use of NIV can improve survival and quality of life if CO2 is reduced. However, other factors seem to be important, besides the decrease in PaCO2. The lack of uniform guidelines or recommendations makes it difficult for clinicians to choose the appropriate device, interface, and ventilation mode.

Educating and encouraging patients, giving them time for accommodation before achieving optimal pressure can increase compliance. Developing a follow-up system for these patients, including telemedicine systems, can further improve compliance and reduce costs.

More studies are needed to determine the ideal candidate for chronic NIV and to explain all the benefits of using NIV.

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CONFLICT OF INTEREST

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