Antonello Nicolini¹, Malcom Lemyze², Antonio Esquinas³, Cornelius Barlascini¹, Maurizio Alessandro Cavalleri⁵
¹Respiratory Diseases Unit, General Hospital, Sestri Levante, Italy
²Department of Respiratory and Critical Care Medicine, Schaffner Hospital, Lens, France
³Intensive Care Unit Hospital Morales Meseguer, Murcia, Spain
⁴Hygiene and Public Health, Sestri Levante, Italy
⁵Internal Medicine Department, Sestri Levante, Italy

Predictors of noninvasive ventilation failure in critically ill obese patients: a brief narrative review
The authors declare no financial disclosure

Abstract
Non-invasive ventilation (NIV) has been used successfully for the management of acute respiratory failure (ARF) more often in the last two decades than previously. Unfortunately, NIV can have failure rates ranging from 5% to 50% and patient selection is the key to success. There are particular groups of patients that are more likely to benefit from NIV. For patients with hypoven tilation syndrome (OHS) this treatment can be beneficial. This review seeks to evaluate the effectiveness of NIV in acute ARF and determine predictors of NIV failure in morbidly obese patients. Only a few studies have investigated NIV success or failure in these patients. NIV was most often effective when patients were carefully selected. Obese patients who exhibited early NIV failure had a high severity score at admission. In contrast, more than half of hypercapnic patients with decompensated OHS exhibited a delayed but successful response to NIV. Patients with decompensation of OHS had better prognosis and response to NIV than other hypercapnic patients. They required more aggressive NIV settings, a longer time to reduce paCO₂ levels, and more frequently a delayed but successful response to NIV which should encourage the use of NIV rather than early intubation. Since clear predictors of NIV failure have not been identified, a strict and prolonged monitoring is mandatory.

Key words: obesity-hypoventilation syndrome, critically ill obese patients non-invasive ventilation, late failure

Introduction
Patients who are likely to benefit from non invasive ventilation (NIV) need to be identified early [1, 2]. Failure to do so often results in increased morbidity and mortality, as well as inappropriate use of limited resources [3]. Before starting NIV, it is crucial to identify good candidates [1]. Non-invasive ventilation efficacy depends on careful patient selection: look for predictors of failure immediately [3–5]. The absence of total alertness and/or an inability to follow instructions are absolute criteria for exclusion. Hypotension, pneumothorax, gastric insufflation, and vomiting, and risk of aspiration must be evaluated; these are relative exclusion criteria. Clinical experience of all persons that form the therapeutic team are vital; changes in patient condition occurs rapidly. The risk of NIV failure determines the intensity of monitoring needed [6, 7]. Moreover, knowing the factors affecting the NIV success may help to decide also the duration of NIV trial. One approach to determine the need for monitoring is to assess the patient’s risk of NIV failure [7, 8]. Some of these are simple bedside assessments, such as ease of arousal, agitation, cough integ-
rity, and respiratory rate. Other methods require simple laboratory tests, such as 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. When a quick decision is required, reliance on simple bedside observations and rapidly obtained laboratory values such as pH are best [8]. Recognition that NIV is failing is an important, but often overlooked, part of clinical management [5, 6]. 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:

1) immediate failure (within minutes to < 1 h)
2) early failure (1 to 48 h), and
3) late failure (after 48 h) [5–9].

Immediate NIV Failure
Immediate NIV failure refers to failure within sixty minutes [9]. 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 been often 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 [6, 8]. The risk of aspiration has been shown to be 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 [9].

Early NIV failure
Nearly 65% of NIV failures occur within the first 48 hours of NIV use [9–11]. 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. [7] found that subjects likely to fail NIV 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 two hours of NIV. Subjects 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% are at risk for early failure. Moreover, patients with excessive respiratory secretions or without improvement of clinical and/or after 60 minutes of NIV have high risk of failure [12–14].

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 subjects 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 [12, 14–18].

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 [1], particularly those resulting from acute exacerbations of chronic obstructive pulmonary disease (COPD), and cardiogenic pulmonary edema [1, 2]. Its usefulness has also been confirmed in patients who are immunocompromised from hematological diseases in which lower rates of endotracheal intubation and mortality rates have been reported in comparison with more invasive therapy [15]. Over the 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) [6]. Since NIV can have failure rates ranging from 5% to 50%, NIV failure may cause intubation delay, increasing morbidity and mortality [11, 12].

More than 30% of patients with OHS are diagnosed initially when hospitalized for acute on chronic respiratory failure [16–18]. 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) [19], increased work of breathing due to decreased thoraco-abdominal compliance, and altered ventilatory drive [20]. Respiratory system compliance in obese subjects 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 [21].

Obesity increases the stiffness of the total respiratory system with consequent development of low lung volume [21]. 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 [20, 21]. 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 [21]. This review seeks to determine which obese patients are good candidates, which patients are poor candidates, and how to gauge the success (or failure) of NIV rapidly. In this review we will address three main issues: 1) evaluation the effectiveness of NIV in ARF 2) calibration of ventilatory settings and selection modes 3) evaluation of predictors of NIV failure.

Methods

The diagnosis and the definition of severity of obesity has been determined by body mass index (BMI), defined as weight in kilograms divided by height in squared meters (kg/m$^2$) [22]. Subjects with BMI greater than 30 are considered obese. Obese is further categorized into class I (BMI 30.0–34.9), class II (35.0–39.9) and class III (BMI ≥40); Class III is referred as severe or extreme or morbid obesity. These standards have been used in studies exploring the relationship between obesity and critical care outcomes [18]. Obesity hypoventilation syndrome (OHS) is defined as a combination of obesity (BMI >30 kg/m$^2$), daytime hypercapnia, PaCO$_2$ > 45 mm Hg, and disordered breathing during sleep [23]. OHS is a chronic disease associated with respiratory and cardio-metabolic impairments leading to a decrease in ability to perform normal human activities including social interactions along with a higher risk of hospitalization and death [16, 21].

Data source

We searched the following electronic databases from their inception from January 2001 to December 2016: MEDLINE, EMBASE, CINHAIL, CENTRAL (Cochrane Central register of Controled Trials), DARE (Database of Abstracts of Reviews of Effectiveness), the Cochrane Database of Systematic Reviews, ACP Journal Club database.

Study selection

We identified studies that included adults admitted to acute care hospitals with acute or acute on chronic respiratory failure who needed NIV. We excluded studies of invasive mechanical ventilation (IMV). We included both randomized controlled trials and prospective studies; we excluded case reports, letters, and editorials. We have found 3738 potential articles regarding NIV and acute respiratory failure. 3542 were excluded because they did not fulfill inclusion criteria (Fig. 1). For the remaining papers we read the full texts. Eight full-text articles were assessed for eligibility. No language restrictions were applied: non-english publications were professionally translated into English.

Results

Only eight studies have investigated NIV success or failure in OHS patients. These are summarized in Table 1. Several observations have emerged from this research:

a) in OHS NIV failed to reversing ARF ranging from 2% to 60% of the time. [3, 4, 8, 10, 24–27]. Two studies were performed in ICU by Lemyze et al. [10] and Contou et al. [26]
and enrolled more severe patients: it can explain higher NIV failure and mortality rate; b) obese patients who exhibited early NIV failure had a high severity score, more comorbidities and a low HCO₃ level at admission and were likely to have hypoxemic ARF caused by pneumonia [8–10]. Low HCO₃ are linked to renal failure and more severe illness [10]; c) factors associated with a successful response to NIV included high PaCO₂ at admission and a diagnosis of idiopathic hypercapnic decompensation of OHS [10]; d) more than half of hypercapnic patients with decompensated OHS exhibited a delayed but successful response to NIV [8, 10]. The obese patients who developed a second episode of ARF despite an initial response to NIV (late NIV failure) had a poor prognosis [10].

In obese patients with ARF neither pH and PaCO₂ accurately predicted patient response to NIV in the first hours of NIV treatment [10, 27]. 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 [7, 13]. No ventilatory mode has been shown to lead to better outcome than any other [28]. Several studies demonstrated no differences between pressure or volume controlled modes [28]. Several modes have been implemented: bilevel positive airway pressure [B-PAP], pressure support ventilation [PSV], B-PAP-spontaneous-timed [ST] with VAPS [volume assured pressure support] and pressure controlled ventilation [PCV] [3, 4, 6, 8, 10, 20, 21, 24–27].

The setting of ventilator is very important because the high thoracic impedance in these patients requires higher inspiratory pressure (IPAP) levels and expiratory positive airway pressure (EPAP) in order to prevent the collapse of the upper airway [20] (Fig. 2).

Delay in the reduction of PaCO₂ may be due to:
1. Inadequate level of IPAP or EPAP levels: in obese patients IPAP should ranged from 12 to 30 cm H₂O or greater and EPAP from 6 to 8 cm H₂O or greater [6, 20].
2. Inadequate duration of NIV: the obese patients as previously explained require longer NIV therapy than non-obese patients especially during the night; their apnea or hypoventilation worsen during hours of sleep [10, 20].

---

Table 1. Studies which have evaluated NIV in critically ill obese patients

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Year</th>
<th>Obese Patients (n°)</th>
<th>Ventilator y mode</th>
<th>NIV failure %</th>
<th>Predictors of NIV failure</th>
<th>Mortality rate %</th>
<th>Type of sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>[3]</td>
<td>2012</td>
<td>42</td>
<td>Pressure support ventilation (PSV) or bilevel positive pressure ventilation spontaneous-timed (ST)</td>
<td>41.0%</td>
<td>Use of home ventilation, higher pressure support levels</td>
<td>0%</td>
<td>Mixed patients</td>
</tr>
<tr>
<td>[8]</td>
<td>2010</td>
<td>15</td>
<td>Bilevel positive airway pressure ventilation ST</td>
<td>20.0%</td>
<td>Higher respiratory rate, higher Apache II score, pneumonia, comorbidities</td>
<td>Not assessed</td>
<td>Mixed patients</td>
</tr>
<tr>
<td>[8]</td>
<td>2010</td>
<td>7</td>
<td>Bilevel positive airway pressure ventilation ST</td>
<td>16.9%</td>
<td>Higher Apache II score, lower Glasgow score, lower pH after 1 h NIV</td>
<td>Not assessed</td>
<td>Mixed patients</td>
</tr>
<tr>
<td>[10]</td>
<td>2014</td>
<td>76</td>
<td>Bilevel positive airway pressure ventilation ST</td>
<td>60.5%</td>
<td>Pneumonia, lower PaCO₂ and HCO₃, higher severity scores at admission</td>
<td>30%</td>
<td>Obese</td>
</tr>
<tr>
<td>[24]</td>
<td>2012</td>
<td>173</td>
<td>Bilevel positive airway pressure ventilation</td>
<td>6.0%</td>
<td>Not assessed</td>
<td>6%</td>
<td>COPD vs Obese patients</td>
</tr>
<tr>
<td>[25]</td>
<td>2011</td>
<td>44</td>
<td>Bilevel positive airway pressure ventilation-ST with AVAPS, Pressure control ventilation, PSV</td>
<td>2.0%</td>
<td>Not assessed</td>
<td>5%</td>
<td>Obese vs non-obese</td>
</tr>
<tr>
<td>[26]</td>
<td>2013</td>
<td>30</td>
<td>PSV</td>
<td>38.0%</td>
<td>Respiratory rate &gt; 30 breaths m', PaO₂/FiO₂ &lt; 200 pH&lt;7.30</td>
<td>14%</td>
<td>Mix patients (15% OHS)</td>
</tr>
<tr>
<td>[27]</td>
<td>2016</td>
<td>189</td>
<td>PSV</td>
<td>7.0%</td>
<td>Respiratory rate &gt; 30 breaths m', PaO₂/FiO₂ &lt; 200 Not assessed</td>
<td>Mix patients (38% OHS)</td>
<td></td>
</tr>
</tbody>
</table>
These findings suggest that NIV settings need to be monitored more aggressively in OHS (when acute illness precipitates respiratory decompensation) than in other syndromes [10, 20]. During NIV therapy, observation and monitoring of the level of consciousness, vital signs, respiratory pattern, oxygen saturation and ABG are crucial [20, 29, 30]. NIV modality and ventilator setting during ARF episode should be adjusted based titration with polysomnography [31].

Complementary use

NIV as weaning strategy

Only few studies address the problem of weaning in critically obese patients [32–34]. Currently, the management of these patients is based on clinical experience and expert opinions [33]. NIV in selected chronic hypercapnic patients if applied within the first 48 hours post-extubation following established weaning protocols reduces hospital mortality. There was also a significant reduction of length of ICU and hospital stay [33]. This study has shown that the use of NIV in the first 48 hours post-extubation might be effective in avoiding respiratory failure.

NIV for obese patients undergoing surgery

Obese patients and particularly those with OHS are more likely to develop post-operative respiratory failure, have higher rates of pneumonia, and development of atelectasis [21, 35–40]. Both upper abdominal and thoracic surgery can result in a restriction of pulmonary function that can persist for several days due to the reduced ability to clear secretions [21]. These problems are often unrecognized. A recent Cochrane review evaluated the effectiveness of NIV and CPAP to prevent or to treat acute respiratory failure after surgery: it concludes that the evidence to support the use of CPAP to reduce pneumonia and re-intubation is not definitively demonstrated and further studies are needed [35]. We found no study that has delineated risk factors for NIV failure in the post-operative period.

Limitations

This study has some limitations: the paucity of studies (always mixed patients do not allow us to provide definitive conclusions. Second, the proposed ventilation strategies are based on expertise of a single center and often derive from COPD patients. The use of the type of interface (oro-nasal mask or helmet) as well as side-effects or managing problems (leakage, gastric inflation) have not been addressed in this review because these were not reported in the studies we have evaluated. We are aware of their importance in the success or failure of any NIV trial.
Conclusion
In conclusion, although few studies are available concerning morbidly obese patients with decompensation of OHS, they suggest that NIV could be safely used in patients with hypercapnic acute respiratory decompensation of OHS. OHS patients require more aggressive NIV settings and a longer time to reduce PaCO₂ levels below 50 mm Hg. They frequently exhibit a delayed but successful response to NIV which should encourage the pursuit of NIV rather than early intubation. Since clear predictors of failure have not been identified, a strict and prolonged monitoring is mandatory because morbidly obese patients often experienced late NIV failure.

Conflicts of interest
The authors declare no conflicts of interest.

References:


