



# Noninvasive ventilation as first-line treatment for acute respiratory distress syndrome: The time is not ripe yet!

Alladi Mohan, J. Harikrishna

Noninvasive ventilation (NIV) is a method of delivering mechanical ventilatory support via an upper airway mask without the need for tracheal intubation. Early reports of the applications of NIV in the treatment of acute respiratory failure date back to the mid-1940s when Motley *et al.*<sup>[1]</sup> used intermittent positive inspiratory pressure ventilation (IPPV) via an anesthesia mask in the treatment of acute respiratory failure caused by pneumonia, pulmonary edema, near-drowning, Guillain-Barré syndrome, and acute severe asthma.<sup>[1]</sup> However, with the emergence of invasive mechanical ventilation, the use of NIV took a back seat. The clinical application of NIV re-emerged in the 1980s when it was successfully used to treat obstructive sleep apnea,<sup>[2]</sup> and respiratory failure in patients with neuromuscular diseases.<sup>[3]</sup> Thereafter, the last two decades have witnessed a phenomenal increase in the clinical applications of NIV in the acute care setting.<sup>[4]</sup> NIV has emerged as a modality of choice in the management of severe acute exacerbation of chronic obstructive pulmonary disease (COPD) and cardiogenic pulmonary edema (Grade 1 [strong] recommendation).<sup>[5]</sup> Evidence is accumulating for use of NIV in patients with acute respiratory failure in the following settings: Immunosuppressed patients, following abdominal surgery and lung resection, for facilitating early extubation in patients with COPD, and as a transition to spontaneous breathing after planned extubation in patients at high risk for recurrent respiratory failure, such as, age >65 years, cardiac failure as the cause of intubation, Acute Physiology and Chronic Health

#### From:

Department of Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, Sri Venkateswara Institute of Medical Sciences, Tirupati, Andhra Pradesh, India

#### Correspondence:

Dr. Alladi Mohan, Department of Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, Sri Venkateswara Institute of Medical Sciences, Tirupati - 517 507, Andhra Pradesh, India.  
E-mail: alladimohan@svims.gov.in

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Evaluation (APACHE) II score greater than 12 at the time of extubation (grade 2 [weak] recommendation).<sup>[5]</sup> NIV has many advantages compared to IPPV. It is easy to administer, avoids the need to secure an invasive airway, is associated with fewer complications, and a shorter hospital stay. Further, the cost of treatment and burden on health care system is also less with NIV.<sup>[5]</sup>

Acute respiratory distress syndrome (ARDS), characterized by acute onset bilateral pulmonary infiltrates and refractory hypoxemia is associated with a high mortality. The standard care for patients with ARDS includes early IPPV with low tidal volume, high positive end-expiratory pressure, among others. The benefits and harms of NIV in ARDS have not been systematically evaluated. For conditions resulting in acute hypoxemic respiratory failure such as acute exacerbation of bronchial asthma, ARDS, severe community-acquired pneumonia (CAP), and chest trauma, NIV is not considered to be the modality of choice.<sup>[5,6]</sup> However,

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in these conditions, including ARDS, NIV has been tried when there were no contraindications. Evidence regarding the use of NIV in acute respiratory failure excluding COPD and cardiogenic pulmonary edema is limited to case series, observational studies and few randomized controlled trials (RCT) that included a heterogeneous, mixed population of patients with various etiological causes which had revealed conflicting results. One RCT<sup>[7]</sup> suggested that in patients with acute hypoxemic respiratory failure which included patients with ARDS, addition of NIV to standard medical management resulted in decreased rate of endotracheal intubation, length of Intensive Care Unit (ICU) stay, and mortality in a subset of patients with arterial partial pressure of carbon dioxide more than 45 mm of Hg compared to patients who received standard medical care and oxygen inhalation. Two other RCTs<sup>[8,9]</sup> also showed beneficial effects of addition of NIV to standard medical therapy compared to oxygen inhalation. Another RCT<sup>[10]</sup> showed NIV neither reduced need for intubation nor improved the clinical outcome. Further, an RCT<sup>[11]</sup> that compared NIV with IPPV concluded that NIV is as effective as IPPV in improving gas exchange and associated with fewer complications in ICU setting. A systematic review<sup>[12]</sup> that compared standard therapy alone with NIV along with standard therapy in patients with acute hypoxemic respiratory failure showed that NIV decreased the rate of endotracheal intubation, length of ICU stay and ICU mortality. In all these studies, the proportion of ARDS patients has been very small and significant heterogeneity observed in the results limits their extrapolation to patients with ARDS.

In patients with moderate to severe ARDS, evidence comparing the use of NIV with IPPV head-on is sparse and is limited to few observational studies and no RCTs. In one observational study<sup>[13]</sup> in patients with acute lung injury (ALI)/ARDS who received a trial with NIV, tracheal intubation could be avoided in 40% of patients; however, a significantly higher mortality was observed in patients who had received NIV trial compared with patients who were intubated early. In patients with ARDS, while on one hand a substantial reduction in the need for tracheal intubation has been observed with the use of NIV, a substantial increase in mortality has been a cause for concern.<sup>[13]</sup> A meta-analysis<sup>[14]</sup> that evaluated on the role of NIV in ARDS showed no significant benefit of the addition of NIV to standard medical therapy. In another meta-analysis,<sup>[15]</sup> it was observed that NIV avoided intubation in 50% of patients; however, the authors concluded that in view of significant heterogeneity these results should be interpreted with caution. Further, a more recent meta-analysis<sup>[16]</sup> had also shown that, in patients with ALI/ARDS, while early

use of NIV can decrease the endotracheal intubation rate, it did not change the mortality of these patients. Further, evidence is also available that failed NIV is associated with intubation-related complications and increased risk of death.<sup>[17]</sup>

In this issue of the IJCCM, Sehgal *et al.*<sup>[18]</sup> reported their experience with NIV in patients with ARDS. In this prospective observational study<sup>[18]</sup> conducted in patients with mild to moderate ARDS, the authors reported that NIV has avoided intubation in 44% of subjects and univariate analysis has shown that baseline APACHE II score >17 and lack of improvement in the ratio of arterial oxygen tension (PaO<sub>2</sub>) to fraction of inspired oxygen (FIO<sub>2</sub>) >150 after 1 h of initiation predicted NIV failure. Further, significantly higher mortality in patients with NIV failure compared with no mortality observed in those with NIV success (19/23 vs. 0/18) is another cause for concern. Patients with NIV failure had more severe disease characterized by a higher median (interquartile range [IQR]) base line APACHE II score and PaO<sub>2</sub>/FIO<sub>2</sub> ratio. The authors report that the median (IQR) time to intubation was 3 (1–4) h. This delay in initiating tracheal intubation and mechanical ventilation in patients with more severe disease could also have contributed to the higher mortality observed in the present study.

While the observations from the present study<sup>[18]</sup> raise hope in terms of avoiding tracheal intubation, the results this study<sup>[15]</sup> should be interpreted with caution. This present study<sup>[15]</sup> where the authors have chosen a “sample of convenience” is underpowered as the sample studied ( $n = 41$ ) is very small. As of now, NIV should be used with caution in patients with ARDS. Use of NIV in patients with ARDS should be considered only in ICUs equipped with facilities for round-the-clock monitoring and carrying out tracheal intubation as soon as it is required. Patients in whom NIV is being considered should be judiciously selected and carefully monitored for NIV failure with an intention to intubate as early as possible in case of NIV failure. At present, sufficient evidence is inadequate to make a strong recommendation to support the routine use on NIV as an initial mode of choice in patients with ARDS. Prospective, randomized, multicentric RCTs with an appropriate sample size are required to generate evidence regarding the role of NIV in patients with ARDS.

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