Noninvasive ventilatory management of the acute respiratory distress syndrome: a new era or just another tease!

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Since its first clinical description, we have made great strides in the management of the patient with the acute respiratory distress syndrome (ARDS). These strides have resulted in a decrease in overall mortality from a rate of about 60% during the 1980's to arguably a rate today in the 40% range for all patients with ARDS regardless of cause or comorbidities (1). This has been accomplished by advances in ventilatory support and careful attention to the setting of delivered tidal volume (4 to 8 mL/kg predicted body weight), maintaining the plateau airway pressure less than 28 cmH_2O, the driving pressure [plateau pressure minus positive end-expiratory pressure (PEEP)] less than 15 cmH_2O and setting the level of PEEP based on the individual patient respiratory system mechanics after a recruitment maneuver (2,3). Still most of us consider a mortality of 40% to high for this syndrome and have explored other approaches to further decrease mortality, such as liquid ventilation, high frequency ventilation, and aerosolized/inhaled agents to modify pulmonary vascular resistance (4,5), none of which have resulted in improved survival and some arguably may actually decrease survival. Many have also promoted the use of extracorporeal membrane oxygenation (ECMO) in patients with severe ARDS, but the best that can be stated regarding ECMO is that ARDS patients should be managed in centers with extensive experience in managing ARDS. Management in the community compared to these centers that do have ECMO capabilities results in poorer patient outcome (6).

We still search for alternate ventilation and oxygenation approaches to managing ARDS patients. Most recently, these approaches have focused on the non-invasive ventilatory management of gas exchange. A number of studies over the last 10 to 15 years have explored the use of noninvasive positive pressure in the form of noninvasive ventilation (NIV) and continuous positive airway pressure (CPAP) to manage gas exchange and avoid intubation in ARDS patients. Although early studies were promising in very small select patient groups, the overall outcome of patients was generally poor with mortality of those failing NIV and requiring intubation back in the 60% range (7). The majority of these studies were not randomized, patients enrolled were very heterogeneous, and none of them compared NIV with invasive ventilation. Consensus documents on NIV state that larger controlled studies are required to determine the potential benefit of adding NIV to standard management of ARDS patients for the avoidance of endotracheal intubation (8). The advice given to many clinicians utilizing NIV was that if their patient's overall clinical status did not change within 1 to 2 hours, NIV has failed and the worse thing we can do for our patient is further delay intubation. Because of the high risk of failure, NIV should be considered only in ARDS patients without extrapulmonary organ failure (8).

The hallmark of ARDS is arterial hypoxemia refractory to the oxygen therapy due to pulmonary shunt. In the last decade a new approach to managing severe hypoxemic respiratory failure and ARDS has emerged, the use of high flow nasal cannulas (HFNC). The HFNC was originally developed for neonatal and pediatric critically ill patients. Basically, the goal is to deliver a very high, heated, and

humidified oxygen-enriched gas flow at body temperature and saturated with water vapor through the nose (9). This modification of the application of the standard nasal cannula has proved highly useful in many settings. In adults, flows of up to 60 liters/min have been recommended.

HFNC have a number of advantages over conventional oxygen delivery systems applied to the non-intubated spontaneously breathing individual. First, gas is delivered at a sufficiently high flow to meet the patients' ventilatory demand and essentially assures that the oxygen concentration in the lungs is equivalent to that inspired by the patient. This is a near impossible target for most other gas delivery systems used to manage the spontaneously breathing patient. Second, based on a number of factors, including the high unidirectional flow via the nose, the diameter of the nasal prongs compared to the diameter of the patients' nares, and the patient's ventilatory demand, PEEP can be established. How much is open to debate but the literature would indicate that upwards to 6 to 8 cmH_2O PEEP can be established with a properly setup HFNC in an adult (10,11). Thirdly, since gas is entering the airway via the nasal route at such high flows, exhalation must be via the mouth. This results in unidirectional gas flow in the upper airway, and decreasing dead space ventilation. Therefore, in addition to being able to increase the end-expiratory lung volume, dead space normally present in the upper airway is eliminated resulting in better CO_2 elimination and a decreased work of breathing.

Frat *et al*. (12) demonstrated superiority of HFNC to standard oxygen therapy and NIV in a randomized comparison of patients with acute hypoxemic respiratory failure defined as a PaO_2/FiO_2 <300 mmHg. The intubation rate trended to be lower with HFNC 38% *vs*. 47% standard oxygen therapy and 50% with NIV and ventilator free days were significantly lower with HFNC (24 *vs*. 22 standard oxygen therapy *vs*. 19 NIV, P=0.02). The hazard ratio for death at 90 days was 2.01 with standard oxygen therapy *vs*. HFNC (P=0.046) and 2.50 with NIV *vs*. HFNC (P=0.006).

Most recently, Patel *et al*. (13) from the University of Chicago Hospital and Clinics published a randomized comparison of NIV with a face mask to NIV delivered via a plastic, transparent helmet for the management of patients with ARDS. Eligible patients were randomized to the two approaches after receiving at least 8 hours on NIV via an oronasal face mask. The study was initially powered for 206 patients, but it was stopped at its first interim analysis (83 patients randomized) because of efficacy of the treatment group. Patients' were followed for 90 days. The use of helmet NIV resulted in a decrease in the number of patients intubated (61.5% *vs*. 18.2%, P<0.001), in the median number of ventilator free days (12.5 *vs*. 28, P<0.001), in hospital mortality (48.7% *vs*. 27.3%, P=0.04) and in 90-day mortality (56.4% *vs*. 34.1%, P=0.02). One must consider these findings highly impressive. The simple changing of the patient interface from a face mask to the helmet resulted in an over 40% absolute reduction in intubation rate and an over 20% reduction in hospital and 90-day mortality.

However, one must look closely at the details to identify possible reasons and sources of bias for these astounding results. The authors indicate that all patients met the Berlin criteria for ARDS. However, the Berlin criteria have three levels of severity: mild, moderate, and severe (14). Although some patients meeting criteria for mild ARDS could initially be managed with NIV, the Berlin criteria mandates invasive mechanical ventilation for classifying patients as moderate or severe ARDS. Since PaO_2/FiO_2 values in patients under NIV are not comparable with those on conventional mechanical ventilation, it is not clear whether patients meeting criteria for mild ARDS on NIV would meet those criteria after intubation and conventional mechanical ventilation (15). There is no data provided to determine the level of ARDS severity at the time of initiation of NIV or randomization. Patel *et al*. stated that the mean PaO_2/FiO_2 were similar in both groups; however a few outliers in either direction can mitigate maldistribution into the three severity categories. Therefore, the use of non-standardized PaO_2/FiO_2 values for enrolment into therapeutic clinical trials may be responsible for patient selection bias, since a treatment that might benefit a subgroup of patients with ARDS is also tested in patients who are unresponsive to the experimental treatment (15).

Thus, were equally sick patients randomized to each group and did all patients truly have ARDS? Were there more severely injured patients randomized to the control group? One must question if all patients actually had ARDS and not simply atelectasis. It is indicated that the median ventilator-free days for the treatment group was 28 days. This means that at least 50% of the patients in the treatment group resolved their ARDS sufficiently within 24 hours to allow removal of the helmet NIV. It is hard to imagine that the intense inflammatory response associated with the presence of moderate to severe ARDS would be reversed within 24 hours. It has been argued that patients should not be classified as ARDS, especially severe and moderate ARDS, unless the syndrome is sustained with a PaO_2/FiO_2 ratio <200 mmHg while receiving an

FiO_2 ≥0.5 and a PEEP ≥10 cmH_2O for at least 24 hours (15,16). The short requirement for NIV in the helmet group is even more surprising since the authors state the patients had a high APACHE II score (~25) and that half of the patients were immunocompromised by virtue of cancer or transplantation, and about 1/3 in each group had an immunocompromised pneumonia. Thus, despite the statistically significant differences in intubation and mortality rates between the two groups, consideration should be given to generalizability and reproducibility of the study because it was not powered to assess whether the combined presence of several determinants of favorable outcome before randomization in patients assigned to helmet NIV (younger, lower median body mass index, asymmetry of etiologies, greater SpO_2 and greater use of steroids) had a plausible impact on the primary and secondary outcomes.

Concerns regarding the use of helmet NIV essentially surround the high capacitance of the helmet. As a result, unless there is adequate gas flow, CO_2 rebreathing has been reported as a problem (17,18). Unfortunately, since no CO_2 data is provided in this report, it is difficult to determine whether the work of breathing was a potential problem in either group. The authors indicate that there was a disproportionate PEEP level applied to the helmet NIV patients (8 *vs.* 5 cmH_2O PEEP, P=0.006). They acknowledge that this higher PEEP level may have favored the helmet NIV group. It is also stated that Positive pressure was provided using either CPAP or NIV but the numbers of patients receiving each approach is not stated for either arm of the study. Was the benefit provided by helmet NIV a result of a larger number of patients actually receiving CPAP at the higher PEEP level than in the face mask group?

The result of the Patel *et al*. (13) study presents us with a welcome dilemma. Clearly, the use of HFNC has demonstrated repeated success in the management of hypoxemic acute respiratory failure and selected patients with ARDS while the NIV literature is filled with studies indicating a failure of NIV to manage ARDS, especially those with moderate or severe ARDS. However, now the simple use of the helmet during NIV changes all of that or does it? We should be cautious not to jump to conclusions and change our practice based on one single center study that has a number of open questions. From the positive side, this study does provide renewed interest in the use of NIV to manage ARDS. Since helmet NIV was not compared with HFNC, what we think is needed is a large, multicenter study comparing the use of helmet NIV to the HFNC for the management of a carefully selected group of patients with ARDS. For if the helmet does provide the benefit defined by Patel *et al*. it is still technically more difficult to use than HFNC, and regardless of how comfortable the helmet is, it is not more comfortable than a nasal cannula (personnel observation). Thus, before we change our practice let's hope some independent groups perform such a study to determine which direction we should go in the non-invasive management of ARDS. Whichever direction that is, it should improve the outcome from ARDS!

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Footnote

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