

Noninvasive Ventilation in Acute Lung Injury: Caution Is Good, More Evidence Is Better

Noninvasive ventilation (NIV) has emerged over the last 2 decades to become the clear choice in the management of patients presenting with respiratory distress secondary to cardiogenic pulmonary edema¹ and exacerbations of COPD.² For these patient groups NIV clearly improves symptoms and, for the latter group at least, NIV is associated with less need for invasive mechanical ventilation and less hospital mortality. NIV has been used in other patient groups presenting with respiratory distress, with the objective of decreasing the need for invasive mechanical ventilation and improving hospital survival.³⁻⁷ The evidence in the literature supporting NIV's use beyond patients with cardiogenic pulmonary edema and COPD, however, is much weaker, especially for those patients presenting with acute lung injury (ALI).⁸ In this issue of the Journal, Agarwal and colleagues report their systematic analysis of the literature on NIV in ALI.⁹ They

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are to be commended for their thorough search of the literature and careful summary of their findings. By pooling the results available they suggest that NIV may decrease the need for intubation by 50%, but acknowledge that their conclusions are limited by the heterogeneity of the studies included, largely composed of small cohort studies. They recommend cautious use of NIV in selected patients with ALI, and in a closely monitored setting that allows prompt intubation. While their recommendations for caution are well founded, a closer look at the literature still cannot dispel a troubling concern that NIV may cause harm in patients with ALI.

The literature on NIV in ALI is very limited. No randomized controlled trials have studied this group alone, leaving us with only small subgroups in the available studies. Cohort studies have described outcomes of patients with ALI who received NIV, but they do not answer the question, "Does the addition of NIV to usual care in patients with ALI improve outcomes (eg, decrease mortality)?" In part to be provocative, I will make a case that there really is no good evidence that NIV improves outcomes in patients with ALI, but that there *is* evidence, admittedly weak, that NIV may cause harm. The need for a randomized controlled trial is paramount.

What evidence is there that NIV may benefit patients with ALI? In their systematic review,⁹ Agarwal and associates pooled the results in the literature and found an average intubation rate of about 50% in patients who received NIV.⁹ But they found substantial clinical and statistical heterogeneity in the studies—so much so that one may wonder about the validity of pooling these studies at all. Clearly, patient selection differed widely among the studies, making the generalizability of the review's results very challenging. While patients with ALI are more prone to deteriorate and require ventilation than patients presenting with respiratory distress from other causes, not all will do so. Making the assumption that the average intubation rate of 50% found by Agarwal et al by pooling study results implies a potential 50% reduction in intubation rate by using NIV assumes that all those patients would have been intubated without NIV. While that is possible, it is unlikely.

A more important point to consider is what is the most important outcome for patients with ALI? Is avoiding intubation the primary outcome of interest? To try to get at this somewhat indirectly, it is necessary to focus on the best evidence available to us. As there are no randomized controlled trials of NIV in ALI, we must move to the next best level of evidence, which are the 2 best cohort studies of ALI patients and NIV (or the closest we can come to it), which I will review.

Antonelli and colleagues,¹⁰ a group with extensive NIV expertise, carefully selected 145 patients with ALI, without shock, and with less than 2 extrapulmonary organ failures, and found an intubation rate of 46%. The hospital mortality in those who avoided intubation was 19%, but for those intubated it was a concerning 54%. Demoule and associates¹¹ conducted a large cohort study in 70 French intensive care units; they included patients presenting with "de novo" respiratory failure, and they excluded all COPD and cardiogenic pulmonary edema presentations, therefore approximating ALI. 209 (70%) of 299 patients with ALI were directly intubated. The remaining 90 patients received a trial of NIV, and 54 (60%) of those were intubated. Demoule et al conducted an adjusted analysis to determine variables associated with hospital mortality, using the mortality of patients intubated without a trial of NIV as the comparator group. A successful NIV trial was associated

with lower hospital mortality, but failing an NIV trial was associated with higher mortality than that among the patients who never received NIV. Taken together, we have a confusing picture that suggests that patients with ALI who succeed in an NIV trial do well, but those who fail NIV do poorly. Is a trial of NIV truly of benefit to some patients, or is tolerance of an NIV trial a marker of patients who are less sick and therefore more likely to survive regardless? One thing to look at that may make us comfortable that an NIV trial is worth a shot would be the overall mortality of those who receive NIV. If it is lower than historical levels for similar patients treated without NIV, this may suggest that there is an overall benefit. However, a previous review that explored this clearly suggested that the mortality in these NIV trials with selected patients, who we would presume represented the less ill end of the spectrum of ALI, is at least as high as mortality in all comers with ALI reported in the literature.⁸

Is there any rationale for why NIV may be harmful? For this we turn to 2 randomized controlled trials for indirect evidence. Declaux and co-workers¹² studied mask CPAP in patients with nonhypercapnic respiratory failure and found no benefit in either the entire study group or the subgroup that probably was largely composed of patients with ALI. Of concern was the increase in adverse events, including 4 cardiac arrests (all in the CPAP arm), that were related to mask disconnects or hypoxemia during intubation. Regardless of whether one opts for NIV in the setting of ALI, the disease process often progresses, leading to worsening hypoxemia. Patients who do not receive NIV are promptly intubated when they become hypoxemic. In those who receive NIV the underlying disease process may progress much further while they are on NIV, and if they fail NIV, they are more prone to hypoxemia and its consequences.

Esteban and colleagues reported an increase in intensive-care-unit mortality in patients randomized to NIV who developed respiratory distress during the first 48 hours after extubation.¹³ This was associated with a prolonged time to intubation, suggesting again the potential for harm when patients receiving NIV are intubated at a later point in the disease course. Finally, theoretically at least, patients with ALI who spontaneously breathe longer because of an NIV trial may sustain further lung injury. It is not possible to control tidal volume in a spontaneously breathing patient, and those who fail NIV are likely to be breathing at tidal volumes that are believed to be injurious.^{14,15}

Agarwal and associates have provided us with an excellent summary of the literature on NIV in patients with ALI.⁹ However, the conclusions we can draw from their analysis are limited. The majority of patients presenting with ALI will probably require urgent intubation for severe hypoxemia or other associated organ failures. The

minority that appear initially stable enough to attempt a trial of NIV should be approached cautiously, as suggested by Agarwal et al. These patients need to be in a setting where they can be closely monitored and promptly intubated if there is any sign of deterioration. It is unclear whether NIV is actually of benefit at all in this patient population, as we do not know whether those patients who do well with NIV balance the possible worse outcomes in those who fail NIV. The latter may have done better if they had never had an NIV trial. We are in desperate need of a randomized trial to inform us on the risks and benefits of NIV in ALI.

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