

Inhaled Prostacyclin as Salvage Therapy for ARDS: Can We Find the Right Patient?

ARDS remains a clinically heterogeneous disorder wherein complex decision-making must be made when considering any salvage therapy. Inhaled nitric oxide and prostacyclin have emerged as an attempt to exploit the portions of the lung where tidal ventilation is preferentially distributed by inducing local pulmonary vasodilation and improving \dot{V}/\dot{Q} matching. Both agents have shown improved oxygenation with their usage,^{1,2} although a mortality benefit has not been clearly demonstrated for either,^{3,4} and fewer data are available for inhaled prostacyclin when compared to nitric oxide.⁴ Given how heterogeneous a disorder ARDS is, more information is needed to help determine which subset of patients may benefit the most from this salvage therapy. For instance, previous studies of inhaled prostacyclin have shown that certain etiologies may benefit more when they are classified as direct versus indirect,⁵ while a study of inhaled nitric oxide noted decreased effectiveness when the underlying etiology was sepsis.⁶

In this issue of *RESPIRATORY CARE*, Kallet et al⁷ sought to answer some of these ongoing questions. They specifically focused on analyzing who had the best response to inhaled prostacyclin by looking at surrogates for aerated parenchyma (ie, the functional residual capacity), including the P_{aO_2}/F_{IO_2} ratio and the compliance of the respiratory system (C_{RS}), as well as analyzing the underlying cause for ARDS and its classification (direct vs indirect).

In this large retrospective study of a hospital's ARDS quality-assurance database spanning 14 years (from June 2002 to April 2016), 279 subjects received aerosolized prostacyclin (PGI₂). After excluding those who died during therapy, had intervening increases in PEEP, recruitment maneuvers, prone positioning, or had missing data, there remained 208 subjects who had an arterial blood gas prior to and after initiation of PGI₂ available for analysis. All subjects underwent ARDSnet ventilatory protocols. The subjects were reclassified post hoc according to the current Berlin definition of ARDS. Logistic regression was

used to determine which variables predicted PGI₂ responders (defined as a >10 mm Hg increase in P_{aO_2}) from non-responders, which is based on a study by Walrath et al.⁸

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Not surprisingly, the subjects from this retrospective study of an ARDS salvage therapy were very ill. The mean APACHE II (Acute Physiology and Chronic Health Evaluation) score was 26.2 and SAPS II (Simplified Acute Physiology Score) was 53. Baseline P_{aO_2}/F_{IO_2} was classified as <60 mm Hg (representing 59% at study onset and 83% at initiation), 60–90 mm Hg (35% at onset, 16% at initiation), and >90 mm Hg (5% at onset, 1% at initiation). Mean in-hospital mortality was 56% for the subjects included in the analysis. When adding in the 12 patients who died during initiation of therapy, the overall mortality for this study approaches 60%, which is higher than most ARDS studies^{9,10} and makes it more difficult to extrapolate this population to others. Overall, inhaled PGI₂ demonstrated an increased P_{aO_2}/F_{IO_2} ratio by 33 mm Hg for the entire cohort and by 56 mm Hg when only responders were considered.

The magnitude of this is consistent with other studies, although higher than others.¹¹ Of those who responded, subjects tended to be less sick with a higher P_{aO_2}/F_{IO_2} ratio at onset. When only looking at responders, the lowest P_{aO_2}/F_{IO_2} group improved by 39 ± 45 mm Hg ($P < .001$), the median group by 58 ± 46 ($P < .05$), and the highest group improved by 70 ± 49 ($P < .05$). The authors emphasized the concept of responders versus non-responders, which is one way to reconcile the clinical relevance of smaller mean improvement but larger improvement in select populations. However, in the absence of mortality data, this brings into question its relevance. On a practical basis, <10 mm Hg improvement logically appears to be of little value in any clinical setting; however, one might argue that marginal improvements of 10–20 mm Hg may be of little value in patients with a P_{aO_2} of >60–70.

In terms of the etiology for ARDS, those with trauma had the biggest increase in P_{aO_2}/F_{IO_2} ratio, while those with sepsis had the least. The average improvement for sepsis was 18 ± 35 mm Hg compared with 40 ± 55 mm Hg for non-sepsis etiologies ($P = .002$), and only 50% of sepsis subjects were responders. These findings are consistent

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with other studies of inhaled nitric oxide^{6,12} and are postulated to be due to dysregulated release of nitric oxide and prostacyclin.¹³ The magnitude of improvement for direct, indirect, and mixed ARDS was 34 ± 51 , 22 ± 45 , and 41 ± 51 mm Hg, respectively. Significance was seen only when comparing the indirect and mixed mechanisms ($P < .05$). In addition, the responder rates ranged from 55–67% and were not significantly different across groups. Ultimately, classifying ARDS as direct, indirect, or mixed did not help in predicting responder rate or the magnitude of improvement as previous studies have done.¹²

While the initial P_{aO_2}/F_{IO_2} ratio predicted proportional increases in oxygenation after inhaled PGI2 therapy, C_{RS} did not demonstrate the same pattern consistently across categories. Nevertheless, the authors noted that, as the C_{RS} improved, it predicted responders to inhaled prostacyclin.

In multivariate regression analysis, the 2 major predictors for response to inhaled PGI2 were the P_{aO_2}/F_{IO_2} ratio (OR 1.10, $P = .042$) and C_{RS} (OR 1.04, $P = .02$). The clinical relevance of these predictors in the absence of mortality analysis or surrogates like the need for extracorporeal membrane oxygenation is harder to interpret. The authors posited that the effectiveness of aerosolized PGI2 is dependent on aerated lung parenchyma (or functional residual capacity) as predicted by surrogate measures like the P_{aO_2}/F_{IO_2} ratio and C_{RS} and therefore should be combined with other strategies to recruit lung parenchyma, such as higher PEEP, prone positioning, and recruitment maneuvers. This is consistent with recent observational studies combining prone positioning and inhaled nitric oxide showing an additive effect of oxygenation.^{14,15} Prone positioning itself has been shown to increase the number of responders to nitric oxide.¹⁵ While we agree with the authors on this concept, we would like to highlight an additional point on recruitment maneuvers.

While the current literature favors higher PEEP and prone positioning as showing improved mortality outcomes for severe ARDS,^{16,17} the data on recruitment maneuvers for ARDS are somewhat mixed. While there are data to support the major methods of recruitment maneuvers (which include sustained, decremental, and stepwise) in the postoperative setting after general anesthesia, sustained and decremental recruitment methods for ARDS have remained controversial. Of primary concern is the relative hemodynamic instability that can result secondary to abrupt increases in intrathoracic pressure, which can lead to decreased cardiac output followed by hypotension and desaturation.^{18,19} For this reason, a stepwise approach has been favored for ARDS utilizing incremental PEEP titration, with PEEP being gradually increased and changes occurring every 3–5 min.¹⁸

The difficulty in reaching a consensus on the use of recruitment maneuvers is likely due to the large heterogeneity of patient populations as well as variability in tech-

niques. Much of the evidence that currently exists focuses on physiologic assessments rather than outcomes. By measuring negative responses to the maneuvers such as hypotension, desaturation, and increased plateau pressure, some argue that the maneuvers may be unsafe and cause detrimental effects. Additionally, of the studies including recruitment maneuvers that do demonstrate improvements in mortality, often other recruitment strategies known to improve outcomes (eg, high PEEP, prone positioning) were being used as well.²⁰ Another important point to highlight is that certain patients seem to respond to lung recruitment while others do not, which adds to the complexity of this process and may be why consistent clinical evidence remains elusive.²¹ The results of ongoing large, multi-center randomized control studies^{22,23} may shed more light on this subject in the future.

Salvage therapy for ARDS is generally defined as additional measures beyond ARDSnet ventilator strategies employed for patients who have deficits in oxygenation despite maximum ventilatory strategies where P_{aO_2} may become limiting and life-threatening. This study clearly gives us more important clinical information on real-world use of inhaled prostacyclin. It is not clear on the basis of this study, however, that we can include or exclude consideration of ARDS patients for this particular salvage technique. It seems that the patients most desperately in need of help appear to be the least likely to improve, and those with the most robust improvement did not appear to have an initial P_{aO_2} that was life-threatening in the first place.

The heterogeneity of ARDS and its complex management strategies clearly complicate evaluation of salvage therapies. The critical end point is mortality, but, in the interim, evaluation of important surrogate end points such as significant reductions in administered F_{IO_2} , decrease in the use or intensity of other salvage therapies, or the need for extracorporeal membrane oxygenation may add important information. Another useful end point may be identifying patients with very little chance of meaningful physiologic improvement where therapy would not be considered a meaningful option. It is hard to clearly outline a population from the data provided by this study, although the authors' emphasis on improving the effectiveness of inhaled prostacyclin by increasing aerated lung parenchyma through higher PEEP, prone positioning, and recruitment maneuvers remain important therapeutic aspects of ARDS. At this time, however, we are still limited in our ability to confidently find the right patient.

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