

Preventing the development of acute cor pulmonale in patients with acute respiratory distress syndrome: the first step

Abhishek Biswas

Division of Pulmonary and Critical Care Medicine, University of Florida, Gainesville 32610, USA

Correspondence to: Abhishek Biswas, MD. Division of Pulmonary and Critical Care Medicine, University of Florida, Gainesville, 1600 SW Archer Road, Gainesville 32610, USA. Email: abhibiswas78@gmail.com.

Submitted Feb 07, 2016. Accepted for publication Mar 10, 2016.

doi: 10.21037/atm.2016.03.18

View this article at: <http://dx.doi.org/10.21037/atm.2016.03.18>

Acute respiratory distress syndrome (ARDS) is a clinical condition characterized by acute hypoxemic respiratory failure that is associated with substantial mortality even 40 years since it was first described. Although hypoxemia appears to be the most conspicuous abnormality noticed with this condition, it isn't the most common cause of death. Conservative oxygen saturation targets of 88–92% have been recently reported to be as effective as targeting saturation above 96%, which indicates that the human body can survive relatively short periods of relative hypoxemia without any lingering effects (1). On the other hand, circulatory failure is frequently encountered and is reported to be one of the major causes of mortality (2). Systemic inflammation drives the shock state to a large extent. Nevertheless, another significant cause of circulatory failure is pulmonary vascular dysfunction and elevated pulmonary vascular resistance that is frequently observed in ARDS. These subsequently lead to failure of the right ventricle and refractory cardiogenic shock in addition to a component of distributive shock state which often coexists. Although hypothesized and agreed upon by many, the direct effect of pulmonary vascular dysfunction on mortality in ARDS has been difficult to demonstrate. Utilizing transesophageal echocardiogram probes (TEE), the demonstration of severe forms of right ventricular dysfunction and acute cor pulmonale (ACP) is relatively easier compared to quantifying pulmonary vascular dysfunction, which requires the use of a pulmonary artery catheter (PAC). Modern intensive care units around the world report the existence of right ventricular dysfunction in about 25–50% of patients with severe ARDS (3). Despite these numbers, current ARDS guidelines do not recommend searching for evidence of ACP or strategies directed at treating elevated

right ventricular pressures as a part of managing ARDS. This is probably because of lack of any high quality evidence that clearly demonstrates the effect of ACP on mortality in ARDS.

Several recent studies have demonstrated strategies that have improved survival rates in ARDS (4–6). Most of these involve advancements in ventilator strategies and measures to protect the lung while attempting to improve oxygenation. However, the pooled mortality rate in ARDS still stands at 40% in spite of best standards of care (7). This invites the question “Is there something else that can be offered to improve mortality in ARDS? Could the early identification and management of ACP associated with ARDS help us save more lives (8)?” Unfortunately, the answer is not entirely clear with the evidence available to us.

As pointed out earlier, although the prevalence of ACP resulting from pulmonary vascular dysfunction has diminished with safer and more effective strategies of mechanical ventilation, it continues to occur in 25–50% of patients with ARDS (3,9–15). Pulmonary vascular dysfunction is a result of acute vascular inflammation that spills over from the alveoli to the microcirculation leading to vessel edema, thrombi as well as vascular remodeling that invariably follows any vascular insult (16). Part of this increased pulmonary vascular pressures may be a result of the way we chose to ventilate our patients. Positive end expiratory pressure (PEEP) has been proven to help oxygenation by keeping diseased alveoli open, thus improving gas exchange and preventing atelectrauma. Unfortunately, it also creates heterogeneity within the lung architecture—some collapsed alveoli because of alveolar filling from ARDS and other relatively normal areas of the

lung that become hyper-expanded as a result of high levels of the PEEP used to keep oxygenation at a level to sustain life. These areas with overstretched alveoli have compressed vessels in the alveolar septa with increase in vascular resistance that leads to the development of pulmonary hypertension (17). On the other end of the spectrum are those areas of the lung with collapsed alveoli. These areas also have high vascular resistance. This results from the loss of radial stretch on the blood vessels resulting in smaller vessel diameters leading to increased vascular resistance. This follows Poiseuille's equation which describes the resistance to be inversely proportional to the radius to the fourth power. Regional hypoxic vasoconstriction in these atelectatic areas also plays a part in increasing vascular resistance. Finally, hypercapnia ($\text{PaCO}_2 > 60$ mm of Hg) has been described to contribute to elevated pulmonary arterial pressures and ACP (14). It is difficult to objectively demonstrate pulmonary vascular dysfunction due to fact that most modern intensive care units have shied away from using pulmonary catheters. In one of the few studies that looked at pulmonary vascular dysfunction in ARDS, Bull *et al.* (18) reported a greater than 70% incidence of pulmonary vascular dysfunction among those with acute lung injury. Right ventricular dysfunction and ACP occurs as downstream effects of pulmonary vascular dysfunction and elevation in pulmonary vascular resistance. The study by Mekontso Dessap *et al.* (19) adds to the growing literature providing evidence to suggest that ACP is common among those with moderate-to-severe ARDS and that it persists even after the implementation of low tidal volume ventilation strategies.

Granted that we do not have clear evidence to prove that ACP affects survival in ARDS, there is sufficient evidence to suggest that it negatively affects the course of the disease. The following studies have investigated the independent effects of ACP on morbidity and mortality. Lheretier *et al.* had demonstrated that patients with ACP required higher levels of inhaled nitric oxide and required proning more often than those without ACP (15). Boissier *et al.* reported statistically significant higher 28-day mortality in those with ACP of 67% (14). Bull *et al.* published data on 470 patients with ARDS demonstrating an increased 60-day mortality with elevated baseline transpulmonary gradient (TPG) > 12 mm of Hg. Both pulmonary vascular resistance index and TPG were determined to be independent risk factors for increased 60-day mortality, number of ICU free days, ventilator free days on multivariate analysis in his study (18).

What does Mekontso Desapp's study add to the current literature?

Mekontso Dessap and colleagues present a retrospective analysis in *Intensive Care Medicine* proposing a risk prediction model to identify those at high risk of developing ACP (19). The authors added 250 new patients to a previously existing dataset to create one of the largest collections of patients (752 patients) with moderate to severe ARDS with focus on the development of ACP and to further characterize the factors predicting its development. They report a 22% prevalence rate of ACP when TEE was performed within 3 days from the diagnosis of ARDS. All patients included in this study were managed with low tidal volume ventilation strategy and plateau pressure were kept below 30 mmHg. The authors defined ACP using a TEE probe that was placed in the mid-esophagus and measured the end diastolic left and right ventricular area (LVEDA and RVEDA). They also looked for evidence of septal dyskinesia at end systole from the transgastric view. The authors defined ACP by a RVEDA/LVEDA ratio greater than 0.6. A cutoff of 1.0 or more was taken to be a marker of severe ACP (7.2% of patients).

The authors identified four variables that stood out as statistically significant predictors of ACP—pneumonia as a cause of ARDS, driving pressure of > 18 cm H_2O , $\text{PaO}_2/\text{FiO}_2 < 150$ mmHg and $\text{PaCO}_2 > 48$ mmHg. These variables were first recognized among 502 patients (called the derivation cohort) and then applied to 250 patients (the validation cohort) confirming their soundness. The authors then used these variables to construct a risk score prediction model for the development of ACP. The prevalence of ACP is approximately 20% when two variables are present and more than 30% when three are present. It goes up to a 75% when all four criteria are met. Based on these results, the authors recommend utilizing TEE to look for evidence of ACP when the risk score is 2 or more. Although the authors report a marginally higher mortality in those with ACP than those without (48% *vs.* 44%; $P=0.17$), statistically significantly higher mortality was noted only in those patients with severe ACP compared to the rest (57% *vs.* 42%; $P=0.03$).

In summary:

- (I) Even with targeted low plateau pressures below 30 mmHg, there is a high incidence of ACP among patients with severe ARDS.
- (II) Defined four variables whose presence could predict the development of ACP:

- (i) pneumonia as a cause of ARDS;
 - (ii) driving pressure of >18 cm H_2O ;
 - (iii) $PaO_2/FiO_2 <150$ mmHg;
 - (iv) $PaCO_2 >48$ mmHg.
- (III) Suggested searching for evidence of ACP with a TEE when the risk score is greater than 2 among patients with ARDS.
- (IV) Mortality was found to be significantly higher in those patients with severe ACP (57% *vs.* 42%).

The question that naturally stems from the results of the study is what would be the next step once we diagnose the existence of ACP? Unfortunately, we do not have evidence to suggest that any therapy targeted towards the management of ACP will actually improve outcomes in ARDS. Hence, it is often left to the institutional intensive care practices to determine management strategies on a case-by-case basis. What we know for sure is that mortality is high once the patient develops ACP (48%) (19). Thus, practices that are known to protect the right ventricle and reduce right ventricular pressures are likely to reduce mortality if applied at the right time and in the right fashion. This study (19) provides evidence to suggest that the same measures that are known to limit lung stretch and damage in ARDS—such as limiting driving pressures to the lower end (20), proning patients with a PaO_2/FiO_2 ratio <150 particularly those with two or more predictors of ACP (4), and preventing the partial pressure of CO_2 to climb above 48 mmHg will decrease the incidence of ACP and subsequent risk of circulatory dysfunction (15). Targeting plateau pressures below 30 cm of H_2O is accepted to be lung-protective based on the results of the ARDSNet results, albeit it still exposes the right heart to considerable strain when plateau pressures are above 28 cm of H_2O (21). Accordingly, it might not be unreasonable to target lower plateau pressures. It is debatable whether one should attempt to treat elevated CO_2 levels by extracorporeal removal. A lack of survival benefit utilizing this modality of treatment limits its applicability in patients with ARDS (22-24). It is important to recognize that none of the studies using extracorporeal CO_2 removal focused on patients with ACP. Prone positioning is also known to help hemodynamics by unloading the right ventricle and hence reduce right ventricular dilatation. This effect is most obvious in patients who have both severe ARDS and ACP (10). Improvements in LVEF are also noted with proning, which might contribute to the improvement in hemodynamics seen with this maneuver (10).

A concept of RV protective ventilation (25) has been proposed to encounter the high risk of ACP in severe ARDS which could be applied to those patients who carry at least two of the high risk determinants as described by the Mekontso Dessap (19). This concept applies those measures known to reduce the chances of developing ACP as described above. PEEP is applied being cognizant of its deleterious effects on the RV (26).

Whether these measures will be effective in improving the survival in severe ARDS is a question for which there are no clear answers. The lack of a clear relationship between ACP and survival stems from the fact that such patient being sicker get the most aggressive treatment including proning which by itself is known to unload the right ventricle and improve right ventricular function (27). It would be unethical to hold treatment from such patients to form a control arm for such a hypothetical study. Having said that, the results of this current study by Mekontso Desapp *et al.* (19) indicates that a severe ACP increases mortality. These results should encourage intensivists to utilize right ventricular protective ventilatory strategies described above to prevent the development of severe ACP. However, whether applying the same principles of treatment after severe ACP has already set in would change outcomes is anybody's guess.

To conclude, it is probably premature to consider the results of this study as definitive proof of a cause-effect relationship between ACP and mortality, but it does indicate that severe ACP increases mortality. Recognition of the four-point clinical variables can help identify those at a high risk of developing ACP. Application of these variables may help us select the right patient for the most aggressive therapy with specific attention given to the state of the right ventricle in order to avoid consequences of hemodynamic compromise resulting from a failing right ventricle.

Acknowledgements

None.

Footnote

Provenance: This is a Guest Commentary Commissioned by Guest Editor Zhongheng Zhang, MD (Department of Critical Care Medicine, Jinhua Municipal Central Hospital, Jinhua Hospital of Zhejiang University, Jinhua, China).

Conflicts of Interest: The author has no conflicts of interest to declare.

References

- Panwar R, Hardie M, Bellomo R, et al. Conservative versus Liberal Oxygenation Targets for Mechanically Ventilated Patients. A Pilot Multicenter Randomized Controlled Trial. *Am J Respir Crit Care Med* 2016;193:43-51.
- Repassé X, Charron C, Vieillard-Baron A. Acute respiratory distress syndrome: the heart side of the moon. *Curr Opin Crit Care* 2016;22:38-44.
- Vieillard-Baron A, Schmitt JM, Augarde R, et al. Acute cor pulmonale in acute respiratory distress syndrome submitted to protective ventilation: incidence, clinical implications, and prognosis. *Crit Care Med* 2001;29:1551-5.
- Guérin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013;368:2159-68.
- Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000;342:1301-8.
- Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 2010;363:1107-16.
- Phua J, Badia JR, Adhikari NK, et al. Has mortality from acute respiratory distress syndrome decreased over time?: A systematic review. *Am J Respir Crit Care Med* 2009;179:220-7.
- Biswas A. Right heart failure in acute respiratory distress syndrome: An unappreciated albeit a potential target for intervention in the management of the disease. *Indian J Crit Care Med* 2015;19:606-9.
- Vieillard-Baron A, Page B, Augarde R, et al. Acute cor pulmonale in massive pulmonary embolism: incidence, echocardiographic pattern, clinical implications and recovery rate. *Intensive Care Med* 2001;27:1481-6.
- Vieillard-Baron A, Charron C, Caille V, et al. Prone positioning unloads the right ventricle in severe ARDS. *Chest* 2007;132:1440-6.
- Fougères E, Teboul JL, Richard C, et al. Hemodynamic impact of a positive end-expiratory pressure setting in acute respiratory distress syndrome: importance of the volume status. *Crit Care Med* 2010;38:802-7.
- Brown SM, Pittman J, Miller Iii RR, et al. Right and left heart failure in severe H1N1 influenza A infection. *Eur Respir J* 2011;37:112-8.
- Mekontso Dessap A, Proost O, Boissier F, et al. Transesophageal echocardiography in prone position during severe acute respiratory distress syndrome. *Intensive Care Med* 2011;37:430-4.
- Boissier F, Katsahian S, Razazi K, et al. Prevalence and prognosis of cor pulmonale during protective ventilation for acute respiratory distress syndrome. *Intensive Care Med* 2013;39:1725-33.
- Lhéritier G, Legras A, Caille A, et al. Prevalence and prognostic value of acute cor pulmonale and patent foramen ovale in ventilated patients with early acute respiratory distress syndrome: a multicenter study. *Intensive Care Med* 2013;39:1734-42.
- Zapol WM, Snider MT. Pulmonary hypertension in severe acute respiratory failure. *N Engl J Med* 1977;296:476-80.
- Schmitt JM, Vieillard-Baron A, Augarde R, et al. Positive end-expiratory pressure titration in acute respiratory distress syndrome patients: impact on right ventricular outflow impedance evaluated by pulmonary artery Doppler flow velocity measurements. *Crit Care Med* 2001;29:1154-8.
- Bull TM, Clark B, McFann K, et al. Pulmonary vascular dysfunction is associated with poor outcomes in patients with acute lung injury. *Am J Respir Crit Care Med* 2010;182:1123-8.
- Mekontso Dessap A, Boissier F, Charron C, et al. Acute cor pulmonale during protective ventilation for acute respiratory distress syndrome: prevalence, predictors, and clinical impact. *Intensive Care Med* 2015. [Epub ahead of print].
- Amato MB, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med* 2015;372:747-55.
- Jardin F, Vieillard-Baron A. Is there a safe plateau pressure in ARDS? The right heart only knows. *Intensive Care Med* 2007;33:444-7.
- Fitzgerald M, Millar J, Blackwood B, et al. Extracorporeal carbon dioxide removal for patients with acute respiratory failure secondary to the acute respiratory distress syndrome: a systematic review. *Crit Care* 2014;18:222.
- Cherpanath TG, Landburg PP, Lagrand WK, et al. Effect of extracorporeal CO₂ removal on right ventricular and hemodynamic parameters in a patient with acute respiratory distress syndrome. *Perfusion* 2015. pii: 0267659115621783. [Epub ahead of print].
- Morimont P, Guiot J, Desaive T, et al. Veno-venous extracorporeal CO₂ removal improves pulmonary hemodynamics in a porcine ARDS model. *Acta Anaesthesiol Scand* 2015;59:448-56.
- Vieillard-Baron A, Price LC, Matthay MA. Acute cor

- pulmonale in ARDS. *Intensive Care Med* 2013;39:1836-8.
26. Repessé X, Charron C, Vieillard-Baron A. Acute cor pulmonale in ARDS: rationale for protecting the right ventricle. *Chest* 2015;147:259-65.
27. Jozwiak M, Teboul JL, Anguel N, et al. Beneficial hemodynamic effects of prone positioning in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2013;188:1428-33.

Cite this article as: Biswas A. Preventing the development of acute cor pulmonale in patients with acute respiratory distress syndrome: the first step. *Ann Transl Med* 2016;4(7):146. doi: 10.21037/atm.2016.03.18