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Mechanical Ventilation in the Obese Patient: Compliance, Pleural Pressure, and Driving Pressure

Obesity is increasingly common in Western societies (1). When critically ill, obese patients present many management challenges, especially during mechanical ventilation (2). As a consequence of the large abdominal and chest wall loads on the diaphragm, they have more atelectasis and hypoxemia and require higher pleural pressure (Ppl) and airway pressure to maintain adequate oxygen saturation as measured by pulse oximetry (Sp_{O_2}). These higher pressures have the potential to decrease $\dot{Q}$. This can negate the benefit of an increase in Sp_{O_2} and result in no change or even a decrease in O_2 delivery (DO_2), which ultimately is what matters for tissues. There is little information on airway pressure management in obese patients because they usually are left out of clinical trials. Accordingly, in this issue of the *Journal*, to evaluate the hemodynamic consequences of higher levels of airway pressure in obese patients with acute respiratory distress syndrome (ARDS), De Santis Santiago and colleagues (pp. 575–584) (3) performed clinical and animal studies to determine if higher positive end-expiratory pressure (PEEP) can improve gas exchange without compromising hemodynamics.

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In a crossover design with 19 obese patients who had an average body mass index of 57 ± 12 kg/m^2, they compared the hemodynamic effects of PEEP based on the standard ARDS network PEEP table (4) versus higher PEEP determined by a lung recruitment procedure and PEEP titrated to respiratory system compliance as in ART (Alveolar Recruitment for Acute Respiratory Distress) (5). In a subset, they also compared changes in regional lung ventilation and perfusion by electrical impedance tomography in these patients and selected nonobese patients from ART (5).

There was no evidence of hemodynamic compromise with the higher PEEP in the obese subjects, nor echocardiographic evidence of right ventricle dysfunction, although the measurements were of limited sensitivity. In the subset with electrical impedance tomography studies, the lung recruitment strategy produced more homogeneous ventilation and reduced lung collapse by 31% without causing overdistention. Respiratory system compliance increased by 24%, driving pressure, which is the difference between the plateau of inspiratory pressure and PEEP, decreased by 30%, and Pa_{O_2}/FI_{O_2} markedly increased. In patients without obesity, overdistention was more common in the nondependent regions and lung perfusion was highly heterogeneous. It was considered too invasive to measure $\dot{Q}$ and DO_2, but unfortunately, these are the key variables needed for interpreting the results.

It was in the animal study that the hemodynamic benefit of higher PEEP is evident. The authors compared PEEP 7 versus 19 cm H_2O in normal swine and swine with obesity and ARDS simulated by placing a weight on the abdomen and lung lavage. It is worth noting some design deficiencies. A weight on the abdomen produces a homogeneous increase in abdominal pressure and misses the effects of intraabdominal fat acting primarily on the dorsal diaphragm and the chest wall load. However, these issues likely give quantitative differences but do not compromise the qualitative response. It also was unfortunate that the authors only compared the equivalent of animals with obesity and ARDS with normal swine rather than a third group with ARDS and no obesity. Without it, the hemodynamic effect of ARDS cannot be fully separated from that of obesity. Ppl was measured with esophageal balloons (6). This allowed vascular pressures to be presented as the transmural pressure (intravascular minus the outside pleural pressure) as well as pressures relative to atmosphere, which is necessary to understand the relationship of the heart to the rest of body. Most importantly, they also measured $\dot{Q}$ and calculated DO_2.

Differences in the hemodynamic responses to the high PEEP between the two groups were striking. Control swine had a marked fall in mean arterial pressure, a rise in pulmonary arterial pressure (PAP), and minimal changes in the transmural central venous pressure (CVP) and wedge pressure. Most significantly, $\dot{Q}$ and DO_2 fell by more than 30%. In contrast, in the obese lung injury swine, PAP fell and there was no change in transmural CVP and wedge pressure and only a modest 12% fall in $\dot{Q}$; DO_2 actually rose. The rise in DO_2 with a fall in $\dot{Q}$ was at first hard to explain, as was the marked rise in mixed venous saturation from a mean of 52–75% with no change in $\dot{V}O_2$. Working backward from the O_2 extraction fraction, it is apparent that this occurred because of a marked increase in arterial Sp_{O_2} from the 65% range before the recruitment to close to 100% after.

What accounts for the marked difference in $\dot{Q}$ response in the obese versus nonobese condition with high PEEP? Mechanical ventilation decreases $\dot{Q}$ either by altering venous return to the heart by increasing CVP relative to atmospheric pressure (and not the transmural CVP) or by loading the RV. In the healthy swine, high PEEP increased CVP by 6 mm Hg relative to atmosphere and, by decreasing venous return, likely was the primary cause of the fall in $\dot{Q}$. There was a small increase in transmural CVP and no change in transmural RV pressure, suggesting only a small inspiratory increase in RV afterload from an increase in transpulmonary pressure (1). Interpretation of the RV load is difficult. A decrease in venous return and $\dot{Q}$ decrease PAP, whereas increased RV load raises PAP, which also lowers $\dot{Q}$ and changes cardiac filling pressures.

In the swine with obesity and ARDS, the recruitment maneuver markedly improved lung compliance so that driving pressure decreased and there only was a modest increase in inspiratory transpulmonary pressure. As a result, there was a smaller fall in venous return and $\dot{Q}$. The recruitment maneuver also resulted in a striking reduction in the inspiratory load on the RV as evidenced by the fall in pulmonary artery pressure and transmural RV systolic pressure.

The major determinant of the inspiratory load on the RV is not the actual Ppl but rather driving pressure. In the obese patients with ARDs, driving pressure dramatically decreased from 13 ± 4 to 9 ± 2 cm H_2O because of the improved respiratory system compliance following recruitment of collapsed lung and better distribution of blood flow. This reinforces the observation that driving pressure is a key variable to follow during ventilator management (7). Based on this study, the argument can be made that a lower driving pressure is not only lung protective but also an important factor for cardiac protection. A second component was the large improvement in Sp_{O_2} from improved V/Q matching.

Two other observations are worth commenting on. By improving V/Q matching, the rise in Sp_{O_2} increased DO_2 and more than compensated for the small fall in $\dot{Q}$. The message is that all parts of the DO_2 equation need to be considered when managing patients. The second is historical. In the 1990s, there was a lot of discussion about supply-dependent $\dot{V}O_2$ (8). Calculated $\dot{V}O_2$ in all animal groups were strikingly similar, indicating that this value most often is regulated by the underlying metabolic activity and not DO_2.

As a cautionary note, although lung recruitment improved DO_2, the same protocol in ART (5) showed net harm. We suggest that it may be safer to use an escalating rather than a deescalating PEEP trial to identify best total thoracic compliance. In this approach, PEEP is increased with a fixed inspiratory pressure until V_T decreases. The PEEP below this value is then used. This likely gives a PEEP value that is lower than that determined by an initial recruitment and deescalation of PEEP because of the hysteresis between inspiration and expiration the curves, but it is safer and likely still adequate for the hemodynamic benefit.

In conclusion, higher levels of PEEP in obese patients with ARDS reduces harmful heart–lung interactions. The primary benefit derives from improving respiratory system compliance, which then allows for a lower driving pressure to ventilate the lung and consequently less compromise of RV function. This further emphasizes the clinical value of following driving pressure. ■

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Getting Near to "Closing the Gap" in the Pediatric Age Group for First Personalized Treatment of Cystic Fibrosis

With the approval of highly effective modulators, the treatment of cystic fibrosis (CF) has been transformed, and the progression of the disease will be further modified in people with CF. CFTR (cystic fibrosis conductance regulator) modulators are small molecules administered orally that treat the basic defect by correcting specific deficiencies in the CFTR protein and therefore restoring CFTR function. Potentiators such as ivacaftor improve the channel opening duration of CFTR in so-called gating mutations.

A phase III study in patients with CF (aged ⩾12 yr) with the G551D mutation demonstrated that ivacaftor improved the percent of predicted FEV_1 ($ppFEV_1$) by 10.6% after 24 weeks of treatment ($P < 0.001$). It reduced the frequency of pulmonary exacerbations by 55% ($P < 0.001$), induced a weight gain of 2.7 kg ($P < 0.001$), and decreased sweat chloride concentration by 48 mmol/L compared with placebo ($P < 0.001$) (1). These results demonstrated that correction of CFTR at the molecular level translates into impressive clinical improvements (2). Ivacaftor became the first CFTR modulator approved in 2012 for people with CF in this age group.

Clinical benefit was also confirmed in further studies. Patients with CF with eight further gating mutations showed improvement in $ppFEV_1$, weight, sweat chloride, and quality of life. Even in children, a patient population with still normal $ppFEV_1$ due to "silent" CF lung disease, a significant improvement in $ppFEV_1$ and lung clearance index was shown (2–4). Furthermore, ivacaftor demonstrated effectiveness in preschool children (5). In this age group, the increase in FE-1 (fecal elastase-1) as an outcome parameter is remarkable, indicating a potential reversal of early pancreatic insufficiency previously thought to be irreversible (5, 6).

Therefore, these promising data, combined with real-life experience, hold promise for its use in very young children when disease manifestations can still be modified. However, new therapies in this vulnerable patient group need careful assessment of pharmacokinetics and safety.

In this issue of the *Journal*, Davies and colleagues (pp. 585–593) provide results of ivacaftor in infants aged 4–12 months with a gating mutation (7). A total of 25 patients received ivacaftor in a phase III, single-arm, two-part multicenter clinical trial.

An important finding of this study was that ivacaftor was generally safe in this very young age group. The majority of infants showed plasma drug concentrations within the accepted range from prior clinical studies consistent with ranges for older children.

This study reveals that most adverse events (AEs) were mild to moderate and considered not related to the study drug, with cough being the most frequent AE (Part B). Five infants had serious AEs, interestingly also all considered not or unlikely related to the study drug.

An important concern regarding CFTR modulators is the risk of inducing abnormalities of liver function in this young population. Fortunately, only one child demonstrated a reversible transaminase elevation. Interestingly, the incidence of liver function abnormalities was lower than expected compared with previous trials.

A striking finding was that one infant aged 3 months had drug levels above the adult 95th percentile, a fact that led to an adjustment of age and dose during the ongoing trial.

This raises the question of whether the dosages need to be adjusted to weight/body composition and whether the ranges are really comparable between the various age groups. The authors

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