Fluid Balance: Another Variable to Consider with Diaphragm Dysfunction?

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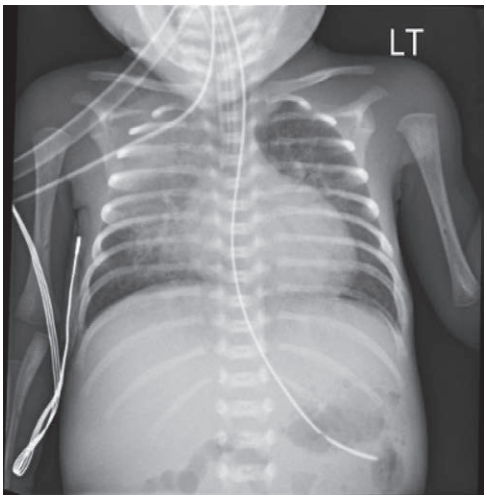
While mechanical ventilation is lifesaving for children with acute respiratory distress syndrome (ARDS), it has become clear that it can lead to significant harm from ventilator-induced lung injury, patient self-inflicted lung injury, and ventilator-induced diaphragm dysfunction.[1] To that end, therapeutic strategies that try to balance lung and diaphragm protection have become a priority in both pediatric and adult ARDS.[2] In this month's issue, Ijland *et al.*[3] provide provocative results evaluating the effect of fluid strategies on diaphragm function in an experimental model of pediatric ARDS. The results highlight that fluid management can have potentially competing effects on the lung and the diaphragm.



"…fluid management can have potentially competing effects on the lung and the diaphragm."

The authors should be commended for an elegant and comprehensive controlled study, conducted in 19 lambs with on average moderate ARDS. The authors hypothesized that lambs managed with a liberal fluid strategy would have more impairment in diaphragm strength, because the liberal strategy would promote more edema in diaphragm myofibrils, impairing force-generating capacity. They found, in contrast to their hypothesis, that lambs managed with a restrictive fluid strategy with use of norepinephrine to maintain blood pressure and cardiac output had a nearly 10 cm H_2O loss in contractile activity of the diaphragm with electrical stimulation, while the liberal fluid strategy group had minimal noticeable change in diaphragm function. Mechanistically, the study found no clear differences in histopathologic findings of size or shape of type I or II myofibrils in the diaphragm between groups and no difference in markers of inflammation or oxidative stress. The authors speculate that potential mechanisms for this observed difference may relate to restrictions in microvascular circulation with the use of norepinephrine and restrictive fluids or disturbances at the level of the neuromuscular junction. While they were unable to test the latter hypothesis, the restrictive fluid group may have had lower density of microvessels, although this was not statistically significant and possibly underpowered for a meaningful effect.

In addition, the authors describe a novel finding related to positive end-expiratory pressure (PEEP) levels and the force-generating ability of the diaphragm. The authors found that as PEEP was increased from 5 to 10, 15, and 20 cm H_2O, there was a dose-dependent reduction in the force-generating capacity of the diaphragm, and this PEEP effect was more important than the impact of fluids when PEEP levels were very high (*i.e.*, 15 to 20 cm H_2O). Certainly, it is highly plausible that the force-generating capacity of the diaphragm will decrease as PEEP is increased if it results in more flattening and elongation of the diaphragm at rest. These higher levels of PEEP may put the diaphragm at more of a mechanical disadvantage, which thereby results in less force. In this experiment, the force was measured with electrical stimulation of the phrenic nerves directly, but these findings corroborate previous investigations in spontaneously breathing adults with vigorous effort where increasing PEEP results in a reduction in large swings in esophageal pressure.[4] There are other potential mechanisms through which increasing PEEP may decrease respiratory effort in spontaneously breathing patients such as lung recruitment and Hering–Breuer reflexes, but the findings from this study highlight the potential impact that diaphragmatic elongation and location have on force generation. This implies that we should be standardizing PEEP levels when measuring the force-generating capacity of the

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diaphragm, regardless of the method (*i.e.*, electrical stimulation, maximal effort maneuvers during airway occlusion, or noninvasive measurements such as ultrasound). We certainly need more mechanistic and clinical studies focused on the interaction between PEEP and diaphragm function in mechanically ventilated adults and children.

So, how can we use these findings to help us at the bedside? Given that these are preclinical data, we certainly should not be changing clinical practice based on these results. However, this study highlights that fluid management is yet another variable that we need to carefully consider as we are investigating risk factors for ventilator-induced diaphragm dysfunction and devising treatment strategies. Controlled trials in adults with ARDS and multiple observational studies in pediatric ARDS have demonstrated improved oxygenation and potential improvements in short-term clinical outcomes when ARDS patients are managed with a restrictive fluid strategy.[5–7] These benefits are likely coming from improved respiratory compliance and oxygenation, leading to less lung stress, and lowering the risk of ventilator-induced lung injury. However, findings from this study have highlighted that these restrictive strategies that try to protect the lung may harm the diaphragm. This is, of course, not the first time that therapeutic strategies developed to protect the lung have had negative consequences on the diaphragm. Controlled ventilation with sedation or neuromuscular blockade is extremely common in adults and children with ARDS, to prevent progression of ventilator-induced lung injury. However, this leads to subphysiologic levels of patient effort, which can lead to overassistance myotrauma of the diaphragm, with atrophy and loss of force-generating capacity.[1] Certainly, protecting the lung should take priority, as ventilator-induced lung injury is clearly associated with multiple organ dysfunction and death. However, as our strategies to prevent ventilator-induced lung injury improve with time, we have an opportunity to try to simultaneously prevent diaphragmatic dysfunction. While some elements of diaphragmatic dysfunction are evident during the acute phase of ventilation (*i.e.*, prolonged weaning, extubation failure), there are longer-term impacts on post–intensive care unit health-related quality of life, respiratory health, and even mortality.[8] Hence, preventing diaphragm dysfunction should be a priority for us at the bedside.

In conclusion, the work by Ijland *et al.*[3] has provided provocative insights into the potential role that fluid balance and management strategies may have on the development of diaphragm dysfunction in ARDS. While this study was conducted in lambs, which are meant to represent pediatric-size patients, the findings are likely applicable more broadly. While these data do not warrant a change in clinical practice, they highlight that we must systematically evaluate the impact of fluid management strategies in all investigations related to ventilator-induced diaphragm dysfunction. Moreover, this study has also highlighted that PEEP levels should be standardized when performing measurements of diaphragmatic strength.

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Competing Interests

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