Ventilator-induced Diaphragm Dysfunction

From Mice (Hopefully) to Men

In the 60 yr since Danish anesthesiologist Bjorn Ibsen initiated the widespread use of positive pressure ventilation during the Copenhagen poliomyelitis epidemic of 1951, the concerns have shifted beyond saving lives to minimizing iatrogenic harm. Webb and Tierney’s seminal 1974 report of ventilator-induced lung injury1 initiated 3 decades of research culminating in the ARDS (acute respiratory distress syndrome) Network trial that confirmed the survival benefit of lower versus higher tidal volumes.2 Although efforts over the last 10–20 yr have concentrated on minimizing damage to the lungs (i.e., ventilator-associated lung injury), harm to the diaphragm caused by mechanical ventilation (i.e., ventilator-induced diaphragm dysfunction [VIDD]) is becoming more widely appreciated. The study of VIDD receives an important boost with the report by Mrozek et al. in the current issue of Anesthesiology of a mouse model that enables reliable exploration of the mechanisms involved.3

The association between mechanical ventilation and respiratory muscle weakness was first reported in baboons by Anzueto et al. in 1997 (although reported in abstract a decade before); several studies have since replicated these findings in multiple species. All the models demonstrate that controlled mechanical ventilation results in significant loss of respiratory (but not peripheral skeletal) muscle strength and endurance after hours or 2–3 days. VIDD is likely an important clinical problem. Diaphragm biopsy specimens from brain dead patients reveal characteristic histologic patterns; indeed, rapidly progressive inspiratory muscle weakness has been reported within 1–2 days of mechanical ventilation in intensive care unit patients. Inspiratory muscle weakness is highly prevalent among mechanically ventilated patients and is associated with a longer duration of ventilation. Because respiratory muscle strength is a key determinant of weaning success (or failure), VIDD probably prolongs mechanical ventilation and increases its associated complications.5

The report by Mrozek et al. provides additional evidence that suppression of respiratory muscle activity during controlled mechanical ventilation leads rapidly to diaphragmatic contractile dysfunction.3 In the study, mice were subjected to controlled mechanical ventilation, continuous positive airway pressure, or control conditions. The results are reassuringly similar to models reported previously: controlled mechanical ventilated mice demonstrated a 40% lower maximal diaphragmatic force versus control, with no impact from continuous positive airway pressure; loss of diaphragm endurance paralleled these findings, and there were no effects on peripheral skeletal muscle.

Ventilator-induced diaphragm dysfunction is characterized by atrophy of type 1 and 2 muscle fibers, as well as by myofibrillar disarray, oxidative injury, and autophagy. Molecular explanations include altered gene expression, with stress-response and proteolytic genes up-regulated and structural and metabolic genes down-regulated.6 Proteolytic systems, such as calcium-dependent proteases (calpain) and caspase, modulate disassembly of the myofilament framework; cleaving these regulatory proteins renders muscle susceptible to ubiquitination and destruction by the ubiquitin-proteasome system. Autophagy, a self-degradative proteolytic pathway has been demonstrated in the diaphragms of brain dead organ donors after 18–69 h of mechanical ventilation. The imbalance between proteolysis and protein synthesis leads to atrophy; myofibrillar disarray produces loss of contractile force that is out of

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proportion to the degree of atrophy. Although the precise events that initiate the cascade of injury within the diaphragm myocyte remain unidentified, oxidative stress resulting in injury to key contractile elements (e.g., myosin and actin) appears to be a key upstream trigger. That antioxidants such as N-acetylcysteine significantly attenuate muscle injury in vitro suggests that oxidative injury plays a role; indeed, reactive oxygen species seem to originate from the myocyte mitochondria, and a mitochondrial-specific antioxidant may attenuate diaphragmatic injury. Many such mechanisms in the pathogenesis of VIDD need to be understood to formulate strategies for prophylaxis or therapy.

In the murine model of VIDD described by Mrozek et al., there was no histologic evidence of muscle atrophy despite a dramatic reduction in contractile function. Such uncoupling of muscle weakness from atrophy has been reported previously in VIDD. This (early) weakness likely results from the initial myofibril disassembly that is required before muscle protein can be ubiquitinatated and degraded. Consistent with previous reports, the caspase-3 proteolytic system was found to be up-regulated in the controlled mechanically ventilated mice. Thus, this model seems to reflect well other models of VIDD.

How will this model facilitate increasing our understanding of VIDD? The beauty of a murine model is that a wide variety of molecular techniques and assays as well as genetically modified animals are available, allowing dissection of potential molecular mechanisms. A pressing example awaiting explanation is how muscle inactivity triggers the cellular changes associated with VIDD. A postulated candidate is titin, a long filamentous sarcomeric protein that functions as a mechanosensor by altering its signaling kinase domain activity in response to mechanical stretch; selective expression of this gene or mutation of its kinase domain would allow exploration of its role in VIDD.

The study also supports the interesting hypothesis that the risk of VIDD is proportional to the rate of protein turnover. The authors predicted that the mice would develop VIDD after only 6 h of mechanical ventilation by extrapolating protein turnover rates from previous VIDD animal models (piglet, rabbit, rat) to mice. They reported contractile dysfunction (but no atrophy) at the 6-h point, suggesting that the muscle injury pathways are not simply related to a local imbalance in cellular protein synthesis and catabolism, at least in the initial stages of VIDD. Nevertheless, organisms with higher protein turnover rates may develop the lesion more quickly; this hypothesis merits further confirmation. Of course, some critically ill patients have extremely high rates of protein catabolism, and these patients may be at higher risk of VIDD; this could help to guide the selection of high-risk patients for study.

One universally reported feature of VIDD is that it is induced by suppression of diaphragm activity during mechanical ventilation, so-called disuse atrophy. The report by Mrozek et al. supports the theory of disuse atrophy; mice subjected to anesthesia and positive airway pressure that maintained diaphragm activity (continuous positive airway pressure mice) had no loss of contractile function. Because maintenance of some respiratory muscle activity attenuates the severity of VIDD, it has been suggested that spontaneous modes of ventilation be used when possible. Multiple factors other than mechanical ventilation affect diaphragm function (e.g., sepsis, corticosteroids, neuromuscular blockade, antibiotics, nutritional deficiency) and may compound the VIDD lesion or limit the benefit of maintaining respiratory muscle activity; here the murine model might provide insights into which conditions contribute most.

Whether attempts at preventing or treating VIDD ultimately will help critically ill patients remains to be seen. But it is likely that insights enabled by careful development of a valid murine experimental model will help guide our pursuit of better care for patients receiving mechanical ventilation. Bjorn Ibsen would be pleased.

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