Invited editorial on “Acquired respiratory muscle weakness in critically ill patients: what is the role of mechanical ventilation-induced diaphragm dysfunction?”

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ACQUIRED WEAKNESS SYNDROMES in critically ill patients have been shown to be a major cause of mortality and long-term morbidity (4, 7). A key component of these syndromes is the development of respiratory muscle weakness, which leads to prolonged duration of mechanical ventilation, difficulty weaning patients from the ventilator, and recurrence of respiratory failure after extubation. Clinical studies (4, 7) have identified sepsis and hyperglycemia as the two major risk factors for development of intensive care unit acquired weakness, including respiratory muscle weakness. In addition to these factors, an extensive literature has recently emerged revealing that mechanical ventilation per se also produces deleterious effects on the diaphragm.

The incidence, prevalence, time course of development, and progression of respiratory muscle weakness in mechanically ventilated patients is not known, as no study has examined these issues in detail in the diverse population of patients who are placed on ventilators. It is important to note that the clinical tools that are used at the bedside to assess respiratory muscle strength in mechanically ventilated patients are often imprecise or inaccurate, as they are highly dependent on the operator and the volitional effort of the patient. Some (14) have argued that even when standardized techniques are used by trained investigators, measurements are unreliable. Because of these issues, it is difficult to diagnose acquired respiratory muscle weakness early in the course of critical illness. In contrast, a limited number of studies (8, 18) have objectively measured respiratory muscle strength in mechanically ventilated patients in the intensive care unit. These studies utilized anterolateral magnetic phrenic nerve stimulation to measure diaphragm pressure generation in response to supramaximal twitch stimulation (TwPdi). Laghi et al. (8) measured TwPdi in patients who were assessed to be ready for weaning from mechanical ventilation; TwPdi values averaged 8–10 cmH2O. Watson et al. (18) also measured TwPdi in 33 critically ill mechanically ventilated patients with values averaging 10.14 cmH2O. In normal individuals, TwPdi values range from 28–39 cmH2O (16, 18). These data show that when assessed objectively, mechanically ventilated patients have marked decrements in TwPdi, indicating profound reductions in respiratory muscle strength.

What then is the role of mechanical ventilation in the development of acquired diaphragm weakness? It is clear from a number of studies using animal models that relatively short durations of controlled mechanical ventilation rapidly produce diaphragm weakness and atrophy. Intensive investigation into the underlying mechanisms responsible for these structural and functional changes reveal that oxidative stress plays a major role in the pathogenesis of mechanical ventilator-induced diaphragm dysfunction (VIDD; Refs. 1, 19). In addition, studies show that multiple proteolytic processes are involved, including activation of caspase-3 (12), calpain (10), and the ubiquitin proteasome pathway (2). Furthermore, Shanely et al. (17) have shown that protein synthesis is decreased. Undoubtedly, the pathogenesis of VIDD is complex, and although much progress has been made to unravel the mechanisms responsible for VIDD, there is still much that is not known.

In this issue of the Journal of Applied Physiology Whidden et al. (19) extend their previous observation that oxidative stress is directly involved in the evolution of VIDD. Using their well-established animal model, the authors hypothesized that xanthine oxidase (XO) is a major source of oxidative stress in the diaphragm during mechanical ventilation. By critically examining multiple parameters, they demonstrate that diaphragm XO activity increased, substrate levels of XO (hypoxanthine and xanthine) decreased, and levels of the end product (urate acid) increased in response to mechanical ventilation. Mechanical ventilation also increased the 130-kDa cleavage product of xanthine oxidoreductase, which represents the active enzyme XO. Furthermore, pretreatment of animals with pharmacological administration of oxypurinol, a XO inhibitor, partially protected the diaphragm from mechanical ventilation-induced dysfunction by preserving specific force generation at higher frequencies as well as reducing oxidative stress. However, XO inhibition did not protect the diaphragm from mechanical ventilation-induced atrophy. These data are similar to those of Matuszczak et al. (11), where administration of allopurinol to mice subjected to hindlimb unloading protected specific force generation in the soleus but had no effect on muscle atrophy.

In previously published data (1) from this group, administration of Trolox, a water soluble vitamin E analog, completely attenuated mechanical ventilation-induced contractile dysfunction by preserving specific force generation in the diaphragm at all frequencies of stimulation and also markedly reduced diaphragm proteolysis. In other studies (12), administration of the caspase inhibitor DVED-CHO was shown to preserve myonuclear domain and mechanical ventilation-induced diaphragm atrophy. Maes et al. (10) showed that calpain inhibition prevents both mechanical ventilation-induced reductions in diaphragm specific force generation as well as diaphragm atrophy. Taken together, these data, along with findings from the current study, suggest that other factors act upstream of caspase-3, calpain, and XO to initiate VIDD dysfunction. One possibility...
is that mechanical ventilation activates diaphragm NADPH oxidase (6). There are data suggesting that NADPH oxidase derived free radicals modulate expression and activity of XO in other tissues (5, 13). Alternatively, mechanical ventilation may enhance diaphragm mitochondrial free radical generation and modulate these downstream processes by redox-mediated events. If these sources of free radicals are activated in the diaphragm as a consequence of mechanical ventilation, theoretically, downstream activation of proteolytic pathways might increase XO activity by either cleaving or oxidizing xanthine oxidoreductase (15). Arguably, further studies are needed to determine if these mechanisms are involved in VIDD and to define the event specifically unique to mechanical ventilation that initiates this cascade.

From a clinical perspective, then, we are left with a number of questions. How are we to use this information in the care of our patients who are receiving mechanical ventilation as a therapeutic treatment for a life threatening condition? Is mechanical ventilation inducing diaphragm dysfunction in our patients? Which pathways are activated in the human diaphragm that are responsible for acquired respiratory muscle weakness? Are some of these processes more important than others? Will we have a treatment for acquired respiratory muscle weakness?

As a practicing critical care physician and a muscle biologist, I realize that these questions can only be partially answered. It is clear that acquired respiratory muscle weakness is a huge clinical problem. An increasing number of patients are being discharged from the intensive care unit to chronic care facilities because they cannot be weaned from mechanical ventilation. While some have argued that studies in animals often do not translate into clinically useful information, a recent study by Levine et al. (9) elegantly showed that the human diaphragm atrophies in response to mechanical ventilation and that caspase-3 activation is involved in this process. These findings were initially discovered in animal studies. With respect to mechanical ventilation as it is typically used in the intensive care unit, where modes of ventilation other than controlled mechanical ventilation are often used (3), it is naïve to presume that by merely using a different mode of ventilation, we will prevent respiratory muscle weakness. The truth is that patients who are critically ill are also critically complex. Many factors, including infection/sepsis, hyperglycemia, and mechanical ventilation, in aggregate, are contributing to the development of respiratory muscle dysfunction. A thorough understanding of the mechanisms involved in producing diaphragm weakness and atrophy is vital. We must embrace the science. Likewise, we are compelled to embrace the complexity of clinical medicine. It is time that we use this knowledge to pursue clinical studies in patients so that we can begin to answer these questions. These studies, however, must be sufficiently rigorous scientifically. This will require a tremendous amount of effort and cooperation between basic scientists and clinicians. Only by proceeding down this path will we be poised to devise effective, targeted therapies to treat acquired respiratory muscle weakness in our patients.

REFERENCES