How Important is Diaphragm Function as a Determinant of Outcomes for MICU Patients in Respiratory Failure?

Overview of the Problem

The number of mechanically ventilated patients in medical intensive care units (MICUs) in the United States has increased dramatically over the past 20 years, with >800,000 patients per year now requiring more than transient mechanical ventilation. Many of these patients die, with a yearly mortality exceeding 200,000. In addition, survivors often require prolonged, expensive hospital stays to achieve liberation from mechanical ventilation. It is commonly thought the outcome of these patients depends primarily on the severity and the temporal evolution of their lung disease. Recent studies indicate, however, that a large majority of MICU patients have severe diaphragm muscle weakness (1, 2, 4–8–10). This finding has raised several questions: 1) What are the clinical consequences of diaphragm weakness in MICU patients? 2) What factors lead to the development of diaphragm weakness in this population? And 3) what potential treatments can or will be found to reverse or prevent weakness in this patient population?

Potential Consequences of Respiratory Muscle Dysfunction in ICU Patients

To elucidate the consequences of respiratory muscle dysfunction in MICU patients, we recently assessed diaphragm strength in a cross section of the MICU patient population and examined the relationship of diaphragm pressure-generating ability to patient outcomes (8). In this study, we used the BAMS technique (assessment of the trans-diaphragmatic twitch pressure, i.e., PdiTw, generated in response to bilateral supramaximal anterior magnetic phrenic stimulation) to assess diaphragm strength (n = 60 mechanically ventilated MICU patients), we assessed lung function from measurements of respiratory system static compliance and inspiratory airway resistance, and we correlated indexes of strength and lung function with the time required to wean patients from mechanical ventilation and patient mortality. In patients who survived their MICU stay, we found there was an inverse correlation between diaphragm strength and the time required to wean patients off of mechanical ventilation. For example, the average duration of mechanical ventilation after PdiTw measurements was 12.3 ± 1.7 days for weaker patients (PdiTw < 10 cmH2O) but only 5.5 ± 2.0 days for stronger patients (PdiTw ≥ 10 cmH2O; P = 0.016). Surprisingly, we also found that the duration of mechanical ventilation did not correlate with the level of lung dysfunction (either respiratory system static compliance or inspiratory airway resistance) but only with the level of diaphragm strength. These data therefore indicate that diaphragm strength may be the major determinant of the duration of mechanical ventilation in ICU patients, with the weakest patients requiring the longest times to wean from ventilators.

We also found that the incidence of death was 49% in the patients with the weakest diaphragms (i.e., with PdiTw < 10 cmH2O) but only 7% for patients with stronger diaphragms (PdiTw levels ≥ 10 cmH2O). To further investigate the relationship between diaphragm weakness and mortality, we determined the circumstances under which patients in our study died. In six patients, there was clear evidence that death was not directly linked to respiratory failure but was due to brain death, cardiopulmonary arrest, or sustained hemodynamic shock. In an additional group of 12 patients, however, death was a consequence of withdrawal of care in patients with sustained respiratory failure. In all of these latter patients, mechanical ventilation was the only form of continuous life support that was being utilized, none had severe neurological impairment, all maintained motor drive to the respiratory pump, none were on vasopressors, none had undergone a cardiopulmonary arrest before care withdrawal, and all had performed at least one ventilator weaning trial and failed to achieve extubation criteria. Importantly, all patients in this latter group had severe diaphragm weakness (PdiTw < 10 cmH2O), and lung mechanics for this group were, on average, equal to values for patients who survived their MICU stays. These 12 patients died when mechanical ventilator support was withdrawn after a discussion between the MICU attending physician and the patient’s family. It seems likely that inability to successfully wean these weak patients with respiratory failure from mechanical ventilation may have influenced decisions about withdrawal of care, accounting for the observed correlation between weakness and mortality.
Numerous previous animal studies have been performed to investigate the biophysical and molecular mechanisms by which infections, inactivity, and systemic inflammation (e.g., acute chemical lung injury) can evoke reductions in respiratory muscle function. This work has examined the subcellular diaphragm organelles altered in response to these stresses (e.g., contractile proteins, mitochondrial electron transport chain function, SR calcium kinetics, action potential propagation), the diaphragm molecular signaling pathways altered by these stresses (e.g., Smase, MAP kinases, PKR, ceramide metabolism, mTOR) and the cellular effector systems modulating alterations in protein structure and function (i.e., proteasomal degradation system, caspase, calpain, oxidative stress, nitrosative stress). All of the organelles, signaling pathways, and cellular effector systems listed in the preceding sentence appear to play a role in modulating the development of diaphragm dysfunction, with many of these processes acting as “common final pathways” that can be activated in parallel by multiple clinical stresses. As an example, both infections and inactivity increase diaphragm oxidative stress, and both of these stresses also activate the proteasomal, calpain, and caspase proteolytic degradation systems. While most of these previous experiments were conducted in animal models, recent studies document that many of these same pathophysiological processes are also present in the diaphragms of critically ill patients, with evidence of increased oxidative stress and proteolytic pathway activation in diaphragm samples from mechanically ventilated MICU patients (7).

**Potential Treatments for Respiratory Muscle Dysfunction in ICU Patients**

Since diaphragm dysfunction appears to play an important role in determining the outcomes of mechanically ventilated MICU patients, it is reasonable to postulate that therapies designed to augment diaphragm function may improve MICU patient outcomes. To date, all of the muscle-directed therapies that have been utilized in MICU patients have involved various forms of volitional or electrically induced exercise directed at various limb and respiratory muscles. Of these therapies, inspiratory muscle training has been shown to directly improve diaphragm function (6). While it is also possible that other forms of targeted or systemic exercise (e.g., walking mechanically ventilated patients, etc.) may also improve diaphragm strength or endurance, we are not aware of a study that has directly shown such an effect.

Although continued development of therapies that utilize various forms of exercise in MICU patients is warranted, another potential approach to the treatment of diaphragm dysfunction in this population is the use of pharmacological agents designed to improve muscle strength and endurance. One group of agents that are potential candidates for this purpose are drugs and biopharmaceuticals that inhibit deleterious pathways (such as the proteasomal, caspase, and calpain proteolytic pathways) previously identified in animal models as potential causes of diaphragm weakness. A second group of agents that could prove efficacious are drugs that alter upstream signaling pathways that regulate muscle protein turnover (e.g., mTOR activators, anti-myostatin receptor antibodies). However, a third group of potential therapies include agents that directly augment contractile protein function, such as levosimendan. Clinical trials to evaluate the effects of these and other potential therapies designed to improve diaphragm function are urgently needed. Treatments that increase diaphragm strength and endurance have the potential to markedly improve MICU patient outcomes by shortening duration of mechanical ventilation and reducing death due to withdrawal of mechanical ventilator support in patients who have failed ventilator weaning.

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**References**


