Commentary

Pressure support ventilation attenuates ventilator-induced protein modifications in the diaphragm

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Abstract

Common medical conditions that require mechanical ventilation include chronic obstructive lung disease, acute lung injury, sepsis, heart failure, drug overdose, neuromuscular disorders, and surgery. Although mechanical ventilation can be a life saving measure, prolonged mechanical ventilation can also present clinical problems. Indeed, numerous well-controlled animal studies have demonstrated that prolonged mechanical ventilation results in diaphragmatic weakness due to both atrophy and contractile dysfunction. Importantly, a recent clinical investigation has confirmed that prolonged mechanical ventilation results in atrophy of the human diaphragm. This mechanical ventilation-induced diaphragmatic weakness is important because the most frequent cause of weaning difficulty is respiratory muscle failure due to inspiratory muscle weakness and/or a decline in inspiratory muscle endurance. Therefore, developing methods to protect against mechanical ventilation-induced diaphragmatic weakness is important.

It is well established that controlled mechanical ventilation (CMV) results in a rapid onset of diaphragmatic proteolysis, atrophy, and contractile dysfunction in a variety of animal models [1-4]. CMV-induced diaphragmatic atrophy occurs due to increased proteolysis and a decreased rate of protein synthesis [5,6]. Importantly, this ventilator-induced diaphragmatic wasting is not limited to laboratory animals as recent evidence confirms that prolonged CMV also results in diaphragmatic atrophy in humans exposed to 18 to 69 hours of mechanical ventilation [7]. Ventilator-induced diaphragmatic weakness is clinically significant because diaphragmatic dysfunction can be an important contributor to weaning difficulties. Therefore, developing strategies to prevent ventilator-induced diaphragmatic weakness is imperative.

Using an animal model of mechanical ventilation, a recent paper by Futier and colleagues [1] reports that the increased diaphragmatic protein turnover observed during CMV can be prevented by using a pressure support mode of mechanical ventilation. Specifically, this study suggests that pressure support ventilation is efficient in maintaining diaphragmatic protein synthesis and retarding CMV-induced diaphragmatic proteolysis. Although this work provides several interesting observations, these experiments did not include direct measurements of diaphragmatic fiber cross-sectional area or the assessment of diaphragmatic contractile function. These additional measures would have greatly improved our understanding of the clinical benefit provided by this mode of mechanical ventilation. For example, in similar experiments, Sassoon and colleagues [8] reported that assist-control mechanical ventilation attenuated the diaphragmatic contractile dysfunction induced by complete diaphragmatic inactivity during CMV. Nonetheless, three days of assist-control mechanical ventilation resulted in a 20% reduction in diaphragmatic peak power output without significant changes in both diaphragmatic contractile proteins and the expression of a key protein (MAF-box) involved in the proteasome system of protein degradation [8]. Therefore, measurement of the rates of protein synthesis and degradation alone do not necessarily reflect the functional status of the diaphragm.

Futier and colleagues [1] also conclude that CMV and pressure-assist mechanical ventilation result in a similar level of diaphragmatic myofibrillar protein oxidation. This argument is based upon the measurement of a single biomarker of oxidative damage (that is, protein carbonyls). We believe that this conclusion is unwarranted for the following reason. Oxidized proteins in cells are rapidly degraded by the 20S proteasome and increased 20S proteasome activity would likely increase the turnover rate of these damaged proteins [9]. This is significant because Futier and colleagues [1] report that the activity of the 20S proteasome is increased in

CMV = controlled mechanical ventilation.

diaphragms from animals exposed to CMV whereas animals ventilated using pressure support do not exhibit elevated 20S proteasome activity. Therefore, protein turnover of oxidized proteins would likely be greater in the diaphragms of CMV animals compared to pressure support animals. It follows that comparing the levels of protein carbonyls from these two experimental groups can not lead to the conclusion that similar levels of protein oxidation existed between these groups.

Finally, Futier and colleagues [1] also state that diaphragmatic protein oxidation probably does not trigger the proteolytic process that occurs during CMV. This postulate may be correct but this report does not provide data to support this supposition. In contrast, studies from our laboratory indicate that the prevention of CMV-induced diaphragm oxidative damage via antioxidants retards CMV-induced diaphragmatic proteolysis and atrophy [10,11]. Moreover, there is abundant evidence to suggest that disturbances in redox balance may play a significant signaling role in several different forms of muscle wasting [12].

In summary, we applaud the authors' attempt to improve our knowledge regarding the impact of different modes of mechanical ventilation on diaphragmatic protein turnover. However, future studies on this topic should include more decisive measures of redox balance along with diaphragmatic contractile measurements and the assessment of muscle fiber atrophy. Moreover, additional mechanistic studies are required to better understand the signaling pathways responsible for the rapid onset mechanical ventilation-induced diaphragmatic wasting and contractile dysfunction.

Competing interests

The authors declare that they have no competing interests.

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