EDITORIALS

Effect of Mechanical Ventilation on the Diaphragm

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It is widely assumed that respiratory-muscle weakness, either intrinsic or due to fatigue, leads to respiratory failure.[1] For the past 30 years, attention has been focused on whether the diaphragm muscle is especially susceptible to fatigue in patients with chronic pulmonary disease and critical illness, increasing the potential for respiratory failure.[2,3] In the 1980s and early 1990s, this concern led to the practice of resting the diaphragm with the use of mechanical ventilation to reverse fatigue. However, in studies examining transdiaphragmatic pressure in patients being weaned from mechanical ventilation, failure to wean was not consistently associated with a decrease in pressure.[4,5] Recently, this idea has been turned on its head with the demonstration that mechanical ventilation may induce diaphragmatic maladaptations leading to muscle weakness, termed ventilator-induced diaphragmatic dysfunction. Thus, for the intensive care physician, the therapeutic decision is not clear: Do you mechanically ventilate your patient to reverse diaphragmatic fatigue, or do you encourage greater diaphragm use to avoid ventilator-induced diaphragmatic dysfunction?

Over the past decade, studies in animals have shown that even relatively short periods of controlled mechanical ventilation (e.g., 18 hours) lead to diaphragm-muscle atrophy and weakness.[6,7] Until now, it has not been clear whether such effects of mechanical ventilation occurred in humans. What was missing were direct measurements of diaphragm fiber size, strength, and fatigue under conditions of diaphragmatic rest. In this issue of the *Journal*, Levine et al.[8] provide important new information showing diaphragm-muscle atrophy in brain-dead organ donors undergoing mechanical ventilation for 18 to 69 hours. They compared muscle fiber size, markers of oxidative stress, and activation of degradation pathways in muscle biopsy specimens obtained from these donors and compared these findings with similar specimens obtained from patients undergoing lung surgery who had received only 2 to 3 hours of mechanical ventilation. The results — consistent with those of studies in animals — revealed marked atrophy of diaphragm fibers, an increase in oxidative stress, and activation of degradation pathways. On the basis of these results, Levine et al. suggest that controlled mechanical ventilation (a mode in which respiratory muscles do not contract and the ventilator provides full ventilatory support) induces oxidative stress that leads to protein degradation and rapid atrophy.

Although the cause of diaphragm-muscle atrophy under conditions of controlled mechanical ventilation is not known, its clinical importance cannot be understated, especially if one considers the prevalence of coexisting conditions associated with the need for mechanical ventilation. A prospective, international study reported that 39% of patients in intensive care units are mechanically ventilated for a median duration of 7 days.[9] More than 80% of these patients presented with acute respiratory failure or acute exacerbation of chronic obstructive pulmonary disease. The effect of ventilator-induced diaphragmatic atrophy and weakening in these patients cannot be ignored.

In considering the effect of mechanical ventilation on diaphragmatic function, it is important to recognize that only a small fraction of the diaphragm's total force-generating capacity is used to sustain spontaneous breathing.[10] Thus, under normal conditions the diaphragm has a very large reserve capacity. It is also important

to recognize that the diaphragm, as compared with other muscles, is very active (approximately 30 to 40% of the time, 24 hours a day). To accomplish this level of activity, the diaphragm fibers used for breathing must be resistant to fatigue. Such fibers are well described and usually classified as slow-twitch fibers. The diaphragm muscle also contains less active but more fatigable fast-twitch fibers that are used primarily for purposes requiring greater force generation and involved in airway clearance (e.g., coughing). In light of this background, a very important observation by Levine et al. was that all diaphragm-muscle fibers atrophied in response to controlled mechanical ventilation. They reported a 57% decrease in the cross-sectional area of slow-twitch fibers, which would almost certainly affect the ability of ventilated patients to sustain spontaneous breathing, requiring recruitment of more fatigable fast-twitch fibers. However, if fast-twitch fibers are repeatedly activated during spontaneous breathing, their subsequent fatigue would only exacerbate muscle weakness. Indeed, variability in recruitment of fast-twitch fibers across patients may account for the inconsistent observations of diaphragm-muscle fatigue in patients being weaned from mechanical ventilation. The 53% atrophy of larger fast-twitch fibers reported by Levine et al. would reduce the diaphragm's reserve capacity and compromise other vital functions, including coughing.

An issue not addressed in this study is whether ventilatory modes other than controlled ventilation have a lesser effect on diaphragmatic atrophy. In studies in animals, assist-mode ventilation, in which the subject makes an effort with the diaphragm to trigger the ventilator's inspiratory cycle, largely alleviates the detrimental effect of controlled mechanical ventilation on diaphragmatic atrophy and strength.[11] Currently, most critically ill patients receiving mechanical ventilation are placed on assist-mode ventilation or synchronized intermittent mandatory ventilation with pressure support[10]; both of these modes require some diaphragmatic work. Whether these modes of ventilation, or others that are under development, will be associated with different degrees of diaphragmatic dysfunction in humans is now unclear.

In this regard, the study of brain-dead organ donors by Levine et al. is not likely to be representative of critically ill patients because brain death completely removes neural activation of the diaphragm. However, in rodents, diaphragmatic inactivity per se is not associated with muscle fiber atrophy.[12] In fact, the benefits of assist-mode ventilation do not appear to depend on the level of diaphragmatic activity, since even short periods of assist-mode ventilation in animal models appear sufficient to reduce detrimental effects.[11] Taken together, the results of studies of animals and humans may reflect the importance of coordinating neural activation with mechanical events in the chest.

Ultimately, hypoventilation, carbon dioxide retention, and respiratory failure during critical illness may not depend simply on impairments in the force-generating capacity of the diaphragm. Any number of other factors associated with mechanical ventilation in critically ill patients — including neuromuscular blocker or corticosteroid use, mitochondrial dysfunction, a generalized inflammatory response to intubation or associated disease, and eccentric muscle injury — may be involved in ventilator-induced diaphragmatic dysfunction. Regardless of the underlying cause, the results reported by Levine et al. certainly argue against the use of controlled mechanical ventilation as a protective, fatigue-reversing intervention for patients requiring ventilatory assistance in intensive care settings. Whether patients undergoing shorter-term procedures (e.g., surgical anesthesia) should also be considered at risk of ventilator-induced diaphragmatic dysfunction remains to be explored, but it is likely that alternative ventilatory strategies will be necessary, especially for patients with decreased reserve capacity at baseline.

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Predicting Cardiovascular Events with Coronary Calcium Scoring

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The thoughtful clinician takes it to be self-evident that intensity of therapy should be proportional to risk of disease.[1,2] Ever since Bigger coined the term "risk stratification" to characterize this intuitive process,[3] more than 3000 articles (according to a recent PubMed literature search) have been published on the subject — at a rate that is doubling every 5 years.[4] Nearly 40% of these articles focus on cardiovascular medicine, where "risk stratification" has become something of a mantra for rational, evidence-based clinical management.

Predicting who will have a cardiovascular event is indeed an important clinical and societal goal. Currently, the United States spends more than $400 billion annually on cardiovascular diseases.[5] However, that disease is common or expensive is not in itself sufficient reason to try to predict it. What is necessary is that reasonable steps can be taken to prevent events. In the case of coronary disease, multiple steps can be taken: patients can stop smoking; they can begin to exercise, control their diet, and lose weight; and when blood lipid levels are abnormal and hypertension or diabetes is present, then pharmacologic therapy can be instituted to reduce risk if nonpharmacologic means fail. The importance of these risk factors has been recognized for more than 45 years, since researchers involved with the Framingham Study published a seminal paper on the subject.[6]

The ability of a risk factor to predict these events as they occur over time may be assessed by the relative risk, or hazard ratio, which is the incidence of events in patients with the risk factor divided by the incidence of events in patients without the risk factor. Models based on the values of risk factors can be created to calculate the probability of an event. How well a model predicts the observed probability of an event across levels of risk is called calibration, while the ability to predict who will and who will not have an event is called discrimination. Thus, calibration and discrimination are not the same, and there is an upper limit to how well a perfectly calibrated model can discriminate.[7] A model's discrimination is often assessed with the c-index (equivalent to the area under the receiver-operating-characteristic curve), which is the fraction of pairs of subjects (one who has an event and one who does not) for which the probability of an event is higher in the subject who has the event. A c-index can vary from 0.5 (no ability to discriminate with half the pairs predicted correctly) to 1.0 (perfect discrimination with all pairs predicted correctly).

The Framingham score remains the most common way to predict cardiovascular risk.[8] By assessment of a few readily available clinical and laboratory variables (age, sex, total cholesterol level, high-density lipoprotein cholesterol level, smoking status, and systolic blood pressure), the 10-year risk of a cardiovascular event can be rapidly and conveniently calculated with a discriminant accuracy of approximately 75%.[8,9] Although this model may be viewed as offering only limited ability to predict individual events, it is inexpensive to assess and provides an opportunity to intervene in cases of cigarette smoking and abnormalities in blood pressure and lipid level.

New risk factors are continually being proposed that could improve discrimination. Popular ones are high-sensitivity tests for C-reactive protein, a biomarker of inflammation, and the