NUMEROUS ANIMAL STUDIES SHOW that controlled mechanical ventilation (CMV) induces diaphragm atrophy and weakness, or ventilator-induced diaphragmatic dysfunction (VIDD) (9). During CMV, oxidative stress activates downstream proteolytic pathways (caspase, calpain, and the proteasome), and diaphragm protein synthesis decreases. Under these experimental conditions, diaphragm contractile dysfunction and atrophy are exacerbated by neuromuscular blockade and low-dose steroids, but attenuated by high-dose steroids, antioxidants, protease inhibitors, hypercapnea, and phrenic nerve stimulation. Additionally, use of other modes of mechanical ventilation (MV), such as pressure support or assist control, as well as intermittent spontaneous breathing (SB) during CMV preserve diaphragm contractility and prevent atrophy, suggesting that maintenance of neural and/or mechanical activation greatly reduces VIDD.

In this issue of the journal, Thomas et al. (11) provide elegant and provocative data indicating that VIDD is rapidly and completely reversible. Specifically, after 24 h of CMV-induced diaphragm weakness, contractile force generation totally recovers within 4–7 h when MV is removed and animals resume SB. This remarkable improvement is associated with complete reversal of type IIX/B diaphragm fiber atrophy, restoration of in vitro diaphragm contractility, and single-fiber contractile force generation/cross-sectional area. Interestingly, these physiological improvements were not associated with reversal of CMV-induced changes in oxidative stress or proteolytic pathway activation, but protein synthesis increased as evidenced by higher levels of phosphorylated-Akt and phosphorylated-eukaryotic initiation factor 4E binding protein. The authors speculate that SB induced rapid resynthesis of myosin, accounting for recovery of type IIX/B cross-sectional area and diaphragm contractile force. These results are fascinating, providing evidence that the diaphragm possesses incredible plasticity. Despite the striking results, questions remain regarding the specific mechanisms responsible for recovery of diaphragm mass and function after VIDD. Additional studies examining myosin heavy chain synthetic rates, quantification of contractile protein content and assessment of biochemical modifications of these proteins, critical appraisal of the role of proteasome, detailed examination of the signaling processes involved, and evaluation of the level of diaphragm activation during recovery should provide additional insights as to how SB improves the dysfunctional diaphragm.

Thomas et al. (11) caution that their findings may not be directly applicable to patients on MV, since they used healthy animals with normal baseline diaphragm function, no medications, and a fully controlled mode. However, the rapid reversibility of VIDD and its potential clinical importance should not be ignored. Several studies suggest that CMV alters the human diaphragm, confirming findings from animal models (6, 8). As a result, most clinicians believe that diaphragm weakness in critically ill patients is primarily due to VIDD (7). Moreover, VIDD has been postulated to be a major problem that limits weaning in mechanically ventilated patients, a concept that is widely endorsed. Nevertheless, there are several important limitations to these human studies that should temper enthusiasm, since VIDD has not been shown to alter patient outcomes. First of all, it is critical to note that most of these human data were obtained from brain-dead organ donors, who, by definition, have no spontaneous diaphragm activity. Brain death induces physiological derangements, including the systemic inflammatory response syndrome, which may have influenced diaphragm alterations (1, 2). Since these data on CMV in humans are based on biochemical assessments of diaphragm biopsies from organ donors, it should not be assumed that they represent the diaphragm dysfunction that occurs in most intubated intensive care unit (ICU) patients. Second, the majority of the human VIDD studies lack physiological data on diaphragm strength or any other index of diaphragm functional capacity. Although muscle atrophy (muscle quantity) is often equated with decreases in function (muscle quality), this is not necessarily true, since atrophy can develop without changes in muscle-specific force generation, and muscle force generation can fall without changes in muscle mass. The absence of such correlative physiological measurements raises questions regarding the clinical applicability of these studies. A third issue is that many, if not all, of these studies failed to separate the effects of MV from the effects of infection on diaphragm dysfunction. The seminal study by Levine et al. (8) provides supporting data that, in the case subjects (organ donors), 43% had an identified source of infection, 93% received antibiotics, and 100% received vasopressors, factors that may have impacted these results. Another report by Hermans et al. (5) argues that the duration of MV affects the level of diaphragm weakness as assessed by measuring transdiaphragmatic pressure generation in response to bilateral anterior magnetic stimulation (Pdi,tw; the gold standard for assessing diaphragm strength in humans). A confounding factor in this study that cannot be discounted is that 9 of 10 of these subjects were septic; interestingly, the patient with the highest Pdi,tw level was the only patient who was not infected.

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**Rapid and complete recovery in ventilator-induced diaphragm weakness—problem solved?**

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Nebroous animal studies show that controlled mechanical ventilation (CMV) induces diaphragm atrophy and weakness, or ventilator-induced diaphragmatic dysfunction (VIDD) (9). During CMV, oxidative stress activates downstream proteolytic pathways (caspase, calpain, and the proteasome), and diaphragm protein synthesis decreases. Under these experimental conditions, diaphragm contractile dysfunction and atrophy are exacerbated by neuromuscular blockade and low-dose steroids, but attenuated by high-dose steroids, antioxidants, protease inhibitors, hypercapnea, and phrenic nerve stimulation. Additionally, use of other modes of mechanical ventilation (MV), such as pressure support or assist control, as well as intermittent spontaneous breathing (SB) during CMV preserve diaphragm contractility and prevent atrophy, suggesting that maintenance of neural and/or mechanical activation greatly reduces VIDD.

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Two recently published large clinical studies (4, 10) that assessed diaphragm strength using nonvolitional techniques in
MV critically ill patients are worth noting, particularly in the context of VIDD. Similar to previous reports, these studies confirm that profound diaphragm weakness is present in many ICU patients. In contrast to the human studies, which implicate MV as the cause of diaphragm weakness, these investigations reveal that infection is the major risk factor. These are the largest reports examining diaphragm dysfunction in a broad-based population of mechanically ventilated, critically ill ICU patients; importantly, both establish that the severity of diaphragm weakness is associated with poor patient outcomes, including increased ICU mortality [40% in the Demoule et al. (4) study, 49% in the Supinski and Callahan (10) study]. We also found that the weakest patients who survived (Pdi,tw < 10 cmH2O) required a longer duration of MV before they were successfully weaned (12.3 ± 1.7 days) compared with patients with Pdi,tw ≥ 10 cmH2O who were successfully weaned (5.5 ± 2.0 days) (10). Taken together, these data underscore that diaphragm weakness is present in many MV critically ill patients, the weakness is often profound, infection is a major risk factor for diaphragm dysfunction, and severe diaphragm weakness results in poor patient outcomes.

In the context of this wealth of animal and human data on diaphragm dysfunction in critical illness, how can we reconcile these data? First, there is no question that diaphragm weakness is a major clinical problem in the ICU. Second, numerous animal studies show that infection profoundly reduces diaphragm function (3), and the two recent clinical studies referenced above provide strong data indicating that infection is a major risk factor for diaphragm weakness in many mechanically ventilated patients (4, 10). Third, data from animal models provide powerful support for VIDD, and studies in brain-dead organ donors suggest that VIDD occurs in this population. Putting this information together, it seems likely that, in some groups of MV critically ill patients, VIDD plays a major role, particularly in individuals on prolonged neuromuscular blockade, those with severe neurological derangements who lack central drive, or those who have little or no spontaneous diaphragm activity. On the other hand, in other MV critically ill patients, infection is a key factor responsible for diaphragm weakness. The present study by Thomas et al. (11) heralds good news for those who have VIDD as the cause for diaphragm dysfunction. Based on their findings, theoretically, VIDD could be readily and rapidly attenuated with implementation of SB trials (T-piece or low levels of pressure support). This would provide a simple, relatively straightforward and safe way to dramatically improve diaphragm function in this subset of patients. Future studies in ICU patients that examine the impact of weaning regimens on diaphragm strength and functional recovery are needed to confirm these findings. It is imperative that such studies examine the contribution of other clinically important variables, including infection, since alternative/additional therapies may be required to improve diaphragm strength in infected patients. These future investigations will provide much needed, clinically relevant, and critically important information.

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AUTHOR CONTRIBUTIONS
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