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UNDERSTANDING THE DISEASE

Myotrauma in mechanically ventilated patients

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In 1988, Knisely et al. "noted marked thinning of the muscular portions of the diaphragm" in neonates following prolonged mechanical ventilation [1]. This provided the first evidence that adverse patient–ventilator interactions can cause deleterious structural changes in the diaphragm, a phenomenon recently termed myotrauma [2]. Extensive experimental and clinical investigation has confirmed the existence of myotrauma and characterized its prevalence and clinical impact [2, 3]. Diaphragm myotrauma is a serious concern because it leads to acute diaphragm weakness (referred to as ventilator-induced diaphragm dysfunction; see Table 1 for terminology) and can therefore impair patients' ability to be liberated from mechanical ventilation. Prolonged mechanical ventilation predisposes patients to nosocomial complications and strongly predicts long-term morbidity and mortality [4]. Preventing myotrauma might therefore accelerate liberation from mechanical ventilation and significantly improve outcomes for critically ill patients. This paper focuses on the adverse patient–ventilator interactions involved in myotrauma and their implications for management; the cellular pathways have recently been reviewed [3, 5].

Mechanisms of myotrauma

Diaphragm myotrauma is thought to result from at least four different adverse patient–ventilator interactions.

- The most well-established mechanism of myotrauma is insufficient inspiratory effort (over-assistance myotrauma), affecting close to 50% of ventilated patients [6]. When diaphragmatic activity falls below the level observed during resting quiet breathing, myofibrillar atrophy and contractile dysfunction rapidly ensue [6, 7]. This atrophy is mediated by oxidative stress, metabolic dysfunction, and an imbalance in proteostasis [5]. Importantly, atrophy can develop during both controlled and assisted or partially assisted ventilation (i.e., pressure support), indicating that the mere presence of "triggering" is insufficient to prevent atrophy [6]. The inspiratory effort level required to prevent atrophy remains uncertain, but several circumstantial observations suggest that a level consistent with resting quiet breathing would be adequate [4, 7, 8].
- Excessive inspiratory effort due to insufficient ventilatory assistance may cause load-induced diaphragm injury (under-assistance myotrauma). Excess loading can cause acute diaphragm weakness [8], delayed muscle inflammation, and proteolysis [9]. Elevated inflammatory cytokine levels have been documented in tissue specimens from patients [5]. Systemic inflammation increases sarcolemmal fragility, increasing susceptibility to load-induced injury. Clinical observations suggest that excessive respiratory effort may lead to load-induced injury, possibly manifesting as an acute increase in diaphragm thickness [10]. Further investigation is required to substantiate the clinical significance of this mechanism.
- Excess contractile loading developed while a muscle is lengthening—eccentric contraction—is particularly injurious (eccentric myotrauma). The diaphragm may contract eccentrically in the context of certain forms of patient–ventilator dyssynchrony where it contracts actively during the ventilator's expiratory phase (reverse triggering, ineffective efforts, premature cycling) [2]. In patients with acute respiratory distress syndrome, the diaphragm may actively contract

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Table1 Terminology for muscle injury and weakness in the critically ill

ICU-acquired weakness	Generalized muscle weakness developing in the context of critical illness and ICU admission; usually employed to refer to axial skeletal muscle weakness but encompasses all forms of muscle weakness
Critical illness-associated diaphragm weakness	Diaphragm weakness (loss of force-generating capacity) occurring in the critically ill regardless of the cause and timing; includes the effects of sepsis, drugs, mechanical ventilation, and other ICU exposures
Ventilator-induced diaphragm dysfunction	An acute loss of force-generating capacity in the diaphragm specifically due to mechanical ventilation
Myotrauma	Various adverse patient–ventilator interactions leading to diaphragm atrophy and injury, resulting in a final common pathway of diaphragm weakness (ventilator-induced diaphragm dysfunction). Analogous to volutrauma or atelectrauma in ventilator-induced lung injury

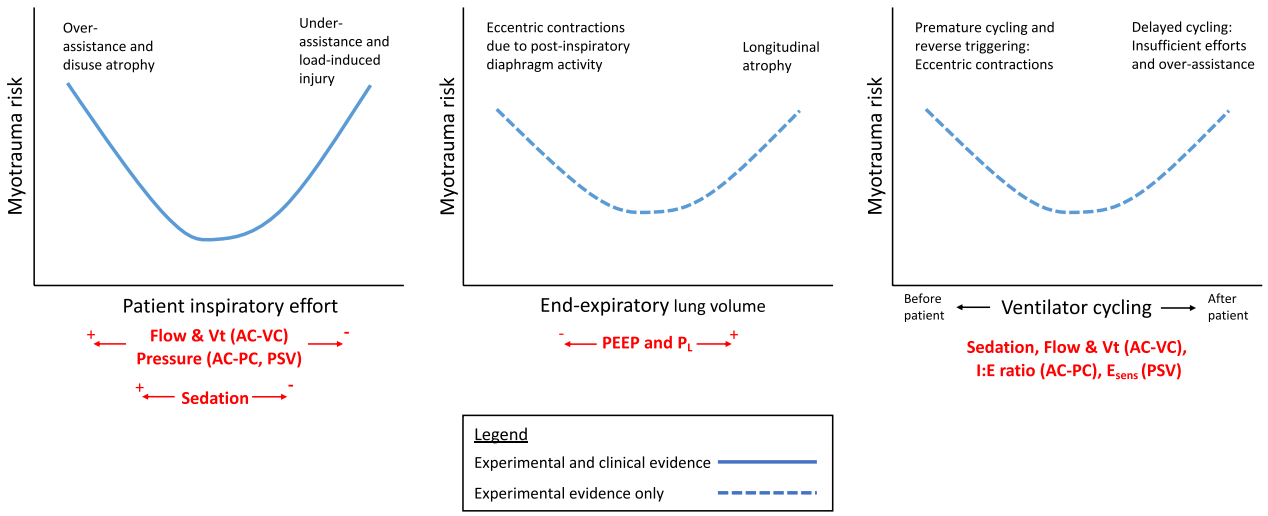

Fig. 1 The risk of myotrauma can theoretically be minimized by optimizing patient inspiratory effort, end-expiratory lung volume, and patient–ventilator synchrony. Optimal levels of inspiratory effort and end-expiratory lung volume likely vary between subjects and over time, though an inspiratory effort level consistent with resting quiet breathing may be optimal under most conditions. The effect of patient inspiratory effort on myotrauma risk is supported by considerable clinical and experimental evidence (solid lines), whereas the effects of end-expiratory lung volume and dyssynchrony on myotrauma risk are supported by experimental evidence and physiological considerations only (dashed lines). Red text indicates specific factors that can be manipulated or targeted. PEEP, positive end-expiratory pressure; P_L, transpulmonary pressure; Vt, tidal volume; ACVC, assist controlled volume control; I:E ratio, inspiratory time to expiratory time ratio; PCV, pressure control ventilation; PSV, pressure support ventilation; E_{sens}, expiratory cycling criterion in PSV

even as it lengthens during expiration to minimize the formation of atelectasis (post-inspiratory activity), particularly if insufficient positive end-expiratory pressure (PEEP) is applied [11]. The frequency and functional impact of eccentric myotrauma in the clinical setting remain uncertain.

- An intriguing recent experimental observation raises the possibility that maintaining the diaphragm at a relatively shorter length with excessive PEEP may cause rapid sarcomere "dropout" resulting in "longitudinal atrophy" [12]. This expiratory myotrauma might alter the optimal length–tension relationship of the muscle and render it acutely weak at an excessive length when PEEP is reduced (as when a spontaneous breathing trial is applied). The clinical significance of this mechanism remains highly uncertain, given very preliminary experimental data.

Evidence of impact on clinical outcomes

Diaphragm weakness is strongly associated with difficult weaning from mechanical ventilation, prolonged ICU admission, and long-term mortality risk [13]. While many factors including severity of illness could account for this association, changes in diaphragm thickness during mechanical ventilation are strongly associated with prolonged ventilation and mediate the association between inspiratory effort and clinical outcomes, suggesting that myotrauma per se impacts clinical outcomes [2, 5].

Implications for ventilator management

Myotrauma might be prevented by optimizing three aspects of ventilator management: patient inspiratory effort, end-expiratory lung volume, and expiratory cycling synchrony (Fig. 1). Absent or insufficient inspiratory effort should be avoided unless muscle relaxation is clinically indicated. Excessive inspiratory effort should also be avoided (particularly since this also causes dyspnea). Sufficient PEEP attenuates respiratory effort and dynamic lung stress during spontaneous breathing [14], but excessive PEEP should be avoided to prevent hyperdistention and longitudinal atrophy. Close attention must be paid to patient–ventilator synchrony: premature cycling or reverse triggering may lead to eccentric muscle injury, while delayed cycling increases the risk of ventilator over-assistance and insufficient efforts.

To achieve such optimization, several clinical advances are required. First, more careful and comprehensive respiratory monitoring is essential. A variety of techniques for monitoring respiratory effort are available, and assessment of inspiratory effort during ventilation should be routine to assess for myotrauma risk (analogous to measurements of plateau and driving pressure to assess for volutrauma risk). Esophageal pressure may be a particularly useful tool to optimize PEEP in spontaneous breathing. Second, better tools to control respiratory drive are needed. Patient respiratory effort is often deliberately suppressed in order to maintain lung-protective tidal volumes because patient drive is significantly elevated. The specific effects of different sedatives on respiratory effort should be considered and studied; partial neuromuscular blockade offers a promising approach (though its safety needs to be established) [15]. The mechanisms responsible for excess respiratory drive in critical illness (deranged chemoreception, mechanoreception, brainstem inflammation, etc.) need to be better delineated to more effectively modulate patient respiratory drive.

In addition to ventilator management to prevent myotrauma, pharmacological interventions acting on cellular pathways that mediate myotrauma are under active investigation [5].

Conclusion: first, do no harm

At least since the time of Semmelweis and Lister, we have come to appreciate that our well-intended medical care may actually harm patients, nowhere more so than for patients in the ICU and on the ventilator. Efforts to avoid barotrauma and volutrauma have dramatically altered outcomes for our patients; it remains to be seen whether myotrauma can be prevented and whether preventing myotrauma can accelerate liberation from the ventilator, attenuate the risk of nosocomial complications, improve survival, and reduce functional disability in patients who survive acute respiratory failure.

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Compliance with ethical standards

Conflicts of interest
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