Diaphragmatic myotrauma: a mediator of prolonged ventilation and poor patient outcomes in acute respiratory failure

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Several mechanisms of diaphragm muscle injury (myotrauma) can result in ventilator-induced diaphragm dysfunction, including ventilator over-assistance, under-assistance, eccentric contractions, and end-expiratory shortening. In this Personal View, we summarise the evidence for the clinical relevance of these mechanisms, and present new data based on mediation analysis supporting the hypothesis that myotrauma due to ventilator over-assistance and under-assistance contribute, in part, to the effect of mechanical ventilation on clinical outcomes. The concept of diaphragmatic myotrauma has important implications for research and clinical practice.

Introduction

Critical care clinicians have long recognised that ventilator settings (mode, pressure, flow, frequency, inspiratory and expiratory cycling triggers) should be selected with care. Inappropriate ventilator settings can decrease efficiency of gas exchange, induce patient–ventilator dyssynchrony, and exacerbate rather than relieve dyspnoea. Importantly, excess volume or pressure applied by mechanical ventilation can injure the lung.[1–5] This insight radically transformed the accepted approach to mechanical ventilation and contributed to substantial improvements in outcomes for mechanically ventilated patients over the past few decades.[6–10] Several mechanisms of ventilator-induced lung injury have been described and specific terms have been designated for each of these mechanisms, including barotrauma, volutrauma, and atelectrauma.[11] The multisystem injury mediated by systemic inflammation from ventilator-induced lung injury is termed biotrauma.[12] Each of these terms helpfully conveys complex biological processes in a manner that facilitates communication between researchers and clinicians and supports clinical decision making at the bedside.

Key messages

- Mechanical ventilation can cause diaphragm (muscle) injury and weakness by several mechanisms collectively referred to as myotrauma
- These mechanisms of myotrauma include over-assistance, under-assistance, eccentric contractions, and excessive end-expiratory shortening
- Myotrauma appears to mediate poor clinical outcomes from abnormally low or high inspiratory effort during mechanical ventilation (mediation analysis)
- Future trials in patients with respiratory failure should account for the possible influence of myotrauma on patient outcomes
- Ventilation strategies designed to optimise patient inspiratory effort might prevent myotrauma and accelerate liberation from the ventilator, resulting in improved long-term functional status in intensive care unit survivors

Ventilator-induced diaphragm dysfunction (VIDD) is another form of iatrogenic injury from mechanical ventilation.[13,14] The diaphragm is the primary muscle of inspiration, with an essential function for the maintenance of adequate ventilation, especially when the respiratory load is elevated. In patients with compromised respiratory mechanics, diaphragm weakness predisposes to prolonged mechanical ventilation.[15] Importantly, VIDD does not result from mechanical ventilation per se; rather, inappropriately applied ventilator support leads to diaphragm injury by a variety of mechanisms. Whereas disuse atrophy (due to ventilator over-assistance) has received a great deal of attention, VIDD can result from several other mechanisms including load-induced injury (due to ventilator under-assistance), eccentric contractile injury (due to dyssynchrony), and excessive shortening (due to high positive end-expiratory pressure [PEEP]). The development of VIDD often constitutes a vicious cycle in which mechanical ventilation leads to diaphragm weakness that, in turn, perpetuates dependence on mechanical ventilation, leading to further diaphragm weakness.

The epidemiology and risk factors for diaphragm weakness during critical illness have been reviewed elsewhere.[16] In this Personal View, we summarise the evidence regarding potential mechanisms underlying diaphragmatic injury due to mechanical ventilation, referring to them as various forms of diaphragmatic myotrauma. The term myotrauma has been used to refer broadly to acute muscle injury,[17,18] or specifically to ventilator-mediated diaphragm injury.[19,20] We present new data supporting the hypothesis that diaphragmatic myotrauma is an important mediator of the effect of mechanical ventilation on clinical outcomes, and we consider the implications of myotrauma for research and clinical practice.

Diaphragmatic myotrauma: mechanisms of diaphragm injury related to mechanical ventilation

Four forms of diaphragmatic myotrauma can be distinguished (figure 1).

The first form is termed over-assistance myotrauma. Excessive ventilatory support by mechanical ventilation or extracorporeal lung support can suppress or reduce respiratory drive, leading to rapid disuse atrophy of the diaphragm. The existence and clinical relevance of this mechanism of injury is well established by experimental studies[21–23] and a series of important clinical studies documenting histological, functional, and imaging evidence of disuse atrophy.[19,24–30] Collectively, these observations showed that suppressing inspiratory effort to very low levels by excessive ventilatory support leads to rapid disuse atrophy and clinically significant diaphragmatic weakness. If over-assistance is avoided during mechanical ventilation, or the diaphragm is activated by phrenic nerve stimulation, disuse atrophy is mitigated.[31–35] Importantly, using a partial assist mode does not guarantee that atrophy will be prevented.[19,36] This form of myotrauma is common and affects nearly 50% of patients that require mechanical ventilation.[19]

The second form is termed under-assistance myotrauma. One of the important aims of providing ventilator support to patients is to reduce the work of breathing to provide sufficient ventilation, reduce oxygen consumption by the respiratory muscles, and avoid diaphragm fatigue. If ventilatory support is insufficient or unable to adequately unload the diaphragmatic work of breathing—eg, when respiratory drive is extremely high[37]—load-induced diaphragm injury could ensue. In the presence of elevated respiratory drive and lung injury, inspiratory effort can redistribute ventilation without increasing tidal volume, generating so-called pendelluft and regional hyperinflation with consequent regional lung injury.[38] Under these conditions the diaphragm can also be injured by the development of excessively high mechanical forces within the muscle. Excessive inspiratory loading can cause acute diaphragm injury and contractile dysfunction, as shown in experimental models and clinical studies.[1–5] Experimentally, acute diaphragm injury is characterised by sarcolemmal rupture, sarcomeric disarray, and inflammatory infiltration,[1,5,39] features that are also reported in diaphragm biopsy samples from critically ill patients.[25,40] Even moderate elevations in respiratory effort for prolonged periods (hours to days) can cause diaphragm injury and weakness,[41] and the propensity for injury is increased in the setting of sepsis and systemic inflammation.[42] Mechanical ventilation mitigates experimental load-induced diaphragm injury.[4] In patients with an

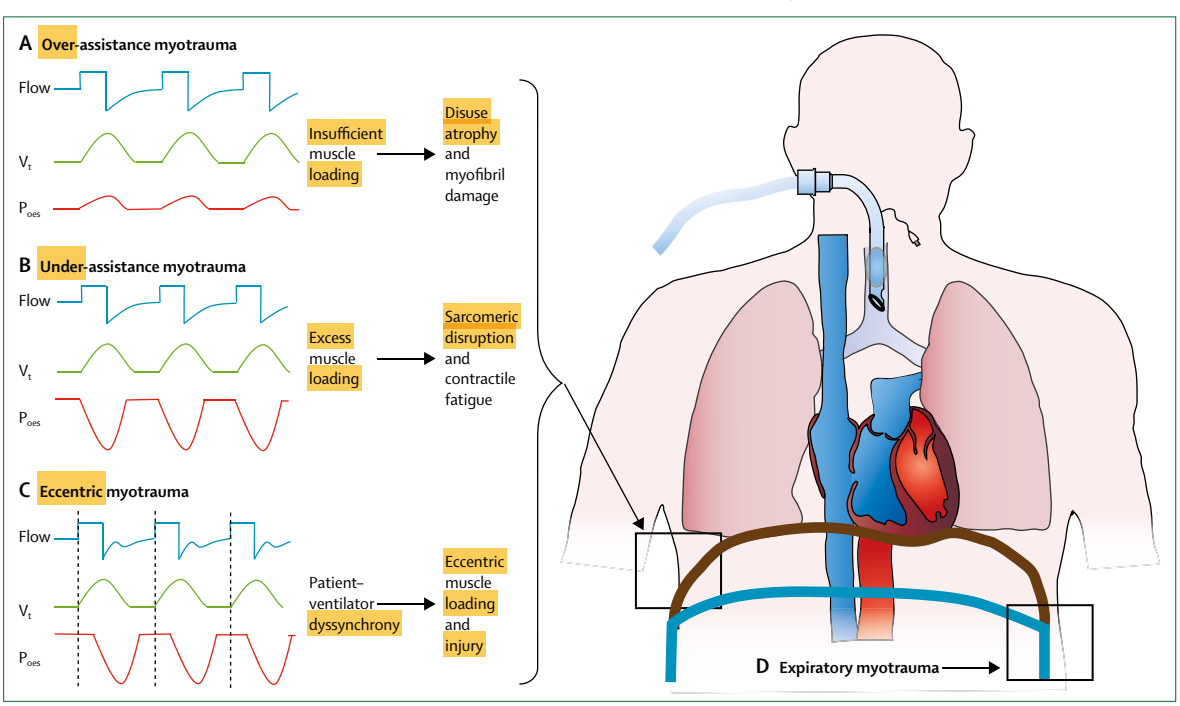

***Figure 1*: Diaphragmatic myotrauma mechanisms leading to ventilator-induced diaphragm dysfunction**
Flow and volume waveforms from the mechanical ventilator (blue and green) are shown in combination with oesophageal pressure tracings (red). (A) When the diaphragm is not sufficiently loaded, because of excess ventilator support or sedation, or both, diaphragmatic atrophy rapidly ensues. The oesophageal pressure tracing shows slight positive deflections during each ventilator breath, reflecting respiratory muscle inactivity. (B) When the diaphragm is not sufficiently unloaded by respiratory support during acute respiratory mechanical loads, then load-induced injury might follow. The oesophageal pressure tracing shows marked negative deflections during each breath, reflecting vigorous inspiratory muscle effort. (C) When the diaphragm contracts eccentrically (while lengthening), muscle injury might follow. Some forms of patient–ventilator dyssynchrony, such as ineffective efforts or reverse triggering (shown by the oesophageal pressure tracing), could predispose patients to eccentric diaphragm contractions. (D) When the diaphragm is maintained at a shortened end-expiratory length for a prolonged period of time by the application of high positive end-expiratory pressure (PEEP), sarcomere dropout and longitudinal atrophy could occur (expiratory myotrauma). When PEEP is removed, the shortened diaphragm might attain a disadvantageous length–tension resulting in acute weakness. V_t=tidal volume. P_{oes}=oesophageal pressure. Brown colouring represents the diaphragm at a longer expiratory length; blue colouring represents the diaphragm at a shorter expiratory length.

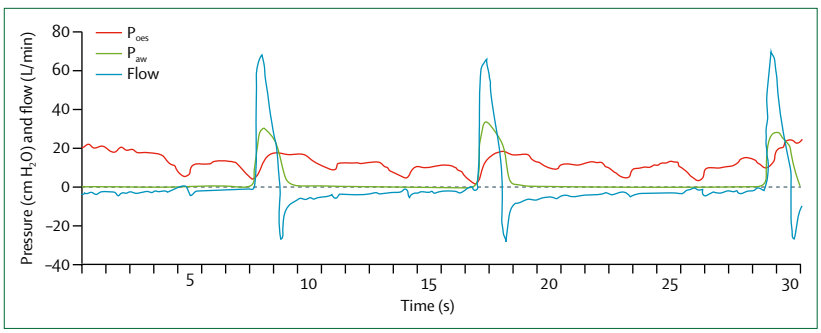

***Figure 2*: Possible eccentric contractions of the diaphragm during ineffective triggering**
Vigorous inspiratory efforts during expiratory flow because of failure to trigger mechanical breaths might result in activation of the diaphragm even while it is lengthening. Reproduced from Chao and colleagues,[51] by permission of Elsevier. P_{oes}=oesophageal pressure. P_{aw}=airway pressure.

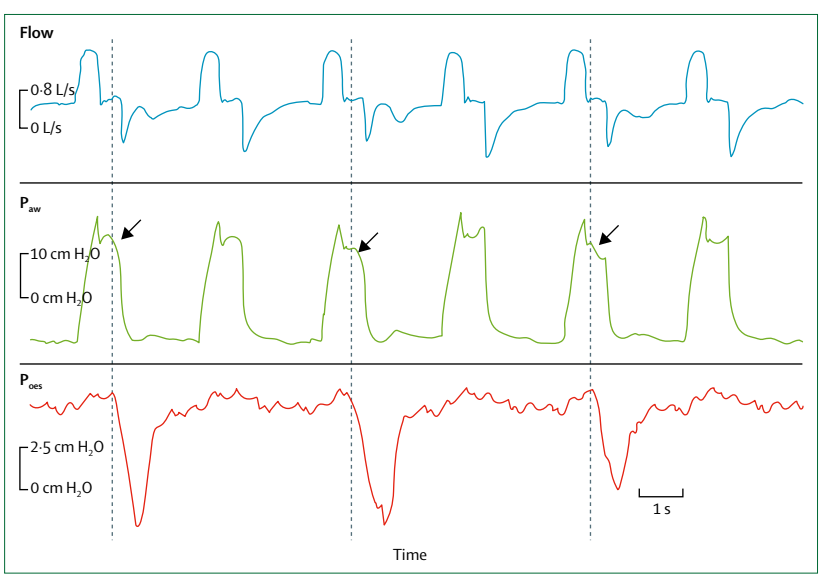

***Figure 3*: Possible eccentric contractions of the diaphragm during reverse triggering**
Inspiratory efforts during expiratory flow can result in diaphragm activation while it is lengthening. Dotted lines show the beginning of neural inspiratory efforts. In the P_{aw} trace, the patient's inspiratory efforts did not trigger the ventilator but managed to insert flow into the lungs (arrows). Reproduced from Akoumianaki and colleagues,[52] by permission of Elsevier. P_{aw}=airway pressure. P_{oes}=oesophageal pressure.

exacerbation of chronic obstructive pulmonary disease (an acute respiratory load), initiating ventilatory support rapidly decreases circulating inflammatory cytokines, suggesting that the elevated respiratory workload can contribute to a generalised systemic inflammatory response.[43]

A large cohort study showed that diaphragm thickness increased abnormally rapidly during the early stages of ventilation in about 25% of patients when respiratory workload increased.[44] This rapid increase in thickness, which was also associated with prolonged ventilator-dependence, might signify load-induced injury with resulting inflammation and tissue oedema. This increase in diaphragm thickness might correspond to the acute increases in muscle thickness observed in other muscle groups that were caused by load-induced injury.[45] Although this hypothesis has not been confirmed histologically, under-assistance myotrauma represents an important and compelling hypothesis based on preliminary clinical observations. Future experimental and clinical studies are required to provide support for this theory.

The third form is referred to as eccentric myotrauma. Contractile loads applied while the muscle is lengthening (eccentric loading) are more injurious than those applied when the muscle is shortening (concentric loading).[46] Eccentric diaphragm contractions lead to immediate, marked diaphragm weakness.[47] In mechanically ventilated patients, eccentric diaphragm contractions typically occur during the ventilator's expiratory phase. First, the diaphragm exerts an expiratory braking effect,[48,49] particularly when lung consolidation or atelectasis are present.[50] This action, which helps to preserve end-expiratory lung volume, requires the diaphragm to generate tension even as it lengthens during expiration. Second, several forms of patient–ventilator dyssynchrony (eg, ineffective triggering, premature cycling, reverse triggering) can produce vigorous diaphragm contractions during expiration, and it is likely that the diaphragm contracts eccentrically during these events (figures 2, 3).[51,52] Myotrauma from such events might explain the reported link between patient–ventilator dyssynchrony and poor outcomes, especially ineffective efforts during expiration.[53,54] Third, in the context of marked inspiratory loading, vigorous accessory muscle activity in the chest wall can pull (ie, lengthen) the diaphragm upward even as it attempts to generate inspiratory flow (ie, shorten), which visibly manifests as an abdominal paradox.[55] Although the pathophysiology underlying eccentric myotrauma seems clear, its effect in patients with acute respiratory failure remains to be fully elucidated.

The fourth form is termed expiratory myotrauma. Experimental evidence published in 2018 suggests that reducing the end-expiratory length of the diaphragm by the application of excessive PEEP can cause sarcomere dropout (a decrease in the number of sarcomeres along the length of diaphragm muscle fibres) resulting in so-called longitudinal atrophy.[56] This atrophy might impair the length–tension relationship of the diaphragm such that when PEEP is withdrawn, the diaphragm contracts from an excessive and disadvantageous initial length.[57] The clinical relevance of this process remains uncertain.

Effect of diaphragmatic myotrauma on clinical outcomes in acute respiratory failure

There are two main findings that suggest that myotrauma might seriously impact both short-term and long-term clinical outcomes for patients with acute respiratory failure.

First, myotrauma is common in mechanically ventilated patients. A cohort study published in 2018 suggests that nearly two-thirds of mechanically ventilated patients

developed rapid early changes in diaphragm thickness (either increases or decreases in thickness).[44] Studies of diaphragm biopsy samples obtained in mechanically ventilated patients and brain-dead organ donors showed consistent structural and functional abnormalities.[25,40,58] Approximately 60% of patients had severe diaphragm weakness at the time of their first spontaneous breathing trial.[59] Although several factors contribute to diaphragm weakness in critically ill patients,[16] we believe that the majority of mechanically ventilated patients will sustain some form of myotrauma during the early stage of respiratory failure.

Second, diaphragm weakness is an important determinant of clinical outcomes. Diaphragm function determines the patient's capacity for unassisted breathing[60] and diaphragm weakness delays liberation from mechanical ventilation.[59,61] Prolonged mechanical ventilation, in turn, portends a poor long-term prognosis, both in terms of risk of death and in functional recovery.[62] Prolonged intensive care unit (ICU) admission is a key risk factor for poor long-term functional outcomes.[63,64] Diaphragm weakness at time of ICU discharge is associated with an elevated risk of readmission to the ICU[65] and mortality at 1 year after discharge.[66] Therefore, by prolonging mechanical ventilation and ICU stay, and predisposing to deleterious nosocomial complications, diaphragm weakness is likely to be causally responsible (in part) for poor long-term functional outcomes and death. Therefore, it is highly plausible that diaphragmatic myotrauma could seriously impact both short-term and long-term outcomes. Indeed, changes in diaphragm thickness specifically related to mechanical ventilation were shown to predict prolonged ventilation, prolonged ICU admission, and an increased risk of complications of respiratory failure including reintubation, tracheostomy, and prolonged ventilation.[44] The foregoing data can be summarised as a putative causal chain of events linking mechanical ventilation to clinical outcomes through diaphragm injury (figure 4).

Myotrauma as a mediator of the clinical outcome of mechanical ventilation

To further evaluate the clinical importance of over-assistance and under-assistance myotrauma, we evaluated whether diaphragm injury mediates the relationship between insufficient or excessive inspiratory effort and clinical outcomes (figure 4).

Mediation analysis quantitatively evaluates the extent to which the relationship between two variables (exposure and outcome) can be explained by a third variable (the hypothesised mediator).[67] The technique was originally developed for use in the social sciences in which theories about causal mechanisms are not always appropriate for testing in experimental designs; mediation analysis allows investigators to explore potential causal mechanisms.[68,69] Importantly, mediation analysis cannot prove causality; rather, it assumes causality (statisticians refer to this as the assumption of sequential ignorability—in other words, the analysis presumes that the possibility of causal effects in the reverse sequence may be ignored or disregarded).[69] By definition, a putative mediator is a variable that is causally responsible for the true association of exposure and outcome—as opposed to a confounder, which gives rise to a false association between exposure and outcome. Mathematically, mediators and confounders are indistinguishable;[70] rather, they are distinguished on a priori grounds on the basis of previous experimental and clinical evidence as evaluated by the research community. Consequently, the fallacy of inferring causality from mediation should be studiously avoided, and putative mediators should be carefully selected on the basis of previous evidence for causality.

If mediation analysis cannot show causality, what is its value? Quantitatively evaluating the potential importance of specific explanatory mechanisms in clinical outcomes can focus the development of new or improved interventions based on putative causal pathways.[71] Although the analysis cannot prove causality, it can strengthen the case for a causal relationship between exposure and outcome.[71] By showing that the relationship between exposure and outcome is partly or fully explained by a variable that is strongly believed on a priori grounds to act as a causal mediator, the probability that the association between exposure and outcome is entirely attributable to confounding is reduced, and the plausibility of a causal association is enhanced.

We used mediation analysis to evaluate whether the association between inspiratory effort and clinical outcome in data from a cohort study[44] published in 2018, was mediated by over-assistance and under-assistance myotrauma (figure 4). First, we examined whether variation in inspiratory effort (quantified by the diaphragm

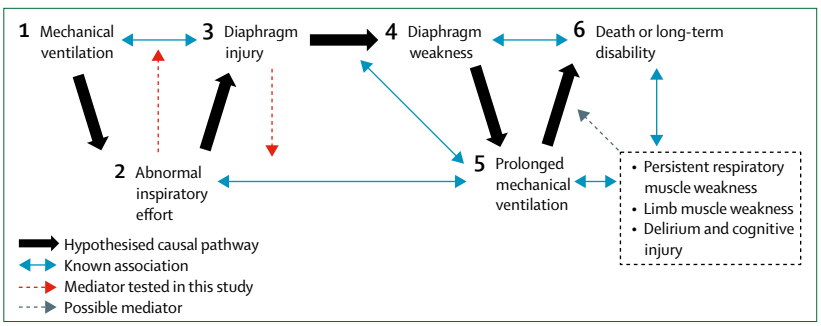

Figure 4: **The putative myotrauma causal pathway leading from mechanical ventilation injury to adverse clinical outcomes**

The mode of mechanical ventilation and the level of assist from the ventilator (step 1) modify the patient's respiratory effort (step 2) and the rate of change in diaphragm thickness (step 3). In turn, the deleterious changes in the diaphragm resulting from insufficient effort or excessive loading (myotrauma) lead to substantially impaired muscle contractile performance (ventilator-induced diaphragm dysfunction; step 4). Finally, both the structural diaphragm changes (seen on ultrasound) and the resulting diaphragm weakness are associated with prolonged mechanical ventilation, prolonged intensive care unit (ICU) stay, and a high risk of complications of acute respiratory failure (a composite of reintubation, tracheostomy, prolonged ventilation for more than 14 days, and death; step 5). These poor ICU outcomes, in turn, predispose to long-term morbidity and mortality (step 6). The black and blue arrows represent links between factors based on evidence from the cohort study.[44] The red arrows represent mediations inferred from the analysis done in this Personal View.

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See Online for appendix

thickening fraction measured on ultrasound) accounts for the effect of mode of ventilation on the change in diaphragm thickness. Second, we examined whether changes in diaphragm thickness account for the relationship between inspiratory effort and clinical outcomes. At each step, the intermediate mediator variable (thickening fraction, changes in diaphragm thickness, respectively) was used on the basis of a priori evidence (summarised above) that these factors play a causal role (see statistical appendix for detailed description of mediation analyses).

Abnormal inspiratory effort was defined as a mean diaphragm thickening fraction value of less than 15% or greater than 30% during the first 3 days of mechanical ventilation, on the basis of thresholds observed in our previous study.[44] Diaphragm injury was quantified as the absolute change in diaphragm thickness from baseline (increases and decreases in thickness were combined, as both of these changes were regarded as forms of injury on the basis of our previous studies); decreases or increases in thickness were analysed separately in sensitivity analyses.[19,44] To assess consistency of mediation across clinical outcomes, we did independent mediation analyses on three separate clinical endpoints—the duration of mechanical ventilation in ICU survivors, the duration of ICU admission in ICU survivors, and the risk of complications of acute respiratory failure (a composite of reintubation, tracheostomy, prolonged ventilation >14 days, or death in hospital). These analyses used either the structural equation approach (for mediated moderation with respect to diaphragm thickness)[72] or the counterfactual framework implemented in the *mediation* package in R (for mediation of clinical outcomes)[69] based on a prespecified analysis plan developed in January, 2016 (before analysis of any study data). All mediation analyses for clinical outcomes were adjusted for potential confounders including age, comorbidities, severity of illness (Simplified Acute Physiology Score II), organ dysfunction (Sequential Organ Failure Assessment score), presence of SEPSIS III criteria, hypoxaemia (ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen), baseline diaphragm thickness, sedation level (Riker Sedation-Agitation Scale), and exposure to neuromuscular blockade.

The findings of the mediation analysis are summarised in the table. The effect of the ventilator mode on the change in diaphragm thickness was mediated by diaphragm thickening fraction. Incorporation of diaphragm thickening fraction as a mediator rendered the effect of ventilator mode non-significant. In turn, changes in diaphragm thickness significantly mediated the relationship between diaphragm thickening fraction and several different related clinical outcomes ($p<0·05$ for mediation). The proportion of the effect of inspiratory effort on outcome mediated by changes in diaphragm thickness ranged between 22% and 28%. The magnitude of mediation effect was similar in sensitivity analyses excluding patients with mean diaphragm thickening fraction of greater than 30% (proportion mediated 28%, $p=0·04$, n=134), or excluding patients with mean diaphragm thickening fraction of less than 15% (proportion mediated 33%, $p=0·33$, n=52), or excluding patients with

Outcome	Mediator	Number available for analysis	p values					Proportion of exposure–outcome association mediated (%, 95% CI; p value for mediation)
			Association before mediation analysis			Mediation analysis		
			Exposure–outcome	Exposure–mediator	Mediator–outcome	Average direct exposure–outcome effect	Average causal mediator effect	
Exposure: mode of ventilation (controlled *vs* partially assisted)								
Diaphragm thickness	Diaphragm thickening fraction	940 patient-days	0·04	<0·0001	<0·0001	0·31	<0·0001	Not computed*
Exposure: diaphragm thickening fraction (15–30% *vs* >30% or <15%)†								
Duration of ventilation in ICU survivors	Changes in diaphragm thickness from baseline	145	0·03	0·01	0·001	0·10	0·02	27% (4–100); p=0·04
Risk of complications of ARF	Changes in diaphragm thickness from baseline	185	0·04	0·01	0·002	0·15	0·01	28% (0–100); p=0·04
Length of ICU stay in ICU survivors	Changes in diaphragm thickness from baseline	143	0·01	0·01	0·002	0·06	0·008	22% (3–95); p=0·02

Cohort data are from a study by our research group.[44] ARF=acute renal failure. ICU=intensive care unit. *The effects of mode (exposure) and diaphragm thickening fraction (mediator) on diaphragm thickness were quantified by their interactions with time (ie, to quantify how they modify the rate of change in diaphragm thickness). The mediating role of diaphragm thickening fraction in the relationship between mode and thickness (mediated moderation) was evaluated by structural equation analysis,[72] which does not permit direct quantification of the proportion of exposure–outcome relation. †Analyses involving clinical outcomes were adjusted for age, number of comorbidities, Simplified Acute Physiology Score II , Sequential Organ Failure Assessment score, presence of SEPSIS III criteria, hypoxaemia (ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen), baseline diaphragm thickness, Riker Sedation-Agitation Scale, and exposure to neuromuscular blockade.

***Table*: Mediation analyses**

both thickening fraction of greater than 30% and greater than 10% increases in diaphragm thickness (proportion mediated 36%, p=0·11, n=103). The mediation effect was smaller and not significant in a sensitivity analysis excluding patients with both thickening fraction of less than 15% and greater than 10% decreases in thickness, although the analysis was limited by an extremely low sample size (proportion mediated 5%, p=0·5, n=36).

These findings suggest that the relationship between insufficient or excessive respiratory effort and clinical outcomes is (at least in part) mediated by changes in the diaphragm. Given the pre-existing experimental and clinical evidence that abnormal inspiratory effort causes diaphragm injury leading to weaning failure, the substantial and consistent mediation signal strengthens (but does not confirm) the hypothesis that patient inspiratory effort during mechanical ventilation has a causal effect on outcome. Furthermore, the mediating role of inspiratory effort in the relationship between ventilator settings and changes in the diaphragm suggests that maintaining a safe level of inspiratory effort could be a promising therapeutic strategy to protect the diaphragm from myotrauma.

Implications of diaphragmatic myotrauma for research and clinical practice

The concept of myotrauma has several implications for research and practice (panel). First, future observational studies and clinical trials regarding acute respiratory failure should consider investigating myotrauma as an explanatory mechanism underlying treatment effects. Interventions that might effect patient inspiratory effort or patient–ventilator synchrony—ie, invasive or non-invasive ventilation strategies, sedation strategies, high-flow nasal cannula, and extracorporeal life support techniques—should account for the possibility of myotrauma as a mechanism of benefit or harm in the design, conduct, and analysis. For example, interventions such as high-flow nasal cannula or helmet non-invasive ventilation might benefit patients by ameliorating under-assistance myotrauma or avoiding the risk of over-assistance myotrauma (by preventing intubation). The benefits of early mobilisation and sedation-avoidance strategies might, in part, result from improved recruitment of respiratory muscle effort and avoidance of over-assistance myotrauma. Ultrasound is a powerful tool used to diagnose myotrauma in the clinical setting—it enables assessment of both respiratory effort and detection of structural changes in the muscle, in addition to the development of muscle weakness. Future studies should consider incorporating simple diaphragm ultrasound measurements to explore the role of the various forms of myotrauma and diaphragm weakness in the determination of outcomes.

Concerns about myotrauma are further increased by the possibility that it might contribute to long-term functional disability in ICU survivors. Indeed, the observation that helmet non-invasive ventilation affects long-term functional outcomes supports the hypothesis that intervention in mechanisms of injury in the early course of respiratory failure can have important downstream effects on long-term functional recovery.[73] Further research is required to confirm these links and to determine whether preventing myotrauma leads to improved long-term outcomes for patients.

Further mechanistic research is required to substantiate the importance of under-assistance, eccentric, and expiratory forms of myotrauma. The hypothesis that the diaphragm is susceptible to load-induced injury needs to be tested in clinically relevant experimental models of spontaneous breathing during lung injury, sepsis, and shock states. The importance of eccentric contractile activity in diaphragm injury, and the role of expiratory resistance and end-expiratory pressure in preventing this injury, require careful investigation.

The major implication of the myotrauma paradigm might be to provide a conceptual framework for how to titrate ventilator support to prevent diaphragm injury. Evidence suggests that the optimal level of respiratory muscle effort might be that of healthy individuals breathing at rest, equivalent to a respiratory muscle pressure swing of 5–8 cm H_2O.[44,74] The aforementioned mediation analyses provide further support for a potential causal relationship between optimal effort and clinical outcome. However, causation can only be shown in the context of a randomised trial—such a trial could examine whether any observed benefit of a diaphragm-protective ventilation strategy is mediated by avoiding changes in diaphragm structure and function. Importantly, the potential magnitude of benefit of modulating inspiratory effort on major outcomes remains uncertain because the confidence intervals for the data regarding effect mediation by diaphragm injury were wide.

Monitoring of respiratory effort should become a routine part of clinical practice in the ICU. Several

Panel: **Research questions for future research related to myotrauma**

- Do different forms of myotrauma account in part for the effects of various ventilation strategies, sedation strategies, or neuromuscular blockade on clinical outcomes?
- What level of inspiratory effort is required to cause under-assistance myotrauma? Does delayed intubation cause under-assistance myotrauma?
- Does patient–ventilator dyssynchrony cause myotrauma?
- How common and how injurious are eccentric and expiratory forms of myotrauma in a clinical setting?
- Can myotrauma be prevented by optimising inspiratory effort and synchrony during mechanical ventilation?
- Do extracorporeal life-support techniques mitigate the risk of myotrauma?
- Does preventing myotrauma improve long-term functional outcomes and quality of life in intensive care unit survivors?

Search strategy and selection criteria

We searched MEDLINE and Google Scholar for articles published before May 1, 2018. We used the search terms "diaphragm weakness", "diaphragm atrophy", "mechanical ventilation", "artificial respiration", "ventilator-induced diaphragm dysfunction", "myotrauma", and "respiratory failure". We largely selected publications from the past 5 years but did not exclude commonly referenced and highly regarded publications from previous years. We also reviewed reference lists and bibliographies and our own personal files for additional relevant articles. Where necessary, review articles are cited to provide readers with further details and references than are published in this Review. Only articles published in English were included. The mediation analyses presented in this Review were done using data previously obtained and reported by our group of investigators.

tools for respiratory muscle monitoring are available to clinicians and researchers, including oesophageal manometry, diaphragm electrical activity recordings, ultrasound, or measurement of airway occlusion pressure.[37,75–77] In view of the current evidence, clinicians should attend to patient inspiratory effort and minimise the duration of diaphragm inactivity during mechanical ventilation. If there is no firm clinical indication for neuromuscular blockade, clinicians should generally aim to maintain a normal level of spontaneous inspiratory effort while concomitantly aiming to minimise the volume and (transpulmonary) pressure applied to the lung.

Contributors

ECG and NDF conceived the study. ECG, LJB, WDR, EF, GDR, and NDF planned the analysis. ECG did the analysis and wrote the first draft of the Personal View. All authors contributed to the interpretation of the findings and critically revised the manuscript for intellectually important content. All authors gave final approval for the publication of the work and all accepted responsibility for the integrity of the work.

Declaration of interests

ECG reports personal fees and non-financial support from Getinge Ventilation. LJB reports grants from Medtronic Covidien, non-financial support from Philips and Air Liquide, and grants and non-financial support from Fisher Paykel. BPK reports a pending patent for a mechanical ventilation device. NDF reports personal fees from Sedana Medical and Getinge Group, outside of the submitted work. All other authors declare no competing interests.

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