REVIEW

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Dysfunction of respiratory muscles in critically ill patients on the intensive care unit

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Abstract

Muscular weakness and muscle wasting may often be observed in critically ill patients on intensive care units (ICUs) and may present as failure to wean from mechanical ventilation. Importantly, mounting data demonstrate that mechanical ventilation itself may induce progressive dysfunction of the main respiratory muscle, i.e. the diaphragm. The respective condition was termed 'ventilator-induced diaphragmatic dysfunction' (VIDD) and should be distinguished from peripheral muscular weakness as observed in 'ICU-acquired weakness (ICU-AW)'.

Interestingly, VIDD and ICU-AW may often be observed in critically ill patients with, e.g. severe sepsis or septic shock, and recent data demonstrate that the pathophysiology of these conditions may overlap. VIDD may mainly be characterized on a histopathological level as disuse muscular atrophy, and data demonstrate increased proteolysis and decreased protein synthesis as important underlying pathomechanisms. However, atrophy alone does not explain the observed loss of muscular force. When, e.g. isolated muscle strips are examined and force is normalized for cross-sectional fibre area, the loss is disproportionally larger than would be expected by atrophy alone. Nevertheless, although the exact molecular pathways for the induction of proteolytic systems remain incompletely understood, data now suggest that VIDD may also be triggered by mechanisms including decreased diaphragmatic blood flow or increased oxidative stress. Here we provide a concise review on the available literature on respiratory muscle weakness and VIDD in the critically ill. Potential underlying pathomechanisms will be discussed before the background of current diagnostic options. Furthermore, we will elucidate and speculate on potential novel future therapeutic avenues.

Keywords VIDD; Diaphragm; Weakness; Cachexia; Sepsis; Mechanical ventilation; ICU-acquired weakness; weaning failure

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Introduction

Historically, respiratory muscle weakness during mechanical ventilation was recognized a state of muscular fatigue. It was thought to be caused by prolonged increased work of breathing. Although first reports of diminished myofibre cross-sectional area in diaphragms because of long term mechanical ventilation date back to the 1980s,[1] direct harmful effects of mechanical ventilation on respiratory muscles were only thoroughly studied, e.g. in animal models in the last two decades. Currently, respective findings from animal models can partially be reproduced in human experiments and find their way to the clinical bedside.[2] Within the complex of critical illness-related weakness,[3–5] the dysfunction of respiratory muscles, particularly of the diaphragm, represents a highly relevant and distinct clinical problem in intensive care units (ICUs). From a clinical perspective, diaphragmatic dysfunction contributes to difficult weaning or even failure to wean from mechanical ventilation in ICU patients. Overall, data indicate that weaning failure may affect up to 25% of mechanically ventilated patients in ICUs today.[6]

Ventilator-induced diaphragmatic dysfunction (VIDD) was previously defined as loss of diaphragmatic force-generating capacity specifically related to the use of mechanical

ventilation.[7] VIDD may typically be observed after variable periods of controlled mechanical ventilation (i.e. ventilation without spontaneous breathing)[7,8] while assisted ventilation modes (i.e. ventilation with preserved diaphragmatic contractions) attenuate the detrimental effects of controlled mechanical ventilation on the diaphragm and seem protective in animal models[9–12] unless high levels of support are used.[8] As preserved muscle activity is protective, it seems conceivable that diaphragmatic contractile inactivity may be the cause for the development of VIDD.[13] Despite the terminology 'VIDD', the condition does not exclusively affect the major respiratory muscle (i.e. the diaphragm), but may also involve the intercostal musculature to a minor degree.[14,15] The diaphragm, however, seems particularly prone to dysfunction under mechanical ventilation while auxiliary respiratory muscles, e.g. pectorales muscles,[16] or skeletal limb muscles (e.g. soleus or extensor digitorum muscles) are typically spared.[17–20]

While many of the pathophysiological aspects of VIDD that were found in animals have also been successfully reproduced in humans, the proof of decreased force generation was so far only performed indirectly in mechanically ventilated patients.[21] Only very recently, direct force generation of isolated human muscle fibres was studied with ambiguous results.[22–24]

Pathophysiology of respiratory muscles dysfunction and VIDD: histological and structural changes

The pathophysiology of VIDD was to a large extent elucidated in models of healthy animals. Under continuous controlled mechanical ventilation, the diaphragm partially loses its force- and pressure-generating capacity, classically assessed in intact animal models with trans-diaphragmatic pressure under maximal phrenic nerve stimulation.[25–27] Data demonstrate that loss of respective force may reach up to 50% within a few days. Importantly, the onset and time course of VIDD may vary between the respective species studied.[25–27] This makes transfer of respective data to the human bedside particularly difficult. However, loss of force seems neither linked to age[28] nor to changes in lung volumes[26] nor to positive end-expiratory pressure (PEEP).[27,29] In addition, phrenic nerve signal transmission and signal transduction at the neuromuscular endplate in VIDD appear normal. This is a distinct difference between VIDD and polyneuropathic forms of ICU-acquired weakness (ICU-AW),[5] as the latter often shows conduction abnormalities in electrophysiological studies. Moreover, loss of force is reproducible in isolated muscle specimens,[18,29] rendering the pathophysiological changes of VIDD to a cellular level. Besides ultrastructural muscle fibre injury,[14,27,30] the most common histopathological correlate is muscle atrophy.[14,18,26,31–33] This is especially the case in regard to type II (fast twitch) muscle fibres within the early course of the disease.[14,19] Remodelling processes with a histopathological increase of hybrid fibres at the expense of (slow twitch) type I fibres can be identified at later stages.[31] However, it must be noted that atrophy alone does not explain the observed loss of force. When force is normalized for cross-sectional area of isolated muscle strips (so-called specific force or tension), the loss is disproportionally larger than would be expected by atrophy alone.[18,27,34]

Overall, protein synthesis in the diaphragm in established VIDD seems dramatically decreased.[35] In murine models, proteolysis is activated as early as 6 h after initiation of controlled mechanical ventilation[36] and loss in myosin heavy chain synthesis of up to 65% may be observed.[19,35] A decrease in anabolic signalling including pathways via insulin like growth factor-1 (IGF-1)[32] and myogenin (MyoD) are found.[37] Proteolysis is significantly increased.[19,38] All four proteolytic systems of the mammalian cell are activated in animal models of VIDD and later found induced in mechanically ventilated humans.[39] Proteolysis is mediated by the calpain [19] and caspase system,[40,41] as well as the ubiquitin–proteasome complex[33,38] and the autophagy–lysosomal system.[42] The biochemical changes of VIDD, mainly examined in healthy murine models, may be augmented or even triggered by oxidative stress pathways,[19,43–45] nuclear factor kB (NFkB),[46,47] or JAK–Stat signalling pathways.[48] Similar to patients with severe sepsis and septic shock, distinct cytokine cascades are upregulated. This includes interleukin (IL)-6, tumour necrosis factor-α, and IL-1β in rat diaphragmatic tissue exposed to mechanical ventilation[47] and may further amplify major inflammatory signalling pathways including NFkB.[47,49] This 'humoral' response is well known to promote systemic immune cellular consequences and may also result in immune phenotypic changes.[50–52] There is experimental proof of diaphragmatic dysfunction directly induced by sepsis.[53–57] This includes free radicals, mitochondrial dysfunction,[54] calpain,[56] and caspase activation.[57] In addition, clinical evidence points to severe sepsis/septic shock as an important risk factor for diaphragmatic dysfunction.[58,59] Interestingly, Maes and colleagues have developed a lipopolysaccharide rat model of controlled mechanical ventilation. They could now show that controlled mechanical ventilation potentiates sepsis-induced diaphragm dysfunction, possibly because of increased pro-inflammatory cytokine production, autophagy, and worsening of oxidative stress.[60] To our knowledge, this is the first study of VIDD in a sepsis model that may indicate an important pathophysiological overlap. It should be clearly noticed that VIDD and sepsis induced diaphragmatic dysfunction are distinctive pathological entities[13] and the findings of overlapping pathophysiology are controversial, even more so as mechanical ventilation was shown to protect rat diaphragms in sepsis.[61] Nevertheless, this shared

 (2016)
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pathophysiology may offer therapeutic options in the future. Strategies to modulate the systemic cytokine and/or immune response by, e.g. blocking respective cascades or by improving host defence, may in theory be beneficial.[62–64] However, because of current lack of respective trials, this remains speculative at this point in time.[65]

Recent data indicate a profound reduction in diaphragmatic blood flow in VIDD.[66] It is therefore speculated that reduced oxygen delivery may lead to formation of reactive oxygen species with consecutive triggering of proteolytic cascades and enhanced oxidative stress.[67] Angiogenetic factors change their expression profile under mechanical ventilation [downregulation of vascular endothelial growth factor (VEGF), upregulation of hypoxia-inducible factor (HIF)-1α], but their role in VIDD remains incompletely understood.[47,68]

Exercise training or a genetically high aerobic capacity—interesting in the context of decreased blood supply—may protect the diaphragm from VIDD. Up-regulation of heat shock proteins and improved antioxidant properties of a 'trained diaphragm' with decreased activation of proteases and respective mitochondrial 'protection' are among the postulated mechanisms.[69,70] Nevertheless, mechanical ventilation may also enhance anti-oxidative pathways, potentially as a counter-regulatory measure.[68,71] Overall, this aspect of VIDD may open new therapeutic avenues as the redox state of a cell might theoretically be influenced positively.[71] Recent data indicate protection from diaphragmatic weakness with N-acetylcysteine via augmented autophagosome formation in mice.[72]

Data from animal VIDD models demonstrate a quick and complete recovery within hours if spontaneous breathing is resumed early. However, this needs to be interpreted before the background of limited times of mechanical ventilation (12 to 27 h.).[73–75] Moreover, the respective kinetics and time course of VIDD are species dependent,[7] and data may therefore not be easily transferrable between species. As pathophysiology of VIDD was investigated mainly in models of healthy animals, it must be kept in mind that in critically ill patients, underlying comorbidities may contribute to diaphragmatic dysfunction.

Pathophysiology of respiratory muscle dysfunction and VIDD: translation to the bedside

Human data are basically available from two groups of patients. The bulk of evidence derives from mechanically ventilated brain dead organ donors. Only very recently, studies were expanded to mixed ICU populations with underlying diseases. Levine and colleagues could show in a seminal study in 14 brain death organ donors that disuse atrophy may occur shortly after start of controlled mechanical ventilation.[16] When compared to controls (i.e. patients with thoracic surgery on 3 h of CMV), muscle biopsies of the costal diaphragm in organ donors (mechanically ventilated for 18 to 69 h) exhibit strongly decreased cross-sectional areas of slow-twitch and fast-twitch fibres (57% vs. 53%, respectively). Atrophy was associated with reduced glutathione levels and up-regulation of caspase-3 and ubiquitin ligases. These changes were limited to the diaphragm and not reproducible, e.g. in pectorales muscles.[16] Findings were later confirmed and linked to up-regulation of autophagic systems via transcription factors (e.g. FOXO-1), activation of the ubiquitin–proteasome complex, NFkB activity, and induction of the calpain system in mechanically ventilated human muscles and diaphragms.[76–80] Hooijman lately documented the activation of the ubiquitin–proteasome complex in a mixed population of critically ill patients.[22] While direct force loss (i.e. loss of performance of isolated muscle strips) is extensively documented in animal models, the condition in humans was until recently only indirectly characterized by airway occlusion pressure responses to phrenic nerve stimulation.[81,82] In the last year, first reports of human muscle fibres appeared and finally documented a loss of specific force in mechanically ventilated human muscles.[22–24] But a clear distinction of the studied populations should be noted. Hooijman initially found no evidence for diminished contractile performance in sarcomeres when studying specimens from brain death organ donors (mean duration of mechanical ventilation of 26 ± 5 h),[23] whereas the group later published data from mixed ICU populations suffering from comorbidities like sepsis or trauma (duration of mechanical ventilation 14 to 607 h) with contractile weakness of human diaphragmatic muscle fibres.[22,24] It is unclear to what extent these underlying conditions have contributed to the documented weakness. So, speaking in strict terms, the formal proof of contractile weakness caused by mechanical ventilation is not yet established.

VIDD appears to be associated with mitochondrial dysfunction. Mechanical ventilation may alter mitochondrial respiratory chain enzyme function (e.g. cytochrome-c oxidase), may induce micro-deletions within mitochondrial DNA, and may decrease levels of mitochondrial scavengers for reactive oxygen species (ROS) culminating in diaphragmatic lipid overload. This metabolic oversupply of resting diaphragms could again trigger ROS production. However, these findings could not be reproduced in biceps muscle specimens.[83] A causative link between lipid overload and mitochondrial dysfunction is not firmly established.[84] Nevertheless, oxidative stress has been linked to activation of apoptic, proteasomal, and autophagocytic pathways,[85] and expression of angiogenetic factors varies with the ventilation mode used.[86]

In conclusion, histopathological and biochemical changes of respiratory muscle dysfunction/VIDD in animal models could now be reproduced to some extent in human experiments.[2] Loss of specific force in isolated human muscle fibres has finally been documented[22,24] in mixed ICU populations

 (2016)
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with underlying comorbidities (but not in brain death organ donors[23]). With VIDD animal models available, this may open up new options for development of specific therapeutic approaches in order to treat or prevent respiratory muscle dysfunction/VIDD.

Clinical approaches to respiratory muscle dysfunction/VIDD

VIDD is diagnosed by exclusion of other causes of weaning failure (e.g. decompensated congestive heart failure) and other specific causes of diaphragmatic weakness such as electrolyte disturbances, malnutrition, drugs, central nervous system disorders, and distinct neuromuscular disorders.[7] Global tests of respiratory muscle strength like measurement of maximum inspiratory pressures[87] or the rapid shallow breathing index (respiratory rate divided by tidal volume)[88] serve as screening tools. However, they lack specificity. Assessment of trans-diaphragmatic pressure in combination with transdermal phrenical nerve (magnetic) stimulation may be considered the gold standard.[82,89,90] However, this approach is invasive with the need for an oesophageal and gastric balloon. Alternatively, twitch tracheal airway pressure avoids balloon placement,[81,82,91] but the accuracy of this approach is debated.[92] The electrophysiological assessment of diaphragmatic electrical activity via a modified nasogastric tube (EAdi)[93,94] is a new promising but almost unexplored technique for VIDD. The electromyographic signal describes the summation amplitude of electrical activity and allows assessment of neuronal respiratory drive and estimation of neuroventilatory efficiency (tidal volume divided by electrical activity).[94–97] Although there is lack of specific VIDD studies, this approach may hold potential for respiratory monitoring as it incorporates the neuronal feedback loop of the respiratory drive.[93,94,97] Further studies are warranted.

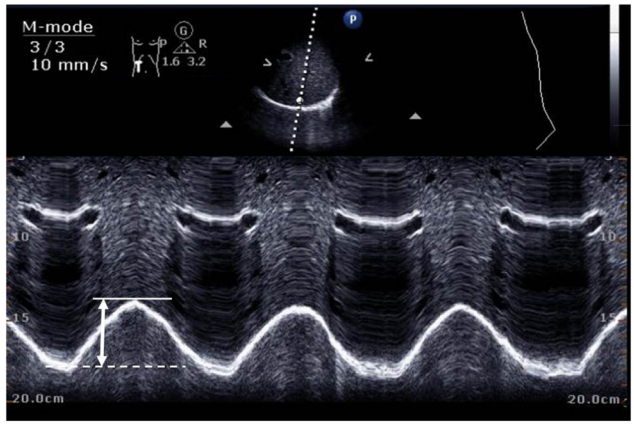
A non-invasive modality for patients with suspected diaphragmatic weakness is ultrasound, readily available at the bedside and most likely free from adverse effects (**Figures** 1 and 2). With reference values established, ultrasound allows both reproducible assessment[98] of diaphragmatic function and structure and may exclude alternative causes of weaning failure.[94,99–102] The inspiratory downward motion of the diaphragm should be greater than one centimetre (**Figure** 1). This was evaluated in ventilated patients during spontaneous breathing trials and predicts successful weaning with an accuracy similar to the rapid shallow breathing index.[103] A thickening fraction (inspiratory minus expiratory thickness divided by expiratory thickness) of ≥30% was shown to exert a positive predictive value of 91% for weaning success[104] (**Figure** 2A and 2B). A sustained loss of diaphragmatic thickness was reported for patients undergoing prolonged mechanical ventilation, most prominent in the first three days.[105] Changes in thickness may be associated with diaphragmatic weakness.[106]

The consequences of application of PEEP (inducing caudal diaphragm displacement) remain unknown.[107] As ultrasound allows dynamic assessment of the diaphragm, it will mainly provide useful insight if performed during unassisted breathing, i.e. during spontaneous breathing trials.[108] Recent data indicate that the thickening fraction is also of use under mechanical ventilation, as thickening is caused by muscular contraction, but not by passive inhalation.[98] Despite a growing body of evidence for the use of ultrasound, it remains a pure imaging technique without direct assessment of ventilation or diaphragmatic force. Ultrasound may also be of limited value in the early course of critical illness, when controlled ventilation needs to be applied.[94] For technical details, please refer to figure legends (**Figures** 1 and 2).

VIDD management: a role for ventilatory and pharmacological interventions?

Human data on interventions for VIDD are sparse. When choosing ventilatory modes, spontaneous breathing efforts during mechanical ventilation seem protective for VIDD in healthy animals.[12,109,110] As most studies on VIDD were performed in healthy animals, questions remain about the applicability in the acute phase of critical illness.[39] The complex

Figure 1 Assessment of diaphragmatic motion (motion mode, phased array 3.5–5 Mhz transducer). Sub-costal position (mid-clavicular line, angle of >70° in supine subjects) with visualization of the posterior diaphragmatic third. The diaphragmatic dome should be hit perpendicularly. Liver/spleen may be used as sound windows for right/left hemi-diaphragm. Diaphragmatic dome excursion at rest should be ≥1 cm (lower limit of normal in healthy controls).[101,108] Inspiratory diaphragmatic position (solid line), expiratory position (dotted line), and excursion (arrow) are indicated.



 (2016)
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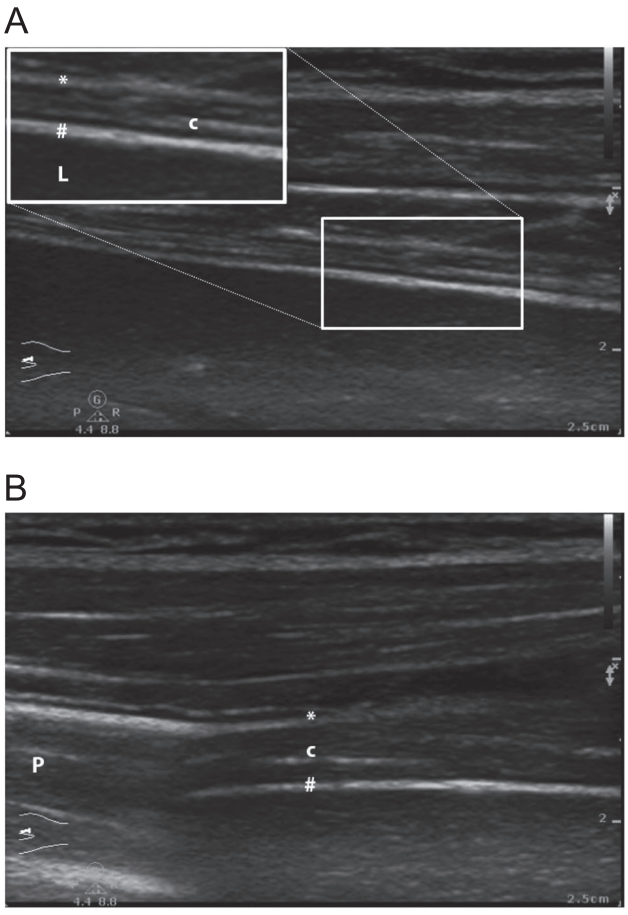
Figure 2 Assessment of (A) expiratory and (B) inspiratory diaphragmatic thickness (brightness mode, linear array high frequency transducer of >10 Mhz, zone of apposition: mid-axillary line). Note in- and expiratory variation (limits of normal may vary).[102,108] The thickening fraction [i.e. (inspiratory–expiratory diameter) / expiratory diameter] can be assessed.[143] Maximum diameters are measured between diaphragmatic pleural line (*) and peritoneal line (#). Central diaphragmatic tendon (c). Liver (L), Lungs (P) are indicated.



and dynamic pathophysiology of respiratory support during critical illness asks for an individually tailored approach. Early in acute critical illness, controlled mechanical ventilation may often be mandatory, but an early switch to an assisted mode seems clearly desirable. Diaphragmatic inactivity is considered to initiate VIDD.[13] Interventions like intermittent spontaneous breathing or respiratory muscle training might be of benefit. Diaphragmatic contractions via phrenic nerve pacing have been successfully used in tetraplegic patients[111,112] and during cardiothoracic surgery[113] with documented increases in mitochondrial respiration.[114] While short periods of intermittent spontaneous breathing had little effect in a rodent model,[12] adding a resistive inspiratory load in order to train the inspiratory muscles has shown promising results for patients in small series[115–117] and improved weaning outcome in a randomized trial.[118]

The period of controlled mechanical ventilation should be kept short.[82,119] Ventilation modes with sustained patient effort should be introduced early,[39] as can be inferred from various animal experiments. Assist Control Ventilation modes (controlled mechanical ventilation with the possibility to trigger additional breaths) and pressure support ventilation (patient's breathing efforts supported by a preset pressure) may attenuate VIDD in animals.[9,109] Nevertheless, partial supportive modes can still cause VIDD in the setting of over-assist,[8] so mode *per se* is not protective. On the contrary, in septic rabbits, controlled mechanical ventilation may protect from VIDD[61] and the use of modes that allow spontaneous breathing is contradictory to the documented benefit of neuromuscular blockers in the early course of severe acute respiratory distress syndrome (ARDS).[120]

The preferred ventilation mode, the optimal level of support ('unloading'), or the rate of support reduction for patients is currently unknown.[39] Spontaneous breathing is well maintained with so-called *effort adapted modes*[121] like neurally adjusted ventilatory assist (NAVA) or adaptive support ventilation (ASV). ASV seems to mitigate deleterious effects of mechanical ventilation on the diaphragm of piglets.[10] NAVA delivers assist in unison with the patient's inspiratory neural effort.[93] As the support level is titrated against the patient's respiratory demand, patients are protected against over-assist.[122,123] This approach was successfully used in various clinical ICU settings[97,122,124,125] but most importantly in patients with critical illness myo-neuropathy.[97]

Currently, no medical treatment for VIDD is available.[126] Anti-oxidants show benefits in animal models[40,71,72,127] and in a randomized trial in critically ill surgical patients.[128] However, human data remain sparse. Targeting of proteolytic (especially proteasome) pathways in rodent models may further elucidate the pathophysiology and theoretically open novel therapeutic avenues. Inhibition of lysosomal proteases and calpain with leupeptin[129] or the proteasome using bortezomib[130] may be of interest as data indicate potential to completely or partially prevent VIDD. However, results could not be reproduced with epoxomicin.[131] Overall, effects may be time dependent.[129–132] Moreover, R548, a JAK/STAT inhibitor, maintained normal diaphragmatic contractility,[133] and a recent FOXO (forkhead BoxO) animal knockout model suggests new potential therapeutic targets.[134]

While the effects of corticosteroids on VIDD seem dose dependent conflicting,[135,136] propofol was accused as a causative agent in animal models.[137] Neuromuscular blockers do not to have additive effects on diaphragmatic dysfunction.[136] Moreover, moderate hypercapnia exerts protective effects on diaphragmatic muscular strength,[138,139] which fits to the overall concept of lung protective ventilation.[140] In addition, the calcium sensitizer Levosimendan may improve diaphragmatic neuro-mechanical efficiency in healthy volunteers, while the fast skeletal troponin activator CK-2066260

 (2016)
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improved diaphragmatic fibre strength *ex vivo* in an experimental human trial.[24] Further studies in critically ill patients with respiratory failure are warranted.[141]

In conclusion, prolonged periods of complete diaphragmatic rest should be avoided and diaphragmatic contractions preserved whenever possible. Respiratory muscle training may lead to improved weaning success.

Respiratory muscle dysfunction in critically ill patients: summary and outlook

Ventilator-induced diaphragmatic dysfunction is an established and specific 'side effect' of prolonged mechanical ventilation. The clinical hallmark is respiratory muscle weakness which contributes to weaning failure and thus implies a significant health care burden. Major pathophysiological changes are disuse atrophy and microstructural changes including decreased protein synthesis, increased proteolysis, and oxidative stress, possibly linked to mitochondrial dysfunction.

For the clinician, bedside ultrasound evaluation and assessment of the electrical diaphragmatic activity are promising tools for the diagnosis and monitoring of respiratory muscle dysfunction/VIDD. Respiratory muscle training may have beneficial effects. Questions remain about the optimal strategy and mode of mechanical ventilation for affected patients. Effort adapted ventilation modes may offer advantages. Whether this may lead to improved clinical outcomes needs to be established.

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