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Ventilator-Induced Diaphragmatic Dysfunction: Diagnosis and Role of Pharmacological Agents

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The use of controlled mechanical ventilation results in a major reduction of diaphragmatic contractile force together with atrophy of diaphragm muscle fibers, which is a condition known as ventilator-induced diaphragmatic dysfunction. Ventilator-induced diaphragmatic dysfunction is one of the major contributors to weaning difficulties and even increased mortality. This review summarizes the current data on the pathogenesis and diagnosis of ventilator-induced diaphragmatic dysfunction, and it outlines the use of ultrasonography for diaphragm evaluation. In addition, current pharmacologic agents used to mitigate ventilator-induced diaphragmatic dysfunction are described, with a particular emphasis on the therapeutic potential of theophylline in patients with ventilator-induced diaphragmatic dysfunction-associated weaning difficulties. *Key words: diaphragm; diaphragm dysfunction; mechanical ventilation; ultrasonography; theophylline; review.* [Respir Care 0;0(0):1–•. © 0 Daedalus Enterprises]

Introduction

Controlled mechanical ventilation is associated with adverse effects on the structure and function of the diaphragm in a condition known as ventilator-induced diaphragmatic dysfunction.[1] The prevalence of diaphragmatic dysfunction has been reported to be up to 2-fold higher than the prevalence of ICU-acquired weakness[2] and as high as 80% in patients with ICU-acquired weakness entering the weaning process.[3] This phenomenon may be exacerbated by the use of neuromuscular blockers and steroids.[4,5] In addition, recent studies have shown that the prevalence of diaphragmatic dysfunction already present at the time of ICU admission is as high as 64%, suggesting that diaphragmatic dysfunction may constitute an under recognized form of organ failure in patients with critical illnesses such as sepsis.[6,7] Ventilator-induced diaphragmatic dysfunction can increase weaning time and is associated with weaning outcome, ICU and hospital mortality, and long-term clinical outcomes.[6,8–12] The duration of mechanical ventilation tended to be higher in patients with persistent

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dysfunction than in those with improving dysfunction.[13] Moreover, maximal inspiratory pressure before extubation below 30 cm H_2O was found to be independently associated with increased risk of mortality at 1 year.[12] This review outlines the current data on the pathogenesis and diagnosis of ventilator-induced diaphragmatic dysfunction, followed by a discussion on pharmacologic agents, in particular theophylline, that are currently used to mitigate ventilator-induced diaphragmatic dysfunction.

Pathogenesis

Controlled mechanical ventilation, even for a few hours, has been found to reduce diaphragmatic contractile force both in vitro and in vivo.[14,15] Prolonged controlled mechanical ventilation in patients was found to trigger significant reductions in the generation of both active and passive diaphragm myofibrillar force by reducing myofibrillar protein levels.[16] In addition to decreased diaphragmatic force, muscle fiber atrophy, resulting from reduction in protein synthesis and increased proteolysis by ubiquitin proteasomes, caspases, and calpains, has been reported in the diaphragms of animals with ventilator-induced diaphragmatic dysfunction.[17–19] A landmark study reported marked atrophy of both slow- and fast-twitch fibers in the diaphragms of brain-dead organ donors who had undergone prolonged mechanical ventilation prior to organ harvest.[20] These changes have been linked to an increased level of oxidative stress in the diaphragm.[21] In addition, prolonged mechanical ventilation was found to trigger diaphragm autophagy via oxidative stress and the induction of Forkhead box O-1, thereby contributing to diaphragm muscle fiber atrophy.[22] Lastly, other comorbidities and metabolic stresses, such as COPD, hyperglycemia, and sepsis, could negatively affect patients with ventilator-induced diaphragmatic dysfunction as well.[6,7,23]

Diagnosis

Accurate evaluation of diaphragmatic function in critically ill patients undergoing mechanical ventilation remains a difficult task. Although measuring maximal inspiratory pressure is relatively easy, this parameter is effort-dependent in that it represents the combined action of all inspiratory muscles, and it may be affected by underlying lung diseases.[24,25] Transdiaphragmatic pressure can be measured by simultaneously recording esophageal and gastric pressures, but the interpretation of results depends on the level of patient cooperation. Phrenic nerve conduction is the accepted standard method of quantifying mechanical function of the diaphragm. However, phrenic stimulation techniques are heavily dependent on patient effort, require expertise and specialized equipment, and are time consuming, making them less than ideal for ICU patients.[26] Diaphragmatic movement can be adequately assessed by fluoroscopy and magnetic resonance imaging[27,28]; however, ionizing radiation, patient transportation, and high cost are limiting factors.

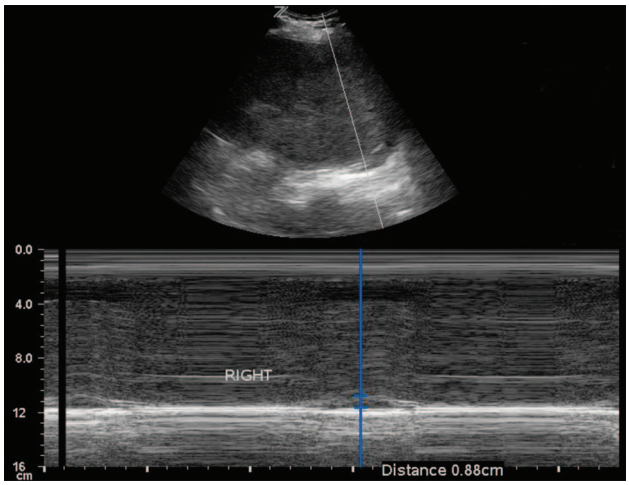

Fig. 1. B-mode was used to find the best approach and to select the exploration line of hemidiaphragm. During inspiration, diaphragmatic contraction was recorded by M-mode tracing, and the amplitude of excursion was measured on the vertical axis of the tracing from the baseline to the point of maximum height of inspiration on the graph.

Ultrasonography

Ultrasonography is increasingly used in the ICU for diagnostic and therapeutic purposes.[29] Ultrasonography does not involve patient transportation or exposure to ionizing radiation. Short examination time and high reproducibility of ultrasonography results are clear advantages in acute care settings. Diaphragmatic ultrasonography at bedside has been shown to be safe and easy to perform, while allowing both morphologic assessment (eg, detection of atrophy) and functional evaluation of the muscle with high inter-observer agreement.[30,31]

Two ultrasonography parameters are mainly used to assess diaphragmatic function: diaphragmatic excursion[32] and thickening fraction of the diaphragmatic muscle[33] during inspiration. Diaphragmatic excursion can be easily measured with a 3–5-MHz probe in either B- or M-mode (Fig. 1). Mean inspiratory diaphragmatic excursion in healthy subjects during quiet spontaneous breathing was found to be 1.34 ± 0.18 cm,[30] with diaphragmatic excursion >2.5 cm in cardiac surgery patients being proposed as a cutoff for excluding severe diaphragmatic dysfunction.[32] However, diaphragmatic excursion depends on the amount of ventilator support and PEEP; accordingly, a recent study indi-

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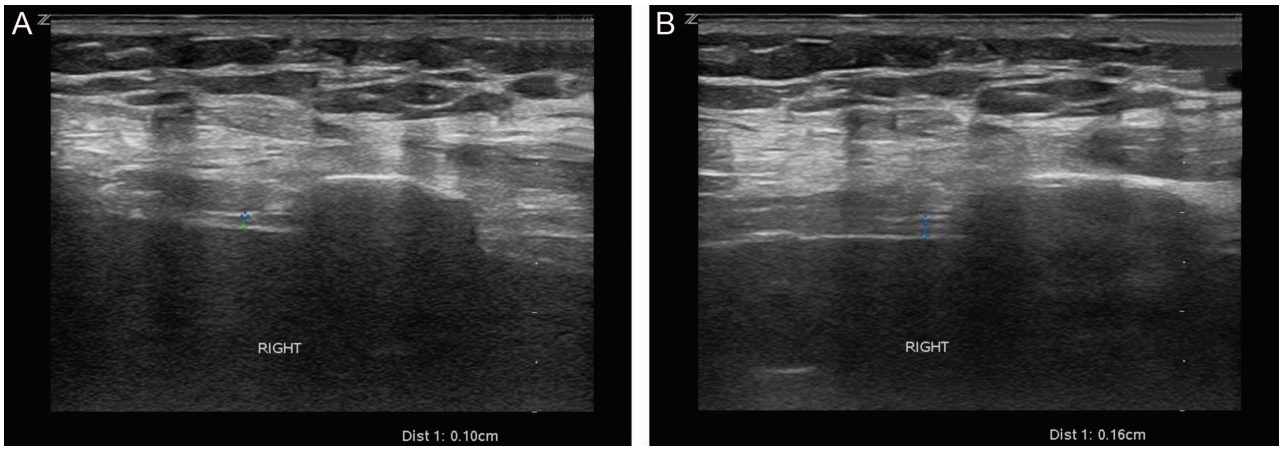

Fig. 2. B-mode view of diaphragm in the zone of apposition during expiration (A) and inspiration (B). The diaphragm is identified as a 3-layer structure (non-echogenic central layer bordered by two echogenic layers, the diaphragmatic pleurae and the peritoneum). Thickening fraction is defined as ([thickness at B − thickness at A]/thickness at A).

cated that diaphragmatic excursion should not be used to assess diaphragmatic contractility in patients receiving mechanical ventilation.[34]

The second parameter, thickening fraction of the diaphragmatic muscle, measures muscle thickening in the zone of apposition of the diaphragm to the rib cage with a probe ≥ 10 MHz in B- or M-mode (Fig. 2). Thickening fraction is defined as [(thickness at end-inspiration − thickness at end-expiration)/thickness at end-expiration].[10,11] The mean normal thickness of the diaphragm at the zone of apposition in healthy, spontaneously breathing subjects while relaxing is 1.7 ± 0.2 mm, increasing to 4.5 ± 0.9 mm when breath is held at total lung capacity.[35] Diaphragm thickness may be regarded as a direct index of diaphragmatic contractility and may detect the presence of atrophy, although diaphragm thickness may also be influenced by lung volume.[33,36] Both diaphragmatic excursion and thickening fraction have been shown to be correlated with functional measurements of diaphragmatic function in spontaneously breathing patients,[32] and studies describing the use of ultrasonography evaluation of the diaphragm in the process of weaning suggest that either method can be a reliable predictor of weaning and extubation outcomes.[8–11] For example, decreased diaphragmatic excursion (<10 mm) was found to be a predictor of weaning failure among subjects in medical ICUs,[9] and a threshold of thickening fraction >30–36% was associated with extubation success.[10,11]

Treatment

Several in vivo and clinical studies have demonstrated that maintaining spontaneous respiratory efforts during mechanical ventilation can alleviate ventilator-induced diaphragmatic dysfunction.[37,38] The diaphragmatic atrophy rate in 40 intubated, critically ill adult subjects was recently evaluated by daily ultrasonography measurements of diaphragm thickness from the first day of mechanical ventilation until transfer to the general ward. Zambon et al[38] found that the daily reductions in thickness were 7.5% during controlled mechanical ventilation, 5.3% during high pressure support ventilation, and 1.5% during low pressure support ventilation. Interestingly, diaphragm thickness increased 2.3% under conditions of spontaneous breathing and CPAP. In another large cohort study, diaphragm thickness during mechanical ventilation over the first week of ventilation was assessed.[39] In this study, diaphragm thickness decreased rapidly during the first several days of mechanical ventilation in > 40% of subjects, and this decreased was predicted by lower levels of inspiratory effort and higher levels of ventilatory support.

Mechanical ventilation has also been associated with increased oxidative stress in the diaphragm, even during pressure support ventilation or intermittent spontaneous breathing.[40] Moreover, the effects of mechanical ventilation on diaphragmatic function may be exacerbated by medications such as steroids and neuromuscular blockers that are commonly used in treating these patients.[4,5] These findings show that diaphragm weakening is inevitable to some extent and that there is a need for alternative therapeutic strategies for ventilator-induced diaphragmatic dysfunction, which might include antioxidants and inotropic agents (eg, theophylline, digoxin, and levosimendan) or phrenic nerve pacing. As for the latter, a recent study in animal models described a novel technology in which a single central-line catheter containing an array of integrated electrodes is used to perform bilateral phrenic nerve pacing in synchrony with the ventilator.[41] The authors of this study reported that intermittent phrenic stimulation

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prevented the decline in diaphragm thickness and also tended to mitigate reductions in diaphragm muscle fiber. In this review, we focus on the use of antioxidants and theophylline for the prevention or treatment of ventilator-induced diaphragmatic dysfunction.

Antioxidants

Prevention of mechanical ventilation-induced oxidative stress with the use of antioxidants can avoid diaphragmatic atrophy and contractile dysfunction that occur during prolonged mechanical ventilation. Aside from countering oxidative stress, antioxidants may also modulate the expression of proteolysis-related genes: eg, administration of high doses of vitamin E to animals reduced the expression of several proteases such as caspase-3 and calpain.[42] Trolox, an analog of vitamin E with antioxidant activity, was found to protect the diaphragm against ventilator-induced diaphragmatic atrophy.[43,44] Mitochondria may be an important source of reactive oxygen species in the diaphragm during prolonged mechanical ventilation, with emission of mitochondrial reactive oxygen species playing a predominant role in mechanical ventilation-induced proteolysis, atrophy, and contractile dysfunction.[45] Treatment of animals with SS-31, a mitochondria-targeting antioxidant, protected rat diaphragms against muscle atrophy that occurs during prolonged mechanical ventilation by countering oxidative stress and preventing protease activation.[46] To date, however, no clinical studies have assessed the efficacy of antioxidants in patients with ventilator-induced diaphragmatic dysfunction.

Theophylline

Theophylline is widely prescribed as an add-on therapy for patients with poorly controlled asthma or COPD. Several molecular mechanisms of its action have been proposed: first, theophylline relaxes airway smooth muscles by inhibiting phosphodiesterase-3 activity, leading to bronchodilation.[47] Second, therapeutic concentration of theophylline antagonizes adenosine A_1 and A_2 receptors, which also results in bronchodilation.[48] Third, theophylline acts as an anti-inflammatory agent, increasing the effect of interleukin-10[49] and preventing the translocation of the pro-inflammatory transcription factor nuclear factor-κB.[50] Theophylline also enhances histone deacetylase-2 activity, which is reduced by oxidative stress, and the increased histone deacetylase-2 activity reduces formation of peroxynitrite radicals.[51,52] In addition to its bronchodilator and anti-inflammatory effects, theophylline stimulates the respiratory neuronal network[53,54] and increases the activity of respiratory muscles, including the intercostal and transversus abdominis muscles, as well as the diaphragm.[55–57]

Taken together, these results suggest that theophylline may be therapeutic in patients with ventilator-induced diaphragmatic dysfunction-associated weaning difficulties. Theophylline was found to dose-dependently increase peak twitch tension in an in vitro model of isolated diaphragmatic fibers.[58] A study using phrenic nerve conduction showed that theophylline infusion rapidly reversed the reduction of transdiaphragmatic pressure resulting from resistive loaded breathing in normal human subjects.[59] Moreover, in subjects with severe COPD, theophylline significantly increased the maximal transdiaphragmatic pressure and suppressed diaphragmatic fatigue when compared with placebo.[60] This phenomenon may be explained by previous findings showing that, under both fresh and fatigued conditions, theophylline is associated with greater improvements in diaphragmatic contractility at short than at long fiber lengths induced by acute hyperinflation.[61] Conversely, a placebo-controlled, double-blind, crossover study investigating the effects of theophylline on recovery of respiratory motor function in subjects after spinal cord injury failed to detect improvements; the null results of this study was attributed to the high dropout rate of subjects due to adverse drug-induced systemic effects.[54]

Numerous studies have demonstrated favorable effects of theophylline on human respiratory muscle function, and the drug is commonly used in patients weaning from mechanical ventilation; however, with the exception of some case reports in patients with tetraplegia, few studies have systematically reported clinical experience with theophylline in adult patients weaning from mechanical ventilation.[62,63] Recently, we demonstrated that low-dose (median, 200 mg/d) theophylline treatment significantly improved the diaphragmatic movements in subjects who required mechanical ventilation for at least 72 h, met the criteria for a spontaneous breathing trial, and had ultrasonography evidence of ventilator-induced diaphragmatic dysfunction.[64] The effects of theophylline were much more prominent in diaphragms with ventilator-induced diaphragmatic dysfunction, consistent with previous studies reporting that the inotropic effect of theophylline was more prominent in fatigued diaphragms.[59,60] In our study, theophylline was well tolerated by the study subjects, with no significant adverse drug reactions that prompted discontinuation. This may be due to a relatively low serum concentration (mean = 4.6 mg/L on day 3) of theophylline compared with studies that used higher doses of theophylline (mean serum concentration $\geq$ 10 mg/L). Even low concentrations of theophylline ($<$ 5 mg/L) have been reported to restore histone deacetylase-2 activity.[51,52] The finding that low-dose theophylline significantly improved diaphragmatic movements is encouraging, considering that the drug is often withheld due to concerns about its adverse effects.[54] However, we cannot conclude at this point that theophyl-

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line is useful for prevention or treating of patients with ventilator-induced diaphragmatic dysfunction. Our study had a small sample size and did not provide supporting molecular mechanisms. In addition, the multiple confounding factors (eg, comorbidity, severity of illness, cause of ICU admission, drugs) generally present in ICU patients may contribute to diaphragmatic dysfunction. Indeed, despite the similar baseline characteristics of the ventilator-induced diaphragmatic dysfunction subjects in the theophylline and non-theophylline groups, most subjects were admitted to the ICU due to severe sepsis or septic shock (91% vs 84%, respectively, $P = .65$), and many of them were treated with sedatives, neuromuscular blockers, and/or steroids.

Summary

Ventilator-induced diaphragmatic dysfunction is believed to be one of the major contributors to the weaning difficulties in ICU patients, and it significantly influences the duration of mechanical ventilation, weaning failure, and mortality. The increasing availability of ultrasonography has provided a simple and effective means of evaluating diaphragm function that may help in the design of adequate treatment. Mounting evidence shows that theophylline increases diaphragmatic contractility in a subset of patients with fatigued diaphragm and hyperinflated lungs; therefore, large prospective clinical trials using theophylline would help physicians choose the appropriate course of therapy for patients with ventilator-induced diaphragmatic dysfunction-associated weaning difficulties.

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