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CROSSTALK

CrossTalk proposal: Mechanical ventilation-induced diaphragm atrophy is primarily due to inactivity

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Mechanical ventilation (MV) is used clinically to maintain adequate alveolar ventilation in patients that are incapable of doing so on their own. Although MV can be a life-saving intervention for patients in respiratory failure, prolonged MV promotes the rapid development of diaphragmatic atrophy and contractile dysfunction. This unfortunate consequence of prolonged MV is referred to as ventilator-induced diaphragm dysfunction (VIDD). Thus, the question arises, 'what factors are responsible for the speedy onset of diaphragmatic atrophy that occurs during MV'? Although a definitive answer to this question does not exist, at least four different physiological mechanisms could make a primary contribution to MV-induced diaphragm atrophy. These include: (1) ventilator-induced lung injury resulting in increased circulating cytokines and the ensuing muscle atrophy; (2) systemic infection (sepsis), a condition often present in patients receiving MV, could promote increased circulating cytokines and subsequent diaphragm atrophy; (3) ventilator-induced paracrine signalling resulting in activation of toll-like receptors leading to diaphragm atrophy; and (4) ventilator-induced diaphragm inactivity resulting in disuse muscle atrophy. Considering the available data, it is our position that the strongest evidence points toward 'diaphragm muscle inactivity' as the primary contributor to MV-induced diaphragmatic atrophy. A brief discussion of the evidence for and against this position follows.

Is ventilator-induced systemic inflammation responsible for MV-induced diaphragm atrophy?

Although chronic elevation of circulating cytokines (e.g. TNFα, IL6, etc.) has the potential to promote skeletal muscle atrophy, recent studies reveal that prolonged MV in healthy rats results in diaphragmatic atrophy in the absence of increased blood levels of cytokines (Maes *et al.* 2008; Hudson *et al.* 2012). Hence, increased circulating cytokines is not a requirement for MV-induced diaphragm atrophy in rats. In contrast to these results in rats, a recent report suggests that 8 h of MV increases plasma concentrations of keratinocyte-derived chemokine (KC) in mice (Schellekens *et al.* 2012). Note, however, that this work does not demonstrate a causal relationship between KC and diaphragm atrophy. Further, if increased blood levels of cytokines were responsible for MV-induced diaphragm atrophy, it would be predicted that increased circulating cytokines would also result in limb muscle atrophy. Nonetheless, limb muscle atrophy does not occur in rats or humans exposed to 15–276 hours of MV (McClung *et al.* 2007; Levine *et al.* 2008; Hussain *et al.* 2010).

Is sepsis responsible for MV-induced diaphragm atrophy?

Clearly, sepsis has been shown to promote skeletal muscle atrophy (Callahan & Supinski, 2009). Nonetheless, both human and animal studies reveal that profound MV-induced diaphragm atrophy occurs in the absence of sepsis (Powers *et al.* 2002; Levine *et al.* 2008; Falk *et al.* 2011). Hence, sepsis is not a requirement for MV-induced diaphragm atrophy.

Is ventilator-induced toll-like receptor (TLR4) signalling responsible for MV-induced diaphragm atrophy?

A recent study reported that prolonged MV (e.g. 8 h) results in a loss of myosin

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heavy chain protein in diaphragm muscle fibres in wild-type mice (Schellekens *et al.* 2012). In contrast, TLR4 knockout mice did not exhibit MV-induced reductions in the myosin heavy chain content in diaphragm fibres. The authors speculated that TLR4 receptors in the diaphragm are activated by ligands released from the ventilated lung and concluded that TLR4 signalling plays an important role in MV-induced diaphragm atrophy via increased expression of cytokines in the diaphragm. A caveat, however, is that numerous TLR ligands exist (Piccinini, 2010) and it is feasible that some TLR4 ligands could originate from skeletal muscle undergoing inactivity-induced fibre atrophy. Also, evidence indicates that prolonged MV does not increase cytokine levels (e.g. TNFα, IL6, etc.) in the human diaphragm (Levine *et al.* 2008). Additional experiments are required to confirm or deny the role that TLR4 signalling plays in MV-induced diaphragm atrophy.

Is ventilator-induced diaphragm inactivity responsible for MV-induced diaphragm atrophy?

Before addressing this topic, it is important to point out that MV support to patients is commonly classified into two general categories: (1) full ventilator support (often referred to as control MV), or (2) partial ventilator support (many modes of partial support MV exist). When a patient is ventilated using full support MV the ventilator provides all the work of breathing and the patient's respiratory muscles are inactive. For example, full support MV in rats results in complete cessation of inspiratory electromyogram activity in the diaphragm (Powers *et al.* 2002). In contrast, during partial ventilator support, the ventilator provides a portion of the work of breathing and the patient's inspiratory muscles (e.g. diaphragm) provide the remainder.

Many studies show that full support MV results in the rapid activation of proteases in diaphragm myofibres which is associated with diaphragm atrophy in both humans and animals (Powers *et al.* 2009; Jaber *et al.* 2011). Importantly, anaesthesia has been eliminated as a cause of diaphragm atrophy in animal studies (Powers *et al.* 2002). In contrast to these full support MV studies, four animal studies conducted in independent laboratories conclude that partial support MV decreases protease activation in the diaphragm and protects against the high level of diaphragmatic atrophy associated with full support MV. For example, compared to full support MV, work by Futier *et al.* reveals that partial support MV prevents protease activation in the diaphragm and also completely eliminates the full support MV-induced depression of diaphragm protein synthesis (Futier *et al.* 2008). A second study demonstrates that, compared to full support MV, partial support MV protects the diaphragm against ventilator-induced diaphragm contractile dysfunction and prevents the increased expression of a key proteolytic protein (i.e. MAF-box) associated with the ubiquitin proteasome system (Sassoon *et al.* 2004). The third study demonstrates that even a low level of pressure support MV delays the development of MV-induced diaphragm atrophy by protecting the diaphragm against oxidative stress and protease activation during the first 12 h of MV (Hudson *et al.* 2012). Finally, Jung *et al.* demonstrated that, compared to full support MV, piglets exposed to 72 h of partial support MV are protected against both MV-induced diaphragm contractile deficits and fibre atrophy (Jung *et al.* 2010). Together, these four independent studies support the notion that diaphragmatic inactivity plays an important role in the development of VIDD during full support MV.

Two additional lines of evidence provide strong support for the position that diaphragmatic inactivity plays a key role in MV-induced diaphragm atrophy. First, Gayan-Ramirez *et al.* demonstrated that adding intermittent periods of spontaneous breathing (5 min h^{-1}) to animals receiving 24 h of full support MV results in significant protection against full support MV-induced diaphragmatic atrophy (Gayan-Ramirez *et al.* 2005). Similarly, a recent paper reveals that short periods of bilateral phrenic nerve stimulation (10 min h^{-1}) protects the diaphragm against full support MV-induced diaphragm contractile dysfunction and increased gene expression of proteolytic proteins (e.g. MuRF1 and MAFbx; Yang *et al.* 2013).

Why does inactivity alone promote the rapid development of diaphragm atrophy? It is well-established that prolonged bed rest or limb immobilization results in skeletal muscle fibre atrophy due to both a decrease in muscle protein synthesis and a rapid increase in proteolysis in the inactive skeletal muscles (Powers *et al.* 2005; Sandri, 2008). Similarly, it is clear that full support MV results in both increased proteolysis and decreased protein synthesis in the diaphragm (Powers *et al.* 2009; Jaber *et al.* 2011). Therefore, it is not surprising that fibre atrophy occurs when a chronically active skeletal muscle like the diaphragm is subjected to prolonged periods of inactivity during full support MV.

In summary, the best evidence that contractile inactivity plays a major role in MV-induced diaphragm atrophy comes from six independent studies indicating that even a small amount of diaphragm contractile activity can protect against full support MV-induced diaphragm fibre atrophy (Sassoon *et al.* 2004; Gayan-Ramirez *et al.* 2005; Futier *et al.* 2008; Jung *et al.* 2010; Hudson *et al.* 2012; Yang *et al.* 2013).

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Competing interests

None declared.