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Respiratory dysfunction in ventilated patients: can inspiratory muscle training help?

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SUMMARY

Respiratory muscle dysfunction is associated with prolonged and difficult weaning from mechanical ventilation. This dysfunction in ventilator-dependent patients is multifactorial: there is evidence that inspiratory muscle weakness is partially explained by disuse atrophy secondary to ventilation, and positive end-expiratory pressure can further reduce muscle strength by negatively shifting the length-tension curve of the diaphragm. Polyneuropathy is also likely to contribute to apparent muscle weakness in critically ill patients, and nutritional and pharmaceutical effects may further compound muscle weakness. Moreover, psychological influences, including anxiety, may contribute to difficulty in weaning. There is recent evidence that inspiratory muscle training is safe and feasible in selected ventilator-dependent patients, and that this training can reduce the weaning period and improve overall weaning success rates. Extrapolating from evidence in sports medicine, as well as the known effects of inspiratory muscle training in chronic lung disease, a theoretical model is proposed to describe how inspiratory muscle training enhances weaning and recovery from mechanical ventilation. Possible mechanisms include increased protein synthesis (both Type 1 and Type 2 muscle fibres), enhanced limb perfusion via dampening of a sympathetically-mediated metaboreflex, reduced lactate levels and modulation of the perception of exertion, resulting in less dyspnoea and enhanced exercise capacity.

Key Words: breathing exercises, ventilator weaning methods

Prolonged mechanical ventilation (MV) is expensive. A recent prospective cohort study of 126 patients in North America reported the mean one-year cost of treatment for prolonged MV patients (defined as greater than four days with a tracheostomy, or greater than 21 days without) as US$306,135 – the majority of which (73%) was attributable to the initial hospitalisation[1]. It is also well-established that prolonged MV is associated with higher mortality, poor functional outcomes, lower quality of life and higher incidence of nursing home placement[2,3]. Clearly ventilator dependence is a significant burden for both individuals and health systems. In this context, there has been surprisingly little research into the mechanisms of ventilator dependence or treatment strategies to facilitate liberation from MV.

There is mounting evidence that MV itself results in pathological changes to the respiratory system which may contribute to prolonged ventilator dependence and the clinical phenomenon of difficult weaning[4]. Potential contributors to ventilator-dependent respiratory dysfunction include inspiratory muscle weakness, polyneuropathy, pharmaceutical influences and nutritional and psychological factors. Recently, inspiratory muscle training (IMT) has emerged as a potential treatment strategy to accelerate ventilatory weaning. The links between IMT and underlying respiratory dysfunction are complex but are of interest to intensive care clinicians around the world who strive to liberate their patients from MV as swiftly as possible.

INSPIRATORY MUSCLE CHANGES WITH MECHANICAL VENTILATION

Muscle atrophy

Animal studies have clearly demonstrated that controlled MV results in measurable changes to the diaphragm. In a study of rats mechanically ventilated

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for 18 hours[5], atrophy of both Type 1 and Type 2 muscle fibres was detected, with greater atrophy of Type 2 fibres, and a concurrent increase in diaphragmatic protease activity and oxidative stress, suggesting muscle catabolism. Another rat study[6], which rigorously excluded any contribution of phenobarbital to muscle changes, found that 12 hours of controlled MV resulted in an 18% reduction in diaphragmatic force, whereas 24 hours resulted in a 46% reduction. Extrapolation of these results to human subjects is limited by the infrequent use of completely controlled MV in contemporary intensive care practice. Nonetheless, a dose-dependent relationship between duration of ventilation and subsequent weakness appears likely.

Observational studies in humans have similarly shown that longer periods of MV are associated with greater weaning difficulty[7-9]. While longer periods of ventilation may be due to the underlying pathology, it is possible that MV further compounds respiratory muscle weakness in these patients, contributing to delayed weaning. Even following successful weaning, prolonged MV appears to affect respiratory muscle endurance. In a study of 20 subjects who received MV for at least 24 hours[10], there was a 12% reduction in endurance detectable approximately one week following weaning. Importantly, those ventilated for longer than seven days showed significantly less fatigue resistance than those ventilated for fewer than seven days. Furthermore, in a recent study of 116 patients ventilated longer than seven days[8], maximum inspiratory pressure (MIP) was found to be reduced and correlated with limb weakness. Although these studies do not provide any direct evidence of muscle atrophy, the results would be consistent with an atrophic response to MV.

Recently, direct evidence for diaphragmatic atrophy with MV has been obtained in mechanically ventilated, brain-dead organ donors[11]. Diaphragmatic biopsies from 14 brain-dead patients ventilated for between 18 and 69 hours were compared with biopsies from eight surgical patients ventilated for no more than three hours. The biopsies from the brain-dead patients demonstrated statistically significant reductions in mean cross-sectional area of Type 1 and Type 2 muscle fibres, reduced glutathione and elevated levels of enzyme active caspase-3, suggesting increased proteolysis. These changes were not detectable in the control muscle studied for each patient (pectoralis major), suggesting that the atrophy and proteolysis observed was specific to the diaphragm and not a generalised phenomenon in skeletal muscle due to the abnormal physiology associated with brain death. As previously discussed, extrapolation of these results to mechanically ventilated patients whose ventilation has not been completely controlled should be done with caution. However, this study provides the most convincing evidence to date that MV has a direct adverse effect on the respiratory muscles[12].

Muscle length-tension changes

The development of inspiratory muscle weakness with prolonged mechanical ventilation is likely to be compounded by other factors that impact on muscle performance. For example, positive end-expiratory pressure (PEEP) is widely used as a therapeutic tool in patients with respiratory failure, but one of its effects is an adverse impact on the length-tension relationship of the diaphragm.

Like all skeletal muscles, the diaphragm's ability to generate force is related to the length of the muscle fibres[13]. The implications of the diaphragm's length-tension relationship are well described in the literature pertaining to patients with chronic obstructive pulmonary disease[14-16]. In this clinical group, chronic hyperinflation, with average intrinsic PEEP of 2.4 cmH_2O[17], results in adaptive shortening of the diaphragm causing a more flattened, less domed structure. This produces an adverse shift along the length-tension curve, so that diaphragmatic contraction generates less muscular force[15].

Mechanically ventilated patients are often prescribed relatively high levels of extrinsic PEEP (typically between 5 and 15 cmH_2O) as a mechanism to maintain alveolar recruitment, enhance oxygenation and counteract autoPEEP[18]. Unfortunately, this extrinsic PEEP may also lead to a flattening of the diaphragm and muscular shortening with disadvantageous shifts along the length-tension curve, further compounding inspiratory muscle weakness (as demonstrated in animal models[19]). Thus, in considering diaphragmatic weakness, the ideal prescription of MV should minimise PEEP wherever possible to reduce the negative impact on diaphragm strength. However, this must be balanced against the potential benefits of PEEP in patients with respiratory failure[20,21]. Both the impairment of the diaphragmatic length-tension relationship associated with excessive PEEP, and the worsening of respiratory mechanics seen with inadequate PEEP, may lead to an increased respiratory drive and impaired neuroventilatory efficiency[22]. Recent work investigating the effects of PEEP in patients receiving neurally adjusted ventilatory assist has shown that while in general, increasing PEEP reduces respiratory drive, the

response is heterogeneous. In addition, it is possible to identify a PEEP level at which breathing occurs with an optimum relationship between tidal volume and diaphragmatic electrical activity[22].

While the effects of MV on the diaphragm are relatively well-studied, the only available evidence regarding the effects of MV and PEEP on the performance of other inspiratory muscles, such as the parasternal intercostals, comes from animal research where positive pressure ventilation has been found to reduce intercostal force generation. However, it has been suggested that this force reduction may be due to rib orientation changes rather than muscular shortening[23]. In ventilator-dependent patients, the relative contribution of intercostal muscle dysfunction to inspiratory muscle weakness remains to be determined.

It has been suggested that when patients fail a spontaneous breathing trial, they typically exhibit rapid shallow breathing which causes a degree of dynamic hyperinflation[12]. As previously discussed, this hyperinflation will impair the length-tension relationship of the diaphragm and thus compromise inspiratory muscle strength[24]. Furthermore, both intrinsic PEEP and dynamic hyperinflation have been demonstrated in ventilator-dependent patients when they are removed from ventilatory support[25], indicating the presence of a high residual inspiratory load. It is yet to be established whether this intrinsic PEEP remains following successful weaning from ventilation.

Thus it is important to consider the possibility that the presence of intrinsic or either inadequate or excessive extrinsic PEEP may be contributing to impaired inspiratory muscle performance and apparent inspiratory muscle weakness.

Muscle weakness and failure to wean

Studies of patients who fail to wean from ventilation have been performed to determine whether there are physiological characteristics which distinguish those who wean from those who fail to wean. A small (n=10) prospective cohort study of ventilator-dependent patients found that those who could be weaned had significantly higher MIPs (mean 40 cmH_2O) than those who failed (mean 20 cmH_2O)[7].Similar results were found in a second prospective cohort study of 30 patients who had failed initial weaning attempts in a weaning centre[26]. In this study, an invasive device at the tip of the tracheostomy tube was used to measure transdiaphragmatic pressures during spontaneous breathing trials. Patients who consistently failed these spontaneous breathing trials concurrently demonstrated lower diaphragmatic pressures than those who weaned successfully, while those who successfully weaned demonstrated significantly higher MIP (mean 57 compared to mean 38 cmH_2O in success and failure groups respectively). The authors concluded that recovery of inspiratory muscle force may be a critical determinant of weaning success in this slow-to-wean population.

A larger prospective cohort study (n=116) of patients ventilated for seven days or longer[8] found that not only was MIP significantly reduced in this group (mean 30 cmH_2O), but a low MIP was an independent predictor of delayed weaning. Yet paradoxically, other researchers have failed to demonstrate that measures of inspiratory muscle strength (e.g. MIP or negative inspiratory force) predict accurately weaning success or failure in the acute setting[27,28]. For example, in a prospective blinded study of 93 patients, neither the MIP values, nor any other parameter investigated, had sufficient predictive power to distinguish between those who would wean successfully and those who would fail[27]. Although inspiratory muscle weakness is a problem for patients undergoing prolonged ventilation, it may be that measures of inspiratory muscle strength only weakly reflect the overall complexity of respiratory dysfunction (and hence readiness to wean) and cannot be considered in isolation.

Implications

The available evidence strongly suggests that even relatively short durations of MV result in diaphragmatic atrophy, with associated abnormally high proteolysis. In healthy subjects, it is well established that high-resistance strengthening exercise causes both muscle anabolism and catabolism in skeletal muscle, with a net anabolic effect[29]. Resultant intra-muscular remodelling and gains in muscle cross-sectional area have been demonstrated in healthy subjects following a three-week high resistance training program[30]. Therefore it is plausible that IMT could reverse or ameliorate inspiratory muscle proteolysis in ventilator-dependent patients, by providing a net anabolic stimulus. The associated inspiratory muscle strength gains could thus enhance weaning. However, appealing as this hypothesis may be, it remains unclear whether the respiratory muscle weakness associated with prolonged MV is reversible. In addition, numerous other factors may contribute to muscle atrophy and apparent weakness in ventilator-dependent patients, which also must be considered.

POLYNEUROPATHY

ICU-acquired weakness (ICUAW) is the current term used to describe the pathophysiological weakness observed in many critically ill patients, and while definitions and diagnostic guidelines have recently been clarified[31], interpretation of data currently available in this area is clouded by the variations in definitions and terminology used prior to this (e.g. critical illness neuromyopathy, critical illness polyneuropathy). Critical illness polyneuropathy (CIP), a subset of ICUAW, is frequently present in critically ill patients but remains relatively under-diagnosed[32]. CIP has long been considered a contributor to difficulty in weaning from MV[33] and in an observational study of 21 patients with 'inability to wean'[34], 62% were found to have neuromuscular disease severe enough to account for ventilator dependence. A subsequent study of 40 patients ventilated for five days or longer[35] found that 83% had polyneuropathy, with a correlation between the severity of the polyneuropathy and weaning duration. In addition, while 25% of patients had reduced central drive, 15% had a combination of disorders. Thus any apparent muscle weakness in critically ill patients may be due to neuropathic as well as myopathic factors.

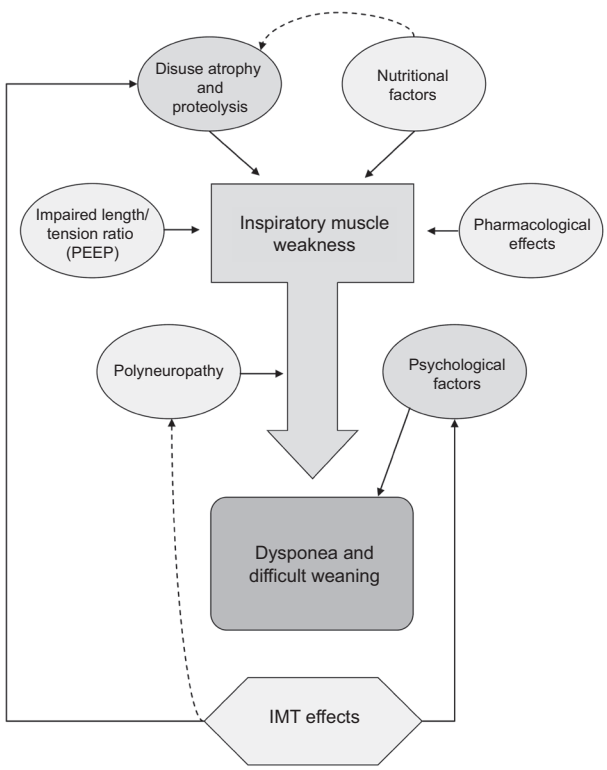

FIGURE 1: Model of inspiratory muscle training and enhanced weaning from mechanical ventilation. PEEP=positive end-expiratory pressure, IMT=inspiratory muscle training.

It has been suggested that as CIP is associated with duration of MV, then measures taken to reduce the period of ventilator-dependence may lessen the potential impact of CIP[32]. While this association is confounded by the likelihood that severity of illness will contribute to both duration of MV and the development of CIP, a recent systematic review has observed that the respiratory muscles in patients with ICUAW may be relatively spared the negative effects observed in peripheral muscles, possibly due to the intermittent stretch provided by the ventilator[36]. However, it is also possible that CIP is a contributor to ventilator dependence, rather than a consequence of it, and while the possible mechanisms for this remain unclear, lack of core stability due to weakness of structural trunk muscles may adversely impact respiratory function. In the absence of data, we believe that it is reasonable to consider CIP as a potential factor contributing to respiratory muscle dysfunction in ventilator-dependent patients.

In addition to ICUAW, pathologies of the peripheral neurological or neuromuscular systems, including myasthenia gravis and Guillain-Barré syndrome, frequently result in long-term ventilator dependence and these underlying pathologies will almost certainly contribute to respiratory dysfunction. There is some limited evidence that IMT may increase inspiratory muscle strength and endurance in non-ventilated patients with myasthenia gravis[37].

Further investigation of the interaction between peripheral neuromuscular disease and muscle retraining would be helpful. In the interim, the possible impact of muscle training on the patho-physiological processes involved in ICUAW must be considered (as suggested in Figure 1).

PHARMACOLOGICAL EFFECTS

The potential effects of pharmacological agents on respiratory muscle strength also must be considered in critically ill patients. Neuromuscular blocking agents (NMBA) and corticosteroids have both been implicated in the development of ICUAW[38]. Although use has declined in recent years, NMBAs are still commonly used in the critical care environment, for management of both intracranial hypertension and ventilator dyssynchrony. It has been suggested that blockade of normal neuromuscular transmission and interference with endplate structure leads to an acceleration of critical illness myopathy; and that muscle will not recover until normal functional stimulation is provided[39].

Corticosteroids are prescribed for a diverse range of indications in the critically ill[40-42], however the effect of corticosteroids on inspiratory muscle function in ventilator-dependent patients has not been studied in detail. In patients without underlying lung disease, extended duration high dose steroids (prednisone 1 to 1.5 mg/kg/day for eight weeks) have been shown to reduce inspiratory muscle strength and endurance[43]. Interestingly, these reductions were reversed when corticosteroid doses were tapered. A subsequent study[44] found that IMT prevented these negative effects of corticosteroid therapy. In contrast, no impact on inspiratory muscle strength was demonstrated in a study of moderate doses of corticosteroids (20 mg daily) in 16 healthy subjects[45]. In asthmatic patients, the combination of corticosteroids and NMBAs may lead to profound and prolonged ICU-acquired weakness[46,47]. Again, the specific effects on respiratory muscles have not been well studied.

It is therefore possible that the administration of either NMBAs or corticosteroids could further compound respiratory muscle weakness in ventilator-dependent patients. The degree to which these changes can be ameliorated by IMT is yet to be investigated.

NUTRITION

A comprehensive analysis of the nutritional requirements of ventilator-dependent patients is beyond the scope of this review. However, while overfeeding has been on the list of factors to be considered in the difficult-to-wean patient for many years[18], inadequate nutrition may also contribute to weaning difficulty. The importance of considering nutrition in the difficult-to-wean patient is illustrated in Figure 1.

It must be acknowledged that there is wide variability in the nutritional requirements between and within patients across their intensive care admission[48]. Trauma, major surgery and short-term starvation are all known to reduce protein synthesis[48]. Furthermore, sepsis impairs mitochondrial function in both respiratory and limb muscles[49]. However, septic patients demonstrate a relative preservation of energy sources (adenosine triphosphate, creatine phosphate) in respiratory muscles[49]. This could enhance the training potential of respiratory muscles relative to peripheral muscles.

In healthy subjects, timing and quality of nutrition (particularly amino acid availability) directly affects muscle synthesis pathways[29]. Thus it would seem reasonable to conclude that adequate nutrition, titrated to account for anabolic muscle development, is necessary for successful IMT in critically ill patients. Conversely, ventilator-dependent patients with inadequate nutrition, or poor baseline metabolic status, may have inadequate substrate availability to match protein synthetic demand, reducing the efficacy of muscle training. However, the determination of nutritional requirements in critical illness remains controversial. There are some limited data from the bed rest (aerospace) literature suggesting that overfeeding may be harmful, with increased inflammatory markers and accelerated muscle atrophy in subjects who do not reduce caloric intake after the initiation of bed rest[50]. Congruent with this, a recent study in critical illness found that permissive underfeeding (goal 60 to 70% of estimated nutritional requirements) resulted in lower hospital mortality compared to those fed with a goal of 100% of estimated requirements[51]. These results are consistent with previous evidence that feeding goals of 33 to 65% of estimated requirements resulted in significantly improved hospital mortality than goals of >66%.

Specific supplementation to augment muscle hypertrophy and overall physical performance in response to training has long been studied in the sports literature, with relatively little crossover work to clinical populations. With particular relevance to muscle weakness and potential training effects, creatine supplements have been shown to augment training effects in healthy subjects[52,53]. However a randomised trial of creatine supplementation in 100 patients with chronic obstructive pulmonary disease undergoing pulmonary rehabilitation failed to find improvements in exercise capacity in the creatine group[54]. To date no studies of creatine supplementation have been performed in critically ill patients.

Thus the interaction between the potential training benefits of IMT and nutritional status is complex. In the absence of clear guidelines regarding overall nutrition goals, or specific supplementation, IMT should be conducted with an appreciation of the potential influence of nutritional factors on resistance training benefits.

PSYCHOLOGICAL FACTORS

Psychological stress has been identified as a potential factor contributing to difficult ventilatory weaning[4,55], yet there are limited data describing the extent of this problem. In a descriptive study of patient experiences of ventilator dependence[56], reported experiences included perceived catastrophic

loss of control, perceiving the ventilator as an extension of one's self, a spectrum of attitudes from depressed passivity to an agitated fight for control, and a dislike or fear of change, particularly with regard to weaning. While it must be acknowledged that this research is relatively old (1985), from a time when ventilators were less synchronised with patient effort, the findings are consistent with more recent studies. A prospective cohort study of 250 ventilator-dependent patients found that 88% of patients described their experience of being intubated and ventilated as moderately to extremely stressful[57]. A follow-up study of these patients focused on memories of intensive care and revealed prominent themes of physical and emotional ventilator-related distress (e.g. feeling unable to breathe, fear and panic, anxiety). Thus psychological distress should not be underestimated in ventilator-dependent patients.

The relationship between psychological stress or anxiety and dyspnoea has not been studied in ventilated patients. However, extrapolation from sports psychology, and specifically the perception of exertion, may be useful here. In athletes it has been proposed that during exercise the perception of exertion is not linear, but rather is best understood as a highly complex system where physiological feedback (e.g. via mechanoreceptors and chemoreceptors) is analysed by a central controller which also considers variables such as time to endpoint (e.g. how long until the end of the race) and previous experience[34,35]. Thus the perception of exertion (and therefore dyspnoea) is conscious and potentially modulated by psychological variables[58,59]. If a ventilator-dependent patient's experience of weaning is analogous to an athlete's exercise conditions (i.e. both characterised by high ventilatory workloads and limited by perceived exertion), anxiety or psychological stress may well modulate the overall perception of effort and manifest as increased dyspnoea.

Although the subjective perception of dyspnoea has not been well studied in ventilated patients, it could be argued that one of the key methods employed to measure or predict weaning failure (i.e. rapid shallow breathing index[60]) may be in fact an attempt to objectively quantify the subjective experience of dyspnoea. If subjective dyspnoea, rather than ventilatory capacity or fatigue, is actually the limiting factor in the context of weaning failure, it is not surprising that physiological-level measurement tools have failed to predict weaning success with great accuracy[27,28]. This is clearly an area requiring further research, but in the interim a possible role for psychological factors as determinants of ventilator-dependence should be considered.

INDICATIONS FOR INSPIRATORY MUSCLE TRAINING

In light of the above evidence regarding ventilator-dependent respiratory dysfunction, clinicians have been urged to minimise controlled ventilation and reduce the doses of drugs known to affect respiratory muscle function[61]. These approaches may reduce inspiratory muscle dysfunction but are unlikely to completely avoid it; even with these strategies, respiratory muscle weakness remains detectable approximately seven days following successful weaning[10]. As skeletal muscle weakness is generally a reversible phenomenon, it seems logical to employ training methods as early as possible to minimise the predictable effects of reduced inspiratory muscle work with MV. Furthermore, as prolonged MV is associated with poor functional outcomes (e.g. 21% complete functional dependency at 12 months[1]), any intervention with the potential to hasten ventilatory weaning, or avoid long-term ventilator dependence, deserves consideration. In this context, the current evidence for the effects of IMT in ventilator-dependent patients will be described. Although this research field is in its infancy, the limited evidence to date has important research and clinical implications.

What is IMT?

IMT uses progressive resistance to provide loading to the inspiratory muscles to achieve a strengthening effect. IMT devices have evolved considerably and now most commonly consist of a commercially available spring-loaded threshold valve which can be easily adjusted to provide incremental resistance. Importantly, the threshold design requires a specified pressure-level to be achieved with each breath, regardless of flow-rate, allowing the intensity of resistance to be titrated and progressed accurately. In non-ventilated patients this device is used with a mouthpiece and nose-clip, but for ventilator-dependent patients it can be attached directly to the tracheostomy or endotracheal tube via a simple connector while patients are briefly removed from ventilatory support.

There is strong evidence that IMT increases muscle strength and reduces dyspnoea in patients with chronic lung disease[62] and also enhances athletic performance in a variety of endurance sports (e.g. rowing[63], cycling[64,65], running[66]). Reduced perception of exertion during exercise has been reported

following IMT[59], as well as reduced estimation of the magnitude of a given respiratory load[67]. There is some preliminary evidence that preoperative IMT may reduce the incidence of postoperative pulmonary complications in high-risk patients undergoing cardiac surgery[68], and may preserve postoperative inspiratory muscle strength in both cardiac[69] and major abdominal surgery[70]. Furthermore, high-intensity IMT has been shown to improve quality of life, both in patients with chronic obstructive pulmonary disease[71] (primarily due to reduction in fatigue and dyspnoea) and chronic heart failure[72].

Mechanisms of improvement with IMT

The mechanisms of improvement with IMT have been studied in patients with chronic lung disease, healthy subjects and also in athletes. In patients with chronic lung disease, five weeks of IMT has been found to increase proliferation of both Type 1 and Type 2 intercostal muscle fibres[73]. IMT may also influence neural pathways, which could explain the significant changes in strength within a four week training period[74] and would be consistent with evidence that IMT affects neural drive in healthy subjects[75].

Further potential benefits of IMT in ventilated patients relate to the influence of IMT on muscle perfusion and metabolic pathways. There is convincing evidence that in healthy subjects IMT enhances limb muscle perfusion. Limb muscle perfusion is inversely related to inspiratory muscle work[76], such that when respiratory muscles become fatigued, blood flow is preferentially redistributed away from limb muscles in order to return blood supply to the fatiguing respiratory muscles, possibly via a sympathetically mediated metaboreflex[76,77]. IMT can down-regulate the impact of this metaboreflex, reducing peripheral fatigue. For example, in healthy subjects fatigue of the inspiratory muscles hastens fatigue of the plantar flexors, but IMT abolishes this effect[78]. Similarly, in patients with chronic heart failure, IMT improves limb blood flow during inspiratory loading[79]. Thus IMT may differentially influence muscle perfusion, thereby improving overall aerobic capacity.

IMT also affects lactate levels, or at least the sympathetic responsiveness to lactate. A randomised trial of IMT in healthy subjects[77] found that IMT resulted in a blunted sympathetic response (i.e. significantly lower heart rate and blood pressures measured in the training group during fatiguing inspiration). These authors suggested that the blunted sympathetic response could be due to a decreased sensitivity to lactic acid produced during fatiguing work, or alternatively an increased aerobic capacity resulting in less lactate production. More recently, in a randomised trial of 22 healthy subjects[80] IMT resulted in significantly lower blood lactate levels in the treatment group during a high intensity voluntary hyperpnoea task. This is consistent with previous studies showing that IMT reduces lactate levels during treadmill running in competitive athletes[81] as well as during cycling in healthy untrained subjects[82].

Together, this evidence suggests that IMT enhances overall aerobic capacity by not just reducing lactate production in the inspiratory muscles themselves (possibly due to an increased ratio of Type 1 muscle fibres), but also by enhancing blood flow to peripheral muscles by attenuating the metaboreflex that would otherwise 'steal' blood flow and redirect it to fatiguing respiratory muscles during high intensity exercise. The consequent enhancement of aerobic capacity may explain the global improvements in exercise performance described as a result of IMT in both healthy subjects and those with chronic disease[62,72]. The potential benefits of enhanced exercise tolerance in ventilator-dependent patients should not be underestimated. Recent evidence suggests that early mobilisation and exercise in intensive care patients can reduce length of stay[83,84]. It is possible that IMT could augment exercise tolerance and thus accelerate recovery in ventilator-dependent patients. Further investigation of this hypothesis is clearly warranted.

Evidence for IMT in ventilated patients

Despite some promising early case studies of IMT in ventilated patients[85-87], a single-centre randomised trial in 2005 concluded that IMT was ineffective this group[88]. However, this study used ventilator manipulations rather than a threshold device and had several limitations. First, the IMT was performed at a relatively low intensity (i.e. 10 to 40% of maximum) which may not have provided an adequate training stimulus; second, the low number of subjects (n=25) may have rendered the study vulnerable to Type 2 errors; third, despite attempts to optimise sedation levels, they reported less than ideal co-operation from some of their subjects, whereas full alert co-operation is considered essential in other training protocols[85-87]; and fourth the equivalence of ventilator manipulations and threshold-device training may be challenged, not least because temporary removal from all ventilatory support may be an essential element of successful IMT. Based on these limitations, the conclusion

that IMT is ineffective for ventilated patients was arguably premature.

In contrast, two recent randomised trials, both providing IMT via a removable threshold device, demonstrated significant improvements in ventilated patients. In a study of 41 patients aged 70 or older, Cader and colleagues used five-minute IMT sessions twice daily, commencing at 30% of MIP and increasing intensity by 10% daily[61]. These researchers found a significant increase in inspiratory muscle strength (mean difference in MIP of 7.6 cmH_2O 95% confidence interval [CI] 5.8 to 9.4), and a decrease in both the rapid shallow breathing index and weaning time, (mean difference 1.7 days, 95% CI 0.4 to 3.0). Subsequently, Martin et al[74] used high intensity interval training (highest tolerable resistance, progressed daily; sets of six to 10 breaths with rests on the ventilator in between) and found that IMT with a threshold device resulted in significant increases in inspiratory muscle strength (from mean 44.4 to 54.1 cmH_2O) whereas no such increase was observable in the control group. The treatment group had significantly more patients successfully weaned than the control group following 28 days of intervention (treatment group 71%, 95% CI 55 to 84%; sham group 47%, 95% CI 31 to 63%). The number needed to treat for these effects was reported as 4 (95% CI 2 to 80). Despite quite different training strategies, both these studies demonstrated that IMT results in increased inspiratory muscle strength and favourable weaning outcomes in ventilator-dependent patients. The optimal training parameters are yet to be established.

The mechanism of improvement with IMT in ventilated patients has not been investigated. The high-intensity training protocols used in both randomised trials described above may have provided an adequate training stimulus to halt or reverse the atrophy and proteolysis that is known to occur in patients undergoing MV (Figure 1). IMT could also attenuate the metaboreflex pathways described above, contributing to enhanced limb muscle perfusion, facilitating early mobilisation and thus accelerating recovery. Investigation of these hypotheses is warranted.

Psychological implications of IMT

Why would IMT with a threshold device be effective in increasing strength and enhancing weaning when ventilator manipulations are not? As discussed above, the psychological aspects of ventilator-dependence can be significant. Threshold-based IMT protocols require patients to gradually develop confidence breathing unassisted (i.e. in short bursts off the ventilator while supervised and encouraged by a physiotherapist). This coached IMT approach may build patients' confidence in breathing without ventilatory support, alleviate weaning-related anxiety, reduce the perception of effort and dyspnoea, and ultimately increase the likelihood of weaning success (Figure 1). This would be consistent with evidence from the sports literature, where perception of effort is considered a critical determinant of performance improvements in the absence of physiological changes in response to IMT[59].

Safety and feasibility of IMT in ventilated patients

The safety of threshold-based IMT in selected ventilator-dependent patients has been recently established, with stable physiological parameters (blood pressure, heart rate, oxygen saturation and respiratory rate) in response to treatment and no adverse outcomes reported in an analysis of 195 treatment sessions[89]. This is corroborated by the two recent randomised trials, neither of which reported adverse outcomes in response to treatment[61,74], but contrasts with the study of IMT using ventilator manipulations[88] which reported 23 cases (14%) of adverse physiological outcomes (i.e. desaturation, tachypnoea, haemodynamic instability and arrhythmia). Careful selection of stable, alert and co-operative patients who are able to psychologically tolerate the temporary high inspiratory workload of IMT should enhance feasibility and reduce potential tachypnoeic or tachycardic responses that could be panic-related.

There are limitations to the usage of IMT using a threshold device in ventilated patients: patients must be alert and able to co-operate with training, they must be medically stable and they must not be heavily reliant on high levels of ventilatory support (e.g. PEEP <10, FiO_2 $<60\%$)[89]. Not all critically ill patients will be suitable for IMT, particularly in the most acute phase of their management. However any patient who is at risk of ventilator-induced respiratory dysfunction, particularly those whose MV has exceeded seven days, should be screened for suitability for IMT. Minimising sedation is essential to maximise training opportunities and will enable the patient to fully participate in comprehensive early physical therapy, of which IMT could be an important element.

CONCLUSIONS

In summary, MV results in respiratory dysfunction, with muscle atrophy, secondary to disuse proteolysis, and inspiratory muscle shortening due to high PEEP leading to impairment of inspiratory muscle force

generation capacity. This weakness may be further compounded by critical illness polyneuropathy, nutritional impairment and the administration of corticosteroids and neuromuscular blocking agents. Psychological distress and anxiety is also likely to contribute to ventilator-dependence and may hamper weaning efforts. IMT improves inspiratory muscle strength and exercise performance in healthy and athletic subjects, as well as those with chronic disease. Early evidence suggests that IMT increases inspiratory muscle strength and reduces weaning times in ventilated patients, with enhanced weaning outcomes. Further research is required to elucidate the mechanisms of these improvements in ventilated patients, but these are likely to be related to enhanced protein synthesis, reduced dyspnoea and psychological readiness to tolerate high respiratory workloads.

Clearly not all ventilator-dependent patients are suitable for IMT. Nonetheless, given the costs of ventilator dependence, for both the patient and the healthcare system[4], clinicians could screen their patients for suitability for IMT and the evidence suggests many may benefit. Indeed, these studies provide further impetus for clinicians to maximise alertness in intensive care patients to facilitate training. Further research is needed to determine the ideal training parameters, and also to establish whether physiological improvements (as reflected in improved inspiratory muscle strength) translate into meaningful improvements in patient-centred outcomes such as quality of life, exercise tolerance and functional performance (i.e. similar to the benefits observed with IMT in chronic lung disease and athletes). Nonetheless, if IMT can hasten ventilatory weaning by even one day, then these early studies suggest IMT may be a wise investment in the modern intensive care unit.

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