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Muscles and lungs: fatal attraction, but time for intervention

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The act of breathing entails the integrity and function of the respiratory muscles [1]; however, diseases of the lung can also influence the muscle pump.

It is well known that neuromuscular damage have a strong impact on respiration [2] and that hyperinflation that accompanies COPD interferes with respiratory muscle function [3]. More recent evidence suggests that even respiratory tract infections can lead directly to muscle weakness [4]. Animal models imply that sepsis is associated with respiratory muscles dysfunction mediated through oxygen-derived free radicals [5]. Moreover controlled mechanical ventilation has been shown to induce diaphragmatic dysfunction [6] creating the possibility of a deleterious additive and/or synergistic with infection [7].

So an examination of the relationship between the Muscle Pump and the Lung can be useful for the clinician.

Although patients with pre-existing Neuromuscular Disease (NMD) are not commonly seen in the ICU [8] and seldom included in randomised controlled trials of Non Invasive Ventilation (NIV) [9], acquired NMD seems very common yet unrecognised [10, 11]. Respiratory failure due to these disorders needs a different approach from the more common obstructive pulmonary diseases [12, 13]. They need a special focus since well established therapeutical protocols may improve the outcomes [14, 15] and may reduce weaning time [16].

Acute Respiratory Failure (ARF) in patients with pre-existing NMD

In Respiratory Intensive Care Units (RICU), ARF due to NMD account for 4-12.5% of cases [17, 18] rising to 25% in weaning centres [19].

In patients with NMD, the development of upper respiratory tract infections significantly reduce respiratory muscle strength (with a mean fall of 12cm H_2O in maximal inspiratory pressure-MIP- and 10 cmH_2O of maximal expiratory pressure-MEP), probably by direct muscle injury [20]. Hypoventilation and hypercapnia ensues and cough efficacy becomes seriously compromised. In this setting, if emphasis is only on improving ventilation, the outcomes will be poor [21]. The use of non invasive mechanical aids to clear bronchial secretions should be added to improve clinical outcomes and avoid intubation or tracheostomy ventilation [14, 22-26]. During weaning, combination a of NIV and mechanical in-exsufflation should also be applied [15, 16].

Acquired NMD in the Intensive Care Unit (ICU)

From multicentre prospective studies it is estimated that 25.3% of patients who underwent mechanical ventilation (MV) for more than 7 days, develop Acquired NMD [10]. Corticosteroid administration is strongly associated with the occurrence of Acquired NMD [10], but neuromuscular blocking agents, aminoglycosides, hyperglycemia and sepsis are also risk factors [11]. Monitoring of respiratory muscle strength should be commonly performed in the ICU [2] and avoiding re-exposure to drugs, strict control of blood glucose levels and infection should be promptly implemented.

It has been shown that ICU-acquired NMD contributes to prolonged MV in critically ill patients [27], so early identification of the disease can have an impact on prognosis. Cough inefficacy and reduction in maximal respiratory pressures have also been reported in these patients [28], suggesting the implementation of secretion clearance techniques together with ventilatory support.

In this issue of the *Journal*, Vitacca *et al* [29] show that one third of patients admitted to an RICU, with severe exacerbation of COPD have a reduction in respiratory muscle strength.

The authors describe their experience with the evaluation of lung and respiratory function at RICU discharge of patients with a severe COPD exacerbation. In their Unit, with a high percentage of COPD admissions (75% of all cases) over one year, these investigators prospectively described a cohort of 42 patients with a severe exacerbation. They showed that at discharge, 33% of cases had significant deterioration of MIP compared with

stable state values. The majority of patients (55%) had required prolonged weaning and ventilation through a tracheotomy. Among patients with tracheotomy, mean RICU stay was 17±5 days, decannulation was possible in only 13% and respiratory muscle decrease was not significantly different from non-tracheotomised patients. Vitacca *et al* also demonstrated that no parameter assessed in stable state could predict lung and respiratory muscle function worsening during exacerbation.

As suggested above, the authors should have mentioned total doses of corticosteroids and neuromuscular blocking agents used before admission into the RICU, as they predominately studied patients from ICU. Although the aetiology of muscle weakness in COPD seems multi-factorial [3, 11], drug-induced neuromuscular damage could also be involved. Moreover, respiratory muscle deterioration in these subset of patients, could also be attributed to failure to significantly decrease lung hyperinflation [30] or ventilator-induced diaphragmatic dysfunction [6] since 55% of cases had long ICU stay (from 10 to 45 days).

This study clearly outlines the importance of evaluating respiratory muscle strength in critically ill patients, a subject that is still under investigated.

According with the work of Vitacca *et al* [29] and previous studies [28], monitoring of respiratory muscles is highly recommended after discharge from RICU in patients in whom neuromuscular damage is identified. This can lead to implementation of early muscle retraining and respiratory rehabilitation. In fact, Weiner *et al* [31], in a small randomized controlled trial, demonstrated that corticosteroid induced muscle weakness was preventable by inspiratory muscle training (IMT) using the Threshold ® trainer. From a meta-analysis, it has been suggested that IMT has a role in COPD patients with inspiratory muscle weakness [32].

The results of Vitacca *et al* are of clinical importance because they raise new questions with respect to the management of COPD: Which patients with acute exacerbations of COPD have clinically significant respiratory muscle weakness? What are the main causes and how should we prevent and treat them? Will the length of the hospital stay increase for patients with more severe muscle function impairment?

Although acquired-NMD was first described in patients with severe acute asthma [33], recent studies also suggest a high prevalence (34.6%) in patients intubated due to exacerbation of COPD [34]. In these patients, total doses of corticosteroids, APACHE score at admission and occurrence of sepsis were considered risk factors for acquired-NMD [34]. Systemic Corticosteroids (specially given in repetitive bursts) have been also directly implicated in the reduction of MIP and MEP in spontaneous breathing COPD patients with an acute exacerbation [35].

Moreover, acute exacerbations *per se*, can decrease peripheral muscle force in COPD patients, related to the production of inflammatory markers like IL-8 and IGF-I [36]. In animal models there is also strong evidence suggesting that TNF-α, a common systemic mediator in COPD, can compromise respiratory muscle function [37].

Where do we go from here? We need to know whether there are specific interventions in this setting…

Treatment of Acquired-NMD in the ICU

Unfortunately there is no specific treatment for Acquired-NMD, although different trials have tested recombinant Growth Hormone [38] in this setting. In COPD, this intervention didn't achieve any significant results [39]. However intensive Insulin therapy does seem to reduce significantly the incidence of Acquired NMD [40].

So, efforts should be made to search for new treatments like agents that inhibit free-radical synthesis, which may be of benefit in preventing the development of respiratory muscle dysfunction and respiratory failure in selected patients with infections [5]. Until then, prevention should be our first goal as much of this acquired-NMD is drug-related. Moreover, to avoid ventilator-induced diaphragmatic dysfunction we should restrain the use of Controlled Mechanical Ventilation to the minimum possible.

Moreover, as Vitacca *et al* suggested, there is growing evidence which is supported by a recent meta-analysis, that Respiratory Rehabilitation initiated immediately after acute exacerbations of COPD reduces the risk for hospital admission and mortality [41].

Further studies are needed to confirm these findings, exploring this expanding field of respiratory failure and neuromuscular damage.

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