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EDITORIAL

Breathing more with weaker respiratory muscles in pulmonary arterial hypertension

R. Naeije

Exertional fatigue and dyspnoea limit the daily activities of patients with pulmonary arterial hypertension [1]. These symptoms are usually explained by the inability of the overloaded right ventricle to perfuse the lungs and to adapt systemic oxygen delivery to oxygen demand. Accordingly, pulmonary hypertension patients present with reductions in peak oxygen uptake, anaerobic threshold, oxygen pulse, ventilatory efficiency and 6-min walk distance [2–8]. This ergospirometric profile is strikingly similar to that of congestive heart failure [8–12], further supporting the notion of impaired cardiac output adaptation to peripheral oxygen requirements as the main cause of decreased exercise capacity. However, in both pulmonary hypertension and heart failure, ergospirometric variables and walk distances are better correlated to functional class and prognosis than to haemodynamic function [3, 6, 7, 10–12]. In addition, impaired skeletal muscle function has been repeatedly reported in heart failure, fuelling a ''muscle hypothesis'' relating dyspnoea and fatigue symptoms to skeletal muscle metaboreceptor and/or ergoreceptor reflexes [13]. The muscle hypothesis implies a persistent sympathetic nervous system activation, which has indeed been shown to occur in heart failure [14] and also, more recently, in pulmonary hypertension [15]. Until now, there have been no studies on skeletal muscle function in pulmonary arterial hypertension.

In the present issue of the *European Respiratory Journal*, MEYER *et al.* [16] report data suggesting that respiratory muscle strength is decreased in pulmonary arterial hypertension. In a prospective study on 37 patients with idiopathic pulmonary hypertension, significant decreases in maximal inspiratory (MIP) and expiratory pressures (MEP) were measured, together with an increased mouth occlusion pressure within first 0.1 s of inspiration ($P_{0.1}$), suggesting inadequate muscle effort with regards to central drive. However, decreased respiratory muscle strength did not appear to be related to haemodynamics, blood gases, lung mechanics, exercise capacity, ventilatory efficiency, or even functional class. This is surprising in view of previous studies by MEYER *et al.* [17] and others [18] that relate respiratory muscle weakness to functional class, exercise capacity and prognosis in heart failure, but this may be explained by a type-II error due to limited patient population size. There was also a close correlation between MIP and MEP, as in chronic obstructive pulmonary disease (COPD) [19], while MIP has been reported to be proportionally more decreased than MEP in heart failure [17, 20]. Accordingly, MEYER *et al.* [16] cautiously speculate that decreased MEP and MIP might be part of generalised skeletal muscle weakness in pulmonary hypertension, possibly related to decreased systemic oxygen transport, leading to a variety of consequences, including muscle atrophy, relative increase in easily fatigable type-IIb fibres, decreased oxidative enzymes and mitochondria, abnormal intracellular calcium profiles and decreased phosphocreatine, all of which are previously reported in heart failure. The authors recognise the overloading of the respiratory muscles in chronically hyperventilating pulmonary hypertension patients, but point out that this is of unclear consequence. In heart failure patients, resting respiratory muscles by the application of continuous positive airway pressure ventilation has been reported to improve respiratory muscle strength [18], but so does selective muscle training [21].

The study by MEYER *et al.* [16] is remarkable because it is the first to report a respiratory muscle dysfunction in pulmonary hypertension, but it has limitations, and, as such, calls for additional experiments. Inspection of the standard deviations and numbers reported in tables 2 and 3 suggests that the matching of controls to the patients could have been better, especially with regards to the relatively limited absolute differences in MIP and MEP, and small patient population size. However, this should not have affected the significances of the differences. A more important reservation is that MIP and MEP measurements are volitional and fraught with variability [22]. The authors could have considered a sniff nasal inspiratory pressure (SNIP) confirmatory test. This measurement is also volitional, but easier, more accurate and reproducible, and also more specific to the diaphragm [22]. Nevertheless, the definite diagnosis of respiratory muscle weakness requires nonvolitional tests, such as transdiaphragmatic pressure (P_{di}) measurements during electrical or magnetic phrenic nerve stimulation [22]. In heart failure patients, MIP, SNIP and P_{di} during magnetic phrenic nerve stimulation have all been reported to be decreased compared with controls, but the magnitude of differences were the greatest for MIP and the smallest for nonvolitional P_{di} measurement [20]. In the study by MEYER *et al.* [16], there was a decreased ratio of MIP to $P_{0.1}$, which argues against a major role of decreased central command accounting for the reported decreases in respiratory muscle strength. Conversely, it would have been interesting to add peripheral muscle measurements to see if altered muscle strength might be limited to respiratory muscles in pulmonary hypertension, or,

Correspondence: R. Naeije, Faculty of Medicine, Free University of Brussels, 808 Route de Lennik, Brussels, Belgium. Fax: 32 25554124. E-mail: rnaeije@ulb.ac.be

as in heart failure or COPD, part of a generalised systemic muscle weakness syndrome. A maximum voluntary contraction of the quadriceps, which is quite reproducible in conscious and motivated patients, or, even better, a nonvolitional test of quadriceps strength by magnetic stimulation, can be conveniently undertaken in a respiratory muscle laboratory [22].

How could respiratory muscle weakness contribute to pulmonary hypertension symptomatology? A decrease in respiratory muscle strength may lead to an impairment in ventilatory capacity, although more important alterations than those suggested by the MIP and MEP measurements reported by MEYER *et al.* [16] appear to be necessary [23]. Patients with pulmonary hypertension hyperventilate at rest and at exercise, but present with a markedly lower than normal peak ventilation at exercise [2–8]. Whether this indicates an impaired ventilatory capacity can be ascertained by a maximum voluntary minute ventilation test and measurement of a decreased ventilatory reserve, which, to our knowledge, has not been done in pulmonary hypertension. However, a ventilatory limitation to exercise in pulmonary hypertension is unlikely because of typical resting and exercise hypocapnia, indicating increased ventilation out of proportion to carbon dioxide production [4, 6], and increased exercise capacity with treatments that decrease pulmonary vascular resistance [24].

Alternatively, a decreased respiratory muscle strength could reflect a generalised skeletal muscle weakness, as repeatedly reported in heart failure [13]. Deconditioning is a well-recognised cause *per se* of decreased aerobic capacity, early lactic acidosis and exertional dyspnoea. Although yet unreported, a skeletal muscle weakness is likely in pulmonary hypertension because of deconditioning and cardiac output limitation, as in heart failure. In addition to peripheral muscle strength measurements, it would be interesting to show that the addition of an arm to maximal leg exercise produces a further increase in peak oxygen uptake in pulmonary hypertension, as has been reported in heart failure [25]. Such an experiment would be proof of the concept of skeletal muscle rather than cardiac output limitation to peak or maximum oxygen uptake.

The muscle hypothesis implies skeletal muscle weakness-related activation of ergoreceptors and metaboreceptors, resulting in sympathetic nervous system activation and increased chemosensitivity [13]. Patients with heart failure hyperventilate at exercise because of increased carbon dioxide output relative to oxygen uptake, owing to bicarbonate buffering of lactic acid, and altered ventilation/perfusion matching with increased dead space [9], but also because of increased chemoreceptor gain and ergoreceptor drive in skeletal muscle [12, 13]. Patients with pulmonary hypertension present with even higher ventilatory equivalents at exercise, but, somewhat surprisingly, careful multiple inert gas-elimination technique studies show relatively well-preserved ventilation/perfusion distributions with normal dead space, at rest as well as during exercise [26–28]. Thus, contrary to heart failure, increased dead space does not seem to contribute to increased ventilation in pulmonary hypertension. Therefore, it appears that in pulmonary hypertension more than in heart failure, hyperventilation is essentially related to increased chemosensitivity and sympathetic nervous activation. Additional experiments, including microneurographic measurements, ventilatory responses to hypoxia and hypercapnia, and measurements of ventilatory variables at exercise, will be necessary to show whether hyperventilation might be nothing more than neurohumoral activation in pulmonary hypertension.

In conclusion, MEYER *et al.* [16] are to be commended, not only for the originality and the quality of their findings, but also for calling attention to pulmonary arterial hypertension as a systemic disease affecting all the components of oxygen transport from the inspired air to muscle mitochondria. Their report will stimulate much needed additional research on skeletal muscle function, and humoral and neural feedback control systems, for a better understanding of the mechanisms accounting for the daily suffering of breathless and fatigued pulmonary hypertension patients.

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