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Respiratory muscle weakness in patients with heart failure: time to make it a standard clinical marker and a need for novel therapeutic interventions?

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Dysfunction of the respiratory muscles (particularly the diaphragm) can compromise ventilation, pulmonary gas exchange, and oxygen delivery to the tissues. This is especially true for patients with heart failure (HF), where a loss in respiratory muscle strength and endurance capacity is common [1-4]. Inspiratory muscle weakness in HF causes heightened breathlessness, exertional intolerance, and reduces health-related quality-of-life [5-7]. The clinical importance of respiratory muscle weakness has also been clearly demonstrated. For example, Meyer et al. [5] reported that maximal inspiratory mouth pressure (MIP) is a strong predictor of survival in patients with HF, and in doing so were the first to highlight reduced inspiratory muscle strength as a novel, independent predictor of prognosis in these patients.

In this issue of Journal of Cardiac Failure, Miyagi and colleagues [8] provide further evidence supporting the clinical significance of diaphragm dysfunction in patients with HF. In a detailed, retrospective study, the authors obtained ultrasonography derived measures of diaphragm muscle thickness in 77 patients (final sample size) hospitalised with a primary diagnosis of HF. Proposing that diaphragm thickness at total lung capacity ("DT-insp") reflects both muscle mass and contractility (i.e. a comprehensive indicator of diaphragm function), it was found that 44% of patients presented with diaphragm dysfunction (DT-insp < 4.0 mm). Intriguingly, compared to 'normal' patients (DT-insp ≥ 4.0 mm), those classified as having diaphragm dysfunction were generally older with higher values of left ventricular ejection fraction (>55%). Indeed, over half of the patients defined as having impaired diaphragm function were HF patients with a preserved ejection fraction (HFpEF), which begs the question: is the pathophysiological development of respiratory muscle dysfunction/weakness particularly prevalent in this distinct clinical syndrome? [9]. Perhaps unsurprisingly, patients with impaired diaphragm function also had worse lung function (vital capacity ~0.4 L lower) and lower MIP (~48 vs. 62 cmH_2O) compared to patients with preserved diaphragm function. Importantly, lower DT-insp was associated with a significant impairment in 6-minute walk distance independent of the presence of dynapenia (i.e. limb muscle weakness unrelated to neurologic or muscular disease) in the patient cohort. In combination, the aforementioned findings suggest that diaphragm thickness may represent a functional index of inspiratory muscle weakness and independently predict exertional limitation in HF. So, given its functional importance and prognostic significance, we ask two questions: 1) should inspiratory muscle dysfunction and/or weakness now be assessed as standard clinical routine; and 2) should future research target the identification of novel interventions to combat respiratory muscle dysfunction to improve short- and long-term outcomes in patients with HF?

To answer our first question; Miyagi et al. [8] evaluate inspiratory muscle function using spirometry and diaphragm muscle ultrasound routinely as part of the standard rehabilitation program for HF patients hospitalised at their facility. However, in our experience, the use of ultrasound to assess inspiratory muscle function is far from standard practice in the vast majority of clinics. In addition, the examination of diaphragm muscle thickness using ultrasound requires in-depth expert training, is time consuming, and relies upon highly specialised (and typically very expensive) equipment. Perhaps more importantly, the definition of impaired diaphragm function presented (i.e. DT-insp < 4.0 mm) seems somewhat arbitrary and potentially rather severe. Indeed, a recent report in healthy humans suggested a lower limit of normal for diaphragm thickness at functional residual capacity and at total lung capacity of 1.5 mm and 1.8 mm, respectively [10]. These considerations, combined with a relative lack of normal reference values for diaphragm thickness in the general population, likely limit the utility of ultrasonography to assess diaphragm dysfunction as standard in the clinical setting. By contrast, the measurement of MIP is non-invasive, straightforward, quick and cost-effective. Despite its dependence upon patient voluntary effort, MIP can provide an accurate indication of the presence and severity of inspiratory muscle weakness when performed in line with current recommendations and expressed relative to normative values [11, 12]. As such, if inspiratory muscle dysfunction and/or weakness is to be assessed as standard clinical routine, we propose that the measurement of MIP represents the most feasible option.

To answer our second question; the data presented by Miyagi et al. [8] provide robust support for implementing therapeutic interventions designed to abate the decline in inspiratory muscle strength in HF patients. Specific inspiratory muscle training has been shown to improve functional indices, reduce symptoms, and decrease hospital readmissions in HF patients [13]. As Miyagi et al. [8] astutely suggested, one mechanism of action for any improvement in exercise capacity following inspiratory muscle training may be through a ‘blunting’ of the respiratory muscle metaboreflex, such that the fraction of cardiac output required by the inspiratory muscles and the reflex vasoconstrictive effects on the limb muscles (secondary to the release of fatigue-induced metabolites from the inspiratory muscles) during exercise would be reduced [14]. While inspiratory muscle training has been recognized as a potential treatment strategy to improve exercise tolerance in HF, it does little to identify the underlying cause of inspiratory muscle dysfunction and/or weakness in these patients.

At the cellular level, most evidence from experimental models has confirmed diaphragm dysfunction in HF is characterized by an increase in reactive oxygen species that act to impair excitation-contraction coupling, which is paralleled by an upregulation in signalling pathways related to atrophy (e.g., ubiquitin proteasome pathway). However, most of these conclusions

have been drawn from our classic HF phenotype. The recent study by Miyagi et al. [8] clearly highlights that more data are urgently needed in relation to HFpEF. We have confirmed that rats with HFpEF similarly demonstrate significant impairments to contractile function in isolated diaphragm fibers [15, 16], with impaired mitochondrial complex I function appearing as one key mechanism. Importantly, this was attenuated by endurance exercise training [16]. We have also revealed that diaphragm weakness in mice with cardiac failure was overcome in vivo following treatment with a small-molecule inhibitor targeting the E3 ligase MuRF1 (i.e. a key step in the atrophy pathway) [17]. Collectively, therefore, these recent data provide encouraging evidence that it is possible to prevent diaphragm dysfunction in HF by in vivo drug treatment in addition to exercise training. However, identifying further underlying cellular mechanisms should remain a key target for future research.

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