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

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

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47 In this issue of *Journal of Cardiac Failure*, Miyagi and colleagues [8] provide further evidence
48 supporting the clinical significance of diaphragm dysfunction in patients with HF. In a detailed,
49 retrospective study, the authors obtained ultrasonography derived measures of diaphragm
50 muscle thickness in 77 patients (*final sample size*) hospitalised with a primary diagnosis of
51 HF. Proposing that diaphragm thickness at total lung capacity (“DT-insp”) reflects both muscle
52 mass and contractility (*i.e. a comprehensive indicator of diaphragm function*), it was found that
53 44% of patients presented with diaphragm dysfunction (DT-insp < 4.0 mm). Intriguingly,
54 compared to ‘normal’ patients (DT-insp ≥ 4.0 mm), those classified as having diaphragm
55 dysfunction were generally older with higher values of left ventricular ejection fraction (>55%).
56 Indeed, over half of the patients defined as having impaired diaphragm function were HF
57 patients with a preserved ejection fraction (HFpEF), which begs the question: is the
58 pathophysiological development of respiratory muscle dysfunction/weakness particularly
59 prevalent in this distinct clinical syndrome? [9]. Perhaps unsurprisingly, patients with impaired
60 diaphragm function also had worse lung function (*vital capacity ~0.4 L lower*) and lower MIP
61 (~48 vs. 62 cmH₂O) compared to patients with preserved diaphragm function. Importantly,
62 lower DT-insp was associated with a significant impairment in 6-minute walk distance
63 independent of the presence of dynapenia (*i.e. limb muscle weakness unrelated to neurologic*
64 *or muscular disease*) in the patient cohort. In combination, the aforementioned findings
65 suggest that diaphragm thickness may represent a functional index of inspiratory muscle
66 weakness and independently predict exertional limitation in HF. So, given its functional
67 importance and prognostic significance, we ask two questions: 1) should inspiratory muscle
68 dysfunction and/or weakness now be assessed as standard clinical routine; and 2) should
69 future research target the identification of novel interventions to combat respiratory muscle
70 dysfunction to improve short- and long-term outcomes in patients with HF?

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

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

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

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

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REFERENCES

- 147
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149 [1] Ambrosino N, Opasich C, Crotti P, Cobelli F, Tavazzi L, Rampulla C. Breathing pattern,
150 ventilatory drive and respiratory muscle strength in patients with chronic heart failure. *Eur*
151 *Respir J.* 1994;7:17-22.
- 152 [2] Lindsay DC, Lovegrove CA, Dunn MJ, Bennett JG, Pepper JR, Yacoub MH, et al.
153 Histological abnormalities of muscle from limb, thorax and diaphragm in chronic heart failure.
154 *Eur Heart J.* 1996;17:1239-50.
- 155 [3] Mancini DM, Henson D, LaManca J, Levine S. Respiratory muscle function and dyspnea
156 in patients with chronic congestive heart failure. *Circulation.* 1992;86:909-18.
- 157 [4] McParland C, Krishnan B, Wang Y, Gallagher CG. Inspiratory muscle weakness and
158 dyspnea in chronic heart failure. *Am Rev Respir Dis.* 1992;146:467-72.
- 159 [5] Meyer FJ, Borst MM, Zugck C, Kirschke A, Schellberg D, Kubler W, et al. Respiratory
160 muscle dysfunction in congestive heart failure: clinical correlation and prognostic significance.
161 *Circulation.* 2001;103:2153-8.
- 162 [6] Ribeiro JP, Chiappa GR, Neder JA, Frankenstein L. Respiratory muscle function and
163 exercise intolerance in heart failure. *Curr Heart Fail Rep.* 2009;6:95-101.
- 164 [7] van der Palen J, Rea TD, Manolio TA, Lumley T, Newman AB, Tracy RP, et al. Respiratory
165 muscle strength and the risk of incident cardiovascular events. *Thorax.* 2004;59:1063-7.
- 166 [8] Miyagi M, Kinugasa Y, Sota T, Yamada K, Ishisugi T, Hirai M, et al. Diaphragm Muscle
167 Dysfunction in Patients With Heart Failure. *J Card Fail.* 2017.
- 168 [9] Yamada K, Kinugasa Y, Sota T, Miyagi M, Sugihara S, Kato M, et al. Inspiratory Muscle
169 Weakness is Associated With Exercise Intolerance in Patients With Heart Failure With
170 Preserved Ejection Fraction: A Preliminary Study. *J Card Fail.* 2016;22:38-47.
- 171 [10] Boon AJ, Harper CJ, Ghahfarokhi LS, Strommen JA, Watson JC, Sorenson EJ. Two-
172 dimensional ultrasound imaging of the diaphragm: quantitative values in normal subjects.
173 *Muscle Nerve.* 2013;47:884-9.
- 174 [11] American Thoracic Society/European Respiratory S. ATS/ERS Statement on respiratory
175 muscle testing. *Am J Respir Crit Care Med.* 2002;166:518-624.
- 176 [12] Sclauser Pessoa IM, Franco Parreira V, Fregonezi GA, Sheel AW, Chung F, Reid WD.
177 Reference values for maximal inspiratory pressure: a systematic review. *Can Respir J.*
178 2014;21:43-50.
- 179 [13] Cahalin LP, Arena RA. Breathing exercises and inspiratory muscle training in heart failure.
180 *Heart Fail Clin.* 2015;11:149-72.
- 181 [14] Chiappa GR, Roseguini BT, Vieira PJ, Alves CN, Tavares A, Winkelmann ER, et al.
182 Inspiratory muscle training improves blood flow to resting and exercising limbs in patients with
183 chronic heart failure. *J Am Coll Cardiol.* 2008;51:1663-71.

184 [15] Bowen TS, Brauer D, Rolim NPL, Baekkerud FH, Kricke A, Ormbostad Berre AM, et al.
185 Exercise Training Reveals Inflexibility of the Diaphragm in an Animal Model of Patients With
186 Obesity-Driven Heart Failure With a Preserved Ejection Fraction. *J Am Heart Assoc.* 2017;6.
187 [16] Bowen TS, Rolim NP, Fischer T, Baekkerud FH, Medeiros A, Werner S, et al. Heart failure
188 with preserved ejection fraction induces molecular, mitochondrial, histological, and functional
189 alterations in rat respiratory and limb skeletal muscle. *Eur J Heart Fail.* 2015;17:263-72.
190 [17] Bowen TS, Adams V, Werner S, Fischer T, Vinke P, Brogger MN, et al. Small-molecule
191 inhibition of MuRF1 attenuates skeletal muscle atrophy and dysfunction in cardiac cachexia.
192 *J Cachexia Sarcopenia Muscle.* 2017;8:939-53.
193