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PERSPECTIVES

Unpreserved muscle function in heart failure with preserved ejection fraction: Diffusion limitations defused

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Fifty percent of all heart failure patients are diagnosed with heart failure with preserved ejection fraction (HFpEF), of whom 80% are obese (Shah *et al.* 2016). Muscle dysfunction is a major contributor to the exercise intolerance in patients with HFpEF (Haykowsky & Kitzman, 2014) and many clinical trials fail to show beneficial outcomes with cardiac-oriented medication (Shah *et al.* 2016). One of the outstanding questions concerns the cause of the skeletal muscle dysfunction during HFpEF. In this issue of *The Journal of Physiology*, Espino-Gonzalez *et al.* (2021) investigated locomotor and respiratory muscle morphology, contractile function and blood flow in obese rats with HFpEF to address this question comprehensively.

Although hypertrophy of the diaphragm of obese rats with HFpEF was also seen in obese rodents, the lower mass of hind limb muscles in rats with HFpEF compared to that in lean control rats contrasts with the higher hind limb muscle mass in obese rodents (Messa *et al.* 2020). This suggests that the loss of hind limb muscle mass is a result of systemic changes with HFpEF rather than obesity. The loss of muscle mass was accompanied by proportional reductions in twitch and maximal tetanic force, and an earlier onset of muscle fatigue during force-matched repeated contractions. This was the case, irrespective of whether the muscle was stimulated via the nerve or directly, indicating that the neuro-muscular interaction, force generating

capacity and fatigue resistance of the remaining muscle tissue are preserved during HFpEF.

Espino-Gonzalez *et al.* (2021) did observe, however, that muscle quality was not entirely preserved because the maximal power per unit muscle mass was lower in HFpEF. It would be expected that such a reduction in the face of a maintained force generating capacity must be the result of a lower maximal shortening velocity of the muscle because power is the product of force and velocity. Surprisingly, however, the maximal shortening velocity was not altered. Yet, it was seen that, at any proportion of maximal isometric force, the muscles of the animals with HFpEF had a lower shortening velocity. This can only be explained by an increased curvature of the force-velocity relationship, something rarely considered, yet having potentially a significant impact on the power that a muscle can generate. An increase in curvature may increase the efficiency of power generation at the expense of maximal power (Woledge, 1968). This intriguing observation may thus be an adaptation to the impaired oxygen delivery to the exercising muscles in rats with HFpEF. The cause of the increase in curvature remains elusive, however, and is an area for further investigation.

A major contentious issue is whether (oxygen) diffusion limitation contributes to the skeletal muscle dysfunction in HFpEF. Espino-Gonzalez *et al.* (2021) used morphological parameters of local capillary supply and tissue oxygenation modelling to address this question comprehensively. At first glance, the lower capillary to fibre ratio, indicating capillary rarefaction, lends support to the idea that diffusion limitation contributes to the muscle dysfunction during HFpEF. However, concomitantly, the fibres atrophy proportionally more than the loss of capillaries, resulting in a higher capillary density that facilitates, rather than limits, diffusion. That there was no problem with oxygen diffusion in the muscles of animals with HFpEF was confirmed by their modelling of tissue oxygenation during exercise, which revealed similar and, if anything, even better oxygenation in HFpEF. The data in this paper thus provide ample evidence that diffusion limitations do not underlie the muscle dysfunction during HFpEF.

One thing to note is that the blood flow following a series of contractions was severely diminished in rats with obese HFpEF ($\sim 3 \text{ mL min}^{-1}$ vs. $\sim 5.2 \text{ mL min}^{-1}$). This demonstrates that at least one factor contributing to the muscle dysfunction in HFpEF is a diminished oxygen delivery during exercise.

In conclusion, the comprehensive study by Espino-Gonzalez *et al.* (2021) has provided strong evidence that muscle dysfunction during HFpEF is not attributable to diffusion limitations. Rather, it is almost entirely attributable to muscle atrophy with some contributions of a lower oxygen delivery. Another unexpected, and often ignored, factor is the increased curvature of the force-velocity relationship that results in a lower power generating capacity that exceeds that expected from the loss of muscle mass. This is an intriguing observation that deserves further research.

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Additional information

Competing interests

No competing interests declared.

Author contributions

Paul Hendrickse and Hans Degens were responsible for the conception and design of the work, as well as the acquisition, analysis and interpretation of data. Both authors drafted the manuscript and revised it critically for important

intellectual content. Both authors approved the final version of the manuscript submitted for publication and agree to be accountable for all aspects of the work.

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