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Authors: Rehan Junejo

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Author: Rehan T Junejo

Liverpool Centre for Cardiovascular Science, University of Liverpool, and Liverpool Heart & Chest Hospital, Liverpool, UK

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Address for correspondence:

Rehan T Junejo, PhD

Liverpool Centre for Cardiovascular Science, adjacent out-patient department, Liverpool Heart and Chest Hospital, Thomas Drive, Liverpool. L14 3PE.

Email: r.junejo@liverpool.ac.uk

Thinly myelinated group III and unmyelinated group IV skeletal muscle afferents are important tools in the armoury of homeostasis. Activated by mechanical and/or metabolic stimuli, they are part responsible for reflex increases in cardiac and peripheral sympathetic output during exercise. Their activity helps maintain a balance between vasoconstriction and vasodilatation, respectively preventing unsuitable increases in local vascular resistance and generalised hypotension. However, aberrant skeletal muscle afferent activation has been implicated in the genesis of exercise intolerance in heart failure (HF) patients. Therefore, in a recent issue of *Journal of Physiology*, Smith *et al.* (2020) scrutinised the contribution of feedback afferents on cardiac and peripheral hemodynamics to determine which mechanisms are responsible for reduced exercise capacity in HF.

Eleven (61±9 years) reduced ejection fraction HF patients performed incremental cycling exercise until volitional fatigue with and without 50 µg lumber intrathecal (subarachnoid) fentanyl (µ-opioid receptor agonist) injection; participants were asked to remain seated to prevent cephalic migration of fentanyl. Resting cardiovascular, ventilatory, and blood gas parameters were not affected by fentanyl suggesting minimal contribution of muscle afferents to resting cardiorespiratory parameters in HF. Crucially, fentanyl improved peak workload, peak oxygen (O_2) uptake (VO_2), and minute ventilation. Improved exercise capacity was accompanied by lower venous (femoral) O_2 content, O_2 saturation, and pH alongside increased venous CO_2 content at peak workload, suggesting muscle afferent overactivity is an important contributor to VO_2 and exercise capacity limitations in HF patients. Systolic, diastolic, and mean blood pressure (BP) at peak workload were lower. Importantly, afferent blockade with fentanyl decreased resistance to stroke volume in HF patients subsequently increasing stroke volume and cardiac output. When matched for peak placebo workload, intrathecal fentanyl was again shown to improve stroke volume and lower heart rate in HF patients. Systolic, diastolic, and mean BP were all lower while leg vascular conductance was improved. Collectively, these novel findings indicate exaggerated locomotor afferent activity constrains VO_2 and exercise capacity / tolerance by restricting central / cardiac hemodynamic contributions in HF patients.

Amann *et al.* (2014) used intrathecal fentanyl with a one-leg knee extensor model to show afferent blockade reverses the inappropriate increases in noradrenaline spill-over and vascular resistance to improve tissue perfusion in HF patients. Moreover,

this increased leg VO_2 and lowered the ratings of perceived exertion. Exercise induced increases in cardiac output and stroke volume were found to be attenuated with fentanyl, suggesting positive / necessary inotropic contributions of muscle afferents to perfusion dynamics in HF. Using two-leg cycling until fatigue, Smith *et al.* (2020) also show aberrant afferent activity contributes to exercise intolerance in HF. However importantly, their novel findings show that exercise intolerance in HF is a direct consequence of a decrease in stroke volume, which itself is a function of inappropriately exaggerated vascular resistance. This recent work, in agreement with numerous previous findings, also suggests pressor responses in HF are primarily maintained by a vasoconstrictor sympathetic influence that can negatively impact cardiac inotropic activity. The conflicting inotropic / cardiac output contributions of muscle afferents between Amann *et al.* (2014) and Smith *et al.* (2020) may reflect discrepant exercise models, which may be differentially affecting peripheral sympathetic activity, cardiac autonomic function, baroreceptor function, renal and/or splanchnic redistribution of perfusion. Indeed, when matched for workload with and without fentanyl, both studies show divergent exercise induced inotropic and chronotropic effects. Moreover, it is also possible that the single-leg knee extensor exercise simply failed to significantly increase peripheral resistance to an extent that could negatively impact cardiac afterload and stroke volume. Nonetheless, in accord, Amann *et al.* (2014) and Smith *et al.* (2020), both show that afferent blockade in HF patients with fentanyl increases vascular conductance of the exercising muscles which enhances their VO_2 and general exercise capacity / tolerance. Therefore, inadequate muscle perfusion and O_2 transport, driven by amplified peripheral resistance and/or cardiac insufficiency, may be the “principal” determinant of exercise intolerance in HF.

As reviewed by Vianna and Fisher (2019), muscle atrophy and shift towards glycolytic fibres are important aspects of the “muscle hypothesis of HF*”*. Besides the fore mentioned discussion on Smith *et al.* (2020), their results also suggest that the direct role of muscle atrophy and a fibre-type switch may be of less importance to exercise intolerance in HF compared to centrally and peripherally mediated reductions in nutritive muscle perfusion. Separately, mechanical cardiac dysfunction may pre-sensitise feedback afferents due to muscle under-perfusion, hypoxia and/or ischemia. Normally, exercise leads to intra- and extravascular release of vasodilator

metabolites to cause functional hyperaemia and sympatholysis. However, some of the vasoactive metabolites also stimulate and sensitize group III and IV muscle afferents. It is possible that the dysfunctional activity of vasoactive metabolites and/or their receptors alongside pre-sensitised muscle afferents is partly to blame for inadequate muscle perfusion. Additionally, patient inactivity may also be adding to the muscle perfusion and sympatholysis limitations. In agreement, improvements in VO_2 and exercise tolerance have been observed with cardiac resynchronisation therapy, which are further enhanced by structured exercise therapy (Conraads *et al.*, 2007).

Design considerations

Fentanyl is a selective μ-opioid receptor agonist and fails to influence δ-opioid receptors. Further, at the administered dosage fentanyl probably only partially disrupts μ-opioid signalling. Therefore, the results described reflect partial / incomplete afferent blockade, enhancing the importance of recognising aberrant restrictive afferent influences on nutritive muscle / tissue perfusion during exercise in HF patients. Observations of Smith *et al.* (2020) reflect combined attenuation of group III and group IV afferent activity; magnitude of their individual contributions remains unknown and is an area of active exploration / discussion. Most HF patients have comorbidities which are independently associated with exercise intolerance. Acknowledging the group homogeneity, Smith *et al.* (2020) do not report any specific comorbidities in their subjects. Some of their participants are on anti-hypertensive medications and the reported body-mass-index is also somewhat higher than normal. Therefore, possible additional influence of hypertension, diabetes, and/or metabolic diseases cannot be excluded from their observations. Lastly, group III and group IV afferents depress motor cortical excitability to restrict motor neurons and locomotor output, at least in young healthy individuals performing cycling time trials (Amann *et al.*, 2020). Paucity of clear information exists regarding the role of central neural fatigue in HF. From the few studies that have attempted to investigate, most have failed to register it as a major contributor whilst one observed significant correlation between muscle fatigability and attenuated surface electromyograph activity. Therefore, exercise intolerance in HF may reflect some motoneuronal output inhibition / central fatigue, which is at least part-reversed with intrathecal fentanyl. This hypothesis and the central neural mechanisms of fatigability in HF warrant

123 further direct exploration. In conclusion, Smith *et al.* (2020) show exercise
124 intolerance in HF is a function of stroke volume constraints due to aberrant
125 vasoconstrictor activity of muscle afferents. Their novel work offers interesting
126 insights and provides direction for many future follow-up studies.

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