

#### Please cite the Published Version

Junejo, Rehan T (2021) Muscle afferent contributions to exercise intolerance in heart failure. The Journal of Physiology, 599 (3). pp. 733-734. ISSN 0022-3751

DOI: https://doi.org/10.1113/jp280757

Publisher: Wiley

Version: Accepted Version

Downloaded from: https://e-space.mmu.ac.uk/626849/

Usage rights: C In Copyright

**Additional Information:** This is an Author Accepted Manuscript of a paper accepted for publication in Journal of Physiology, published by and copyright Wiley.

#### Enquiries:

If you have questions about this document, contact openresearch@mmu.ac.uk. Please include the URL of the record in e-space. If you believe that your, or a third party's rights have been compromised through this document please see our Take Down policy (available from https://www.mmu.ac.uk/library/using-the-library/policies-and-guidelines) The Journal of Physiology

https://jp.msubmit.net

### JP-JC-2020-280757R1

Title: Muscle afferent contributions to exercise intolerance in heart failure

# Authors: Rehan Junejo

#### Author Conflict: No competing interests declared

Author Contribution: Rehan Junejo: Conception or design of the work; Acquisition or analysis or interpretation of data for the work; Drafting the work or revising it critically for important intellectual content; Final approval of the version to be published; Agreement to be accountable for all aspects of the work

# **Running Title:**

# **Dual Publication:** N/a

Funding: N/A: Rehan T Junejo, N/A N/A

1	
2	
3	Muscle afferent contributions to exercise intolerance in heart failure
4	
5	Author: Rehan T Junejo
6	
7 8 9 10	Liverpool Centre for Cardiovascular Science, University of Liverpool, and Liverpool Heart & Chest Hospital, Liverpool, UK
11	Words: 1133
12	Figures: 0
13	
14	Key words:
15 16	Muscle afferents, Exercise intolerance, Muscle Perfusion, Stroke Volume, Heart failure
17	
18	Address for correspondence:
19	Rehan T Junejo, PhD
20 21 22	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
23	

Thinly myelinated group III and unmyelinated group IV skeletal muscle afferents are 24 important tools in the armoury of homeostasis. Activated by mechanical and/or 25 metabolic stimuli, they are part responsible for reflex increases in cardiac and 26 peripheral sympathetic output during exercise. Their activity helps maintain a 27 balance between vasoconstriction and vasodilatation, respectively preventing 28 unsuitable increases in local vascular resistance and generalised hypotension. 29 However, aberrant skeletal muscle afferent activation has been implicated in the 30 genesis of exercise intolerance in heart failure (HF) patients. Therefore, in a recent 31 32 issue of Journal of Physiology, Smith et al. (2020) scrutinised the contribution of feedback afferents on cardiac and peripheral hemodynamics to determine which 33 mechanisms are responsible for reduced exercise capacity in HF. 34

35 Eleven (61±9 years) reduced ejection fraction HF patients performed incremental cycling exercise until volitional fatigue with and without 50 µg lumber intrathecal 36 37 (subarachnoid) fentanyl (µ-opioid receptor agonist) injection; participants were asked to remain seated to prevent cephalic migration of fentanyl. Resting cardiovascular, 38 39 ventilatory, and blood gas parameters were not affected by fentanyl suggesting minimal contribution of muscle afferents to resting cardiorespiratory parameters in 40 HF. Crucially, fentanyl improved peak workload, peak oxygen (O<sub>2</sub>) uptake (VO<sub>2</sub>), and 41 minute ventilation. Improved exercise capacity was accompanied by lower venous 42 (femoral) O<sub>2</sub> content, O<sub>2</sub> saturation, and pH alongside increased venous CO<sub>2</sub> content 43 at peak workload, suggesting muscle afferent overactivity is an important contributor 44 to VO<sub>2</sub> and exercise capacity limitations in HF patients. Systolic, diastolic, and mean 45 blood pressure (BP) at peak workload were lower. Importantly, afferent blockade 46 with fentanyl decreased resistance to stroke volume in HF patients subsequently 47 increasing stroke volume and cardiac output. When matched for peak placebo 48 workload, intrathecal fentanyl was again shown to improve stroke volume and lower 49 50 heart rate in HF patients. Systolic, diastolic, and mean BP were all lower while leg vascular conductance was improved. Collectively, these novel findings indicate 51 exaggerated locomotor afferent activity constrains VO<sub>2</sub> and exercise capacity / 52 tolerance by restricting central / cardiac hemodynamic contributions in HF patients. 53

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

this increased leg VO<sub>2</sub> and lowered the ratings of perceived exertion. Exercise 57 induced increases in cardiac output and stroke volume were found to be attenuated 58 with fentanyl, suggesting positive / necessary inotropic contributions of muscle 59 afferents to perfusion dynamics in HF. Using two-leg cycling until fatigue, Smith et al. 60 (2020) also show aberrant afferent activity contributes to exercise intolerance in HF. 61 However importantly, their novel findings show that exercise intolerance in HF is a 62 direct consequence of a decrease in stroke volume, which itself is a function of 63 inappropriately exaggerated vascular resistance. This recent work, in agreement with 64 65 numerous previous findings, also suggests pressor responses in HF are primarily maintained by a vasoconstrictor sympathetic influence that can negatively impact 66 cardiac inotropic activity. The conflicting inotropic / cardiac output contributions of 67 muscle afferents between Amann et al. (2014) and Smith et al. (2020) may reflect 68 discrepant exercise models, which may be differentially affecting peripheral 69 sympathetic activity, cardiac autonomic function, baroreceptor function, renal and/or 70 splanchnic redistribution of perfusion. Indeed, when matched for workload with and 71 without fentanyl, both studies show divergent exercise induced inotropic and 72 chronotropic effects. Moreover, it is also possible that the single-leg knee extensor 73 74 exercise simply failed to significantly increase peripheral resistance to an extent that could negatively impact cardiac afterload and stroke volume. Nonetheless, in accord, 75 Amann et al. (2014) and Smith et al. (2020), both show that afferent blockade in HF 76 patients with fentanyl increases vascular conductance of the exercising muscles 77 78 which enhances their  $VO_2$  and general exercise capacity / tolerance. Therefore, inadequate muscle perfusion and O<sub>2</sub> transport, driven by amplified peripheral 79 resistance and/or cardiac insufficiency, may be the "principal" determinant of 80 exercise intolerance in HF. 81

As reviewed by Vianna and Fisher (2019), muscle atrophy and shift towards 82 glycolytic fibres are important aspects of the "muscle hypothesis of HF". Besides the 83 fore mentioned discussion on Smith et al. (2020), their results also suggest that the 84 direct role of muscle atrophy and a fibre-type switch may be of less importance to 85 exercise intolerance in HF compared to centrally and peripherally mediated 86 reductions in nutritive muscle perfusion. Separately, mechanical cardiac dysfunction 87 may pre-sensitise feedback afferents due to muscle under-perfusion, hypoxia and/or 88 89 ischemia. Normally, exercise leads to intra- and extravascular release of vasodilator

metabolites to cause functional hyperaemia and sympatholysis. However, some of 90 the vasoactive metabolites also stimulate and sensitize group III and IV muscle 91 afferents. It is possible that the dysfunctional activity of vasoactive metabolites 92 and/or their receptors alongside pre-sensitised muscle afferents is partly to blame for 93 inadequate muscle perfusion. Additionally, patient inactivity may also be adding to 94 the muscle perfusion and sympatholysis limitations. In agreement, improvements in 95 VO<sub>2</sub> and exercise tolerance have been observed with cardiac resynchronisation 96 therapy, which are further enhanced by structured exercise therapy (Conraads et al., 97 98 2007).

99 Design considerations

Fentanyl is a selective  $\mu$ -opioid receptor agonist and fails to influence  $\delta$ -opioid 100 101 receptors. Further, at the administered dosage fentanyl probably only partially disrupts µ-opioid signalling. Therefore, the results described reflect partial / 102 incomplete afferent blockade, enhancing the importance of recognising aberrant 103 restrictive afferent influences on nutritive muscle / tissue perfusion during exercise in 104 HF patients. Observations of Smith et al. (2020) reflect combined attenuation of 105 group III and group IV afferent activity; magnitude of their individual contributions 106 remains unknown and is an area of active exploration / discussion. Most HF patients 107 have comorbidities which are independently associated with exercise intolerance. 108 Acknowledging the group homogeneity, Smith et al. (2020) do not report any specific 109 comorbidities in their subjects. Some of their participants are on anti-hypertensive 110 medications and the reported body-mass-index is also somewhat higher than 111 112 normal. Therefore, possible additional influence of hypertension, diabetes, and/or metabolic diseases cannot be excluded from their observations. Lastly, group III and 113 114 group IV afferents depress motor cortical excitability to restrict motor neurons and locomotor output, at least in young healthy individuals performing cycling time trials 115 (Amann et al., 2020). Paucity of clear information exists regarding the role of central 116 neural fatigue in HF. From the few studies that have attempted to investigate, most 117 have failed to register it as a major contributor whilst one observed significant 118 correlation between muscle fatigability and attenuated surface electromyograph 119 120 activity. Therefore, exercise intolerance in HF may reflect some motoneuronal output inhibition / central fatigue, which is at least part-reversed with intrathecal fentanyl. 121 This hypothesis and the central neural mechanisms of fatigability in HF warrant 122

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

127	Competing Interests: None.
128	
129	Author Contributions: Sole author.
130	
131	Funding: Not applicable.
132	
133	Acknowledgements: When the article was commissioned and reviewed, author
134	was a postdoctoral research fellow in the Liverpool Centre for Cardiovascular
135	Science, Liverpool, UK. He has since accepted an academic position in Manchester
136	Metropolitan University, Manchester, UK and may have started when the article is
137	published. Associate Professor James P. Fisher, University of Auckland, is
138	acknowledged for helpful discussion and insightful feedback on this article.
139	

140	References
141	
142 143 144	Amann M, Venturelli M, Ives SJ, Morgan DE, Gmelch B, Witman MAH, Jonathan Groot H, Walter Wray D, Stehlik J & Richardson RS (2014). Group III/IV muscle afferents impair limb blood in patients with chronic heart failure. <i>International Journal of Cardiology</i> <b>174,</b> 368-375.
145 146 147 148	Amann M, Wan H-Y, Thurston TS, Georgescu VP & Weavil JC (2020). On the Influence of Group III/IV Muscle Afferent Feedback on Endurance Exercise Performance. <i>Exercise and Sport Sciences</i> <i>Reviews</i> <b>48,</b> 209-216.
149 150 151 152 153	Conraads VMA, Vanderheyden M, Paelinck B, Verstreken S, Blankoff I, Miljoen H, Sutter JD & Beckers P (2007). The effect of endurance training on exercise capacity following cardiac resynchronization therapy in chronic heart failure patients: a pilot trial. <i>European Journal of Cardiovascular Prevention and Rehabilitation</i> <b>14</b> , 99-106.
154 155 156 157	Smith JR, Joyner MJ, Curry TB, Borlaug BA, Keller-Ross ML, Van Iterson EH & Olson TP (2020). Locomotor muscle group III/IV afferents constrain stroke volume and contribute to exercise intolerance in human heart failure. <i>The Journal of Physiology</i> <b>n/a</b> .
158 159 160	Vianna LC & Fisher JP (2019). Reflex control of the cardiovascular system during exercise in disease. <i>Current Opinion in Physiology</i> <b>10,</b> 110-117.
161	
162	