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**Muscle afferent contributions to exercise intolerance in heart failure**

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

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

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

57 this increased leg  $\text{VO}_2$  and lowered the ratings of perceived exertion. Exercise  
58 induced increases in cardiac output and stroke volume were found to be attenuated  
59 with fentanyl, suggesting positive / necessary inotropic contributions of muscle  
60 afferents to perfusion dynamics in HF. Using two-leg cycling until fatigue, Smith *et al.*  
61 (2020) also show aberrant afferent activity contributes to exercise intolerance in HF.  
62 However importantly, their novel findings show that exercise intolerance in HF is a  
63 direct consequence of a decrease in stroke volume, which itself is a function of  
64 inappropriately exaggerated vascular resistance. This recent work, in agreement with  
65 numerous previous findings, also suggests pressor responses in HF are primarily  
66 maintained by a vasoconstrictor sympathetic influence that can negatively impact  
67 cardiac inotropic activity. The conflicting inotropic / cardiac output contributions of  
68 muscle afferents between Amann *et al.* (2014) and Smith *et al.* (2020) may reflect  
69 discrepant exercise models, which may be differentially affecting peripheral  
70 sympathetic activity, cardiac autonomic function, baroreceptor function, renal and/or  
71 splanchnic redistribution of perfusion. Indeed, when matched for workload with and  
72 without fentanyl, both studies show divergent exercise induced inotropic and  
73 chronotropic effects. Moreover, it is also possible that the single-leg knee extensor  
74 exercise simply failed to significantly increase peripheral resistance to an extent that  
75 could negatively impact cardiac afterload and stroke volume. Nonetheless, in accord,  
76 Amann *et al.* (2014) and Smith *et al.* (2020), both show that afferent blockade in HF  
77 patients with fentanyl increases vascular conductance of the exercising muscles  
78 which enhances their  $\text{VO}_2$  and general exercise capacity / tolerance. Therefore,  
79 inadequate muscle perfusion and  $\text{O}_2$  transport, driven by amplified peripheral  
80 resistance and/or cardiac insufficiency, may be the “principal” determinant of  
81 exercise intolerance in HF.

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

90 metabolites to cause functional hyperaemia and sympatholysis. However, some of  
91 the vasoactive metabolites also stimulate and sensitize group III and IV muscle  
92 afferents. It is possible that the dysfunctional activity of vasoactive metabolites  
93 and/or their receptors alongside pre-sensitised muscle afferents is partly to blame for  
94 inadequate muscle perfusion. Additionally, patient inactivity may also be adding to  
95 the muscle perfusion and sympatholysis limitations. In agreement, improvements in  
96  $VO_2$  and exercise tolerance have been observed with cardiac resynchronisation  
97 therapy, which are further enhanced by structured exercise therapy (Conraads *et al.*,  
98 2007).

### 99 Design considerations

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