The Journal of Physiology

JOURNAL CLUB

The role of muscle sympathetic nerve activity in limiting exercise capacity in heart failure

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Elevated resting muscle sympathetic nerve activity (MSNA) and a marked reduction in exercise tolerance are two important outcomes in heart failure with reduced ejection fraction (HFrEF). The release of noradrenaline as a result of increased sympathetic activity stimulates vaso-constriction in peripheral blood vessels, restricting muscle perfusion. Physical activity in patients with heart failure further stimulates the activation of central and peripheral sympathetic tone, exacerbating the adverse effects on the already compromised heart. Therefore, this neurogenic response is believed to be the key factor underlying the limited exercise capacity observed in patients with HFrEF. Previous studies investigating the effects of exercise on MSNA have only been carried out involving handgrip exercise, which does not reflect the true exercise capacity of a patient with heart failure. Consequently, even though an inverse relationship between resting MSNA and exercise capacity has been documented by previous studies, future study was warranted to provide more compelling evidence that will further validate the role of MSNA in limiting exercise capacity in heart failure.

In a recent prospective cohort study led by Notarius *et al.* (2015), 16 individuals with HFrEF (history of ischaemic or non-ischaemic cardiomyopathy) and 13 healthy age-matched controls were recruited to assess and determine the changes in sympathetic conduction in the fibular nerve during dynamic leg exercise. The authors aimed to determine the relationship between exercise capacity and MSNA responses during dynamic leg exercise in HFrEF. Notarius *et al.* (2015) were the first to investigate changes in MSNA response during leg exercise. Their exercise protocol involved single-legged cycling exercise while the other leg remained stationary to measure changes in sympathetic conduction. The study's authors revealed that the heart failure cohort had a significant relative increase in MSNA when compared to healthy controls. This observation further supports the role of MSNA responses as a neurogenic determinant of exercise capacity in patients with HFrEF. The potential implications revolve around whether this increase in MSNA can be corrected by improving heart function through regular physical activity.

Guyatt *et al.* (1985) have shown that the 6 min walking test is a more efficient and accurate approach to assess maximal oxygen consumption in individuals with heart failure. Nevertheless, Notarius *et al.* should not be penalized for using the cycle ergometer to assess participants' maximum consumption of oxygen in milliliters per kilogram every minute ($\dot{V}_{O_2max}$) and thus exercise capacity. The approach they used enabled a direct comparison between the patients with heart failure and their age-matched healthy controls as well as improving the feasibility of MSNA measurements. This also provides consistency throughout the study in results and analysing changes in MSNA compared to baseline. However, peripheral muscle limitations due to an elevated MSNA and lack of familiarization with the exercise protocol in patients with HFrEF may have limited their true exercise capacity to a greater extent.

Although the authors successfully assessed the role of MSNA responses as being one of the key determinants in measuring exercise capacity in patients with HFrEF, the results should be viewed in light of certain confounding factors. Patients remained on a variety of prescribed heart failure medications, including the use of combinations of heart failure medications. At the time of the study, patients were reported to be on β-adrenergic receptor antagonists (100%), aspirin (88%), diuretics (75%), angiotensin-converting-enzyme (ACE) inhibitors (62%) and anticoagulants (44%). Interestingly, Grassi *et al.* (1997) were able to quantify the extent to which ACE inhibitors reduce the sympathetic outflow in patients with heart failure. They demonstrated that ACE inhibitor treatment elicited significant decreases in MSNA measurements by an average of 30.5% and thus attenuates the adverse effects imposed by elevated sympathetic activation in patients with heart failure. As a result, many of the quantitative values are potentially underestimated. In addition, the healthy controls are explicitly not on any medications therefore demonstrating that medication(s) being taken by study subjects is a significant variable that was not controlled for.

Furthermore, the differential effects of different types of β-blockers were shown by Metra *et al.* (2000) in patients with heart failure. β-Blockers were shown to differ significantly in their clinical efficacy as well as chemical properties. Patients treated with metoprolol had a significantly higher maximal exercise capacity and increased exercise tolerance than patients treated with carvedilol. However, patients treated with carvedilol showed greater improvements in cardiac performance with a significant increase in left ventricular ejection fraction and reduced left ventricular chamber size. Hence, these differential clinical effects between the two treatments contribute largely to the background variability of the variable of interest being investigated in the recently published study.

Although Notarius *et al.* (2015) have compared heart failure subjects with healthy age-matched controls, they had only used the mean age to determine if there was a lack of significance in age difference. This is problematic as they state the age range within the heart failure group to be 42–79 years (difference of 37 years), while that of the healthy control group was 48–69 years (difference of 21 years). The healthy control group has a narrower age range (21 years). We are also not given the age distribution and are left unsure if there is a normal, even, or bimodal distribution. This information is significant as MSNA values differ between age groups and respond to exercise differently based on age as well. If more individuals are skewed toward one age group than another this would render the data not truly age-matched.

Finally, the authors had test subjects perform the single-legged cycling exercise at 50% of their peak $\dot{V}_{O_2}$, which was

 DOI: 10.1113/JP270345

determined via a two-legged cycling ergometry protocol. However, Ogita *et al.* (2000) had demonstrated that peak $\dot{V}_{O_2}$ values are significantly greater in those who performed a two-legged cycling protocol as opposed to the single-legged protocol. Specifically, people who performed the two-legged cycling exercise achieved a work rate of 324 W in conjunction with their peak $\dot{V}_{O_2}$ as opposed to a work rate of 204 W attained by those who performed the one-legged cycling exercise. This accounts for an approximately one-and-a-half times greater work load during the single-legged exercise. As a result, when subjects performed the one-legged cycling exercise at 50% of their peak work rate, the intensity selected could in actuality have been as high as 75% of their peak work rate. Ultimately, this overestimation would result in inaccurate quantitative values obtained for fibular nerve MSNA.

In conclusion, Notarius *et al.* (2015) have demonstrated that exercise capacity in heart failure is significantly limited due to decreased peripheral sympathetic vasoconstriction as a consequence of increased MSNA response. The author's previous study implementing handgrip exercise demonstrated the same phenomena; however, this study provides more compelling evidence as a dynamic leg exercise protocol will provide data more accurately representative of a person's peak $\dot{V}_{O_2}$. However, the imbalanced ratio of male and female subjects (4:1) in the study could have precluded any significant effects modulated by sex. Elucidation of the mechanisms underlying exercise intolerance in heart failure may allow future studies to investigate the potential beneficial effects of a regular exercise regimen on exercise capacity in heart failure.

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Additional information

Competing interests

None declared.

Funding

None.