To the Editor: Muscle sympathetic nerve activity (MSNA), as measured during supine rest, is similar between patients with chronic heart failure (HF) due to left ventricular systolic function with relatively preserved capacity for exercise (percentage of peak oxygen uptake \( [\text{VO}_2\text{peak}] \) predicted by age, sex, and weight >56%) and healthy control subjects but is augmented in those patients whose peak \( \text{VO}_2 \) is <56% of predicted (1). We previously identified an inverse relationship between resting calf MSNA and \( \text{VO}_2\text{peak} \) in patients with HF but not in age-matched healthy untrained control subjects (2). This relationship was specific to skeletal muscle sympathetic nerve traffic; there was no correlation between cardiac norepinephrine spillover and \( \text{VO}_2\text{peak} \) (3). In patients with HF performing dynamic handgrip exercise, fibular MSNA increased. Sympathetic activation was elicited at a lower-intensity threshold than in age-matched control subjects, was greatest in those with low \( \text{VO}_2\text{peak} \), and bore no relationship to left ventricular ejection fraction (LVEF) (1).

To date, there have been no published reports of sympathetic recordings from the fibular nerve of patients with HF during leg exercise. Thus, whether peripheral sympathetic vasoconstriction elicited by exercise could limit the capacity to exercise by restricting skeletal muscle blood flow or normal blood flow redistribution is as yet unknown. We hypothesized that \( \text{VO}_2\text{peak} \) is a function of MSNA elicited by moderate dynamic leg exercise. To test this hypothesis, we recruited a cohort comprising subjects both with and without HF.

We studied 11 patients with HF (61 ± 3 years of age [mean ± SE]; 2 women) with a mean LVEF of 32 ± 2% and 11 healthy control subjects (55 ± 2 years of age; 2 women) on 2 separate days. Inclusion criteria were sinus rhythm, diagnosis of HF due to left ventricular systolic dysfunction and LVEF <40%. Those with diabetes were excluded. Patients were maintained on stable optimum therapy for HF. All received beta-adrenoceptor antagonists. No subject was participating in an exercise training program. On the first day, \( \text{VO}_2 \) was assessed on a cycle ergometer during a 15 W/min ramped protocol to peak effort and expressed as a percentage of that predicted based on age, sex, and weight (3). On the second day, we recorded MSNA by microneurography (2) (left fibular nerve) at rest and during 1-legged cycling (right leg) for 4 min (2 at 0 load and 2 at 50% \( \text{VO}_2\text{peak} \)) and determined MSNA frequency (bursts/min) and incidence (bursts/100 heart beats). Heart rate, blood pressure, and rating of perceived exertion (RPE; Borg scale 0 to 10) were also assessed. Multiple linear regression was performed with exercise MSNA burst frequency (minute 4 of exercise at 50% \( \text{VO}_2\text{peak} \)) and resting MSNA as the independent variables and percent of predicted \( \text{VO}_2\text{peak} \) achieved as the dependent variable (SigmaStat, version 3.5, Systat Software Inc., Chicago, Illinois).

For patients with HF and control subjects, respectively, mean age, weight (76.6 ± 3.1 kg vs. 79.3 ± 2.8 kg), body mass index (27.0 ± 0.8 kg/m² vs. 26.2 ± 0.9 kg/m²), resting heart rate (60.0 ± 2.4 beats/min vs. 66.0 ± 3.2 beats/min), blood pressure (111 ± 4/66 ± 2 mm Hg vs. 114 ± 4/69 ± 2 mm Hg) were not significantly different between groups. Also, there was no significant difference in MSNA burst frequency between groups (50.6 ± 2.7 bursts/min vs 44.3 ± 2.6 bursts/min; \( p = 0.12 \)). \( \text{VO}_2\text{peak} \) was significantly lower in patients with HF, whether adjusted for weight (19.0 ± 2.3 vs. 32.7 ± 3.2 ml/kg·min; \( p = 0.004 \)) or normalized as percent of predicted \( \text{VO}_2 \) achieved (71% ± 8% vs. 117% ± 9%; \( p = 0.002 \)). The mean heart rate response during the second minute of cycling at 50% \( \text{VO}_2\text{peak} \) was similar in both groups (HF +13.5 ± 2.1 beats/min vs. control +17.4 ± 2.7 beats/min; \( p = 0.27 \)), and mean RPE, equivalent to a moderate work rate, was comparable (HF 4.2 ± 0.5 vs. control 4.0 ± 0.5).

Multiple linear regression analysis demonstrated a significant inverse relationship between exercise MSNA (minute 2 at a work rate of 50% \( \text{VO}_2\text{peak} \)) and \( \text{VO}_2\text{peak} \) (predicted) across a broad range (31% to 173%) of the latter variable that was not influenced by resting values for MSNA: \( \text{VO}_2\text{peak} \) predicted (% of predicted) = 160.229 – (0.0816 × resting...
MSNA burst frequency) = (1.303 × exercise MSNA burst frequency) 
\( r = -0.59; p = 0.02 \) (Fig. 1). VO2peak percent predicted also correlated with the absolute change in MSNA burst frequency elicited by exercise \( r = -0.59; p = 0.02 \) (not shown).

The novel finding presented in this correspondence is that in middle-aged subjects, peak exercise capacity relates inversely (and independently of resting MSNA) with the magnitude of MSNA elicited by moderate-intensity leg cycling exercise: approximately one-third of the predicted VO2peak could be attributed to exercise-induced MSNA. This also represents the first report of fibrilar MSNA recorded during contralateral dynamic leg exercise in patients with HF. An augmented neurogenic vasoconstrictor response to dynamic exercise in patients with HF, as has been demonstrated for handgrip (1), could impair exercise capacity by limiting muscle blood flow or altering its distribution. Whether exercise training attenuates exercise MSNA of patients with HF merits investigation.

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Letters to the Editor

Effects of Habitual Coffee Consumption on Vascular Function

We read with interest the article by O’Keefe et al. (1). The authors reviewed existing data regarding the effects of chronic coffee consumption, with a focus on cardiovascular (CV) health. They concluded that coffee can be included as part of a healthy diet for the general public and for those with elevated CV risk or CV disease. However, the authors did not present the vascular effects of chronic coffee consumption. In this setting, we examined the association between habitual coffee intake and endothelial function in elderly inhabitants of Ikaria Island. We found that habitual coffee consumption was associated with improved endothelial function in elderly individuals (2). Moreover, there was no association among coffee consumption, endothelium-independent vasodilation, and baseline brachial artery diameter, highlighting the association of coffee consumption with endothelial-dependent dilation (3). Interestingly, this correlation of daily coffee consumption with endothelial function was also constant in hypertensive patients and was not affected by other parameters related to general health (e.g., smoking, diabetes mellitus, hypercholesterolemia) (3). Our findings present a further explanation how chronic coffee consumption can favorably affect CV risk, providing a new connection between nutritional habits and CV health.

It should be noted that the favorable effects of coffee on vascular function appear to be attributed to a synergy among multiple, intricate mechanisms involving its phenolic antioxidant properties, the prevention of low-density lipoprotein cholesterol oxidation and the inhibition of platelet aggregation (4). Moreover, caffeine has a direct effect on endothelial function, stimulating the production of nitric oxide (NO) and the release of calcium from the reticulum, favoring the activation of endothelial NO synthase (4). Furthermore, caffeine enhances endothelial cell migration and re-endothelialization, partly through an AMP protein kinase-dependent mechanism, suggesting a beneficial role of caffeine on endothelial repair (5). Importantly, other substances of coffee beverages, beyond caffeine, can affect endothelium. Caffeic and ferulic acids appear to improve vascular function by reducing reactive oxygen species production and enhancing the bioavailability of NO. Last, coffee consumption not only exhibits inherent antioxidant properties but also activates the endogenous antioxidant defense system by increasing plasma levels of glutathione. Thus, daily coffee consumption seems to be beneficial for vascular function, and this may affect cardiovascular prognosis.

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