Peak oxygen uptake is not determined by cardiac
noradrenaline spillover in heart failure

C. F. Notarius, E. R. Azevedo, J. D. Parker and J. S. Floras

Division of Cardiology, Department of Medicine, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada

Aims We recently found that resting muscle sympathetic nerve activity is inversely related to peak oxygen uptake (VO2 peak) in patients with heart failure, suggesting a peripheral neurogenic limit to exercise in heart failure. No such relationship was observed in healthy controls. To determine whether this observation is specific to sympathetic discharge to skeletal muscle, we tested the null hypothesis that VO2 peak would not relate to resting cardiac noradrenaline spillover, which is also elevated in heart failure.

Methods and Results We measured cardiac noradrenaline spillover at rest by a radiotracer technique and VO2 peak, during cycle ergometry, by open circuit spirometry in 49 heart failure patients (mean age 54.4 ± 1.4 (SE)). There was a significant relationship between age and peak VO2 (P = 0.022). There was no significant relationship between cardiac noradrenaline spillover and either absolute or relative VO2 peak (P = 0.136), with age included in a multiple linear regression model, and none between cardiac noradrenaline spillover and the percent predicted VO2 peak achieved (P = 0.34).

Conclusions Reduced exercise capacity in heart failure relates more closely to sympathetic traffic to skeletal muscle than to cardiac sympathetic outflow, as assessed by noradrenaline spillover. This finding lends further support to the concept of a predominately peripheral neurogenic limit to exercise.

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Introduction

Increased sympathetic activity and reduced exercise tolerance are characteristic features of patients with heart failure[1–8] and independent risk factors for foreshortened survival[9–11].

The sympathetic nervous system of patients with left ventricular systolic dysfunction displays differential regional activation. Increases in sympathetic discharge to the heart, as measured by cardiac noradrenaline spillover, precede any increases in both muscle and renal sympathetic nerve activity or in total body noradrenaline spillover[12]. There is considerable regional variation in the magnitude of sympathetic activation in heart failure. Total body noradrenaline spillover increases by twofold, cardiac noradrenaline spillover by tenfold and renal noradrenaline spillover increases by two- to threefold[6,13]. In contrast, sympathetic discharge to the cutaneous circulation is not augmented[14,15].

Elevated cardiac noradrenaline spillover is associated with high left and right filling pressures, low cardiac output[16,17] and premature mortality[11]. The consequences of increased sympathetic drive to the heart include beta receptor downregulation and uncoupling of G-proteins. These result in chronotropic incompetence[18–20], decreased contractile response to catecholamines[20], and a diminished sympathetic reserve during exercise in heart failure, due more to end-organ refractoriness than to inadequate neural stimulation[21]. These observations provide several potential mechanisms by which cardiac sympathetic activation may contribute to exercise intolerance in heart failure[19].

The concept that there exists a peripheral neurogenic limit to exercise tolerance in heart failure is supported by several lines of evidence, including our recent observation that sympathetic nerve traffic to muscle at rest is inversely related to both peak oxygen uptake and the extent to which exercise tolerance is reduced in such patients[8]. It remains unclear whether this relationship is
limited to muscle or whether it may also be generalizable to vascular beds exposed to increased sympathetic activity in heart failure. The possibility that increased sympathetic drive to the heart might limit exercise capacity in this condition was suggested by Grassi and Mancia[22] and by a previous study using imaging techniques[23].

We therefore tested the null hypothesis that there is no relationship between sympathetic outflow directed to the heart, as measured by cardiac noradrenaline spillover, and absolute or normalized peak oxygen uptake in patients with left ventricular systolic dysfunction. If rejected, this would suggest that exercise tolerance is limited by a generalized increase in sympathetic activity, and a function of both central cardiac and peripheral factors. If confirmed, this would argue for a predominately peripheral limit to exercise tolerance in patients with heart failure.

Methods

Subjects

Heart failure patients
We studied 49 stable patients (46 men and 3 women) (age 54·4 ± 1·4 years; mean ± SE) with moderate to severe left ventricular systolic dysfunction (ejection fraction by radionuclide ventriculography 19% ± 2%), due to ischaemic or dilated cardiomyopathy, in the context of protocols approved by the Ethical Review Committee for Human Experimentation of the University of Toronto. Written informed consent was obtained from all patients. Patients were on optimal drug therapy for heart failure as determined by their treating cardiologist at the time of each study. Medications included beta-blockade (16·3% of patients), angiotensin converting enzyme inhibition (83·7%), diuretic therapy (79·6%), digitalis (61·2%), vasodilators (22·4%), and anticoagulation (36·7%). Patients were maintained on their medications including beta-blockade, diuretics, and digitalis therapy while undergoing the exercise protocol. Drug therapy was continued to avoid any withdrawal effects that might impact negatively on both cardiac sympathetic activity and peak oxygen uptake, with the exception of diuretics which were withheld on the morning of the right heart catheterization study for comfort.

Study protocol

One experimental day included right heart catheterization during which measurements of cardiac and systemic noradrenaline kinetics were acquired. On a separate day patients underwent a graded exercise tolerance test to a symptom-limited maximal effort, with continuous breath by breath measurement of oxygen uptake. The median time between visits was 72 days.

Noradrenaline spillover measurements

Systemic and cardiac-specific sympathetic activity was estimated according to the radiotracer technique described by Esler et al.[13]. This method provides the rate at which noradrenaline released from the nerve terminal appears in plasma and is therefore an indirect biochemical index of efferent sympathetic nervous activity. For the assessment of noradrenaline clearance and spillover, a steady-state plasma concentration of a tracer dose of tritium-labelled noradrenaline is required. Total body noradrenaline spillover is calculated as follows:

\[
\text{Total body NE spillover (pmol.min}^{-1}) = \left[\frac{\left[^{3}H\right] \text{NE infusion rate}}{\text{Plasma NE specific activity}}\right] \times \text{CSPF}
\]

where NE indicates noradrenaline; \(\left[^{3}H\right]\text{NE}\), tritium-labelled noradrenaline. Cardiac noradrenaline spillover is calculated according to the Fick principle, with a correction for the extraction of tritium-labelled noradrenaline across the heart:

\[
\left[^{3}H\right] \text{NE}_{\text{cs}} = \frac{\left[^{3}H\right] \text{NE}_{\text{art}} - \left[^{3}H\right] \text{NE}_{\text{ext}}}{\text{[}^{3}\text{H}]\text{NE}_{\text{art}}}
\]

Cardiac NE spillover (pmol.min}^{-1}) = \left[\text{[NE}_{\text{cs}} - \text{[NE}_{\text{art}} + \left[^{3}H\right] \text{NE}_{\text{ext}} \times \text{NE}_{\text{art}}\right] \times \text{CSPF}
\]

where \(\left[^{3}H\right] \text{NE}_{\text{ext}}\) indicates tritium-labelled cardiac noradrenaline extraction; \(\text{NE}_{\text{cs}}\), coronary sinus noradrenaline concentration; \(\text{NE}_{\text{art}}\), arterial noradrenaline concentration; CSPF, coronary sinus plasma flow, calculated from coronary sinus blood flow and haematocrit.

Radiotracer preparation and infusion

Tritium labelled noradrenaline (L-[2,5,6-3H]NE; New England Nuclear) was diluted in sterile 0·2 mol.l}^{-1} acetic acid in saline solution with 10 mmol.l}^{-1} ascorbate, sterilized by filtration through a 0·22 µm Millex-GV filter and packaged in 4 ml aliquots that were stored at −70 °C until use. The radiotracer was administered intravenously as a 16 mCi.min}^{-1}. Control measurements were performed 20 min after initiation of the radiotracer infusion to ensure steady-state concentration in plasma.

Exercise tolerance test

Exercise capacity was assessed on a separate day by means of a graded exercise test performed on a bicycle ergometer. Subjects maintained their normal medication schedules and were studied at least 2 h after a meal. Patients began to exercise at a work rate of 17 watts with step increases of 17 watts every minute until a maximal effort was achieved. The test was terminated when the pedal speed could no longer be maintained and the respiratory exchange ratio (\(\text{\(\Delta\)}\text{CO}_{2}/\text{\(\Delta\)}\text{O}_{2}\)) exceeded 1·1. Oxygen consumption at peak exercise (\(\text{\(\Delta\)}\text{VO}_{2}\) peak) was obtained by open circuit spirometry (Horizon MMC System or Vmax Series 229, Sensormedics, CA, U.S.A.). Heart rate was monitored by a 12-lead
statistical analysis

All data are summarized as mean ± standard error. The relationship between peak oxygen uptake (VO\textsubscript{2} peak) and resting cardiac or total body noradrenaline spillover was examined first by linear regression. Subsequently, a multiple regression analysis (SigmaStat\textsuperscript{®} for Windows, Ver.1.0, Jandel Scientific Corp., San Rafael, CA, U.S.A.) was applied in order to determine the extent to which the dependent variable, VO\textsubscript{2} peak, could be predicted by the two independent variables, resting cardiac or total body noradrenaline spillover and age. The latter was included in order to account for possible age-related effects on both VO\textsubscript{2} peak and cardiac noradrenaline spillover in heart failure patients. Since age is included in the calculation of percent predicted VO\textsubscript{2} peak, linear regression was used to describe the relationship between the percent of predicted VO\textsubscript{2} peak achieved (dependent variable) and resting cardiac or total body noradrenaline spillover (independent variable).

Results

Group mean data showing resting haemodynamics, cardiac and total body noradrenaline spillovers and peak oxygen uptake appear in Table 1. Corresponding values for subjects of similar age, but with normal left ventricular function, studied in our laboratory, are 73 ± 13 pmol . min\textsuperscript{-1} for cardiac noradrenaline spillover and 1.8 ± 0.2 nmol . min\textsuperscript{-1} for total body noradrenaline spillover\textsuperscript{[16]}.

Patients exercised to a mean peak heart rate of 137 ± 4 beats . min\textsuperscript{-1}, which was 84 ± 2.5% of their age-predicted maximal heart rate. This observation indicates maximal effort and suggests that these patients were not limited by chronotropic incompetence or beta-adenergic blockade. Thirty-five of 49 patients (71.4%) stopped exercise because of fatigue, 12 (25.5%) due to dyspnoea and two because of chest discomfort. The respiratory exchange ratio (RER) at peak exercise was 1.14 ± 0.02.

There was no significant difference between the body weight of these subjects on the two study days. There was a significant negative linear relationship between VO\textsubscript{2} peak (l . min\textsuperscript{-1}) and cardiac noradrenaline spillover (CANASP) (P=0.03) and a trend towards significance between VO\textsubscript{2} peak (ml . kg\textsuperscript{-1} . min\textsuperscript{-1}) and CANASP (P=0.052), but these were not significant when age was added in a multiple regression model. VO\textsubscript{2} peak (ml . kg\textsuperscript{-1} . min\textsuperscript{-1}) could be predicted from a linear combination of resting cardiac noradrenaline spillover and age by the regression equation: VO\textsubscript{2} peak=28.2 – (0.182*age) – (0.007*CANASP).

In this equation, only the slope of the age variable was significantly different from zero (P=0.02) (Fig. 1). Similar results were obtained when absolute VO\textsubscript{2} peak (l . min\textsuperscript{-1}) was used as the independent variable.

When the relationship between exercise limitation (i.e. percent of predicted VO\textsubscript{2} peak achieved) and cardiac noradrenaline spillover was examined by linear regression, the correlation was not significant (r=–0.14, P=0.34) (Fig. 2).

In addition, there was no relationship between resting total body noradrenaline spillover and VO\textsubscript{2} peak (r=0.04, P=0.79) or percent of predicted VO\textsubscript{2} peak achieved (r=0.07, P=0.63).

There were no clear differences in these relationships between the subgroup with ischaemic and the subgroup with non-ischaemic dilated cardiomyopathy, or in those whose two study dates occurred less than or greater than the median between-study interval.

There was no relationship between central haemodynamics, specifically right atrial pressure, pulmonary artery wedge pressure (and thus left ventricular end-diastolic pressure), and either absolute peak oxygen uptake (r=0.02, r=0.12 respectively) or peak oxygen uptake normalized for either body weight (r=0.05, r=0.15) or for that predicted by age, sex and body size (r=0.14, r=0.01), in these patients.

Discussion

The principal new finding of this study is that peak exercise capacity, whether expressed in terms of absolute (i.e. 1 . min\textsuperscript{-1}), relative (per kg of body mass) or as a percentage of predicted peak oxygen uptake, is unrelated...
to resting cardiac noradrenaline spillover in patients with heart failure. These findings contrast with our previous demonstration that the same measures of exercise capacity are significantly related to direct measures of sympathetic nerve traffic to muscle in a smaller cohort of patients with left ventricular systolic dysfunction. Grassi and Mancia suggested that the relationship described in our previous study could imply causality provided it was specific to sympathetic traffic directed to muscle and was not present for other organs subject to sympathetic activity, such as the heart. The present study was undertaken in order to address this question using the cardiac noradrenaline spillover technique, which, at present, is the most direct measure of cardiac sympathetic activity in conscious humans.

These results contrast with the only previous work on this subject by Atsumi et al. These authors reported a significant inverse relationship between VO₂ peak and cardiac sympathetic nervous activity, as estimated non-invasively by the ¹²³I-MIBG (meta-iodobenzylguanidine), in 24 heart failure patients with dilated cardiomyopathy or valvular disease. Their study differs from the present work in three distinct aspects. First, their method of assessing cardiac sympathetic activity may be problematic in that the tracer used differs from noradrenaline with respect to storage, release, metabolism and clearance. Therefore, it is unclear what this method signifies in terms of cardiac noradrenaline kinetics and neuroeffector transduction. Second, significant correlations between variables were only achieved when both heart failure and healthy control
subjects were considered as a single group, providing a broad enough range of their independent variable to establish a positive correlation, that may simply represent changes in their dependent variable arising from the disease state. Their proposed relationship did not appear to be present if analysis was restricted to the heart failure group. Third, over one half of the patients in their study had valvular disease and suffered from atrial fibrillation, which can independently reduce exercise tolerance by as much as 20% in heart failure patients[^27]. In contrast, in the present study of a much larger cohort of heart failure patients of dilated or ischaemic aetiology, less than 15% of whom had atrial fibrillation, there was no relationship between cardiac sympathetic activity, as measured by a more accurate and direct method, and absolute or relative VO\textsubscript{2} peak.

In healthy subjects, cardiac noradrenaline spillover increases with age and peak oxygen uptake decreases with age[^24,25,28–30]. Therefore, as anticipated, there was a significant decrease in peak oxygen uptake with age in the present heart failure population.

The lack of relationship between total body noradrenaline spillover and VO\textsubscript{2} peak in heart failure patients is similar to the findings of Adamopoulos et al[^31], who noted a lack of association between spectral indices of cardiac sympathovagal balance, using heart rate variability, and peak VO\textsubscript{2}, not inconsistent with our previous work using microneurography[^8]. This is because only a small fraction of the total body noradrenaline spillover at rest is derived from skeletal muscle[^32]. Although it may not be appropriate to extrapolate from neural regulation of sino-atrial discharge to sympathetic drive to the myocardium as a whole, the observations of Adamopoulos et al[^31], also argue against an association between cardiac sympathetic activity and exercise intolerance in heart failure.

While beta-adrenoreceptor downregulation may contribute to diminished sympathetic reserve during exercise in heart failure[^21], the patients in this study showed no obvious chronotropic incompetence. As well there is evidence that the transcardiac noradrenaline gradient and systolic cardiac function can be enhanced by blocking inhibitory alpha-adrenoreceptors[^33], suggesting inotropic reserve in patients with heart failure of varying severity. There is an inverse relationship between stroke work index and sympathetic nerve traffic to skeletal muscle[^7]. Although our previous data and that of others has shown that cardiac noradrenaline spillover increases relate to higher cardiac pressures and lower cardiac output[^16,17], an inverse relationship between cardiac noradrenaline spillover and stroke work index has not been described. These several observations are consistent with the concept that any neurogenic limit to exercise capacity in heart failure is primarily peripheral in origin and linked specifically to excessive sympathetic nerve traffic directed at skeletal muscle, rather than due to enhanced global, non-specific sympathoexcitation. Sympathetic nerve traffic to muscle is augmented during both isometric and dynamic exercise in heart failure compared with control subjects[^34]. Increased sympathetic outflow to resistance vessels in muscle adversely affects muscle blood flow and in particular, its distribution to muscle during exercise[^35]. An important contributing mechanism could be stimulation of muscle afferents via the muscle metaboreflex, which we recently demonstrated occurs at a lower threshold in heart failure patients compared with healthy subjects, and is also a function of peak VO\textsubscript{2}[^14].

Because of the difficulty in performing these tracer methods during maximal bicycle exercise, our study was neither designed nor intended to address the issue of how exercise-induced cardiac sympathetic activation correlates with peak oxygen consumption. Patients with heart failure are capable of increasing their cardiac norepinephrine spillover in response to bicycle exercise at 50% of VO\textsubscript{2} peak, similar to subjects with normal ventricular systolic function, despite having higher basal levels[^21]. A second limitation is that peak oxygen uptake and cardiac noradrenaline spillover measurements were performed on separate days with variable time between studies. However, the similar body weights, and comparable results between those subjects studied at less than the median between-study interval and results in the group as a whole, suggest that patients were stable clinically throughout this period.

In conclusion, this study found no association between cardiac sympathetic outflow as assessed by cardiac noradrenaline spillover, and absolute or relative peak oxygen uptake or extent of exercise intolerance in patients with heart failure. In the context of our previous work, this study diminishes the potential contribution of increased sympathetic outflow to the heart to exercise intolerance in heart failure. This finding lends support to our hypothesis of a peripheral limit to exercise arising from increased sympathetic nerve traffic directed at skeletal muscle.

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**References**


[^4]: Francis GS, Benedict C, Johnstone DE *et al.* Comparison of neuroendocrine activation in patients with left ventricular


