Caffeine Prolongs Exercise Duration in Heart Failure

CATHERINE F. NOTARIUS, PhD, BEVERLEY MORRIS, RN, AND JOHN S. FLORAS, MD, DPhil

Toronto, Ontario, Canada

ABSTRACT

Background: Caffeine increases submaximal exercise performance in healthy young subjects; its effects on exercise tolerance in heart failure (HF) have not been characterized.

Methods and Results: To determine whether caffeine increases exercise tolerance in HF, caffeine (4 mg/kg intravenously, equivalent to 2 cups of coffee) or vehicle were infused into 10 treated HF patients (left ventricular ejection fraction 25 ± 2 %), and 10 age-matched normal subjects (N) on 2 separate days in a double-blind, randomized, crossover design. We measured heart rate, blood pressure, and ventilation at rest and during graded cycling (15 W/minute) to peak effort. Peak oxygen consumption was unaffected in either group. Mean exercise time was unchanged in N (1013 ± 87 versus 988 ± 107 seconds; $P = .86$) but was significantly increased by caffeine in HF (from 511 ± 28 to 560 ± 37 seconds; $P = .004$) despite an increase in peak minute ventilation ($P < .05$). Resting and peak blood pressures were higher after caffeine ($P < .05$) in HF, not N.

Conclusion: Caffeine allows HF patients to exercise longer at peak effort.

Key Words: Blood pressure, exercise tolerance, normal subjects, symptoms.

Oral caffeine or coffee as a potential ergogenic aid has been studied extensively in healthy young subjects, in whom it has been shown to significantly increase submaximal exercise performance,[1] but not peak oxygen uptake.[2] Whether caffeine exerts similar actions in chronic heart failure (HF) patients is unknown. The most recent American Heart Association/American College of Cardiology guidelines concerning the management of heart failure do not address, in general, the issue of caffeine consumption.

Exercise intolerance is a cardinal feature of the heart failure syndrome and impacts adversely on patients' perceived quality of life. Of the several potential mechanisms contributing to exercise intolerance in HF, neurogenic vasoconstriction in skeletal muscle has been the focus of our laboratory. Previously, we reported an age-independent inverse relationship between muscle sympathetic nerve activity (MSNA), measured at rest, and peak oxygen uptake in heart failure, but not in healthy subjects, and demonstrated that increases in MSNA, elicited reflexively by ischemic and nonischemic handgrip exercise, occur at a lower threshold in HF patients with impaired peak oxygen uptake than in either HF patients with preserved peak oxygen uptake or age-matched control subjects with heart failure.[3] When infused intravenously at a dose of 4 mg/kg (equivalent to 2 cups of coffee),[4] caffeine increased both systolic and diastolic blood pressure of HF patients without affecting either heart rate, or MSNA, indicating the absence of sympathetically mediated peripheral vasoconstriction.[5] Importantly, caffeine abolished MSNA responses to post-handgrip ischemia in HF, but not in healthy subjects, a finding consistent with blockade of muscle metaboreflex-mediated sympathoexcitation. These findings led us to consider the possibility that caffeine might also improve exercise tolerance in HF. Moreover, caffeine in doses of 4 to 9 mg/kg can also induce analgesia,[6] reduce fatigue sensations,[7] and improve neuromuscular function,[6] all of which could prolong time to fatigue during muscular exercise. In healthy young subjects, caffeine has also been reported to exert a positive inotropic effect.[8] With this background, our objective in the present study was to test the hypothesis that caffeine would increase peak oxygen uptake and total exercise time in patients with HF but not healthy normal subjects.

From the University Health Network and Mount Sinai Hospital, Division of Cardiology and Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada.

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Reprint requests: Catherine F. Notarius, PhD, Division of Cardiology, Toronto General Hospital, 6 Eaton South, Room 414, 200 Elizabeth St., Toronto, Ontario M5G 2C4, Canada.

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Methods

Subjects

Heart Failure Patients (HF). We recruited 10 stable patients (3 women) with impaired left ventricular systolic function of ischemic (n = 4) or nonischemic dilated (n = 6) etiology. Their mean age was 56 ± 4 (range 38–73) years and mean LVEF 25 ± 2%. Patients were maintained on their regular medication schedule to ensure clinical relevance and to avoid any adverse responses to withdrawal. All 10 patients were taking angiotensin-converting enzyme inhibitors, 9 β-adrenoceptor antagonists, 4 diuretics, and 3 anticoagulants. Four were in NYHA symptom class I, five in class II and one in class III.

Normal Subjects (N). Ten healthy, age-matched, medication-free volunteers (1 woman) were recruited, through local advertisement, and screened by medical history. Their mean age was 50 ± 4 (range 30–69) years.

Procedures and Protocol

This protocol was approved by our Institution's Research Ethics Board and informed written consent was obtained from all subjects. Subjects were studied in a quiet, temperature-controlled laboratory on 2 separate days, 1 week apart, 2 hours after the last food intake. To avoid the effects of caffeine tolerance, 72 hours of caffeine abstinence was mandated.[9] Blood pressure was monitored from the right arm manually every minute by sphygmomanometer. Heart rate was derived from lead II of a 12-lead electrocardiogram (Marquette Instruments, Denver, CO.). An antecubital venous catheter was inserted in the right forearm for infusions and for blood sampling.

Following a double blind placebo-controlled randomized crossover design, each subject received, over approximately 20 minutes, an intravenous infusion of 4 mg/kg caffeine (equivalent to 2 cups of coffee) diluted in 5% dextrose solution (a total volume of 50–60 mL) or the same volume of vehicle (5% dextrose) as in our previous studies.[5] The infusions were stopped and the subjects performed a graded ramped bicycle ergometer test (15 watts/minute) until peak effort, as indicated by the inability to maintain pedal speed despite verbal encouragement, and a respiratory exchange ratio (carbon dioxide production/VO_2) > 1.1. Monitoring continued for 10 minutes after exercise.

Oxygen uptake at peak exercise (VO_{2peak}) was calculated breath by breath on line using expired gas analysis by open circuit spirometry (Horizon MMC System or Vmax Series 229, Sensormedics, CA). VO_{2peak} was expressed both as L/minute, $mL \cdot kg \cdot min^{-1}$, and as percent of predicted VO_{2peak}, to account for age, sex, body weight, and height.

Venous blood was sampled at 5 time points: preinfusion; postinfusion; at submaximal exercise (50%–60% of peak oxygen consumption); at peak exercise; and after 10 minutes of recovery postexercise. Submaximal exercise time ranged from 3 to 5 minutes in HF patients and from 5 to 7 minutes in healthy subjects. The samples were subsequently submitted to plasma norepinephrine and epinephrine determination by high-performance liquid chromatography.[10] The measurement of total (protein-bound and free) serum caffeine concentration by a homogeneous enzyme immunoassay technique was also performed on samples before and after infusion, using a commercially available kit (Emit Caffeine Assay, Syva Canada, Kanata, Canada). The limit of detection of this assay is 5 μg/mL. In our clinical laboratory, the batch-to-batch coefficient of variation is 4.2% at a concentration of 77.2 μmol/L.

Statistical Analysis

Data are presented as mean ± standard error. Unpaired *t*-tests were performed to test for differences between group means for dependent variables. The effect of the infusions alone on resting dependent variables was determined in the HF and healthy subject groups separately by means of a repeated measures 2-way analysis of variance, which examined main effects of time (pre- and postinfusion) and infusion (vehicle and caffeine) (SigmaStat for Windows, Ver.1.0, Jandel Scientific Corp, San Rafael, CA). A similar analysis was applied for the exercise protocol to assess the effects of vehicle and caffeine on dependent measures during upright rest, submaximal exercise (50%–60% of peak oxygen consumption) and peak exercise. Prespecified hypotheses were then assessed by a post-hoc Student Newman-Keuls test.

Results

Characteristics of HF and Healthy Normal Subjects

When compared with N, those with HF had a significantly reduced VO_{2peak} (Table 1). Otherwise, there was no significant difference between groups with respect to age, height, resting heart rate, blood pressure, or catecholamines. HF patients were heavier ($P = .03$). All subjects reported complete compliance with caffeine abstinence. Indeed, no caffeine was detected in the plasma of any subject before infusions.

Effect of Caffeine on Responses to Exercise

Infusion achieved similar mean plasma caffeine levels in HF patients (68.2 ± 8.4 μmol/L) and normal subjects (56.6 ± 7.8 μmol/L) ($P = .17$). Except for an occasional premature ventricular contraction and 1 couplet during exercise in 1 HF patient, no arrhythmias were observed.

Caffeine infusion increased resting supine blood pressure (Fig. 1) and pulse pressure in both groups ($P < .05$), but the magnitude of this rise was approximately 2-fold greater in HF (for SBP: +19 versus +8.5 mm Hg, $P = .04$)(Table 2). Infusion of vehicle had no effect on these variables.

Upright blood pressure before exercise was higher on the caffeine day in HF ($P < .05$) but not in N (Fig. 1). No

Table 1. Subject Characteristics

	Normal (n = 10)	Heart Failure (n = 10)
Height (cm)	175.0 ± 2.6	172.0 ± 2.1
Weight (kg)	70.3 ± 2.6	78.8 ± 2.5*
HR (beats/min)	65.8 ± 2.2	67.6 ± 3.5
SBP (mm Hg)	114.0 ± 3.2	113.5 ± 6.4
DBP (mm Hg)	73.5 ± 2.0	73.0 ± 3.3
PNE (nmol/L)	1.33 ± 0.2	1.93 ± 3.2
Plasma epinephrine	0.28 ± 0.2	0.17 ± 0.04
VO_2 peak ($mL \cdot kg^{-1} \cdot min^{-1}$)	33.4 ± 3.0	18.1 ± 1.0†
VO_2 peak (% predicted)	109.0 ± 13.0	66.3 ± 4.6‡

Mean ± SE, standard error; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; PNE, plasma norepinephrine; VO_{2peak}, peak oxygen consumption.
*$P = .03$.
†$P < .001$.
‡$P < .006$.