Effect of adenosine receptor blockade with caffeine on sympathetic response to handgrip exercise in heart failure

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Adenosine (Ado) increases muscle sympathetic nerve activity (MSNA) reflexively. Plasma Ado and MSNA are elevated in heart failure (HF). We tested the hypothesis that Ado receptor blockade by caffeine would attenuate reflex MSNA responses to handgrip (HG) and posthandgrip ischemia (PHGI) and that this action would be more prominent in HF subjects than in normal subjects. We studied 12 HF subjects and 10 age-matched normal subjects after either saline or caffeine (4 mg/kg) infusion during isometric [30% of maximal voluntary contraction (MVC)] and isotonic (10%, 30%, and 50%) HG exercise, followed by 2 min of PHGI. In normal subjects, caffeine did not block increases in MSNA during PHGI after 50% HG. In HF subjects, caffeine abolished MSNA responses to PHGI after both isometric and 50% isotonic exercise (P < 0.05) but MSNA responses during HG were unaffected. These findings are consistent with muscle metaboreflex stimulation by endogenous Ado during ischemic or intense nonischemic HG exercise (22). Isometric and isotonic handgrip (HG) and posthandgrip ischemia (PHGI) evoke a further increase in MSNA. This reflex sympathetic activation is elicited by a lower workload, and is of greater magnitude in those with moderate-to-severe left ventricular systolic dysfunction than in age-matched healthy subjects (23). Patients with the lowest \( \dot{V}O_2 \) peak and resting forearm blood flow achieve the highest MSNA during isotonic and isometric HG and during PHGI. These observations are consistent with the concept that the muscle metaboreflex elicits a greater MSNA response to both ischemic and intense nonischemic exercise in HF. If so, augmented neurogenic vasoconstriction in skeletal muscle may further limit exercise capacity in this condition. The exact stimulus, or stimuli, responsible for this reflex sympathetic activation during HG exercise is uncertain.

Adenosine is one potential candidate. Microdialysis studies involving healthy volunteers demonstrate interstitial accumulation of adenosine during dynamic leg exercise (17), intense nonischemic HG, and even low-level HG exercise, if accompanied by ischemia (6). Endogenous adenosine could activate the metaboreflex by stimulating thin-fiber muscle afferents that constitute its afferent limb (5). Although its local actions include vasodilation and prejunctional inhibition of norepinephrine (NE) release, the intravenous or intra-arterial infusion of this purine elicits marked reflex increases in central sympathetic outflow by stimulating adenosine-sensitive afferent nerve endings in skeletal muscle, kidney, and the heart (1, 2, 4, 7, 8, 19, 28, 30, 35, 37). For example, in healthy volunteers, infusion of adenosine into the brachial artery increases total body NE spillover into plasma without affecting NE release into the experimental forearm (26). The contribution of these reflex excitatory actions to short-term cardiovascular regulation is most evident 36 h or more after abstinence from the nonspecific adenosine A1 and A2 receptor antagonist caffeine (3, 13, 27, 34).

Such actions of endogenous adenosine may be particularly relevant to moderate-to-severe HF, in which relative tissue hypoperfusion at rest or during exercise could stimulate the local production of adenosine in higher concentrations or at a lower workload than in healthy subjects. Indeed, plasma adenosine concentrations are increased in HF, relative to symptom class (14) and correlate inversely with \( \dot{V}O_2 \) peak (24). Plasma hypoxanthine concentrations (a major product of adenosine metabolism) increase during submaximal treadmill exercise in congestive HF patients, in parallel with lactate and NE (18). Thus the excitatory reflex elicited by adenosine may be an important additional mechanism contributing to generalized sympathetic activation in HF (12) and could also account for the lower threshold required to activate reflex increases in MSNA in response to HG in these patients (23). If stimulation, by adenosine, of afferent nerve endings in skeletal muscle
during exercise elicits a sympathoexcitatory response via this reflex, this action should be most evident during ischemic exercise and PHGI, and attenuated or inhibited by adenosine receptor blockade.

In the present experiments, subjects therefore performed isometric exercise and three levels of isotonic exercise to test the hypotheses that caffeine would attenuate reflex MSNA responses to isometric exercise and to forearm ischemia after intense rhythmic exercise, two stimuli to local adenosine production and its interstitial accumulation, and that these effects would be more prominent in HF than in age-matched healthy subjects.

METHODS

Subjects

HR patients. We studied 12 stable patients (11 men and 1 woman) (age 50.5 ± 4.3 yr; means ± SE) with moderate-to-severe impairment of left ventricular function (ejection fraction by radionuclide ventriculography 19.0 ± 2.5%). Five patients had ischemic and seven had dilated cardiomyopathy. Of these, 9 (75%) were receiving β-adrenoceptor antagonists; 10 (83%), angiotensin-converting enzyme inhibitors; 6 (50%), digitals; 10 (83%), diuretics; and 3 (33%), anticoagulants. Diuretics were withheld on the morning of each micrographie study.

Normal subjects. Ten healthy volunteers (nine male and one female) were screened by medical history. None were taking medication. Their mean age was 48.0 ± 3.9 yr.

Procedures

Subjects were studied supine in a quiet temperature-controlled laboratory on two separate days, 2 h after the last food intake, and after 72 h of caffeine abstinence. Blood pressure was monitored from the left arm every minute by an automated device (model 200 Lifestat, Physio-Control; Redwood, WA). Heart rate (HR) was derived from lead II of the electrocardiogram. Signal output was to an ink recorder (model 2800S, Gould; Cleveland, OH) and a computer using a LabVIEW software platform (National Instruments, Austin, TX). An antecubital venous catheter was inserted into the right forearm for infusions and blood sampling. Venous blood was submitted to plasma NE and epinephrine determination by HPLC (11), and the measurement of total (protein-bound and free) serum caffeine concentration by a homogeneous enzyme immunoassay technique 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.

Sympathetic nerve recordings. Multiunit recordings of postganglionic muscle sympathetic nerve activity were obtained with a unipolar tungsten electrode inserted selectively into a muscle nerve fascicle of the right or left peroneal nerve, posterior to the fibular head as previously described (30). MSNA was expressed as burst frequency (bursts/min) and integrated (burst frequency times amplitude) MSNA.

Venous occlusion plethysmography. Resting blood flow in the left forearm (FBF) was determined by venous occlusion plethysmography (model 270A, Parks Electronics Laboratory; Beaverton, OR) using a Whitney mercury-in-Silastic strain gauge (38).

Exercise capacity. Oxygen uptake at peak exercise (VO₂ peak) was determined on a separate day by open circuit spirometry (Horizon MMC System or V max Series 229, Sensormedics) during a graded bicycle ergometer test (17 W/min) performed until the pedal speed could no longer be maintained and the respiratory exchange ratio (VO₂/VO₂ peak) exceeded 1.1. VO₂ peak was expressed as both milliliters per kilogram per minute and percentage of predicted VO₂ peak, accounting for age, sex, body weight, and height.

Protocol

Determination of maximal voluntary contraction (MVC) (handgrip dynamometer, model 78010, Lafayette Instrument) in the nondominant forearm (average of three trials), was made before a 20-min stabilization period and subsequent 7- to 10-min baseline recording. Baseline measures were obtained during the last 2 min of this period, and venous blood was sampled.

In a double-blind, placebo-controlled, randomized crossover design, each subject then received, over a 20-min period, 4 mg/kg iv caffeine diluted in 5% dextrose solution for a total volume of 50–60 ml or the same volume of 0.9% sodium chloride (saline) solution. A second 7- to 10-min postinfusion baseline recording was obtained.

Subjects then performed the following in random order: 2 min of isometric or ischemic (sustained) HG exercise at 30% MVC; and 2 min each of isotonic or nonischemic (rhythmic) HG exercise at 10, 30, and 50% MVC. Each bout of exercise was followed immediately by 2 min of PHGI, achieved by the inflation of an upper arm cuff to 200 mmHg, so as to trap metabolites released by the muscle contraction and dissociate the mechanics of the muscle contraction (mechanoreceptor reflex) and volitional effects (central command) from stimulation of metabolically sensitive muscle afferents (metaboreflex). Dependent variables were measured during each minute of HG and averaged over the 2-min PHGI period and the subsequent 2-min recovery interval.

Graded doses (35, 70, and 140 μg·kg⁻¹·min⁻¹) of adenosine (Adenoscan; Fujiyama) were infused after the exercise protocol in a subgroup of HF patients (n = 5) and normal subjects (n = 4). These infusions were administered as an internal control to confirm blockade of adenosine receptors by caffeine.

This protocol was approved by the Human Subjects Review Committee of the University of Toronto. Informed written consent was obtained from each subject before participation.

Statistical Analysis

Data are presented as means ± SE. 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 two-way ANOVA which examined main effects of time (pre- and postinfusion) and infusion (saline and caffeine) (SigmaStat for Windows, Version 1.0, Jandel Scientific, San Rafael, CA). A similar analysis was applied for the exercise protocol to assess the effects of saline and caffeine on responses to each minute of HG, PHGI, and recovery. Prespecified hypotheses were then assessed by a post hoc Student-Newman-Keuls test.

RESULTS

Characteristics of HF and Control Subjects

These subjects were similar in age, height, weight, resting HR, blood pressure, and forearm blood flow...
Table 1. Subject characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal, n = 10</th>
<th>Heart Failure, n = 12</th>
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<tr>
<td>Age, yr</td>
<td>48.0 ± 4.0</td>
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<td>Height, cm</td>
<td>176.0 ± 3.0</td>
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<tr>
<td>Weight, kg</td>
<td>75.5 ± 5.8</td>
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<td>SBP, mmHg</td>
<td>114.6 ± 3.0</td>
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<td>DBP, mmHg</td>
<td>72.8 ± 2.5</td>
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<td>HR, beats/min</td>
<td>67.8 ± 3.1</td>
<td>68.6 ± 4.6</td>
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<tr>
<td>FBF, ml/min⁻¹·100g⁻¹</td>
<td>3.3 ± 0.5</td>
<td>3.4 ± 0.5</td>
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<tr>
<td>MSNA, burst/min</td>
<td>33.0 ± 2.5</td>
<td>53.1 ± 3.0†</td>
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<tr>
<td>MSNA, bursts/100 beats</td>
<td>50.3 ± 4.6</td>
<td>78.5 ± 3.1†</td>
</tr>
<tr>
<td>V̇O₂peak, ml·kg⁻¹·min⁻¹</td>
<td>34.4 ± 2.0</td>
<td>18.7 ± 1.9*</td>
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<tr>
<td>V̇O₂peak,% predicted</td>
<td>104.0 ± 3.2</td>
<td>95.7 ± 5.2</td>
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</table>

Values are means ± SE; n, number of subjects. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; FBF, forearm blood flow; MSNA, muscle sympathetic nerve activity; V̇O₂peak, peak oxygen uptake. *P < 0.0001; †P < 0.002.

Those with HF had significantly higher resting sympathetic nerve burst frequency and burst incidence (P < 0.0001) and lower V̇O₂peak and percentage of predicted V̇O₂peak (P < 0.002) (Table 1).

All subjects reported successful caffeine abstinence. No caffeine was detected in plasma in any subject, with the exception of one HF patient in whom concentrations were 9.1 and 12 µmol/l before the saline and caffeine infusions, respectively. Both concentrations fell below the level required for blockade of adenosine receptors (13).

Effect of Caffeine on Resting Values

Infusion achieved comparable increases in mean plasma caffeine levels in HF (67.7 ± 11.5 µmol/l, n = 10) and normal subjects (54.7 ± 10.8 µmol/l, n = 9) and had no immediate effect on plasma catecholamine concentrations in either group.

Resting HR, blood pressure, and sympathetic nerve activity before and immediately after these infusions appear in Table 2. Caffeine increased systolic and diastolic blood pressure in both groups (P < 0.05), whereas saline had no effect on either variable. Mean HR fell in normal subjects (P < 0.05) but did not change in HF patients.

In control subjects, caffeine reduced MSNA (P < 0.05), whereas saline had no effect. Neither infusion altered MSNA in HF patients. Of note, baseline values for MSNA burst frequency were significantly lower before the caffeine infusion than before the saline infusion in this group (P < 0.05) (Table 2).

Effect of Caffeine on Response to Adenosine

Plasma caffeine concentrations immediately before adenosine (about 2 h after its infusion) were similar in HF and normal subjects (38.8 ± 2.4 and 30.3 ± 3.5 µmol/l, respectively). The sympathoexcitatory response to incremental adenosine infusion was significantly attenuated by prior administration of caffeine in both groups (for MSNA burst frequency main effect: P = 0.03 for HF, n = 5; P = 0.02, for control subjects, n = 4) (Fig. 1), indicating blockade of adenosine receptors by caffeine. In control subjects, adenosine caused a significant reduction in diastolic blood pressure under saline conditions (P = 0.05); this was abolished by prior infusion of caffeine (P = 0.02). In HF subjects adenosine had no effect on diastolic blood pressure on either study day, indicating that attenuation of this sympathoexcitatory response by caffeine occurred independently of the arterial baroreflex.

Effect of Caffeine on Responses During Handgrip Exercise

Control subjects. In normal subjects, the highest workloads (isometric and 50% isotonic HG) evoked significant increases from resting values in both mean arterial pressure (MAP) (P < 0.05) (Fig. 2) and in HR during the second minute of exercise on the two study days (P < 0.05; data not shown). After caffeine infusion, MAP was significantly higher than after saline during 30% isometric HG and 10% and 50% rhythmic HG (Fig. 2) (P < 0.05). Both 30% isometric and 50% isotonic exercise increased HR during the second minute of HG, but HR was significantly lower after caffeine throughout 50% rhythmic HG (P < 0.05). As previously documented (21, 36), MSNA burst frequency was not increased significantly by HG under saline conditions, but after caffeine infusion, there was a significant increase in MSNA during the second minute of 50% rhythmic HG (Fig. 3).

HF patients. In contrast to normal subjects, caffeine had no effect on the MAP response to any level of HG exercise (Fig. 2). The highest workloads (isometric and

Table 2. Hemodynamic and muscle sympathetic nerve activity response before and immediately after infusions in normal and heart failure subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal, n = 10</th>
<th>Heart Failure, n = 12</th>
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<tr>
<td></td>
<td>Before</td>
<td>After</td>
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<tr>
<td>HR, beats/min</td>
<td>67.8 ± 3.1</td>
<td>69.4 ± 3.8</td>
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<tr>
<td>SBP, mmHg</td>
<td>114.6 ± 3.0</td>
<td>116.2 ± 4.6</td>
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<tr>
<td>DBP, mmHg</td>
<td>72.8 ± 2.5</td>
<td>72.7 ± 3.5</td>
</tr>
<tr>
<td>MSNA, bursts/min</td>
<td>33.2 ± 2.4</td>
<td>36.3 ± 2.7</td>
</tr>
<tr>
<td>MVC, kg</td>
<td>46.1 ± 2.6</td>
<td>46.4 ± 3.0</td>
</tr>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
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<td>68.8 ± 4.6</td>
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<td>61.7 ± 4.5</td>
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<td></td>
<td>74.2 ± 4.5</td>
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<tr>
<td></td>
<td>53.1 ± 3.0</td>
<td>53.2 ± 3.2</td>
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</tbody>
</table>

Values are means ± SE; n, number of subjects. MVC, maximal voluntary contraction. *P < 0.05 vs. respective precondition; †P < 0.05 from saline precondition.
50% isotonic HG) elicited significant increases from resting values in HR during the second minute of exercise on both study days (P < 0.05; data not shown). All HG protocols evoked significant increases in MSNA burst frequency compared with preexercise values under both caffeine and saline conditions (P < 0.05), with the exception of 10% HG, where the increase was only significant on the saline day (P < 0.05) (Fig. 3).

Effect of Caffeine on Responses During PHGI

Control subjects. Consistent with previous literature (21, 36), the pressor effects of 30% isometric and 50% isotonic HG were sustained during PHGI after saline infusion. These increases were not attenuated by caffeine. HR increases observed during HG were not sustained during PHGI. After saline infusion, MSNA remained at preexercise values during PHGI, but after caffeine infusion, the increase in MSNA burst frequency elicited by 50% isotonic HG was sustained during PHGI (Fig. 3).

HF patients. In contrast to normal subjects, increases in MAP with 30% isometric, and 50% rhythmic HG (Fig. 2) as well as the increase in HR with 50% rhythmic HG were sustained during PHGI on the day of the saline infusion (P < 0.05) but not after caffeine. Consistent with this observation, increases in MSNA burst frequency evoked by 30% isometric and 50% isotonic HG in HF were maintained during PHGI after saline but not after caffeine (Fig. 3). Thus caffeine antagonized both the pressor and the sympathoneural responses to stimulation of the muscle metaboreflex by PHGI in these HF patients.

DISCUSSION

The present experiment yielded three novel findings. The principal new observation was the inhibitory effect

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**Fig. 1.** Integrated muscle sympathetic nerve activity (IntMSNA) responses to graded infusions of adenosine after saline (open circles) and caffeine (closed circles) preinfusion (Pre) in normal subjects (A; n = 4) and patients with heart failure (HF) (B; n = 5). Sympathoexcitatory effect of adenosine was attenuated in a dose-dependent manner by caffeine preinfusion in both groups (interaction P = 0.03 in normal subjects, P = 0.02 in HF).

**Fig. 2.** Mean arterial pressure (MAP) response to 30% isometric (A), 10% isotonic (B), 30% isotonic (C), and 50% isotonic (D) handgrip (HG) exercise after saline (circles) or caffeine (triangles) infusion in normal subjects (open symbols) and patients with HF (closed symbols). HG1 and HG2, handgrip exercise periods; PHGI, posthandgrip ischemia, REC, recovery. *P < 0.05 vs. pre-HG in both saline and caffeine; #P < 0.05 vs. pre-HG in saline only; $P < 0.05 vs. pre-HG in caffeine only; $P < 0.05 saline vs. caffeine. Symbols above plots apply to HF patients and symbols below plots apply to normal subjects.
of caffeine in HF patients on the reflex increase in MSNA elicited by forearm ischemia after the most intense forms of exercise, i.e., 30% isometric and 50% rhythmic HG. This maneuver was incorporated into the protocol to examine the effects of the muscle metaboreflex on the sympathetic response to HG exercise, free from any effects of volition or of the mechanical effect of muscle contraction on central sympathetic outflow (21). This previously documented sympathoexcitatory effect of PHGI in HF (23, 33) was abolished by prior infusion of caffeine, at a dose equivalent to the oral intake of two cups of coffee. As anticipated, MSNA increased in response to exogenous adenosine, administered at the conclusion of these studies (5, 30), and this response was prevented by prior infusion of caffeine, confirming adenosine receptor blockade throughout this protocol. Caffeine has additional mechanisms of action, including direct release of intracellular calcium and inhibition of cyclic nucleotide phosphodiesterases, but these are only activated at a much higher plasma concentration (13). Thus the effects of caffeine in the present experiments can be attributed to blockade of the actions of endogenous adenosine at the level of the A1 and A2 adenosine receptor (13, 34).

The attenuation of MSNA and also blood pressure responses, by this nonspecific antagonist, implicates endogenous adenosine as an important stimulus to the muscle metaboreflex during ischemic or intense nonischemic HG. This inhibitory effect of caffeine, and the increase in MSNA elicited by 50% HG on the caffeine (but not the saline) day was sustained during PHGI. These findings imply that of the several known or postulated chemical and mechanical stimuli to the somatic pressor reflex, which include lactic acid and arachidonic acid products (5, 31), adenosine assumes far greater importance in HF than in normal subjects. This may be due to relative tissue hypoperfusion and greater adenosine generation during muscle contraction. Adenosine could augment reflex sympathetic responses to HG exercise in HF (23) by this mechanism.

The second novel finding was the lack of attenuation by caffeine of MSNA burst frequency during HG exercise in HF patients with the exception of 10% isotonic HG. In a previous experiment in young (mean age 25 yr) healthy subjects, brachial artery infusion of aminophylline, a methylxanthine derivative analogous to caffeine, abolished the increase in integrated MSNA elicited by 3 min of 30% isometric HG (5). MSNA burst frequency, which did not increase in the present cohort of middle-aged volunteers, was not reported by those authors (5). As noted previously (23), 10% isotonic HG increased MSNA in HF, but not healthy subjects, indicating a lower threshold for sympathetic activation by exercise in the setting of left ventricular systolic dysfunction. However, in the present series, caffeine had no effect on the MSNA responses to 30 or 50% isotonic exercise, suggesting that any potential antagonism of interstitial adenosine generated during these maneuvers may have been obscured by the recruitment of volitional (i.e., central command), mechanical, and other stimuli to the somatic pressor reflex during these greater workloads.
Aminophylline attenuates markedly the increase in MSNA and HR observed when dipyridamole is administered to inhibit the reuptake of endogenous adenosine (9), but the effect of intravenous caffeine on MSNA in healthy volunteers has not been reported. Thus the third new finding was the inhibitory influence of caffeine on MSNA at rest in these HF patients and on HR in these control subjects. This observation indicates that increases in plasma epinephrine and NE observed previously in response to oral caffeine, in pressor doses similar to that administered in the present protocol (25, 34), arise from adrenal catecholamine discharge, or by blockade of the inhibitory effect of adenosine on neural NE release (29), rather than from an increase in efferent sympathetic discharge to skeletal muscle. Because we did not measure hemodynamics directly, we cannot determine the mechanism responsible for the pressor response to caffeine, but would suggest that this is a function of inhibition of the tonic dilatory effects of adenosine on vasomotor tone (28, 34).

By contrast, caffeine had no effect on MSNA or on HR in HF subjects. Because of the many direct and indirect vascular and neural actions of caffeine, the exact mechanism or mechanisms responsible for this discordance cannot be ascertained with certainty from the present observations, and requires elucidation in future experiments. Regardless of the mechanism, the present observations have two clinical implications. First, they demonstrate that caffeine, in the doses administered in the present experiments, does not increase MSNA, an action with potentially adverse pathophysiological consequences in this condition. Second, they do not support the concept that endogenous adenosine contributes to the increase in MSNA under resting conditions in HF. Rather, the sympathoinhibitory effect of caffeine in HF becomes evident only during forearm ischemia after exercise when interstitial adenosine levels reach their peak (6, 17).

Fatigue is the principal limitation to leg exercise in the majority of patients with left ventricular systolic dysfunction. Although derived from experiments involving forearm HG, the present findings can be considered relevant to whole body exercise in human HF for two reasons. First, they are consistent with the results of experiments demonstrating that exercise intensity and relative skeletal muscle ischemia can elicit the muscle metaboreflex during whole body exercise in conscious healthy dogs (32) and, at a lower threshold, in dogs with experimental HF (15). Second, in patients with HF, muscle sympathetic nerve traffic to the calf muscle at rest is positively correlated with calf vascular resistance (16) and inversely related to whole body peak exercise capacity in patients (22). These findings support the concept of a link among sympathetic neural outflow, relative ischemia, and exercise capacity in this condition.

The possibility that the dose of caffeine administered may have been inadequate to detect an inhibitory effect on MSNA at rest in these HF patients was considered. This is unlikely because this dose was sufficient to inhibit, significantly, the excitatory response to intravenous adenosine in both groups. Subjects abstained from caffeine for 72 h before the study to eliminate the effects of tolerance (27). Patients continued taking medications that might affect baseline values or HR responses to exercise or caffeine. However, the present observations avoid the adverse or confounding effects of drug withdrawal and are directly relevant to the effect of exercise and caffeine in optimally managed HF patients. In our previous study, MSNA responses to rhythmic and static HG were greatest in those HF patients with the lowest forearm blood flow at rest. In the present series, resting blood flow in the left forearm was similar at the start of the study in the two groups. It is possible that we may have underestimated the importance of endogenous adenosine production in mediating the MSNA responses to HG and PHGI in HF by studying patients with well-compensated ventricular systolic dysfunction and relatively normal skeletal muscle blood flow at rest.

This study, therefore, demonstrates that endogenous adenosine is an important stimulus to the muscle metaboreflex evoked by brief ischemic and intense non-ischemic HG exercise in patients with marked systolic dysfunction. Reflex sympathoexcitation evoked by adenosine could thereby contribute to the exercise intolerance of HF (22, 23).

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