Effects of caffeine on blood pressure, heart rate, and forearm blood flow during dynamic leg exercise

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Daniels, Jason W., Paul A. Molé, James D. Shaffrath, and Charles L. Stebbins. Effects of caffeine on blood pressure, heart rate, and forearm blood flow during dynamic leg exercise. *J. Appl. Physiol.* 85(1): 154–159, 1998.—This study examined the acute effects of caffeine on the cardiovascular system during dynamic leg exercise. Ten trained, caffeine-naive cyclists (7 women and 3 men) were studied at rest and during bicycle ergometry before and after the ingestion of 6 mg/kg caffeine or 6 mg/kg fructose (placebo) with 250 ml of water. After consumption of caffeine or placebo, subjects either rested for 100 min (rest protocol) or rested for 45 min followed by 55 min of cycle ergometry at 65% of maximal oxygen consumption (exercise protocol). Measurement of mean arterial pressure (MAP), forearm blood flow (FBF), heart rate, skin temperature, and rectal temperature and calculation of forearm vascular conductance (FVC) were made at baseline and at 20-min intervals. Plasma ANG II was measured at baseline and at 60 min postingestion in the two exercise protocols. Before exercise, caffeine increased both systolic blood pressure (17%) and MAP (11%) without affecting FBF or FVC. During dynamic exercise, caffeine attenuated the increase in FBF (53%) and FVC (50%) and accentuated exercise-induced increases in ANG II (44%). Systolic blood pressure and MAP were also higher during exercise plus caffeine; however, these increases were secondary to the effects of caffeine on resting blood pressure. No significant differences were observed in heart rate, skin temperature, or rectal temperature. These findings indicate that caffeine can alter the cardiovascular response to dynamic exercise in a manner that may modify regional blood flow and conductance.

angiotensin II; forearm vascular conductance; adenosine receptors

BECAUSE OF ITS PURPORTED ROLE as an ergogenic aid (8, 19, 35), the use of caffeine during exercise is a common practice among both athletes and nonathletes (35). Although numerous studies have examined the effects of this methylxanthine on metabolism during exercise, few have focused on its concomitant action on the cardiovascular system.

Under resting conditions, caffeine has been shown to cause increases in blood pressure (25, 27, 38) and systemic vascular resistance (6, 38). Moreover, it can provoke elevations in plasma renin activity (5, 27, 39, 41) and presumably in plasma ANG II concentrations. Enhanced blood pressure and systemic vascular resistance responses have also been observed during dynamic exercise (cycling exercise) (38, 39). However, potential mechanisms underlying these effects are unclear.

Caffeine is a well-known adenosine-receptor antagonist (15, 16), and adenosine can cause vasodilation in several regional circulations (particularly in the forearm) (32–34) as well as attenuate the release of renin (2). As a result, blockade of adenosine receptors could cause cardiovascular and hormonal effects similar to those induced by caffeine. Because muscle contractions cause the release of adenosine (20), blockade of adenosine receptors might account for caffeine's reported cardiovascular effects during exercise.

In light of these observations, we tested the hypothesis that caffeine-induced augmentations in blood pressure during dynamic exercise are associated with reductions in regional blood flow [i.e., forearm blood flow (FBF)] and increases in plasma ANG II concentrations.

METHODS

Ten trained cyclists (7 women and 3 men) gave written informed consent to participate in this study, which was approved by the Human Subjects Committee of the University of California, Davis. Trained cyclists were chosen to increase the reliability of measuring the cardiovascular response during exercise because reliability is greater in highly trained subjects than it is in the less well trained (19). The mean physical characteristics of the subjects were as follows: age, 30 ± 0.3 (SE) yr; weight, 60 ± 0.2 kg; body fat, 19 ± 0.4%; and maximal oxygen uptake ($\dot{V}O_{2max}$) 49.0 ± 0.2 ml·kg^{-1}·min^{-1}. Subjects selected for this study were nonhabitual caffeine users (<100 mg or the equivalent of 1 cup of coffee per day), nonsmokers, and non-oral-contraceptive users (women) and were actively cycling between 100 and 300 miles/wk.

Experimental Design

Each subject performed four separate 100-min protocols arranged in a double-blind, 2 × 2 arrangement of exercise (bicycle ergometer at 65% $\dot{V}O_{2max}$) or rest with placebo or caffeine treatment. On experiment days, each subject reported to the Human Performance Laboratory between 6 and 10 AM after a 12-h fast. All subjects abstained from consumption of caffeinated foods/beverages for at least 4 days before each session. The first session consisted of a body composition analysis by means of underwater weighing and a graded maximal exercise test on an electronically braked bicycle ergometer (SensorMedics, Ergo-metrics 800s) to volitional fatigue. Before the remaining four test protocols, each subject was familiarized with the testing equipment and fitted with a custom mercury-in-Silastic strain gauge for measurement of FBF via venous occlusion plethysmography. In addition, each subject completed a 3-day diet assessment before each session, which was analyzed with FoodProcessor II (E.S.H.A. Macintosh version 2.1) to determine any caffeine consumption. Each of the four remaining sessions was separated by at least 1 wk.

To control for potential alterations in thermogenic (37) and hemodynamic (22) responses to dynamic exercise during different phases of the menstrual cycle, female subjects

performed their protocols during the follicular phase of menses (*days 1–10* of cycle). Therefore, female subjects performed the first two sessions within a 10-day period, followed 1 mo later by the final two sessions.

Each subject was instructed to abstain from any form of exercise for 24 h before each testing session. Immediately on arrival at the laboratory, the subject rested quietly in a chair, followed by withdrawal of a venous blood sample taken from the median cubital vein for measurement of baseline concentrations of plasma caffeine and ANG II. The subject was then fitted with the custom strain gauge, skin and rectal thermistors, blood pressure cuff, and three-lead electrocardiogram (ECG).

The following measurements were assessed at 20-min intervals throughout the entire protocol in the following sequence: skin temperature (T_{sk}), rectal temperature (T_{re}), heart rate (HR), arterial blood pressure, and FBF. Because previous studies have shown that plasma caffeine levels peak at 60 min postingestion (6, 27, 34), blood samples for the measurement of both plasma caffeine and plasma ANG II were taken at baseline and again at 60 min postingestion.

Caffeine (6 mg/kg body wt; Sigma Chemical) and fructose (6 mg/kg) were administered in gel capsules with 250 ml of water. All protocols were separated by at least 4 days to allow for resensitization of each individual to the physiological effects of caffeine (13, 28). During the exercise protocol, after 45 min of rest, subjects performed 55 min of continuous exercise on an electronically braked bicycle ergometer (SensorMedics, Ergo-metrics 800s) at a workload of 65% of $\dot{V}O_{2max}$. All protocols were conducted in an environmental chamber controlled at 25°C.

Measurement of cardiovascular variables. HR was determined from ECG recordings by averaging R-R intervals over 15-s time periods. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were obtained from the left brachial artery via manual auscultation. Mean arterial pressure (MAP) was calculated (⅔DBP + ⅓SBP) for both rest and exercise.

FBF was measured by using the indirect plethysmographic venous occlusion technique of Whitney (45). A strain gauge was mounted on the right forearm, 2 in. distally from the elbow joint, and set at a tension of 15 g. The forearm was suspended above the venostatic point (by a wrist sling during exercise or a platform during rest). Flow recordings were taken during the first 4 min of each 20-min interval. Blood flow to the hand was abolished by occlusion of the radial artery by using a wrist cuff inflated to 250 mmHg. A venous occlusion cuff, which cycled on and off at 50 mmHg every 15 s, was placed over the brachial artery. The strain gauge was calibrated on the arm before and after each bout of exercise. Forearm vascular conductance (FVC) was calculated as FBF divided by MAP during both rest and exercise.

Body temperature was monitored by using surface thermistors (model 409A, Yellow Springs Instruments) for T_{sk} and a rectal thermistor probe (model 401, Yellow Springs Instruments) for T_{re}. Skin thermistors were placed at five different locations (forearm, thigh, chest, abdomen, and forehead). The arithmetic mean of each site was used to calculate mean T_{sk} (1).

Blood Analysis

Plasma caffeine was determined by HPLC. Plasma (1 ml) was deproteinized by using 1 ml of an internal standard solution consisting of 40 mg/l 7-(2-hydroxyethyl)theophylline acetonitrile. After centrifugation, 15 ml of supernatant were injected onto an isocratic HPLC system by using a Waters Spherisorb ODS-2-column (150 × 4.6 × 5 mm). The mobile phase consists of 7% (vol/vol) acetonitrile in deionized water pumped at a flow rate of 2.5 ml/min by using a Perkin-Elmer LC 250 pump. Caffeine and the internal standard were detected at 278 nm by using a Perkin-Elmer LC-95 visual spectrum variable wavelength detector. Elution of caffeine occurred at 5.09 min. The lower limit of caffeine detection was 2.5 μg/ml.

ANG II levels were determined in blood samples obtained from the median cubital vein. Samples were collected in tubes containing 100 μl EDTA and centrifuged at 3,000 *g* for 10 min at 4°C. Before measurement, ANG II was extracted from the plasma by adsorption onto octadecylsiyl columns (Sep-Pak, C_{18}). The columns were prepared by washing with 6 ml of 1% trifluroacetic acid in 99% distilled water and eluted with 3 ml of 60% acetonitrile in 1% trifluroacetic acid in 39% distilled water. A radioimmunoassay was performed on the extracted plasma by using a peptide radioimmunoassay kit (radioimmunoassay kit RIK 7002, Peninsula Laboratories). The lower limit of detection was 1 pg/ml.

Statistical Analysis

Significant differences between rest vs. exercise and placebo vs. caffeine conditions were determined by using Friedman's one-way ANOVA with repeated measures on rank sums. When a significant interaction occurred between mode (i.e., rest or exercise) and supplement (caffeine or placebo), the location of pairwise differences was determined by using Neuman-Keuls post hoc analysis. Significant differences in plasma caffeine or ANG II concentrations were determined by using a Mann-Whitney nonparametric test. Data are presented as means ± SE. Statistical significance was accepted at $P \leq 0.05$.

RESULTS

Because there were no significant differences in the response to caffeine between genders, both male and female data were pooled for analysis. Before any treatment, plasma levels of caffeine were below the lower limit of detection by HPLC (<2.5 μg/ml) (Table 1). Sixty minutes after caffeine ingestion, plasma caffeine levels were 9.4 ± 1.1 and 8.8 ± 1.0 μg/ml at rest and during exercise, respectively (Table 1).

Table 1. *Plasma caffeine and angiotensin II values at baseline and 60 min after ingestion of a single-dose administration of caffeine or placebo*

	Rest		Exercise	
	Baseline	60 min Postingestion	Baseline	60 min Postingestion
		Placebo		
Plasma caffeine				
μg/ml	≤2.5	≤2.5	≤2.5	≤2.5
μM	≤12.8	≤12.8	≤12.8	≤12.8
Angiotensin II				
pg/ml			7.7±1.0	15.0±2.3*
pM			7.4±0.9	14.3±2.2*
		Caffeine		
Plasma caffeine				
μg/ml	≤2.5	9.4±1.1*†	≤2.5	8.8±1.0*†
μM	≤12.8	49.0±5.6*†	≤12.8	45.0±4.9*†
Angiotensin II				
pg/ml			12.1±1.9	25.3±2.3*†
pM			11.5±1.8	24.2±2.2*†

Values are means ± SE. Measurements were taken at baseline and at 60 min postingestion. *$P \leq 0.05$ vs. baseline values. †$P \leq 0.05$ placebo vs. caffeine values.

Before exercise, caffeine caused significant increases in SBP (20 and 40 min postingestion) and MAP (40 min post ingestion) compared with placebo conditions (Fig. 1). During dynamic exercise plus caffeine, SBP and MAP were higher than in placebo conditions at 60 min postingestion. However, the magnitudes of caffeine-induced increases in resting and exercise blood pressure were not significantly different from respective control conditions. Furthermore, no statistical interaction was found between the effects of caffeine and exercise on blood pressure. Finally, DBP and HR were unaffected by caffeine (Fig. 1).

At rest, there were no significant differences between placebo and caffeine conditions in T_{re} [36.8 ± 0.2 °C (placebo) and 37.0 ± 0.2 °C (caffeine)] or T_{sk} [32.7 ± 0.2 °C (placebo) and 32.4 ± 0.2 °C (caffeine)]. During exercise, T_{re} increased to peak values of 37.8 ± 0.5°C (placebo) and 37.3 ± 0.5°C (caffeine) at 80 min. Additionally, T_{sk} increased to peak values of 34.0 ± 0.2°C (placebo) and 34.3 ± 0.2°C (caffeine) at 80 min. There were no significant differences between placebo and caffeine conditions during exercise.

Resting FBF and FVC were unaffected by caffeine consumption. However, during dynamic exercise, caffeine attenuated the rise of FBF after administration of caffeine at 60 and 80 min posttreatment and diminished FVC after 60, 80, and 100 min (Fig. 2).

Compared with placebo conditions, ANG II levels were elevated during dynamic exercise plus caffeine (Table 1). There were no significant differences between baseline values (Table 1).

DISCUSSION

The results of this investigation provide evidence that caffeine alters the hemodynamic response to dynamic exercise. Specifically, ingestion of 6 mg/kg caffeine attenuated exercise-induced increases in FBF and FVC and enhanced the concomitant increase in plasma ANG II. In addition, arterial blood pressure was higher during exercise compared with placebo conditions. However, we found no significant interaction between the two conditions (caffeine vs. placebo). Because caffeine caused similar increases in resting and exercise blood pressure, we concluded that the effects of caffeine on resting blood pressure were responsible for the higher blood pressures observed during exercise.

The dose of caffeine used in this study (6 mg/kg) was selected on the basis of its similarity to doses (3–6 mg/kg) previously shown to increase blood pressure (at rest or during exercise) without provoking side effects, intolerance, or a decrease in exercise performance (27, 35, 38, 39). A dose of 6 mg/kg caffeine is similar to that contained in two to three cups of drip brewed or Italian coffee (23). This dose of caffeine also produced plasma concentrations of the drug (8.8–9.4 μg/ml) that were within the range (4.7–11.5 μg/ml) of those observed in previous studies (5, 6, 27).

We also controlled for potential tolerance to the effects of caffeine consumption because hemodynamic responses to caffeine may be blunted in regular users (6, 13, 14). In fact, tolerance to caffeine can occur after only 3 consecutive days of use (6, 14). Consequently, all subjects in the present study refrained from consumption of caffeine for at least 4 days before participating in any of the protocols to resensitize the system to the effects of this drug (13).

It is possible that the action of caffeine on FBF, FVC, and ANG II was caused by a reduction in plasma volume induced by the mild diuretic effects of this drug (3). These effects are related to increases in glomerular

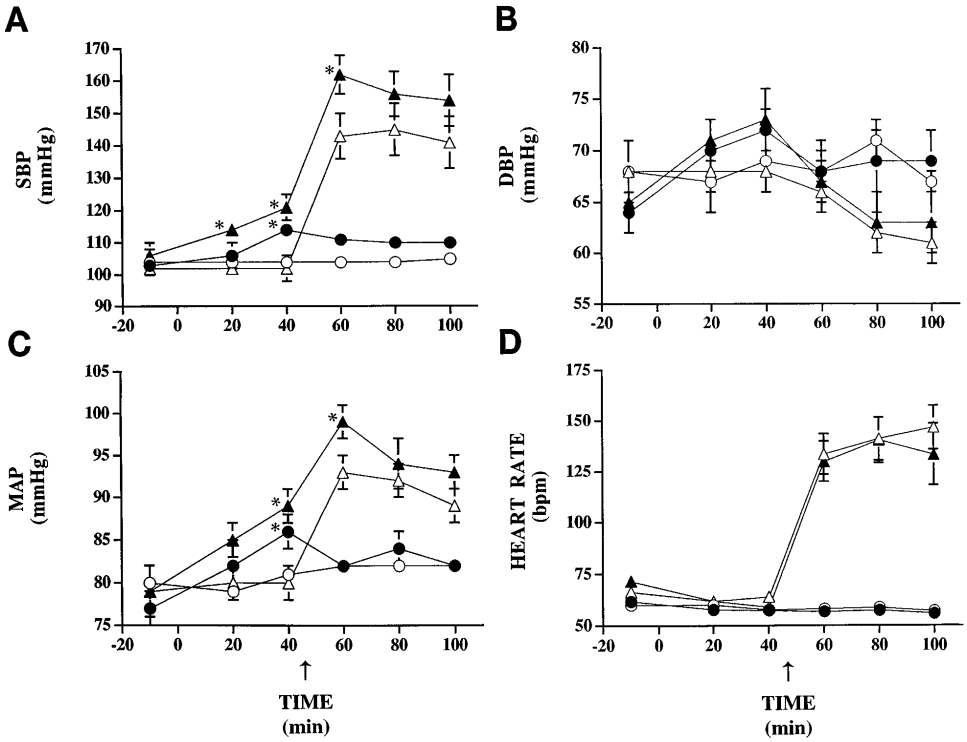

Fig. 1. Mean changes in systolic blood pressure (SBP; *A*), diastolic blood pressure (DBP; *B*), mean arterial pressure (MAP; *C*), and heart rate (*D*) in response to ingestion of 6 mg/kg caffeine during rest and 65% maximal oxygen consumption. bpm, Beats/min. ○, Rest-placebo; ●, rest-caffeine; △, exercise-placebo; ▲, exercise-caffeine. Arrows, onset of exercise. *$P \leq 0.05$ caffeine vs. respective placebo at same time point.

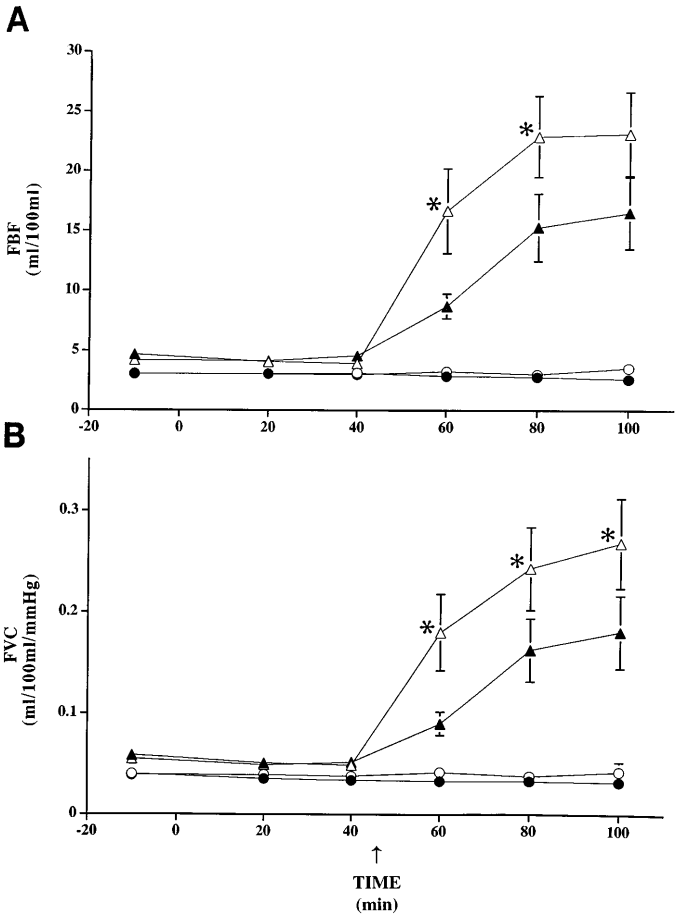

Fig. 2. Mean changes in forearm blood flow (FBF; *A*) and forearm vascular conductance (FVC; *B*) in response to ingestion of 6 mg/kg caffeine during rest and 65% maximal oxygen consumption. ○, Rest-placebo; ●, rest-caffeine; △, exercise-placebo; ▲, exercise-caffeine. Arrow, onset of exercise. *$P \leq 0.05$ caffeine vs. respective placebo at same time point.

filtration rate and inhibition of tubular reabsorption (3). This series of events was unlikely, however, because caffeine has been found to have no effect on plasma volume during dynamic exercise of similar or greater intensities and durations than those performed in the present study (12, 18, 42).

The caffeine-induced attenuation of FBF during exercise may have involved reductions in skeletal muscle and/or cutaneous blood flow. On the basis of our results, we cannot dismiss either possibility. However, it is not unreasonable to assume that cutaneous blood flow was reduced by caffeine, because vasoconstriction occurs in inactive skeletal muscle in response to exercise (44). Consequently, a reduction in cutaneous blood flow could lessen the dissipation of body heat and adversely affect temperature regulation and exercise performance. Nevertheless, in agreement with Falk et al. (12), we observed no effect of caffeine on T_{sk} or T_{re} during exercise. Thus it appears that potential caffeine-induced reductions in cutaneous blood flow during exercise were not of a magnitude capable of affecting temperature regulation.

The caffeine-induced alterations in hemodynamics during exercise in this study were probably due to antagonism of adenosine receptors. Caffeine has been shown to inhibit both A_1 and A_2 adenosine receptors (31). The A_2 receptors are primarily responsible for adenosine's vasodilatory effects (29). In this regard, infusions of adenosine in humans can cause increases in blood flow in the forearm and in the splanchnic and coronary circulations (11, 32). Our observation that caffeine attenuated the increase in FBF during exercise suggests that this drug also may offset adenosine-provoked dilation in other regional circulations under these circumstances.

The effects of caffeine on exercise hemodynamics may also have been due to its inhibitory action on A_1 receptors. For example, stimulation of A_1 receptors diminishes plasma renin activity (2), resulting in a reduced production of ANG II (29). During dynamic exercise, plasma ANG II is elevated to levels that can augment the corresponding pressor response, attenuate increases in myocardial blood flow, and enhance reductions in splanchnic and renal blood flow (36). Moreover, the cutaneous circulation is responsive to the vasoconstrictor effects of ANG II (17, 26). Consequently, the caffeine-induced increase in ANG II concentrations during exercise could account, at least in part, for the concomitant increase in blood pressure and relative reduction in FBF observed in the present study.

A_1-receptor activation also causes presynaptic inhibition of norepinephrine release from postganglionic sympathetic nerve endings (43). In humans, inhibition of nucleoside transport causes accumulation of adenosine in the synaptic cleft that is associated with enhanced forearm norepinephrine appearance rate and forearm vascular resistance in response to lower body negative pressure (30). Thus inhibition of A_1 receptors by caffeine may have enhanced norepinephrine release in our subjects and contributed to the enhanced pressor response to exercise. Nonetheless, this possibility is unlikely because previous research has found that caffeine does not enhance the plasma norepinephrine response to dynamic exercise (19).

Adenosine additionally attenuates the release of epinephrine from the adrenal medulla (41). Epinephrine, which is an α- and β-adrenergic-receptor agonist, is a potent vasoconstrictor in the skin because this organ does not possess β_2-receptors (44). In addition, exercise-provoked increases in plasma epinephrine concentrations can be enhanced by caffeine treatment (19, 41). Thus we speculate that our finding of caffeine-reduced FVC during exercise may have been due, in part, to a reduction in cutaneous blood flow that was secondary to an increase in the release of epinephrine from the adrenal medulla.

Another action of adenosine is its excitatory effect on carotid and aortic chemoreceptors (4) and sensory nerves in the kidney (21), heart (10), and skeletal muscle (7). Activation of these afferent nerves results in increases in sympathetic nerve activity, blood pressure, and HR (4, 7, 9). If caffeine had modified the reflex effects of adenosine on the cardiovascular system in the present study, attenuation of the blood pressure and HR responses to exercise would have been expected.

The fact that this outcome did not occur suggests that our dose of caffeine did not block the reflex effects of adenosine on the cardiovascular system and/or that adenosine levels were below the threshold necessary to cause cardiovascular reflexes. In any case, it is apparent that any inhibitory action of caffeine on adenosine-induced cardiovascular reflexes did not play a predominant role in the overall effect of this methylxanthine on the hemodynamic response to exercise.

Although caffeine can inhibit phosphodiesterase, which could mediate the action of hormones and neurotransmitters via increased cAMP (3), this mechanism of action probably did not contribute to the outcome of our study. This is because phosphodiesterase inhibition only occurs at large caffeine concentrations that would be toxic in vivo (3), and we observed no such effects.

In summary, the results of this investigation indicate that caffeine can modify cardiovascular and hormonal responses to dynamic exercise. We found that ingestion of 6 mg/kg of caffeine enhanced plasma ANG II levels and attenuated corresponding increases in FBF and FVC. Caffeine also caused increases in SBP and MAP during dynamic exercise that were secondary to increases in resting blood presure. Interestingly, reductions in FBF and FVC were not associated with any changes in body temperature. Because caffeine antagonizes the cardiovascular effects of adenosine, these results suggest that the effects of this purported ergogenic aid on exercise hemodynamics are mediated by inhibition of adenosine receptors.

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