Caffeine Decreases Exercise-Induced Myocardial Flow Reserve

Mehdi Namdar, MD,* Pascal Koepfli, MD,* Renate Grathwohl, MD,* Patrick T. Siegrist, MD,* Michael Klainguti, MD,* Tiziano Schepis, MD,* Raphael Delaloye, MD,* Christophe A. Wyss, MD,* Samuel P. Fleischmann, MD,* Oliver Gaemperli, MD,* Philipp A. Kaufmann, MD*†
Zurich, Switzerland

OBJECTIVES We studied the acute effect of caffeine on myocardial blood flow (MBF) at rest and exercise in healthy volunteers at normoxia and during acute exposure to simulated altitude.

BACKGROUND Caffeine is a widely consumed stimulant, although its cardiovascular safety remains controversial and its effect on MBF is unknown.

METHODS 15O-labeled H2O and positron emission tomography (PET) were used to measure regional MBF at rest and immediately after supine bicycle exercise in healthy volunteers at normoxia (n = 10; mean workload, 175 W; 98% predicted; mean age, 27 ± 6 years) as well as during hypoxia, simulating an altitude of 4,500 m by inhalation of a mixture of 12.5% oxygen (n = 8; 148 W; 78% predicted; mean age, 29 ± 4 years). Measurements were repeated 50 min after oral ingestion of caffeine (200 mg). Myocardial flow reserve (MFR) was calculated as the ratio of hyperemic to resting MBF.

RESULTS Resting MBF was not affected by caffeine at normoxia (1.05 ± 0.36 ml/min/g vs. 1.17 ± 0.27 ml/min/g; p = NS), although it was significantly increased at hypoxia (1.71 ± 0.41 ml/min/g vs. 2.22 ± 0.49 ml/min/g; p < 0.001). By contrast, exercise-induced hyperemic MBF decreased significantly at normoxia (2.51 ± 0.58 ml/min/g vs. 2.15 ± 0.47 ml/min/g; p < 0.05) and hypoxia (5.15 ± 0.79 ml/min/g vs. 3.98 ± 0.83 ml/min/g; p < 0.005 vs. baseline; p < 0.005 vs. normoxia). The MFR decreased by 22% at normoxia (2.53 ± 0.69 to 1.90 ± 0.49; p < 0.01) and by 39% at hypoxia (3.13 ± 0.60 to 1.87 ± 0.45; p < 0.005; p < 0.05 vs. normoxia).

CONCLUSIONS In healthy volunteers, a caffeine dose corresponding to two cups of coffee (200 mg) significantly decreased exercise-induced MFR at normoxia and was even more pronounced during exposure to altitude. (J Am Coll Cardiol 2006;47:405–10) © 2006 by the American College of Cardiology Foundation

Because coffee is consumed in large amounts all over the world (1), characterization of its cardiac effects in people is important. Coffee drinking has been associated with increased cardiovascular morbidity and mortality in some (2–4) but not all (5) prospective and epidemiological studies, whereas a recent trial found a beneficial effect of coffee (6). Similarly, the role of coffee in the development of cardiovascular risk factors is controversial. Coffee drinking has been linked to both elevated (7) and reduced (8) but also to unchanged blood pressure (9) and serum cholesterol levels (10), depending on the brewing method (11).

The influence of caffeine on myocardial blood flow (MBF) during physical stress is largely unknown. Caffeine might directly affect MBF by blocking coronary adenosine A2 receptors (12) or, indirectly, via catecholamine release causing alpha-2 receptor-mediated coronary vasomotion (7). Because caffeine consumption has been found to blunt dipyridamole-induced hyperemia via adenosine A2 receptor antagonism (13), caffeinated foods or beverages must be avoided before pharmacologic radionuclide stress perfusion imaging. Nothing is known, however, about the impact of caffeine on exercise-induced hyperemia. Although during exercise extravascular resistive forces (14) might in part counteract adenosine-mediated metabolic vasodilation, hyperemic response to exercise may largely depend on intrinsic adenosine production (15). Because adenosine is released by myocytes inversely related to myocardial oxygen tension to act via adenosine receptors on coronary vascular smooth muscle cells to induce coronary vasodilation, this mechanism might be susceptible to adenosine receptor antagonism by caffeine. This could be even more pronounced during states of decreased oxygen delivery because adenosine production is linked to myocardial partial oxygen tension (pO2) (16) and the major stimulus for adenosine production seems to be an imbalance between oxygen delivery and oxygen demand.

Thus, the goals of the present study were: 1) to assess the effect of caffeine on resting and exercise-induced hyperemic MBF and on the resulting myocardial flow reserve (MFR), and 2) to study the impact of caffeine on exercise-induced MBF during simulated hypoxia mimicking comparable states of oxygen deprivation in ischemic coronary artery disease (CAD) (17).
Study population. Eighteen healthy volunteers (7 women, 11 men) were included in the study. The patients had no history of and low clinical probability for CAD (18). Normal lipid profiles were found in each individual. All patients were habitual coffee drinkers (at least two cups of coffee per day) but refrained from ingesting caffeinated beverages or food for 36 h before the study.

Study protocol. For group 1 (n = 10; mean age, 27 ± 6 years), with the patient’s feet attached to a bicycle ergometer (model 380 B, Siemens-Elema AG, Bulach, Switzerland), MBF was measured at rest and during supine bicycle exercise-induced hyperemia at normoxia corresponding to 450 m above sea level (i.e., Zurich ground altitude). Exercise was started at 60 W, and workload was increased every minute to target the same protocol used at baseline. During the 50-min break, a 20-min transmission scan was acquired for the purpose of attenuation correction of all emission scans.

Group 2 (n = 8; mean age, 29 ± 4 years) underwent the same study protocol as group 1 while exposed to a hypoxia simulating an altitude of 4,500 m throughout the study. Altitude simulation (hypoxic hypoxia) was achieved by inhalation of moistened hypoxic gas mixture (through a mouthpiece) consisting of approximately 12.5% oxygen (O₂) in nitrogen (N₂), resulting in an oxygen pressure of 90 mm Hg (17,21). Heart rate and peripheral arterial oxygen saturation (SₐO₂) were recorded with a finger pulse oximeter (Nellcor N-200E, Nellcor Inc., Hayward, California). After achieving a cardiorespiratory steady state as assessed by a steady end-tidal CO₂ partial pressure, SₐO₂, and heart rate, positron emission tomography (PET) measurements were performed as previously reported (17,21). Exercise was started at 60 W, and workload was increased every minute to target the same average rate-pressure product (RPP) values as found at normoxia to allow meaningful comparison as previously reported (17). During the examination, blood pressure was continuously monitored by a Finapress BP Monitor (BOC Inc., Englewood, Colorado) and recorded at one-minute intervals. The electrocardiogram was monitored continuously throughout the procedure, and a 12-lead electrocardiogram was recorded at baseline and every minute during exercise at each level as well as during five minutes of recovery. Venous blood samples to determine serum caffeine concentration and lipid values were drawn before baseline resting scan and before post-caffeine bicycle exercise.

Image acquisition. The MBF was assessed at the PET Center of the University Hospital in Zurich on a GE Advance positron emission tomograph (GE Medical Systems, Milwaukee, Wisconsin). An intravenous bolus of 500 to 700 MBq ¹⁵O-water was infused over 20 s at a rate of 10 ml/min to assess MBF. The line was then flushed for another 2 min. The dynamic image sequences were: 14 × 5 s, 3 × 10 s, 3 × 20 s, and 4 × 30 s.

Image processing. The obtained sinograms were corrected for attenuation and reconstructed on a Sun workstation (Sun Microsystems, Mountain View, California) using standard reconstruction algorithms. Images were transferred to a Transtec 2200 PC (Transtec Computer AG, Bulach, Switzerland) and analyzed with the pmod software package (PMOD Technologies Ltd., Zurich, Switzerland) designed and validated at our institution (19,22,23) using myocardial images generated directly from the dynamic ¹⁵O-water study by means of linear dimension reduction of the dynamic sinograms. Regions of interest were drawn within the left ventricular cavity and myocardium on consecutive image planes and projected onto the dynamic ¹⁵O-water images to generate blood time-activity curves. These curves were fitted to a single tissue compartment tracer kinetic model to give values of regional and global MBF (ml/min/g) (24–26).

Coronary resistance and MFR. To account for the variability of coronary driving pressure, the ratio of mean arterial pressure to MBF was calculated as an index of coronary resistance as previously described (25,26). The MFR was defined as the ratio of MBF during physiologic hyperemia (induced by exercise) to MBF at rest and was calculated for baseline and repeated measurements.

Statistical analysis. Data are reported as mean values ± standard deviation. Hemodynamic and PET data at rest and during stress were compared using the paired Student t test; p values of <0.05 were considered to indicate statistical significance. Based on an expected standard deviation in minimal coronary resistance of 5 (19), a minimum clinically relevant difference in minimal coronary resistance of 20% between baseline and caffeine, alpha = 0.05 and a power (1-beta) of 0.8, the number of patients necessary (in each group) was calculated to be fewer than 10.

RESULTS

All patients tolerated the simulated altitude subjectively well and without objective impairment.

Hemodynamic findings. In both groups, heart rate, blood pressure, and RPP were not affected by caffeine, neither at
rest nor at peak exercise (Table 1). This holds true also for the post-exercise period during MBF measurement in group 1 (RPP baseline, 11,868 ± 1,933 vs. caffeine, 13,073 ± 2,534; p = NS) and group 2 (RPP, 12,827 ± 2,350 vs. 12,361 ± 1,890, p = NS). In group 1, 98% (= 175 W), and in group 2, 78% (= 148 W) of the predicted maximum workload was achieved.

**Serum caffeine and lipid levels.** At baseline, caffeine level averaged 0.52 ± 1.28 μmol/l in 3 patients but was immeasurably low in 15 patients. Fifty minutes after caffeine ingestion, serum caffeine was 14.5 ± 8.9 μmol/l. Caffeine had no influence on total cholesterol (4.4 ± 0.8 mmol/l vs. 4.3 ± 0.8 mmol/l; p = NS), nor on low-density lipoprotein (2.4 ± 0.7 mmol/l vs. 2.5 ± 0.7 mmol/l; p = NS), nor high-density lipoprotein levels (1.5 ± 0.5 mmol/l vs. 1.4 ± 0.3 mmol/l; p = NS).

**Respiratory parameters.** There was a significant hypoxic hyperventilation in patients at 4,500 m with a decrease in end-tidal CO2 partial pressure from 36 ± 2 mm Hg to 33 ± 2 mm Hg (p < 0.01). Exercise induced an increase in respiratory frequency (p < 0.01). Respiratory frequency during hypoxia was not affected by caffeine, neither at rest (15 ± 3 breaths/min at baseline vs. 14 ± 1 breaths/min after caffeine, p = NS) nor during exercise (23 ± 6 breaths/min vs. 24 ± 5 breaths/min, p = NS).

**MBF and MFR. GROUP 1 (NORMOXIA).** Mean resting MBF showed a non-significant trend to increase (p = 0.14) after caffeine ingestion, whereas bicycle exercise-induced hyperemic MBF decreased significantly by 13% (p < 0.05) (Figs. 1 and 2), resulting in a decrease in physiological (bicycle exercise-induced) MFR of 22% from 2.53 ± 0.69 to 1.90 ± 0.49 (p < 0.01) (Fig. 3) (Table 2).

**GROUP 2 (HYPOXIA).** The MBF values during hypoxia were significantly higher than those found in group 1 at normoxia. Mean resting MBF increased significantly after caffeine ingestion (+31%, p < 0.001), whereas bicycle exercise-induced hyperemic MBF decreased by 22% (p < 0.005) (Table 2). Physiological (bicycle exercise-induced) MFR (Fig. 3) decreased by 39% from 3.13 ± 0.6 to 1.87 ± 0.45 (p < 0.005; p < 0.05 vs. normoxia).

**Coronary resistance. GROUP 1 (NORMOXIA).** Coronary resistance at rest showed a non-significant decrease after caffeine ingestion (110 ± 23 to 98 ± 19; p = NS). After bicycle exercise, resistance decreased significantly compared with rest (p < 0.001), but was higher after caffeine compared with baseline (46 ± 15 vs. 54 ± 15, p < 0.001).

**GROUP 2 (HYPOXIA).** Coronary resistance was lower during hypoxia throughout the study compared with normoxia. Caffeine further decreased resistance at rest from 68 ± 18 to

---

**Table 1. Hemodynamics**

<table>
<thead>
<tr>
<th></th>
<th>Normoxia</th>
<th>Caffeine</th>
<th>p</th>
<th>Hyoxia</th>
<th>Caffeine</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SBP (mm Hg)</strong></td>
<td>124 ± 12</td>
<td>120 ± 11</td>
<td>NS</td>
<td>129 ± 12</td>
<td>125 ± 16</td>
<td>NS</td>
</tr>
<tr>
<td><strong>DBP (mm Hg)</strong></td>
<td>73 ± 10</td>
<td>71 ± 11</td>
<td>NS</td>
<td>69 ± 8</td>
<td>70 ± 11</td>
<td>NS</td>
</tr>
<tr>
<td><strong>MAP (mm Hg)</strong></td>
<td>107 ± 10</td>
<td>104 ± 9</td>
<td>NS</td>
<td>109 ± 10</td>
<td>104 ± 14</td>
<td>NS</td>
</tr>
<tr>
<td><strong>HR (beats/min)</strong></td>
<td>66 ± 13</td>
<td>65 ± 11</td>
<td>NS</td>
<td>77 ± 11</td>
<td>78 ± 21</td>
<td>NS</td>
</tr>
<tr>
<td><strong>RPP (mm Hg × beats/min)</strong></td>
<td>8,179 ± 1,933</td>
<td>7,771 ± 1,037</td>
<td>NS</td>
<td>9,996 ± 2,265</td>
<td>9,860 ± 3,362</td>
<td>NS</td>
</tr>
</tbody>
</table>

| Peak exercise     |                |                |      |                |                |      |
| **SBP (mm Hg)**   | 152 ± 21       | 159 ± 19       | NS   | 152 ± 11       | 154 ± 10       | NS   |
| **DBP (mm Hg)**   | 90 ± 9         | 95 ± 4         | NS   | 88 ± 5         | 92 ± 6         | NS   |
| **MAP (mm Hg)**   | 152 ± 8        | 156 ± 5        | NS   | 163 ± 5        | 167 ± 7        | NS   |
| **HR (beats/min)**| 153 ± 4        | 154 ± 8        | NS   | 168 ± 9        | 164 ± 8        | NS   |
| **RPP (mm Hg × beats/min)** | 23,173 ± 3,487 | 24,382 ± 2,360 | NS   | 25,591 ± 1,774 | 25,274 ± 2,287 | NS   |

DBP = diastolic blood pressure; HR = heart rate; MAP = mean blood pressure; RPP = rate pressure product; SBP = systolic blood pressure.
After bicycle exercise, resistance was significantly decreased compared with rest \( (p < 0.001) \), but was higher after caffeine compared with baseline \( (20.5 \text{ vs. } 28 \pm 7, p < 0.005) \).

**DISCUSSION**

Caffeine decreases exercise-induced hyperemic MBF, resulting in a significant decrease in physiologic MFR. This is significantly more pronounced at high-altitude exposure, where resting flow significantly increases and hyperemic flow response is blunted significantly more by caffeine than at normoxia. Although the long-term effect of caffeine consumption on human health is the subject of an ongoing controversy \( (27,28) \), we have studied the acute impact of caffeine consumption on MBF and found no significant increase in resting MBF by caffeine during normoxia, in agreement with Bottcher et al. \( (13) \). By contrast, at hypoxia—with which resting MBF was higher than at normoxia, in line with our previous results \( (21) \)—we found an increase in resting MBF after caffeine. This may in part be explained by the fact that caffeine might stimulate local and systemic catecholamine release \( (7) \), adding to the hypoxia-induced sympathetic activation, which contributes importantly to the regulation of MBF \( (29) \).

Because MBF is mainly determined by cardiac workload (i.e., RPP) at rest and during physical exercise \( (30) \), bicycle exercise workload at altitude (group 2) was stepwise increased to target the same RPP as at normoxia (group 1) to allow meaningful comparison of the hyperemic MBF responses between the two groups \( (17) \). At hypoxia, target RPP was attained with a significantly lower workload level than at normoxia because of the hypoxia-induced increase in sympathetic tone. Nevertheless, exercise-induced hyperemic flow response at altitude was significantly increased compared with normoxia, despite the lower workload. Caffeine caused an increase in coronary resistance resulting in a decrease in exercise-induced hyperemic MBF, which was more pronounced during altitude exposure than at normoxia, supporting that compensatory mechanisms of hypoxia-induced increase in MBF are in part adenosine-mediated and, thus, susceptible to caffeine. This is in line with previous reports in experimental animals in which an increase in MBF after aminophylline infusion has been attributed to a stimulation of alpha-1-adrenoreceptors at baseline conditions \( (31) \), whereas during situations with increased adenosine release, the inhibitory effect of aminophylline on adenosine receptors predominated over the beneficial effects of alpha-1-adrenoreceptor stimulation.

Although we found a significantly increased coronary resistance and decreased MFR after caffeine consumption, our study design does not allow comment on the long-term effect of caffeine. Nevertheless, because impairment of coronary endothelial function \( (32) \) and specifically impaired MFR response as assessed by PET \( (33) \) have been shown to be independent predictors of unfavorable cardiovascular outcome, our results may at least raise questions about safety in patients with impaired MFR, such as CAD patients. Furthermore, our results support that exercise-induced hyperemic flow response may at least in part be antagonized by caffeine, indicating that in people, adenosine seems involved in the regulation of MBF at exercise. This may suggest that the advice to refrain from methylxanthine-containing foods and beverages before undergoing a radionuclide perfusion scan should not be confined to pharmacological stress \( (34) \), but could possibly be extended to physical exercise stress.

Although caffeine has been shown to impair pharmacologically induced hyperemia by adenosine-receptor antagonism, no data exist so far on the impact of caffeine on MBF at exercise, reflecting daily life activity. Therefore, we have used bicycle exercise stress for stimulation of hyperemic MBF.

**Study limitations.** A first limitation of this study is that patients did not exercise at their individual but rather at the maximal predicted level of effort, however, this was because exercise workload in the supine position usually matches approximately 70% of the workload achieved in the upright position.
position (35,36). In addition, physical capacity at high altitudes of 4,500 m has been found to match 70% of the capacity at sea level (37). Thus, the workload in the present study was reasonably high, because 98% and 78% of the predicted workload was achieved at normoxia and at hypoxia, respectively.

Second, data acquisition was obtained in the immediate post-exercise period when the cardiac power output is considerably decreased and when flow is also expected to decrease rapidly. Therefore, we assessed the impact of caffeine on an MBF value representing the average value over five minutes of recovery, rather than the peak MBF value at maximal exercise. These suboptimal conditions were chosen as a compromise to avoid excessive motion artifact during scanning. However, the fact that every patient was used as his or her own control strengthens our results, and the validity of this method has been recently documented in a repeatability study (19).

Furthermore, no patients with CAD were included, because this would have been beyond the scope of testing our hypothesis on the interaction of caffeine and myocardial perfusion during exercise stress. Certainly, further studies will now need to assess the impact of caffeine in CAD patients.

In summary, our results show that within 50 min, oral intake of a common caffeine dose corresponding to two cups of coffee (200 mg) significantly decreases bicycle exercise-induced hyperemic myocardial flow response at normoxia and is even more pronounced during exposure to simulated altitude. Although these findings seem not to have a clinical importance in healthy volunteers, they may raise safety

### Table 2. Myocardial Blood Flow, Flow Reserve, and Coronary Resistance

<table>
<thead>
<tr>
<th></th>
<th>Normoxia</th>
<th></th>
<th>Hyoxia</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Caffeine</td>
<td>p</td>
<td>Baseline</td>
</tr>
<tr>
<td>MBF rest (ml/min/g)</td>
<td>1.05 ± 0.36</td>
<td>1.17 ± 0.27</td>
<td>NS</td>
<td>1.71 ± 0.41</td>
</tr>
<tr>
<td>MBF bicycle (ml/min/g)</td>
<td>2.51 ± 0.58</td>
<td>2.15 ± 0.47</td>
<td>&lt;0.05</td>
<td>5.15 ± 0.79</td>
</tr>
<tr>
<td>Coronary resistance, rest (mm Hg/ml/min/g)</td>
<td>110 ± 23</td>
<td>98 ± 19</td>
<td>&lt;0.05</td>
<td>68 ± 18</td>
</tr>
<tr>
<td>Coronary resistance, bicycle (mm Hg/ml/min/g)</td>
<td>46 ± 15</td>
<td>54 ± 15</td>
<td>&lt;0.001</td>
<td>20 ± 5</td>
</tr>
<tr>
<td>MFR (relative values)</td>
<td>2.53 ± 0.69</td>
<td>1.9 ± 0.5</td>
<td>&lt;0.01</td>
<td>3.13 ± 0.6</td>
</tr>
</tbody>
</table>

MBF = myocardial blood flow; MFR = myocardial flow reserve.

REFERENCES


