Caffeine Reduces Dipyridamole-Induced Myocardial Ischemia

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The mechanism of action of coronary vasodilation after dipyridamole may be based on inhibition of cellular uptake of circulating endogenous adenosine. Since caffeine has been reported to be a competitive antagonist of adenosine we studied the effect of caffeine on the outcome of dipiridamole-^{201}Tl cardiac imaging in one patient. During caffeine abstinence dipyridamole induced myocardial ischemia with down-slope ST depressions on the ECG, and reversible perfusion defects on the scintigrams. When the test was repeated 1 wk later on similar conditions, but now shortly after infusion of caffeine (4 mg/kg), the ECG showed no, and the scintigrams only slight signs of ischemia. We conclude that when caffeine abstinence is not sufficient, the widespread use of coffee and related products may be responsible for false-negative findings in dipyridamole-^{201}Tl cardiac imaging.

In the diagnostic workup of suspected coronary artery stenosis thallium-201 (^{201}Tl) myocardial scintigraphy after dipyridamole infusion has been reported to be a valuable alternative for patients who are unable to exercise adequately (*1*). Moreover, dipyridamole infusion with cardiac imaging may be of value both in determining cardiac risks in patients undergoing peripheral vascular surgery (*2*), and in predicting future cardiac events after acute uncomplicated myocardial infarction (*3*). Dipyridamole elicits strong vasodilation, which may induce subendocardial ischemia in regions with coronary stenosis as a result of an increased pressure gradient and a decrease in the distal coronary pressure (*1*). The vasorelaxing effect of dipyridamole may be based on inhibition of cellular uptake of adenosine, resulting in increased plasma concentrations of this endogenous vasoactive nucleoside (*4*). In in vitro studies it has been shown that xanthine derivatives like caffeine and theophylline act as competitive antagonists of adenosine, and recently we have reported on the antagonism between caffeine and exogenous adenosine within the human cardiovascular system (*5*). This case report now shows indirect evidence for an antagonism

between caffeine and endogenous adenosine within the specific vascular bed of the human heart, thereby calling forth practical as well as theoretic implications.

CASE REPORT

A 46-yr-old man, who had been treated for essential hypertension for more than 12 yr, experienced a myocardial infarction in April 1988. Electrocardiographically, the infarction was located in the inferior wall. Laboratory analysis showed elevated plasma enzyme levels of CK (1340 U/l, normal < 180 U/l) and SGOT (209 U/l, normal < 45 U/l). The patient recovered well without signs of heart failure or angina pectoris. The antihypertensive medication (atenolol 50 mg o.d., nifedipine retard 20 mg o.d.) was continued because of hypertension. Further physical examination revealed no abnormalities.

Two months after the infarction a dynamic exercise test was performed. At a load of 130 W on a bicycle ergometer the exercise test was stopped because of ST depressions on the precordial leads of the electrocardiogram (ECG). The heart rate measured 134 bpm and the patient had no complaints. For further evaluation dipyridamole-^{201}Tl myocardial imaging was performed to prove the suspected silent ischemia. This test was done after a caffeine abstinence of 36 hr and on the day of the test no medication was taken. Basal plasma caffeine concentration was measured by reversed phase high performance liquid chromatography (HPLC) (*6*) and was < 0.1 mg/l. Before, during, and after dipyridamole administration blood pressure and heart rate were recorded at 2-min intervals by a

dinamap 1846 (Critikon). Dipyridamole (0.56 mg/kg in 10 ml NaCl 0.9%) was infused intravenously in 4 min by an infusion pump with the patient in the supine position. Seven minutes after the start of dipyridamole infusion 3.0 mCi (110 MBq) of [^{201}Tl]chloride were injected i.v. rapidly. During and after dipyridamole an ECG was registered every minute for 12 min. Subsequently, initial ^{201}Tl scintigraphy was performed with a gamma camera (Siemens ZLC 370) with a converging collimator in the anterior (0°), 40°, and 70° left anterior oblique (LAO) position, each for 9 min. Delayed (redistribution) images were obtained after 3 hr.

Dipyridamole clearly induced signs of ischemia with downslope ST depressions on the precordial leads of the ECG, maximally 6 mm in the seventh minute after finishing the infusion of dipyridamole (Figure 1). The patient had only slight complaints of tiredness and being not well. Compared to basal values, mean arterial blood pressure (mean ± s.d.) remained unchanged (102.5±3.5 vs. 101.6±3.2 mmHg) but heart rate increased from 73.9±3.9 to 102.3±9.5 bpm after dipyridamole. The left part of Figure 2 represents the initial and delayed cardiac images and shows a reversible inferoseptal defect on the anterior view, a reversible inferoapical defect on the 40° LAO view, and a reversible inferoposterior defect on the 70° LAO view indicating local myocardial ischemia. In the LAO 40 view there is also evidence for a residual defect on the delayed images, consistent with the old inferior infarction.

One week later, dipyridamole-^{201}Tl myocardial scintigraphy was repeated on exactly the same conditions, with one exception: 30 min before the dipyridamole infusion, caffeine (4 mg/kg in 20 ml Nacl 0.9%) was administered intravenously within 15 min. Before and just after caffeine infusion plasma caffeine concentrations were determined, and amounted to < 0.1 and 8.8 mg/l, respectively. During this test no changes in blood pressure or heart rate occurred as a result of caffeine infusion. After dipyridamole the heart rate increased from 78.8±3.6 to 88.3±2.5, but mean arterial blood pressure remained unchanged (108.5±11.3 vs. 108.4±4.7). The ECG showed no abnormalities at all during this test (Figure 1). The right part of Figure 2 illustrates that the initial and delayed cardiac images were almost similar, with only a minor reversible inferoseptal defect on the anterior view.

For quantitative analysis of the myocardial scintigrams regional defects were scored as a percentage of maximal activity (7). After caffeine abstinence the percentage scores differed between the initial and delayed images with 2%, 2%, and 5% in the anterior, LAO 40 and LAO 70 view, respectively. After pretreatment with caffeine these differences were zero in the LAO 40 and LAO 70 view, and numbered 4% in the anterior view. These quantitative data agree with the visual analysis of the images. Later on coronary angiography was performed and showed severe three-vessel disease with impaired left ventricular function. Consequently, the patient underwent subsequent coronary revascularization.

COMMENTS

This case report illustrates that caffeine in a plasma concentration of 8.8 mg/l reduces dipyridamole-induced myocardial ischemia. Plasma caffeine concentrations up to 14 mg/l have already been reported after drinking two cups of coffee (6). In healthy subjects plasma caffeine half-life shows a large range and may be as long as 8.5 hr (8), and this may even be prolonged by oral contraceptive drugs, cimetidine, or impaired hepatic function. Therefore, more attention should be paid to both the duration and the compliance of caffeine abstinence (no coffee, tea, coca cola, chocolate, cocoa, and caffeine containing analgesics) before dipyridamole-^{201}Tl myocardial scintigraphy is performed in order to exclude false-negative findings. Further studies with larger groups of patients and with different dose schedules for caffeine are needed to draw up justified criteria with respect to the required duration of caffeine abstinence prior to dipyridamole thallium imaging. As reported recently maintenance oral theophylline ther-
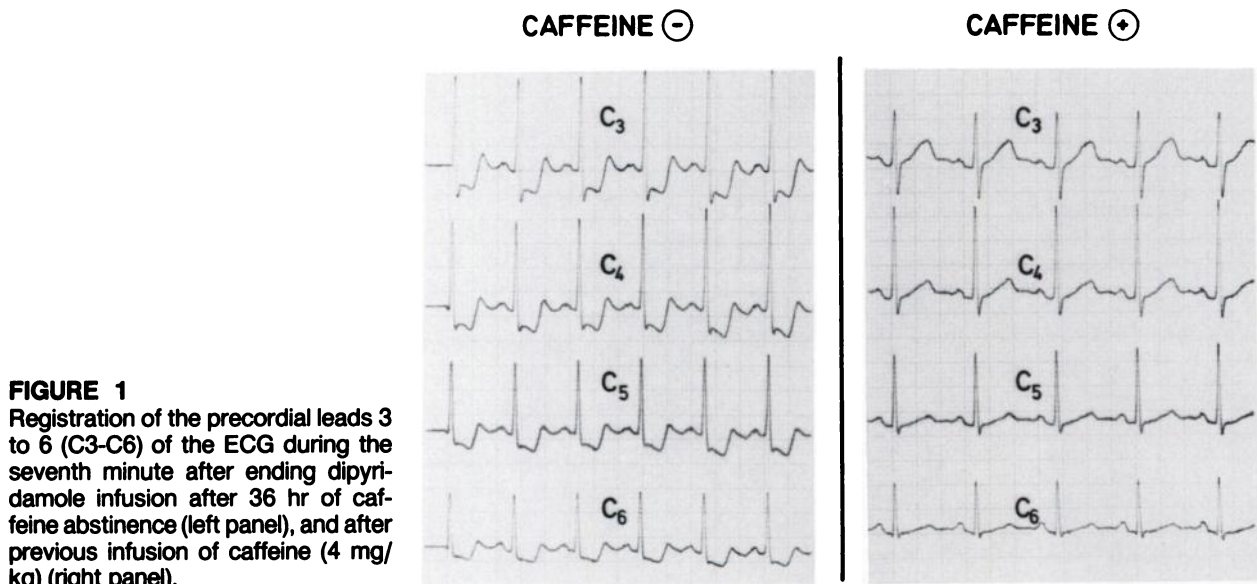
CAFFEINE ⊖   CAFFEINE ⊕

FIGURE 1
Registration of the precordial leads 3 to 6 (C3-C6) of the ECG during the seventh minute after ending dipyridamole infusion after 36 hr of caffeine abstinence (left panel), and after previous infusion of caffeine (4 mg/kg) (right panel).
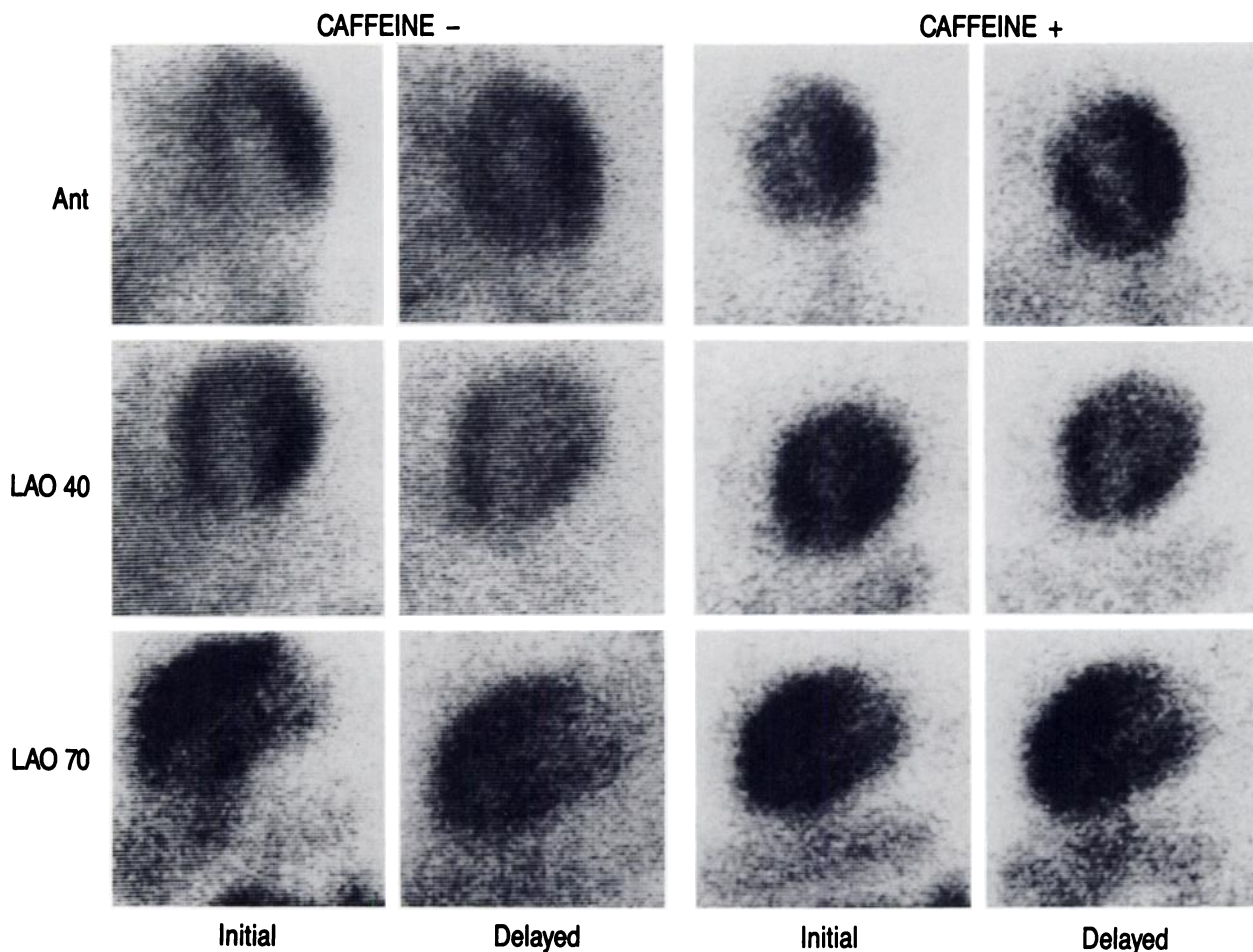
FIGURE 2
Initial and delayed dipyridamole-^{201}Tl images of the myocardium from three directions (anterior (ANT), 40° LAO (LAO 40), 70° LAO (LAO 70) after 36 hr of caffeine abstinence (left part) and shortly after infusion of caffeine (4 mg/kg) (right part). Despite small differences in the level of contrast between both panels, the figure clearly shows that the initial images reveal reversible perfusion defects on all views after caffeine abstinence, whereas only one minor reversible defect in the anterior view was observed after caffeine.

apy has to be stopped temporarily because of similar reasons (*9*).

Possible pharmacologic mechanisms for the coronary vasodilation after dipyridamole include (a) inhibition of the enzyme phosphodiesterase; (b) potentiation of prostacyclin-induced effects; (c) an increase of prostacyclin biosynthesis; or (d) a reduction of the reuptake of adenosine by inhibiting the nonspecific symmetric nucleoside transporter in red blood cells and the endothelium, thereby increasing the plasma levels of the endogenous vasodilator adenosine (*10*). The currently observed antagonism between caffeine and dipyridamole supports the latter mechanism since caffeine shows adenosine-antagonistic properties within the human cardiovascular system. Like dipyridamole, caffeine has also been reported to inhibit the enzyme phosphodiesterase. However, if this mechanism would have been of relevance a synergism rather than antagonism between caffeine and dipyridamole was expected to occur.

Besides practical consequences, the current results also elicit some interesting theoretic implications. Endogenous adenosine has been hypothesized to play an important role in several physiologic and pathophysiologic processes of the human heart. For instance, adenosine may be involved in the regulation of coronary blood flow during ischemia (*11*), and in the regulation of cardiac stress tolerance via presynaptic inhibition of noradrenaline release (*12*), whereas an altered adenosine sensitivity may be of importance in the development of the sick sinus syndrome (*13*), and of hypertrophic cardiomyopathy (*14*). Since we have now found evidence for an antagonism between endogenous adenosine and caffeine within the human heart, the widespread use of coffee and other caffeinated beverages might be of more interest in the management of cardiovascular diseases.

The aforementioned implications all are based on observations in only one patient. However, the results of dipyridamole cardiac imaging during caffeine absti-

nence were strongly positive, electrocardiographically as well as scintigraphically, whereas the results of the same test on similar conditions were impressively reduced after caffeine. Realizing that the reproducibility of ^{201}Tl myocardial imaging is as high as 91% (15), the extreme differences between both tests can not be attributed to chance.

In conclusion, caffeine, in plasma concentrations which are likely to occur in daily life, may significantly reduce the myocardial ischemia induced by dipyridamole in patients with coronary artery disease. Consequently, this widely used drug may be responsible for false negative findings in dipyridamole-^{201}Tl cardiac scintigraphy. This single observation warrants further systematic research on the interaction between caffeine and dipyridamole.

ACKNOWLEDGMENT

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