False-Negative Dipyridamole-Thallium-201 Myocardial Imaging After Caffeine Infusion

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The vasodilator effect of intravenously administered dipyridamole may be caused by an increase in endogenous plasma adenosine levels. We evaluated the effect of caffeine, an adenosine receptor antagonist, on the diagnostic results of dipyridamole-^{201}Tl myocardial imaging in eight patients with coronary artery disease. Caffeine infusion significantly attenuated the dipyridamole-induced fall in blood pressure and the accompanied increase in heart rate. The infusion of dipyridamole alone resulted in chest pain and ST-segment depressions on the electrocardiogram in four patients, whereas none of these problems occurred when the tests were repeated after caffeine. In six of eight patients, caffeine was responsible for false-negative dipyridamole-^{201}Tl tests. Semiquantitive scores of the dipyridamole-induced ^{201}Tl perfusion defects were decreased by caffeine from 9.0 ± 0.9 to 2.0 ± 1.1 points ($p < 0.05$). Computerized analysis revealed a caffeine-mediated reduction in the percent reversibility of the images from 46% ± 16% to 6% ± 10% ($p < 0.05$). We conclude that the use of caffeinated products prior to dipyridamole-^{201}Tl testing may be responsible for false-negative findings.

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The use of intravenous dipyridamole in conjunction with ^{201}Tl myocardial perfusion imaging has been well established as a diagnostic procedure in cardiology for several years (*1*). This method is especially useful for evaluation of the presence of coronary artery disease in patients who are unable to perform physical exercise (*1*). In particular, dipyridamole-^{201}Tl imaging has been shown to be useful in determining cardiac risks prior to elective peripheral vascular surgery (*2*) and in predicting future cardiac events after acute uncomplicated myocardial infarction (*3*). The basic principle underlying the use of dipyridamole in these diagnostic tests is the induction of nearly maximal coronary vasodilation, resulting in a (relative) hypoperfusion of substenotic regions, which subsequently can be visualized by ^{201}Tl imaging (*1*).

The mechanism of action of dipyridamole-induced vasodilation appears to be an inhibition of cellular uptake of adenosine, resulting in increased plasma concentrations of this endogenous vasodilating nucleoside (*4*). Caffeine, a widely used stimulant, has potent adenosine antagonistic properties, both in vitro (*5*), as well as in human in vivo studies (*6,7*). The pharmacologic interaction between caffeine and dipyridamole and its potential effect on ^{201}Tl imaging has, to the best of our knowledge, never been studied. A recently described case report on this item initiated the present study (*8*). Accordingly, we investigated the potential inhibitory effect of caffeine on dipyridamole-^{201}Tl imaging in man. Our findings indicate that the use of caffeine prior to dipyridamole infusion may result in false-negative findings on ^{201}Tl scintigraphy.

PATIENTS AND METHODS

Eight patients (3 men, 5 women) were studied. The results of one of these patients have been described previously (*8*). Their mean (±s.d.) age was 59.3 ± 6.9 yr (range: 46–66 yr). The patients were referred for clinically indicated ^{201}Tl myocardial scintigraphy with dipyridamole infusion, and they were asked to abstain strictly from caffeine for at least 36 hr prior to the scheduled test. Patients who had reversible perfusion defects on this first test were asked to participate in the study. Eight patients consented and had a second dipyridamole-^{201}Tl test 1 wk after the first test. The protocol of the second test was performed identically to the first one, however, caffeine was infused prior to the test.

Some relevant characteristics of the patients are given in Table 1. Informed consent was obtained after explanation of the protocol. The study protocol was approved by the local Hospital Ethical Review Board.

Dipyridamole-^{201}Tl Imaging

Before each test, theophylline-containing preparations and dipyridamole medication were stopped for 36 hr. All tests were performed in the morning hours after an overnight fast with the patients in the supine position. The patients were not allowed to take any medication on the test day until scintigraphy was completely finished. Dipyridamole-^{201}Tl imaging was performed according to a standardized protocol. After cannulation of an antecubital vein, dipyridamole (0.56 mg/kg) was infused in 4 min by an automatic syringe infusion pump. Before, during, and after dipyridamole infusion, blood pressure (by a Dinamap 1846, Critikon), heart rate, and a 12-lead electrocardiogram were recorded each minute until the start of ^{201}Tl imaging. For the second test, the administration of caffeine (4 mg/kg intravenously in 10 min) was started 30 min before the start of dipyridamole

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infusion. Oral ingestion of caffeine was not employed because this potentially could have complicated the interpretation of the results by an additional coffee-induced increase in the uptake of ^{201}Tl in the splanchnic region. Plasma-caffeine concentrations were measured by reversed-phase HPLC (*9*) at the beginning of each test and for an additional 20 min after completion of caffeine infusion.

Three minutes after completion of the dipyridamole infusion, 90 MBq of ^{201}Tl were administered as a bolus injection. Myocardial scintigraphy (initial images) were started 3 min later. Imaging was performed in three different positions using a gamma camera (Siemens ZLC 370) with a converging collimator in the anterior (0°) and in the 40° and 70° left anterior oblique (LAO) position for 9 min each. Delayed redistribution images were obtained in identical views.

Analysis of ^{201}Tl Myocardial Scintigrams

Myocardial images were analyzed subjectively by blinded observers without background correction or computer processing according to the method described by Rigo et al. (*10*). Briefly, the *caffeine-free* tests images were mixed with the scintigrams of the *caffeine* tests. Subsequently, the matching initial and delayed views were displayed as pairs and interpreted by two observers (one cardiologist and one nuclear medicine physician) without knowledge of the test dates and conditions (caffeine abstinence or caffeine infusion), as well as without knowledge of any personal or clinical characteristic. Each image was divided into five equal segments. Thus, a total of 15 segments were available for analysis in a three-view study. The images were interpreted by consensus and the degree of reversibility was scored on a semiquantitive scale: 0 = no redistribution, 1 = mild redistribution, and 2 = (near) complete redistribution. The ^{201}Tl images were judged as positive when there was at least one segment with a score of 2 or two or more (not adjacent) segments with a score of 1. Slight perfusion defects at the location of the apex were interpreted as "apical thinning," being a normal finding in the human heart.

In addition to the semiquantitive analysis, all images were stored on magnetic tape and mailed to the Cardiovascular Nuclear Imaging Laboratory at Yale University (New Haven, CT), for uniform processing and quantitation with use of a previously validated computer program (*11*). After modified interpolative background substraction, circumferential count distribution profiles were generated, displaying mean count density in 36 segments. The segment with the highest mean density was designated as 100%, and all remaining segments were displayed relative to this maximal value. This allowed comparison of the relative distribution of ^{201}Tl uptake in serial studies. The size of the myocardial perfusion defect was defined by integrating the hypoperfused area under the lower limit of normal curves (mean − 2 s.d., derived from a data base of rest ^{201}Tl images in normal healthy subjects). The hypoperfused area was expressed as a proportion (×100) of the total potentially visualized normal myocardium. This value is unitless and reflects both the extent and severity of the myocardial perfusion defect. The total defect size was defined as the sum of defects on the three views.

TABLE 1
Patient Characteristics (n = 8)

Age (year)	59.3 ± 6.9 (46–66)
Weight (kg)	81.0 ± 15.5 (59.0–90.7)
Height (m)	1.70 ± 0.08 (1.61–1.87)
Quetelet index (kg/m^2)	28.0 ± 3.9 (22.8–31.8)
Sex (Male/Female)	3 M/5 F
Electrocardiography	ST-T abnormalities (5 patients)
	cLBBB† (1 patient)
	Old myocardial infarction (2 patients)
Coronary artery disease*	Proven in five patients

* Definite coronary artery disease proven by coronary angiography and/or by a history of myocardial infarction. In the remaining three patients with suspected coronary artery disease, coronary angiography was not yet performed.

† cLBBB: complete left bundle branch block.

Statistical Analysis

Results are presented as a mean values ± s.e., unless indicated otherwise. The semiquantitive scores and the computerized data of the myocardial images were analyzed by a paired Wilcoxon test. Since the data on blood pressure and heart rate showed a Gaussian distribution, analysis was performed by paired Student t-tests. Differences were considered to be statistically significant at p values < 0.05 (two-tailed).

RESULTS

Caffeine Blood Levels

The baseline plasma-caffeine concentrations were below the level of detection (<0.1 mg/liter) in 14 tests. In the other two tests, the plasma-caffeine levels were 0.7 and 1.1 mg/liter, indicating an acceptable compliance with respect to caffeine abstinence in all tests. In the second test, plasma-caffeine concentrations averaged 9.7 ± 1.3 mg/liter after the infusion of caffeine.

Hemodynamic Response

During the first (caffeine-free) test, baseline systolic and diastolic blood pressure were 165.2 ± 8.6 mmHg and 89.6 ± 3.3 mmHg, respectively. During dipyridamole infusion, systolic and diastolic blood pressure gradually decreased to 144.8 ± 9.2 mmHg and 76.8 ± 3.2 mmHg in the tenth minute, respectively ($p < 0.01$ versus baseline for both parameters). Mean heart rate increased from 71.2 ± 3.1 bpm to 86.5 ± 4.6 bpm ($p < 0.001$). Because of the change of systolic blood pressure and heart rate in opposite directions during dipyridamole infusion after caffeine abstinence, the rate pressure product did not change significantly: 11,794 ± 830 at the beginning versus 12,480 ± 934 mmHg bpm at the end (p = not significant).

During the second test, baseline values of systolic and diastolic blood pressure prior to dipyridamole infusion, but after caffeine administration were slightly but not significantly higher than in the first test: 178.2 ± 7.9 mmHg and 92.1 ± 2.8 mmHg, respectively. In the tenth minute of dipyridamole infusion, these values were not different: 177.1 ± 7.9 and 88.8 ± 2.8 mmHg, respectively. After previous administration of caffeine, mean heart rate increased during dipyridamole infusion from 70.3 ± 3.2 bpm to 73.4 ± 3.5 bpm (p = not significant). Figure 1 shows the course of the percentage dipyridamole-induced changes of blood pressure and heart rate with and without prior infusion of caffeine.

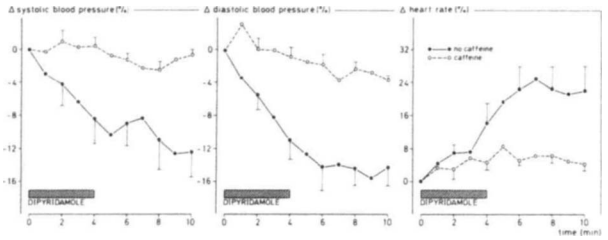

FIGURE 1. The course of the mean (±s.e.) percentage changes in blood pressure and heart rate during and after infusion of dipyridamole (0.56 mg/kg), with (dashed lines) and without (solid lines) previous administration of caffeine (4 mg/kg i.v.). During the 10-min period, the mean percentage fall in systolic blood pressure in the first versus the second test numbered −8.5% ± 2.6% versus −0.6% ± 0.6% ($p < 0.05$), respectively. For diastolic blood pressure and heart rate, these values amounted to −11.3% ± 1.2% versus −1.2% ± 0.9% ($p < 0.01$), and 16.6% ± 4.3% versus 5.4% ± 1.3% ($p < 0.05$), respectively.

Electrocardiogram

Dipyridamole-induced ST-segment depressions (≤1 mm) associated with chest pain, suggestive of myocardial ischemia, occurred in four patients after caffeine abstinence. However, after caffeine administration, none of those patients showed ST-segment depression nor experienced retrosternal discomfort as a result of dipyridamole infusion.

Thallium-201 Scintigraphy

Figure 2 summarizes the results of the blinded semiquantitive analysis of the eight pairs of ^{201}Tl images. After caffeine abstinence, all dipyridamole-^{201}Tl tests showed reversible ^{201}Tl defects and were judged as positive. In contrast, after caffeine administration, six of eight patients had negative tests. In two patients, near complete redistribution occurred in more segments after caffeine, but both patients showed an obvious decline in the number of segments showing mild redistribution (Fig. 2). During the first caffeine-free test, the semiquantitive score of the scintigrams averaged 9.0 ± 0.9 points (range: 6–12), and this score decreased to 2.0 ± 1.1 points (range: 0–7) in the second test after caffeine ($p < 0.05$).

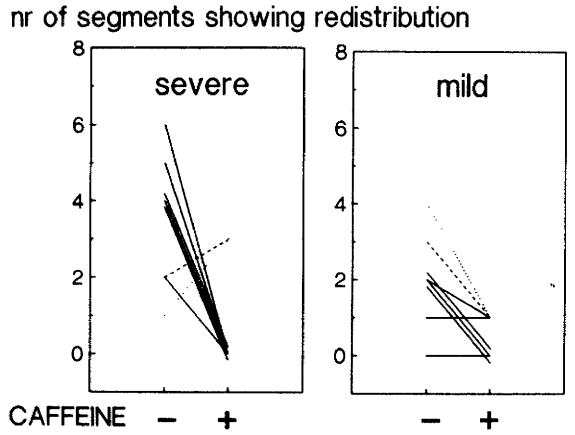

FIGURE 2. Individual data on the number of segments showing (near) complete (left panel) or mild (right panel) redistribution in the dipyridamole-^{201}Tl images. Two individuals with deviant responses are presented by dotted and dashed lines, respectively, to show the corresponding data in the two panels.

The results of computer quantification of the images revealed comparable data. After caffeine abstinence, reversible perfusion defects were detected in seven patients, whereas after caffeine administration only one patient showed a (quantitively less pronounced) reversible perfusion defect. The quantitated mean percent reversibility of the perfusion defects in the first series of caffeine-free dipyridamole-^{201}Tl tests numbered 46% ± 16%, whereas this was only 6% ± 10% in the second series of tests after caffeine infusion (first versus second test: $p < 0.05$).

DISCUSSION

In this study, the systemic vasoactive effects of dipyridamole are clearly visualized by the distinct fall in blood pressure and the accompanied increase in heart rate. Furthermore, the coronary vasodilation after dipyridamole was visualized indirectly by showing reversible perfusion defects in the ^{201}Tl myocardial scintigrams. The present study shows that caffeine, at concentrations lower than 10 mg/liter, attenuates these dipyridamole-induced effects. Previous studies have shown that plasma-caffeine concentrations after drinking regular coffee range from 4.9 to 14.1 mg/liter (*9,12*). Therefore, the use of caffeinated products like coffee, tea, cacao, chocolate, and caffeine-containing analgesics prior to dipyridamole-^{201}Tl imaging potentially can be responsible for false-negative findings.

The current results might have been expected on theoretical grounds, especially because we previously described a false-negative test after caffeine ingestion in one patient with proven coronary artery disease (*8*). However, until now, neither the interaction between caffeine and dipyridamole, nor the effects of caffeine on the outcome of dipyridamole-^{201}Tl scintigrams have been studied systematically. Our findings have practical implications for the daily practice of dipyridamole-^{201}Tl imaging. In order to avoid false-negative test results, a caffeine-free interval prior to dipyridamole-^{201}Tl scintigraphy is recommended. One should consider that some patients referred for dipyridamole-^{201}Tl scintigraphy may have congestive heart failure and impaired hepatic function. This might prolong plasma half-lives for methylxanthines (*13*). Furthermore, according to the literature, caffeine already inhibits adenosine-induced vasodilation in man at plasma-caffeine concentrations below 5 mg/liter (*14*), and preliminary results from our department show that the hemodynamic response to dipyridamole infusion in healthy subjects is already attenuated at plasma-caffeine concentrations of 1 mg/liter (unpublished data). Thus, small amounts of caffeine may interfere with the pharmacologic mechanisms underlying dipyridamole-^{201}Tl imaging. Based on these aforementioned observations, one can calculate that a caffeine-free interval of 24 hr or more is needed to prevent

false-negative test results. However, we realize that this recommendation is rather speculative, and consequently more studies are needed to validate this point of view.

Dipyridamole-induced myocardial ischemia was observed in four of eight patients. Again, pre-treatment with caffeine completely abolished these dipyridamole-mediated effects. The maximal vasodilation of small arteries associated with a structural coronary stenosis may result in a reduction of subendocardial flow mediated by a coronary steal phenomenon or by a decreased perfusion pressure (*1*), and these mechanisms may account for the dipyridamole-induced myocardial ischemia. Alternatively, the dipyridamole-induced hemodynamic changes might have been responsible for the myocardial ischemia. However, this seems unlikely because cardiac oxygen consumption, as measured by the rate pressure product, was not increased by dipyridamole administration. In this view, the absence of myocardial ischemia in the caffeine tests may solely be based on the caffeine-mediated attenuation of the coronary vasodilation due to dipyridamole, and not on the inhibition of its hemodynamic effects. The finding that the number of segments with redistribution on the dipyridamole-^{201}Tl images was significantly less after caffeine (Fig. 2) supports this explanation.

In conclusion, the use of caffeine prior to dipyridamole-^{201}Tl imaging may result in false-negative test results. In view of the current results and the literature on the pharmacokinetics of caffeine, a caffeine-free interval prior to diagnostic dipyridamole-^{201}Tl testing seems required to maintain the diagnostic yield of this valuable test in patients suspect of coronary artery disease.

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