Serum Caffeine Levels After 24-Hour Abstention: Clinical Implications on Dipyridamole ^{201}Tl Myocardial Perfusion Imaging

Xiao Ming Zheng, PhD[1]; and Robert Charles Williams, CNMT[2]

[1]*School of Clinical Sciences, Faculty of Health Studies, Charles Sturt University, Wagga Wagga, New South Wales, Australia; and*
[2]*Wangaratta Nuclear Medicine, Base Hospital, Wangaratta, Victoria, Australia*

Background: Caffeine binds to the A2 receptors and inhibits adenosine's action of vasodilation or dipyridamole-induced vasodilation. Patients scheduled for ^{201}Tl myocardial perfusion using pharmacologic stress with dipyridamole or adenosine are advised to abstain from caffeine for 24 h before the test. This article reports on the residual serum caffeine levels of 36 patients after 24-h caffeine abstention and the clinical implications on dipyridamole ^{201}Tl myocardial perfusion imaging.
Methods and Results: Heart rate, diastolic blood pressure, and systolic blood pressure were recorded before and after dipyridamole infusion. Sixty-six percent of the patients had detectable plasma caffeine but all values were within the range of 0.1–0.8 mg/L. No statistically significant change in diastolic and systolic blood pressures after dipyridamole infusion has been observed. The mean heart rate was increased by 18% after dipyridamole infusion in patients with zero caffeine, and the heart rate increase was inversely correlated with the serum caffeine levels ($r = -0.22$) with 81% confidence.
Conclusion: A serum caffeine level of 2 mg/L is predicted to be the lower limit for false-negative dipyridamole ^{201}Tl myocardial perfusion. The increase of heart rate after dipyridamole infusion could be the simple indicator for the serum caffeine level. Rescheduling of the patient study or further adenosine challenge is necessary only if the heart rate increase is <5% after dipyridamole or adenosine infusion.
Key Words: caffeine; myocardial perfusion; dipyridamole; ^{201}Tl

Caffeine has been shown to induce false-negative ^{201}Tl myocardial perfusion using the pharmacologic stressor dipyridamole (*1,2*). Twenty-four or 12-h abstention from caf-

For correspondence or reprints contact: Xiao Ming Zheng, PhD, School of Clinical Sciences, Faculty of Health Studies, Charles Sturt University, Wagga Wagga, New South Wales 2678, Australia.
E-mail: xzheng@csu.edu.au

feine is recommended for patients undergoing dipyridamole- or adenosine-induced ^{201}Tl stress tests (*3–6*). The residual caffeine levels after 24-h abstention have been reported by Jacobson et al. (*7*) in a group of 86 patients, where 60% had no measurable caffeine and 6% had serum caffeine concentrations up to 5 mg/L. The residual caffeine levels after 12-h abstention have also been reported by Majd-Ardekani et al. (*8*) in a group of 70 patients. Only 36% of their patients had residual caffeine levels of zero. It has been suggested that a 12-h abstention from caffeine-containing products is insufficient and may result in false-negative myocardial perfusion scans (*8*). However, it is unclear what the lower limit of the plasma caffeine level is that would produce false-negative dipyridamole ^{201}Tl myocardial perfusion. The reported false-negative images were based on a high caffeine concentration of 9.7 ± 1.3 mg/L resulting from intravenous caffeine administration (*1,2*). Furthermore, it was implied that a lower caffeine concentration, as low as 1–5 mg/L, could inhibit the vasodilation effect of adenosine or dipyridamole (*1*).

Patients scheduled for dipyridamole ^{201}Tl myocardial perfusion are often reported to have inadvertently ingested beverages or medications that contain caffeine. Hurwitz et al. (*9*) reported an adenosine challenge protocol for such patients to avoid patient rescheduling and its associated costs. They claimed 96% success over a 3-y period. However, it is unclear how many of such patients actually had false-negative myocardial perfusion imaging without an adenosine challenge, given the half-life of plasma caffeine (4.9–5.7 h) (*7,10*). In other words, should the adenosine challenge protocol be used solely on the basis of the words of patients? It would be useful to have a simple indicator of the serum caffeine level and the likelihood of false-negative ^{201}Tl myocardial perfusion without any invasive blood test. Indeed, it would be very helpful to know the lower limit of serum caffeine level above which false-negative imaging would likely be produced.

In this article, we report on the residual serum caffeine

levels of 36 patients after a 24-h abstention, who were scheduled for dipyridamole ^{201}Tl stress tests, as well as the changes of heart rate and blood pressure associated with dipyridamole infusion. We predicted that a caffeine level of 2 mg/L be the lower limit for false-negative ^{201}Tl myocardial perfusion using dipyridamole and suggest that the change in heart rate be the simple indicator of serum caffeine level and the likelihood of false-negative myocardial perfusion.

MATERIALS AND METHODS

The experiment was designed to not change the current dipyridamole protocol in which supplemental exercise (bicycle ergometer) is routinely added to the dipyridamole stress (5,6). Thirty-six patients (21 female, 15 male; mean age, 69 ± 9 y; mean weight, 78 ± 16 kg) were recruited for this study. Data are expressed as mean ± SD.

Informed consent was obtained before the test. Five milliliters of blood were taken for analysis of the serum caffeine level before dipyridamole infusion. The plasma caffeine concentration was determined by standard high-performance liquid chromatography (i.e., liquid solvent extraction, evaporation, and concentration) (1,7,11).

Patients were given dipyridamole at 0.56 mg/kg over 3.5 min, and the blood pressures and heart rates were recorded at 0 and 4 min. Four minutes was used as an endpoint as we added supplemental exercise to dipyridamole stress.

RESULTS

Figure 1 shows a histogram of patient numbers and their residual serum caffeine levels. Sixty-six percent of the patients had detectable caffeine, but the detected caffeine concentrations were all within the range of 0.1–0.8 mg/L.

Figure 2 shows the diastolic and systolic blood pressure changes after dipyridamole infusion. The averaged diastolic and systolic blood pressures of all patients were decreased by 3 ± 10 mm Hg and 4 ± 13 mm Hg, respectively, but the changes were statistically insignificant. There is no correlation between the blood pressure and the serum caffeine level; this finding also can be seen in Table 1.

Figure 3 shows the percentage increases of heart rate associated with dipyridamole infusion versus the serum caffeine levels. The increase of heart rate was inversely correlated with the serum caffeine level ($r = -0.22$) with 81% confidence ($P = 0.19$).

Table 1 lists the percentage heart rate increases averaged for patients with small caffeine ranges of 0, 0–0.5, and 0.5–1.0 mg/L together with the systolic and diastolic blood pressure changes after dipyridamole infusion. The inverse linear relationship between the percentage heart rate increases and the serum caffeine levels is clearly seen, but it is not seen between the blood pressures and the plasma caffeine levels.

DISCUSSION

The number of our patients with detectable serum caffeine levels (66%) is significantly higher than the 40% of patients reported by Jacobson et al. (7) after 24-h caffeine abstention. Ninety-five percent of the general population has detectable caffeine levels without the caffeine abstention restriction (12). The caffeine levels detected from our patient group are all <0.8 mg/L, which is consistent with that of Jacobson et al. except for 5 of their 86 patients who had caffeine levels of 1.9–5.0 mg/L. Jacobson et al. reported that these 5 patients with high-level plasma caffeine had documented aortocoronary bypass surgery and liver function tests. Whether the aortocoronary bypass surgery
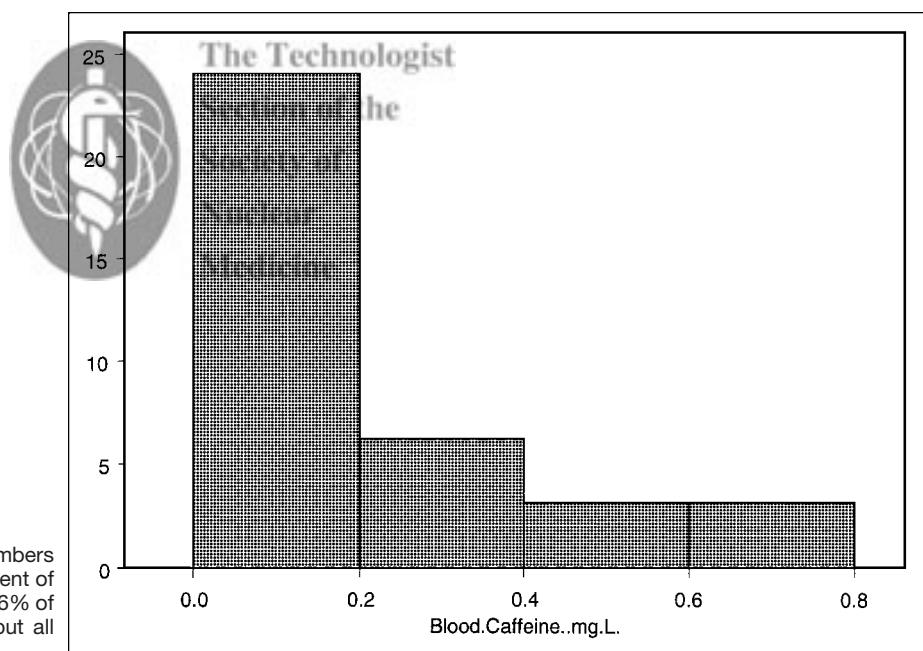

FIGURE 1. Histogram of patient numbers vs. serum caffeine levels. Thirty-four percent of patients have zero plasma caffeine, and 66% of patients have detectable caffeine level but all are <0.8 mg/L.
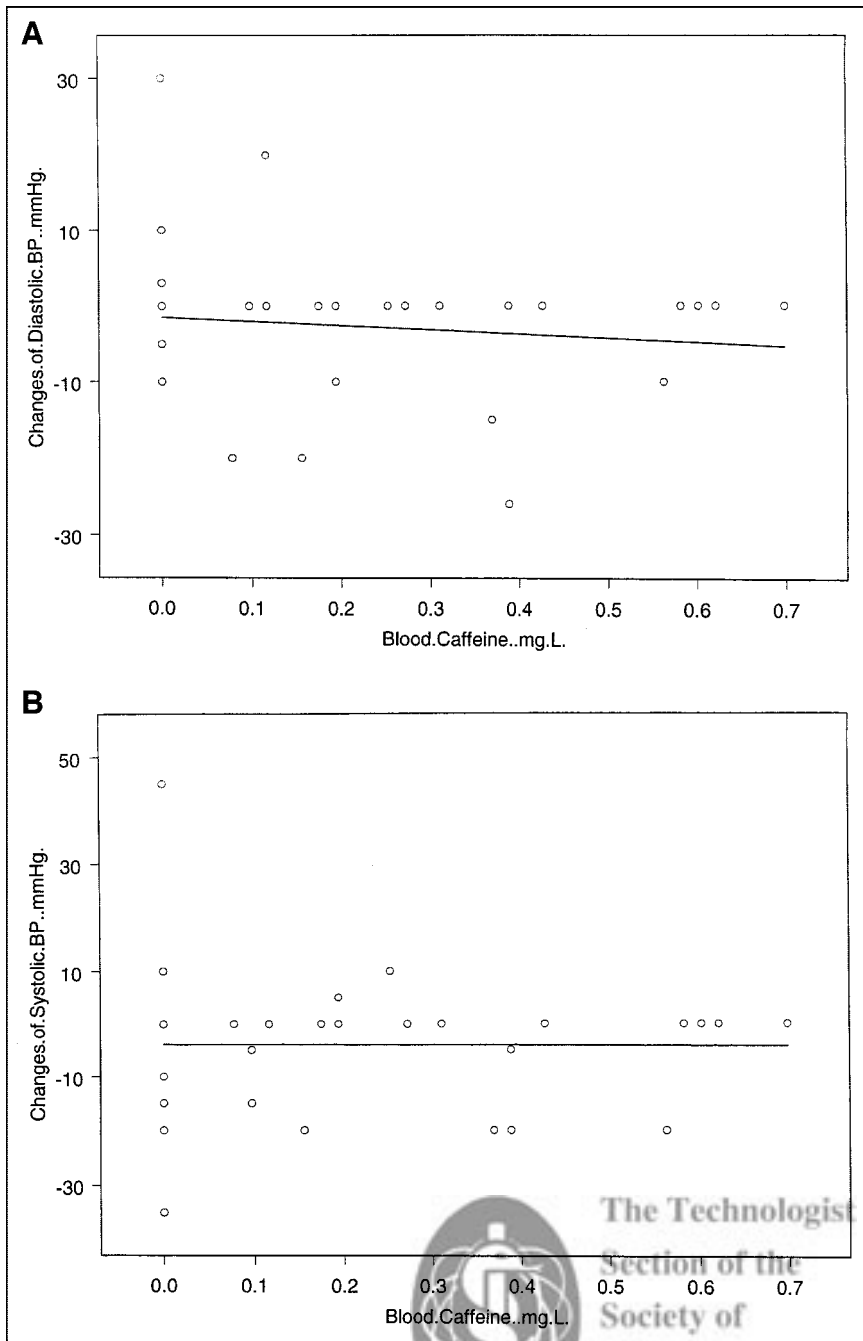
FIGURE 2. Changes of diastolic (A) and systolic (B) blood pressures ([BP] mm Hg) associated with dipyridamole infusion vs. serum caffeine levels. Averaged diastolic and systolic blood pressures of all patients are decreased by 3 ± 10 mm Hg and 4 ± 13 mm Hg, respectively, but changes are statistically insignificant.

and liver function tests caused the high residual caffeine is unclear. Otherwise, our patients and those of Jacobson et al. with detectable caffeine levels were all within the range of

TABLE 1
Averaged Percentage Heart Rate (HR) Increase and Systolic and Diastolic Blood Pressures (BP) Versus Range of Serum Caffeine Levels

Caffeine level (mg/L)	0	0–0.5	0.5–1.0
HR increase (%)	17.6 ± 9.2	16.3 ± 8.9	11.0 ± 4.5
Systolic BP (mm Hg)	−4.6 ± 19	−3.7 ± 8.6	−4.0 ± 8.9
Diastolic BP (mm Hg)	−0.2 ± 11	−4.3 ± 10	−2.0 ± 4.5

0.1–0.8 mg/L. We believe that, under normal circumstances, the plasma caffeine levels would be <1 mg/L after a 24-h caffeine abstention; therefore, a 24-h abstention from caffeine-containing products should be sufficient, which is in contrast with that of a 12-h abstention (*8*).

Our data showed no statistically significant change in diastolic and systolic blood pressures after dipyridamole infusion, although there were small decreases by averaging the data of all of our patients. This finding is in general agreement with Jacobson et al. (*7*) and others (*1,4,8,13*), although the averaged decreases of Jacobson et al. were slightly more than ours. The existing data in the literature on the changes in blood pressure after dipyridamole infusion
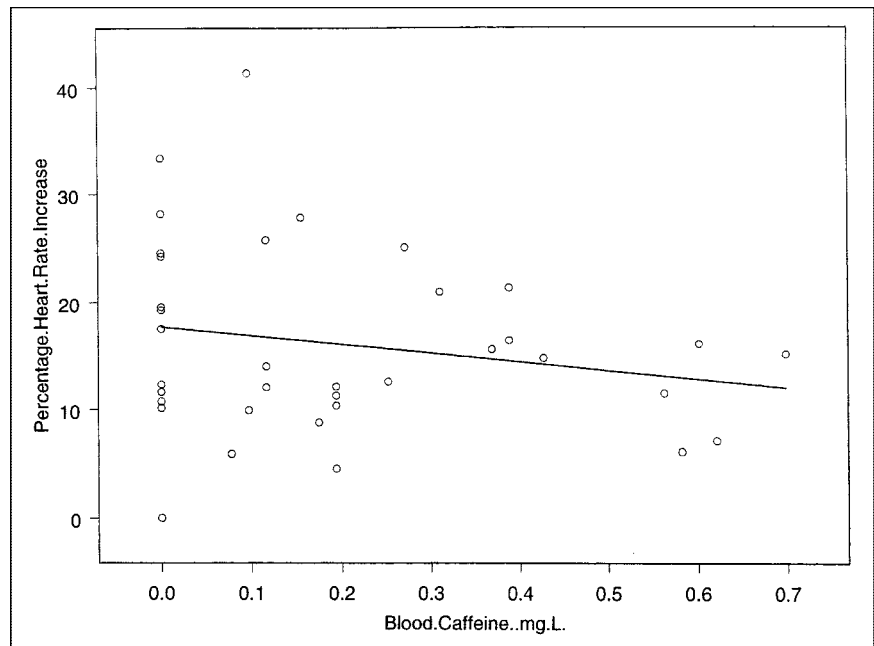
FIGURE 3. Percentage increases of heart rate associated with dipyridamole infusion vs. serum caffeine levels. Heart rate increases are inversely correlated with serum caffeine levels, with $r = -0.22$ and confidence level of 81% ($P = 0.19$).

are not all in agreement: Both increased (*14*) and decreased (*1,8,13*) blood pressures as well as no changes (*11,15,16*) have been reported. Vascular vessel dilation rather than increased oxygen demand are believed to cause adenosine- or dipyridamole-induced increases of blood flows (*3,17,18*). This contrasts with the belief of increased blood flows caused by physical exercise or dobutamine-induced stress (*3–6*). We expect that a reflex increase in heart rate and a modest fall in systolic and diastolic blood pressures is in response to dipyridamole or adenosine infusion (*5*). Therefore, it would be inappropriate to consider the product of heart rate and the systolic blood pressure as an indicator for the stressor dipyridamole or adenosine (*11*) because this product is an indicator of oxygen demand (*3*).

The most consistent result is the heart rate increase after dipyridamole infusion (*1–18*) and the inverse correlation between the percentage heart rate increases and the plasma caffeine levels (*7,11*). Bottcher et al. (*11*) reported a correlation coefficient ($r = -0.68$) and a probability value ($P < 0.05$) that were much higher in confidence than our values ($r = -0.22$; $P = 0.19$). We believe that the discrepancy is caused by the fact that our data were from a small range of residual caffeine levels, whereas the data of Bottcher et al. were based on a wider range of caffeine levels resulting from intravenous infusion of caffeine. Table 1 shows the heart rate percentage increases averaged on small intervals of caffeine concentration following Jacobson et al. (*7*) together with the changes in diastolic and systolic blood pressures. Both our data and those of Jacobson et al. showed a clear linear relationship between the percentage heart rate increases after dipyridamole infusion and the serum caffeine levels, whereas the blood pressures showed no such relationship. The 18% averaged heart rate increase for patients with zero caffeine is in excellent agreement with that of Smits et al. (*1,2*) and others (*4*). We believe that the per-

centage heart rate increase after dipyridamole or adenosine infusion could be a simple indicator for the serum caffeine level. A plot of the averaged percentage heart rate increases versus the serum caffeine levels is shown in Figure 4.

Smits et al. (*1,2*) reported that the false-negative dipyridamole ^{201}Tl myocardial imaging resulted from a plasma caffeine level of 9.7 ± 1.3 mg/L. Daley et al. (*13*) reported that theophylline at $10–20$ µg/mL abolished the hemodynamic effects of intravenous dipyridamole and rendered dipyridamole ^{201}Tl imaging ineffective. What Smits et al. and Daley et al. have in common is the fact that the percentage heart rate increase after dipyridamole infusion is reduced from 18% to only 5%, on average, when dipyridamole produced no stress effect on ^{201}Tl myocardial perfusion (*4*). If we extend our plot of Figure 4 to intercept the 5% heart rate increase, we have a serum caffeine level of 2 mg/L. In other words, we predict that the serum caffeine level of ≥ 2 mg/L would produce false-negative dipyridamole ^{201}Tl myocardial perfusion. This prediction is in fact consistent with the expectation that a serum caffeine level of <5 mg/L could induce false-negative dipyridamole ^{201}Tl perfusion (*1*).

It follows that the percentage heart rate increase after dipyridamole infusion is a simple clinical indicator for the serum caffeine level or the likelihood of false-negative dipyridamole ^{201}Tl perfusion imaging. We also believe that the adenosine challenge protocol of Hurwitz et al. (*3*) is necessary only if the percentage heart rate increase is $\leq 5\%$ (or 9%, half of the 18% to be conservative) after a standard dipyridamole infusion of 0.56 mg/kg, regardless of the patient reports on 24-h abstention. Future work is required to verify these predictions because the patients in our study were imaged using a combination of dipyridamole stressor and partial physical exercise (*6*).
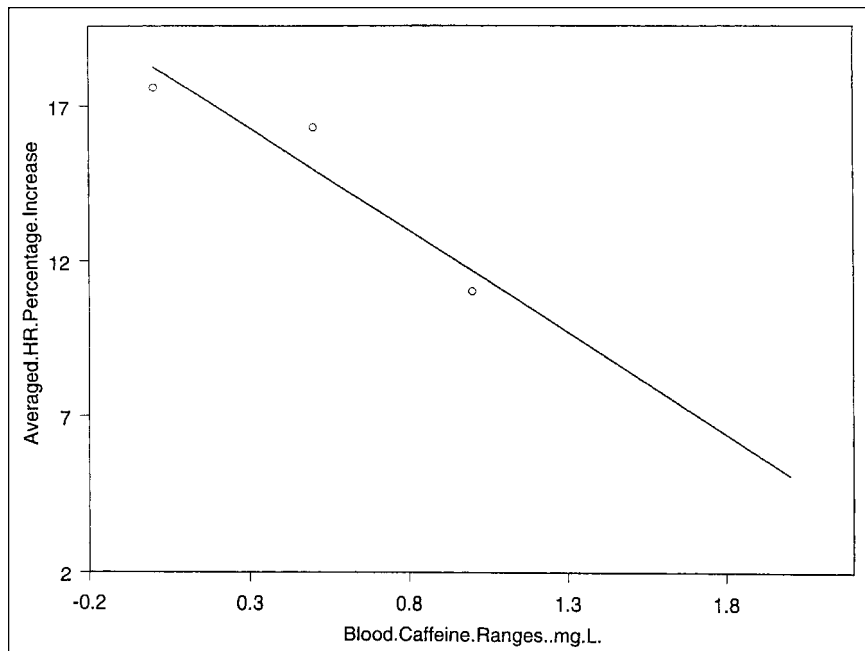
FIGURE 4. Averaged heart rate (HR) percentage increases vs. serum caffeine ranges. At point of 5% heart rate increase, serum caffeine level of 2 mg/L is predicted to be lower limit for false-negative dipyridamole ^{201}Tl myocardial perfusion.

CONCLUSION

Serum caffeine levels after 24-h abstention were found to be <0.8 mg/L for all 36 sample patients, with 34% of the patients having zero plasma caffeine. There was no statistically significant change in diastolic and systolic blood pressures induced by dipyridamole, although all patients' averaged diastolic and systolic blood pressures showed small decreases after dipyridamole infusion. Patients who had caffeine levels of 0 mg/L had an average heart rate increase of 18% after dipyridamole infusion. The percentage heart rate increase was inversely correlated with the plasma caffeine level ($r = -0.22$; $P = 0.19$). The percentage heart rate increase after dipyridamole infusion could be a simple indicator for the serum caffeine level, and the adenosine challenge protocol of Hurwitz et al. (3) may be used if the percentage heart rate increase is <5%. A caffeine concentration of 2 mg/L is predicted to be the lower limit above which false-negative dipyridamole ^{201}Tl myocardial perfusion would be produced. Further work is required to verify these predictions.

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