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# Comparison of myocardial blood flow induced by adenosine triphosphate and dipyridamole in patients with coronary artery disease

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Myocardial perfusion imaging with adenosine triphosphate (ATP) has been used increasingly to diagnose coronary artery disease (CAD) and assess risk for this disease. This study compared absolute myocardial blood flow (MBF) and myocardial flow reserve index (MFR) with ATP and dipyridamole (DIP) in patients with CAD. MBF was quantified by $^{15}O$-$H_2O$ PET in 21 patients with CAD (17 male, 4 female), aged 55 to 81 years. MBF was measured at rest, during intravenous injection of ATP (0.16 mg/kg/min), and again after DIP infusion (0.56 mg/kg). Regions of interest were drawn in nonischemic and ischemic segments based on findings from thallium-201 ($^{201}Tl$) scintigraphy and coronary angiography (CAG). Absolute MBF values and indexes of MFR were calculated in nonischemic and ischemic segments. Intravenous injection of ATP and DIP significantly increased MBF in nonischemic (2.4 ± 0.9 and 2.1 ± 0.8 m*l*/g/min, respectively; $p < 0.01$, for both) and in ischemic segments (1.3 ± 0.4 and 1.5 ± 0.4 m*l*/g/min, respectively; $p < 0.01$, for both). There was a significant difference in MBF values between ATP and DIP in nonischemic segments ($p < 0.05$), which was not observed in ischemic segments. In nonischemic segments, ATP produced higher MFR than DIP (2.1 ± 0.8 and 1.8 ± 0.7, respectively; $p < 0.05$), while no significant difference was observed in ischemic segments (1.5 ± 0.6 and 1.7 ± 0.3, respectively). ATP produced a greater hyperemia than DIP between the ischemic and nonischemic myocardium in patients with CAD. ATP is as effective as DIP for the diagnosis of CAD.

**Key words:** ATP, DIP, myocardial blood flow, $^{15}O$-$H_2O$ PET, coronary artery disease

## INTRODUCTION

THE DYNAMIC NATURE of coronary artery disease (CAD) is defined by atherosclerotic plaque, endothelial function, and an interaction of cellular elements with the vessel wall.[1–10] However, angiographically defined coronary lesions reflect an advanced disease state, with structural alterations resulting from a longstanding atherosclerotic process. Many patients with CAD may have a limited ability to achieve maximal exercise stress. Patients with suspected CAD who cannot perform an exercise test can be diagnosed with an alternative method called pharmacologic coronary vasodilation.

Dipyridamole (DIP) is frequently used for myocardial flow reserve measurements, and for the noninvasive detection and risk assessment of CAD in patients with exercise limitations.[11–15] Recently, ATP has been used increasingly as an alternative agent for pharmacologic stress imaging.[15–17] It has been reported that ATP has a diagnostic value similar to that of DIP for myocardial perfusion scintigraphy in patients with CAD.[15,16] However, few data are available on the magnitude of hyperemia produced by intravenous infusion of ATP in comparison with DIP in patients with CAD. Therefore, this study compared absolute myocardial blood flow (MBF) and myocardial flow reserve index (MFR) during ATP infusion and after DIP administration in patients with CAD.

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## MATERIAL AND METHODS

*Patient population*

Subjects were 21 patients with angiographically proven CAD who were admitted to Kyoto University Hospital for clinical follow-up. Ten of the patients had experienced a previous myocardial infarction. Seventeen patients had undergone some interventional procedure in their coronary arteries, such as percutaneous transluminal coronary angioplasty (PTCA) and/or coronary artery bypass graft surgery (CABG). The clinical characteristics of each patient are provided in Table 1. Written informed consent was obtained from each subject before the study, which had been approved by the Kyoto University Ethics Committee.

All patients underwent a dynamic positron emission tomography (PET) with intravenous oxygen-15 labeled water ([$^{15}$O]-$H_2O$) for MBF quantification at rest, during intravenous ATP infusion, and after DIP administration. Coronary artery angiography (CAG) was performed in all patients within 2 weeks before or after PET study. All cardiovascular medications were discontinued at least 24 hours before the PET studies, and all subjects were carefully instructed to refrain from consuming caffeine-containing beverages or foods within 24 hours before the study.

*PET imaging*

Two catheters were inserted in each patient; one for pharmacologic agent infusion and the other for blood sampling and infusion of [$^{15}$O]-$H_2O$. The subject was positioned in the gantry of the PET camera (Advance; General Electric Medical Systems, Milwaukee, WI) with their arms out of the field of view. The characteristics of this camera have been described previously.[18]

A 10-minute transmission scan using 2 rotating $^{68}$Ge pin sources was made for the attenuation correction. After a transmission scan, the subjects were asked to inhale $^{15}$O-CO for 2 minutes. Three minutes later, a 4-minute static scan was started. During the scan, 3 blood samples were drawn at 2-minute intervals and the radioactivity was measured. Ten minutes was allowed for decay of $^{15}$O-CO radioactivity before the flow measurements. At baseline, approximately 740 MBq of $^{15}$O-$H_2O$ was injected intravenously over 2 minutes, and a 20-frame dynamic PET examination consisting of 6 × 5-s, 6 × 15-s, and 8 × 30-s frames was performed for 6 minutes.[19]

Ten minutes later, ATP was infused intravenously for 9 minutes at a constant rate of 0.16 mg/kg/min.[15,17] Three minutes after the start of ATP infusion, [$^{15}$O]-$H_2O$ was administered again and a second set of dynamic PET images was acquired. Ten minutes after the ATP administration, DIP was infused intravenously at a rate of 0.56 mg/kg over 4 minutes.[11,14] Three minutes after the DIP infusion, a third dose of [$^{15}$O]-$H_2O$ was administered with acquisition of dynamic PET image. Heart rate, blood pressure, and electrocardiogram (ECG) readings were monitored continuously during the PET studies. Each subject was carefully monitored and questioned during and after the infusion of pharmacologic agents to check for adverse events. Aminophylline was available during the study.

*Analysis of PET images*

All data were corrected for dead time, decay, and photon attenuation. The analysis of PET images was conducted with an image analysis package (Dr. View; Asahi-Kasei, Tokyo, Japan) and a special dedicated software package.[20] The arterial input function was obtained from the left ventricular time-activity curve using a previously validated method.[21]

The PET images, including transmission images, [$^{15}$O]-CO images, and [$^{15}$O]-$H_2O$ dynamic images, were reoriented into short-axis planes. For the regional analysis of MBF, the left ventricle was divided into 11 segments based on the model recommended by the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association.[22] Figure 1 illustrates the 11 myocardial segments used to generate the tissue time-activity curves and their respective vascular territories. Values of the MBF (ml/g/min) were calculated according to the previously published method using the single-compartment model.[23]

Because the baseline MBF is closely related to rate-pressure product (RPP), known to be a marker of cardiac work, MBF at rest was corrected for the RPP,[5] an index of myocardial oxygen consumption, according to the following equation[8]: Corrected MBF = MBF × (mean RPP at rest in PET study/individual RPP). The magnitude of the flow response, called the myocardial flow reserve (MFR), during ATP infusion and after DIP administration was defined as the ratio of MBF during or after pharmacologic stress using ATP or DIP to MBF at rest (not corrected for the RPP).

*SPECT images (retrospective study)*

To better characterize ischemic and necrotic lesions in the myocardium, a retrospective analysis using $^{201}$Tl single photon emission computed tomography (SPECT) images (stress and re-injection) was performed. All of the SPECT studies were done within 2 months before the PET study. Two groups of patients were identified: exercise/re-injection (13 patients) and DIP/re-injection (8 patients).

For each patient, regional $^{201}$Tl activity was measured on the short-axis tomograms. To objectively compare relative regional $^{201}$Tl uptake, 11 myocardial regions of interest were drawn on each visually selected $^{201}$Tl stress tomogram and on each corresponding $^{201}$Tl re-injection tomogram (Fig. 1). The myocardial region on the $^{201}$Tl re-injection images that corresponded to the region with the highest uptake on the $^{201}$Tl stress image series was used as the reference region for computing relative $^{201}$Tl uptake.

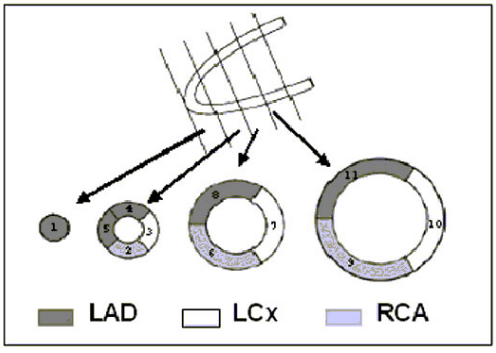


**Fig. 1** Schematic presentation of ROI definition. Eleven ROIs were determined in the 4 short-axis slices and their respective vascular territories.
*Footnote:* The left ventricle was divided into 11 segments based on the model recommended by the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association.

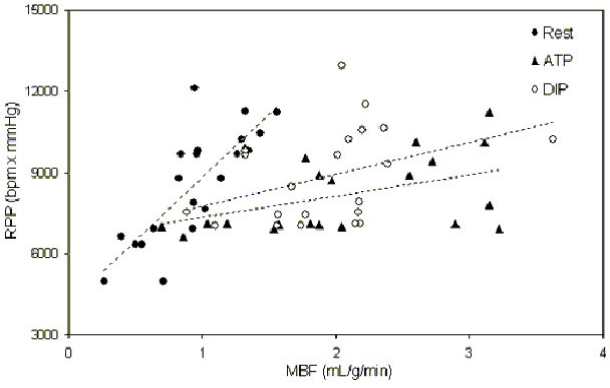


**Fig. 2** Correlations between myocardial blood flow and rate pressure product (RPP) in patients with advanced CAD at rest (RPP-corrected MBF), during ATP infusion, and after DIP administration.
*Footnotes:* 1. Values are expressed in ml/g/min and its correspondent bpm × mmHg; 2. RPP: rate-pressure product (bpm × mmHg); 3. ATP: adenosine triphosphate; 4. DIP: Dipyridamole; 5. At rest, RPP-corrected MBF correlated linearly with RPP ($r = 0.801$, $p < 0.01$); 6. After DIP and ATP, hyperemic blood flows were no longer correlated with RPP.

$^{201}$Tl uptake in all other myocardial regions was expressed as a percentage of the activity in this reference region. The presence of a $^{201}$Tl defect on the stress images was defined as $^{201}$Tl activity <85% of the normal reference region.[24] A defect was considered reversible when relative $^{201}$Tl activity on the subsequent re-injection images increased by ≥10% above the initial value and the final defect activity was ≥50%.[24] Persistent defects were defined as $^{201}$Tl activity <50% of maximal activity and were considered necrotic regions or scars. These regions were further excluded from our analysis for MBF.

*Definition of ischemic and nonischemic segments*
In order to evaluate the effects of ATP and DIP on the MBF of ischemic and nonischemic regions in patients with CAD, two groups of segments in the myocardium were characterized. The definition was based on the $^{201}$Tl images and the coronary angiography images following the left ventricular segmentation shown in Figure 1. Nonischemic segments were defined as the myocardial region showing 85% to 100% of the highest uptake on stress $^{201}$Tl images. Ischemic segments were defined as areas with signs of redistribution of ≥10% improvement on the $^{201}$Tl re-injection images and a final defect activity of ≥50% with the CAG showing narrowing of the referent coronary artery (>75%). Regions in the myocardium that received invasive treatment (PTCA and/or CABG) in their supplied coronary arteries were excluded in the present study regardless of the findings on the $^{201}$Tl scintigraphy. Finally, 58 ischemic segments and 24 non-ischemic segments were analyzed.

*Statistical analyses*
Statistics were calculated with a commercially available personal computer software program (SPSS 12.0). Values are expressed as mean ± SD. One-way analysis of variance (ANOVA) was used to compare the groups with respect to changes in hemodynamic data, MBF, and MFR. The statistical significance of intergroup differences was assessed using the independent Student's t-test. Differences during ATP infusion and after DIP infusion were compared with Student's paired t-test. Correlations were sought using least-squares analysis. Probability values less than 0.05 were considered statistically significant.

## RESULTS

*Hemodynamic findings*
The hemodynamic findings at rest, during ATP infusion, and after DIP administration are shown in Table 2. The heart rate increased significantly during ATP infusion ($p < 0.01$) and after DIP administration ($p < 0.01$). While heart rate after DIP administration tended to be higher than during ATP infusion, statistically significant differences were not observed ($p = 0.21$). The systolic and diastolic blood pressures decreased significantly with ATP or DIP (for p values, see Table 2). Lower blood pressure (systolic and diastolic) values were noted during ATP than after DIP ($p < 0.01$ for both). The RPP with ATP was lower than that with DIP ($p = 0.071$ and $p = 0.759$, respectively).

*Regional MBF*
Table 3 summarizes the findings of MBF, during ATP and after DIP for groups of nonischemic and ischemic myocardium. In the group of nonischemic segments, the MBF increased significantly with ATP and DIP ($p < 0.01$ for both). Higher values of MBF were observed during

**Table 1** Profile of patients of CAD

| Patient number | Age (y) | Gender | NYHA | DM | HT | HL | Number of dis. vessels | Coronary artery | MI | Region of MI | PTCA | CABG |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| #1 | 59 | M | I | | | X | 2 | RCA + LAD | X | Inf-lateral | X | |
| #2 | 74 | M | II | | | | 2 | RCA + LAD | X | Inferior | X | A – LAD + RCA |
| #3 | 72 | M | I | | X | | 2 | LAD + LCx | | | X | |
| #4 | 77 | F | I | | X | X | 2 | LAD + LCx | | | | |
| #5 | 68 | M | II | X | | X | 3 | RCA + LAD + LCx | | | X | |
| #6 | 58 | M | I | | X | X | 2 | RCA + LAD | X | Inferior | X | |
| #7 | 67 | F | I | X | X | | 3 | RCA + LAD + LCx | | | | A – LAD + RCA |
| #8 | 69 | M | I | | X | | 1 | LAD | X | Ant-septal | X | |
| #9 | 57 | F | II | X | | | 2 | RCA + LAD | | | X | A – LAD + RCA |
| #10 | 68 | M | I | | | | 2 | RCA + LAD | | | X | |
| #11 | 78 | M | I | | | | 3 | RCA + LAD + LCx | X | Inf-septal | X | |
| #12 | 74 | M | III | | | | 2 | LAD + LCx | | | | |
| #13 | 55 | M | I | X | | | 3 | RCA + LAD + LCx | X | Inf-lateral | | A – LAD + LCx, V – RCA |
| #14 | 76 | M | II | X | | | 3 | RCA + LAD + LCx | | | | |
| #15 | 61 | M | I | | | | 2 | LAD + LCx | X | Inferior | X | |
| #16 | 74 | M | I | | | | 3 | RCA + LAD + LCx | X | Inf-lateral | X | V – LAD + LCx |
| #17 | 78 | M | I | X | | | 3 | RCA + LAD + LCx | | | X | |
| #18 | 72 | M | I | X | | | 2 | RCA + LAD | X | Ant-apical | X | |
| #19 | 67 | F | I | X | | | 2 | LAD + LCx | | | X | |
| #20 | 72 | M | I | X | X | X | 2 | RCA + LAD | | | | |
| #21 | 81 | M | IV | | | | 2 | RCA + LAD | X | Inferior | X | |

NYHA: New York Heart Association classification, DM: Diabetes mellitus; HT: Hypertension; HL: Hyperglycemia; Number of dis. Vessels: number of diseased vessels (CAG showing >75% of narrowing of the referent coronary artery); MI: Myocardial infarction; Region of MI: Region of myocardial infarction; PTCA: percutaneous transluminal coronary angioplasty; CABG: coronary angioplasty bypass graft; M: male; F: female; RCA: right coronary artery; LAD: left anterior descending coronary artery; LCx: Left circumflex coronary artery; Inf-lateral: infero-lateral region; Ant-septal: antero-septal region; Inf-septal: infero-septal region; Ant-apical: antero-apical region; A: arterial bypass graft; V: venous bypass graft.

**Table 2** Hemodynamic data

| Parameter | Rest | ATP | DIP |
|---|---|---|---|
| Heart rate (bpm) | 71.1 ± 10.4 | 78.1 ± 8.3 ** | 79.7 ± 10.0 ** |
| Systolic BP (mmHg) | 129.8 ± 25.3 | 109.7 ± 17.8 ** | 117.3 ± 19.3 * £ |
| Diastolic BP (mmHg) | 70.1 ± 11.2 | 59.6 ± 10.2 ** | 63.3 ± 11.0 ** £ |
| RPP (bpm × mmHg) | 9218.2 ± 2016.0 | 8538.9 ± 1530.0 | 9335.9 ± 1903.1 £ |

ATP: adenosine triphosphate; DIP: dypiridamole; bpm: beats per minute; BP: blood pressure; RPP: Rate pressure product; * represents $p < 0.05$ between rest and ATP or DIP; ** represents $p < 0.01$ between rest and ATP or DIP; £ represents $p < 0.01$ between ATP and DIP.

**Table 3** Myocardial blood flow and coronary vascular resistance

| | Nonischemic | Ischemic | Nonischemic vs. Ischemic |
|---|---|---|---|
| MBF (ml/min/g) | | | |
| Rest | 1.20 ± 0.35 | 0.92 ± 0.31 | $p < 0.05$ |
| ATP | 2.39 ± 0.94 * £ | 1.31 ± 0.43 * | $p < 0.01$ |
| DIP | 2.11 ± 0.79 * | 1.47 ± 0.39 * | $p < 0.05$ |
| Myocardial Flow Reserve | | | |
| Flow reserve (ATP) | 2.09 ± 0.85 £ | 1.49 ± 0.57 | $p < 0.05$ |
| Flow reserve (DIP) | 1.83 ± 0.68 | 1.66 ± 0.29 | NS |

MBF: myocardial blood flow; ATP: adenosine triphosphate; DIP: dypiridamole; Myocardial Flow Reserve: defined as the ratio of MBF enhanced with ATP or DIP and rest; * represents $p < 0.01$ between rest and ATP or DIP; £ represents $p < 0.05$ between ATP and DIP; NS: not significant.

infusion of ATP compared with DIP administration ($p < 0.05$). As for the ischemic segments, MBF also increased significantly with ATP and DIP ($p < 0.01$ for both). MBF values after DIP were slightly higher than those for ATP; however, no statistically significant difference was observed.

Comparisons were made between groups of nonischemic and ischemic segments at rest, during ATP infusion and after DIP administration (Table 3). At rest and after pharmacologic stress with ATP or DIP, MBF in ischemic segments showed lower values compared with the nonischemic segments ($p < 0.05$, $p < 0.01$, and $p < 0.05$, respectively).

At rest, RPP-corrected MBF correlated linearly with RPP ($r = 0.801$, $p < 0.01$) (Fig. 2), systolic and diastolic blood pressures ($r = 0.856$, $p < 0.01$ and $r = 0.693$, $p < 0.01$, respectively), and heart rate ($r = 0.508$, $p < 0.05$). After DIP and ATP, hyperemic blood flows were no longer correlated with the RPP, SBP, DBP, or HR.

*Regional MFR*

Table 3 summarizes the results of regional MFR during ATP and after DIP. The pharmacologic stress with ATP had significantly higher values of MFR compared with DIP in nonischemic segments ($p < 0.05$). In ischemic segments, MFR during ATP infusion and after DIP administration did not differ significantly ($p = 0.195$). Accordingly, MFR by ATP in ischemic segments was lower than that in nonischemic segments ($p < 0.05$). This finding was not statistically significant for DIP.

*Adverse events*

None of the patients reported any major adverse reactions (chest pain, heart block, or acute asthmatic attack). Minor adverse reactions, including shortness of breath, headache, anxiety, nausea, and dyspnea, occurred in 5 patients during ATP infusion and in 4 patients after DIP administration. The minor reactions to ATP subsided soon after the infusion was stopped, and those associated with DIP administration disappeared promptly after aminophylline infusion.

## DISCUSSION

These data demonstrate that ATP is useful in comparing ischemic with nonischemic myocardium and is therefore effective for diagnosis and risk assessment of patients with CAD.

DIP has been used extensively in perfusion imaging for the diagnosis and risk assessment of patients with CAD.[12,14] DIP increases the level of circulating adenosine by inhibiting phosphodiesterase, and activating adenylate cyclase and preventing its cellular reuptake.[25–27] Therefore, DIP induces the vasodilator effect indirectly. It is known that intravenous DIP elicits submaximal coronary hyperemia, which varies among subjects.[12] Its duration of action is quite long (>30 minutes) and, therefore, precludes repeated measurements during the same study. Even though the vasodilator effects can be attenuated by methylxanthines, prolonged ischemia is presumably due to coronary "steal."[11,13]

Recently, ATP has been increasingly used as an alternative agent for pharmacologic stress imaging.[15–17] It has been reported that ATP has a diagnostic value similar to that of DIP for myocardial perfusion scintigraphy in patients with CAD.[15,16] The short half-life of ATP (<20 sec) compared with that of DIP may lessen the risk of prolonged coronary ischemia due to vasodilator-induced coronary steal and reduce the time required for redistribution of the isotope. Although the precise role of ATP in regulating coronary blood flow is still not certain, several aspects of its mechanism of action in causing microvascular vasodilation are known and should be considered when the drug is used in diagnostic studies. To our knowledge, this is the first study using ATP and DIP that evaluates MBF by $^{15}O$-$H_2O$ PET in patients with CAD.

In the present study, the hemodynamic results were in concordance with results published previously.[15–17] ATP and DIP infusions resulted in slight increases in heart rate and decreases in blood pressure. The change in the double product (heart rate multiplied by pressure) is modest for both. Adenosine-induced sympathetic stimulation of the chemoreceptors in the carotid body may explain the tachycardia and improvement in cardiac performance.[28] The decrease in blood pressure during ATP and DIP infusion is probably caused by direct vasodilation in the systemic circulation.

On the other hand, evidence is also presented for ATP acting as an excitatory co-transmitter with noradrenaline from sympathetic perivascular nerves and causing vasoconstriction via excitatory $P_2$-purinoceptors located on vascular smooth muscle.[29,30] ATP released as a cotransmitter may also act as a prejunctional modulator of nerve activity.[31–33] Clearly, the responses produced by ATP in this study are the sum of its inhibitory action at $P_1$- and $P_2Y$-purinoceptors located on the endothelium and its excitatory action at $P_2$-purinoceptors located on the smooth muscle. Therefore, the net effect of the actions and interactions may depend on the structural integrity of the vascular wall.

The earliest abnormality associated with CAD is the demonstration of abnormal MFR, an integrating parameter of endothelial function and vascular smooth muscle relaxation.[1] Quantitative analysis with $^{15}O$-$H_2O$ PET permits noninvasive measurements of MBF and MFR.[6,7] This procedure is commonly used to detect early CAD and altered endothelial function and to assess functional responses to physiological or pharmacologic stimuli in patients with and without CAD.[7,34]

ATP seems to be more effective than DIP in increasing MBF in nonischemic segments. ATP showed a 2-fold increase in the MBF. However, this result was lower than

the 5-fold increase presented in a previous study.[17] This divergence can be explained by the differences in the subjects evaluated. Kubo et al.[17] studied normal subjects with no history or signs of CAD who had a very low probability of endothelial damage. Therefore, the vascular response to ATP was expected to be greatest in this group. In fact, in the group of nonischemic segments, the negative angiographically-proven CAG does not exclude the presence of some impairment on the endothelium-dependent vasodilation of the microcirculation to ATP and DIP.[3,4,10]

As for the ischemic segments, ATP and DIP were less likely to increase the MBF, and there was a significant difference between the ischemic and nonischemic segments for ATP. In addition to stenosis in the epicardial coronary arteries, multiple alterations at the vascular smooth muscle and endothelial cell level might have contributed to the markedly decreased responsiveness of coronary vessels to ATP compared with DIP in ischemic myocardium. Thus, compared with DIP, the vasodilatory effect of ATP seems to be more dependent on the structural integrity of the vascular wall. This fact was also seen in terms of MFR. In ischemic myocardium, ATP significantly reduced MFR compared with that in nonischemic myocardium (not seen for DIP).

The RPP-corrected MBF at rest correlated linearly with the rate-pressure product, systolic and diastolic blood pressures, and heart rate. After DIP and ATP, hyperemic blood flows (not RPP-corrected) were no longer correlated with them. The agents therefore uncouple blood flow and oxygen demand and consequently, cardiac work. Accordingly, hyperemic blood flows were found to be unrelated to the rate-pressure product.

For ATP to replace DIP, however, it must safely cause coronary hyperemia sufficient to differentiate myocardium perfused by a stenotic artery from that supplied by a normal vessel. Based on this hypothesis and by using MFR as a marker of viable myocardium, the present study suggests that clinically tolerable doses of ATP can differentiate between areas with significant stenosis and coronary arteries angiographically normal in patients with advanced CAD, which was not observed for DIP.

## LIMITATIONS

Our study had some limitations. First, the order of drug administration was not random. However, performing DIP scans before ATP scans would be impractical, because DIP has a much longer half-life than ATP and it would interfere with the action of ATP for a few hours. On the other hand, due to ATP's short half-life (<20 sec), the measurement of MBF after DIP administration would not be compromised by the vasodilation occurring during ATP infusion. Second, we did not compare MBF between ATP and adenosine because adenosine is not approved for clinical use in Japan. Further investigation comparing ATP and adenosine using $^{15}O$-$H_2O$ PET, as well as studies on groups of patients with suspected CAD, should be undertaken. Third, we have determined the ischemic and non-ischemic segments based on findings from CAG and $^{201}Tl$ scintigraphy. It is well known that reduction of MFR frequently occurs even without coronary stenosis in patients with diabetes or hyperlipidemia. MFR reduction is not detectable in thallium scintigraphy. Therefore, nonischemic segments determined by CAG or thallium scintigraphy can be a potential limitation of our study.

## CONCLUSIONS

ATP produced a greater hyperemia than DIP between the ischemic and nonischemic myocardium in patients with CAD. ATP is considered effective for the diagnosis of patients with CAD.


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## REFERENCES


1. Gould KL, Lipscomb K. Effects of coronary stenoses on coronary flow reserve and resistance. *Am J Cardiol* 1974; 34: 48–55.
2. Furchgott RF. Role of endothelium in responses of vascular smooth muscle. *Circ Res* 1983; 53: 557–573.
3. Creager MA, Cooke JP, Mendelsohn ME, Gallagher SJ, Coleman SM, Loscalzo J, et al. Impaired vasodilation of forearm resistance vessels in hypercholesterolemic humans. *J Clin Invest* 1990; 86: 228–234.
4. Panza JA, Quyyumi AA, Brush JE Jr, Epstein SE. Abnormal endothelium-dependent vascular relaxation in patients with essential hypertension. *N Engl J Med* 1990; 323: 22–27.
5. Czernin J, Muller P, Chan S, Brunken RC, Porenta G, Krivokapich J, et al. Influence of age and hemodynamics on myocardial blood flow and flow reserve. *Circulation* 1993; 88: 62–69.
6. Uren NG, Melin JA, De Bruyne B, Wijns W, Baudhuin T, Camici PG. Relation between myocardial blood flow and the severity of coronary-artery stenosis. *N Engl J Med* 1994; 330: 1782–1788.
7. Uren NG, Crake T, Lefroy DC, de Silva R, Davies GJ, Maseri A. Reduced coronary vasodilator function in infarcted and normal myocardium after myocardial infarction. *N Engl J Med* 1994; 331: 222–227.
8. Marinho NVS, Keogh BE, Costa DC, Lammerstma AA, Ell PJ, Camici PG. Pathophysiology of chronic left ventricular dysfunction; new insights from the measurement of absolute myocardial blood flow and glucose utilization. *Circulation* 1996; 93: 737–744.
9. Vanhoutte PM. The endothelium: modulator of vascular smooth muscle tone. *N Engl J Med* 1998; 319: 512–513.
10. Creager MA, Luscher TF, Cosentino F, Beckman JA. Diabetes and vascular disease: pathophysiology, clinical

consequences, and medical therapy: Part I. *Circulation* 2003; 108: 1527–1532.
11. Homma S, Gilliland Y, Guiney TE, Strauss HW, Boucher CA. Safety of intravenous dipyridamole for stress testing with thallium imaging. *Am J Cardiol* 1987; 59: 152–154.
12. Taillefer R, Amyot R, Turpin S, Lambert R, Pilon C, Jarry M. Comparison between dipyridamole and adenosine as pharmacologic coronary vasodilators in detection of coronary artery disease with thallium 201 imaging. *J Nucl Cardiol* 1996; 3: 204–211.
13. Becker LC. Conditions for vasodilator-induced coronary steal in experimental myocardial ischemia. *Circulation* 1978; 57: 1103–1110.
14. Stratmann HG, Tamesis BR, Younis LT, Wittry MD, Miller DD. Prognostic value of dipyridamole technetium-99m sestamibi myocardial tomography in patients with stable chest pain who are unable to exercise. *Am J Cardiol* 1994; 73: 647–652.
15. Watanabe K, Sekiya M, Ikeda S, Miyagawa M, Kinoshita M, Kumano S. Comparison of adenosine triphosphate and dipyridamole in diagnosis by Thallium-201 myocardial scintigraphy. *J Nucl Med* 1997; 38: 577–581.
16. Miyagawa M, Kumano S, Sekiya M, Watanabe K, Akutzu H, Imachi T, et al. Thallium-201 myocardial tomography with intravenous infusion of adenosine triphosphate in diagnosis of coronary artery disease. *J Am Coll Cardiol* 1995; 26: 1196–1201.
17. Kubo S, Tadamura E, Toyoda H, Mamede M, Yamamuro M, Magata Y, et al. Effect of caffeine intake on myocardial hyperemic flow induced by adenosine triphosphate and dipyridamole. *J Nucl Med* 2004; 45: 730–738.
18. DeGrado TR, Turkington TG, Williams JJ, Stearns CW, Hoffman JM, Coleman RE. Performance characteristics of a whole-body PET scanner. *J Nucl Med* 1994; 35: 1398–1406.
19. Tadamura E, Mamede M, Kubo S, Toyoda H, Yamamuro M, Iida H, et al. The effect of nitroglycerin on myocardial blood flow in various segments characterized by rest-redistribution thallium SPECT. *J Nucl Med* 2003; 44: 745–751.
20. Katoh C, Ruotsalainen U, Laine H, Alenius S, Iida H, Nuutila P, et al. Iterative reconstruction based on median root prior in quantification of myocardial blood flow and oxygen metabolism. *J Nucl Med* 1999; 40: 862–867.
21. Iida H, Rhodes CG, de Silva R, Araujo LI, Bloomfield PM, Lammertsma AA, et al. Use of the left ventricular time-activity curve as a noninvasive input function in dynamic oxygen-15-water positron emission tomography. *J Nucl Med* 1992; 33: 1669–1677.
22. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation* 2002; 105: 539–542.
23. Iida H, Kanno I, Takahashi A, Miura S, Murakami M, Takahashi K, et al. Measurement of absolute myocardial blood flow with $H_2{}^{15}O$ and dynamic positron-emission tomography: strategy for quantification in relation to the partial-volume effect. *Circulation* 1988; 78: 104–115.
24. Dilsizian V, Freedman NM, Bacharach SL, Perrone-Filardi P, Bonow RO. Regional thallium uptake in irreversible defects. Magnitude of change in thallium activity after reinjection distinguishes viable from nonviable myocardium. *Circulation* 1992; 85: 627–634.
25. Klaubunde RE. Dipyridamole inhibition of adenosine metabolism in human blood. *Eur J Pharmacol* 1983; 93: 21–26.
26. West JW, Bellet S, Manzoli UC, Muller OF. Effects of persantine (RA8), a new coronary vasodilator, on coronary blood flow and cardiac dynamics in the dog. *Circ Res* 1962; 10: 35–44.
27. Fitzgerald GA. Dipyridamole. *N Engl J Med* 1987; 316: 1247–1257.
28. Biaggioni I, Killian TJ, Mosqueda-Garcia R, Robertson RM, Robertson D. Adenosine increases sympathetic nerve traffic in humans. *Circulation* 1991; 83: 1668–1675.
29. Muramatsu I, Fujiwara M, Miura A, Sakakibara Y. Possible involvement of adenine nucleotides in sympathetic neuroeffector mechanisms of dog basilar artery. *J Pharmacol Exp Ther* 1981; 216: 401–409.
30. Sneddon P, Burnstock G. ATP as a co-transmitter in rat tail artery. *Eur J Pharmacol* 1984, 106: 149–152.
31. Langer SZ. Presynaptic regulation of the release of catecholamines. *Pharmacol Rev* 1981; 32: 337–362.
32. Paton DM. Presynaptic neuromodulation mediated by purinergic receptors. In: Burnstock G (ed), *Purinergic Receptors: Receptors and recognition*. London; Chapman and Hall, 1981: 199–219.
33. Su C. Purinergic neurotransmission and neuromodulation. *Annu Rev Pharmacol Toxicol* 1983; 23: 397–411.
34. Yokoyama I, Momomura S, Ohtake T, et al. Reduced coronary flow reserve in hypercholesterolemic patients without overt coronary stenosis. *Circulation* 1996; 94: 3232–3238.