Transmural Perfusion Gradient in Adenosine Triphosphate Stress Myocardial Perfusion Computed Tomography

Kohei Hosokawa, MD; Akira Kurata, MD; Teruhito Kido, MD; Fumiaki Shikata, MD; Hiroshi Imagawa, MD; Kanji Kawachi, MD; Akiyoshi Ogimoto, MD; Itsuo Higaki, MD; Tomoyuki Kido, MD; Hiroshi Higashino, MD; Teruhito Mochizuki, MD

Background: The aim of the present study was to assess semi-quantification of myocardial perfusion using adenosine triphosphate (ATP)-stress myocardial perfusion computed tomography (MPCT) in patients with coronary artery disease (CAD).

Methods and Results: Seventeen patients with CAD underwent ATP-stress MPCT, stress myocardial perfusion scintigraphy (MPS) and coronary angiography (CAG). With ATP loading (0.16 mg·kg\(^{-1}\)·min\(^{-1}\), 5 min) and slow infusion of contrast medium (2 ml/s, 100 ml), stress images were acquired using prospective electrocardiogram-gated 64-slice CT. Stress MPCT images were analyzed according to the transmural perfusion gradient (TMPG; difference between subendocardial and epicardial attenuation, divided by wall thickness; Hounsfield units [HU]/mm) per segment, and summed TMPG was compared with those of stress MPS and CAG per territory and patient, respectively. There were 36 CAG-proved stenotic vessels in 51 (17×3) territories. There were significant correlations between TMPG and MPS stress score per segment, per territory and per patient, respectively (P<0.05). Summed TMPG in territories with and without >70% coronary stenosis was 32.3 HU/mm (–1.9–90.9) and 14.5 HU/mm (–5.6–38.4; P<0.05). For detecting coronary artery stenosis, sensitivity, specificity, positive and negative predictive values using the summed TMPG were 72%, 87%, 93% and 57%, in comparison with summed MPS (64%, 73%, 85%, and 46%).

Conclusions: Semi-quantification of myocardial perfusion using TMPG has great potential to evaluate the severity of myocardial ischemia, similarly to MPS score. (Circ J 2011; 75: 1905–1912)

Key Words: Adenosine triphosphate; Computed tomography; Myocardial perfusion; Stress test; Transmural extent
Methods

Subjects
The Human Research Committee approved the present study and waived the requirement for informed patient consent. Between December 2007 and July 2009, 17 patients with severe CAD, who had been scheduled for coronary artery bypass grafting at Ehime University Hospital were prospectively included. All the patients underwent pharmacological stress MPCT and MPS, respectively, within 3 days, and final diagnosis was confirmed on invasive CAG.

The exclusion criteria for the present study were as follows: (1) acute myocardial infarction; (2) unstable angina; (3) history of previous revascularization therapy; (4) atrioventricular block greater than first degree; (5) deteriorated renal function (serum creatinine >1.5 mg/dl); (6) pregnancy, hyperthyroidism, or a known allergic reaction to contrast media; (7) severe lower cardiac function (left ventricular (LV) ejection fraction <20%); (8) known history of bronchial asthma; and (9) New York Heart Association class IV congestive heart failure.

Stress MPCT
A 64-multi-detector row CT (Brilliance 64, Philips Healthcare, Andover, MA, USA and Best, The Netherlands) was used, with 64×0.625-mm collimation and a gantry rotation time of 0.42 s. Scan parameters were as follows: voltage 120 kV, tube current 210 mAs (500 mA), field of view 150–250 mm, matrix 512×512 and XCB reconstruction filter, respectively.

The scanning protocol of stress MPCT is shown in Figure 1. First, adenosine triphosphate (ATP 20 mg; Daiichi Sankyo, Tokyo, Japan) was infused over 5 min at a constant rate of 0.16 mg·kg\(^{-1}\)·min\(^{-1}\) through a peripheral venous catheter on the opposite side into the cubital vein for contrast infusion. Second, 3 min after the ATP infusion, contrast medium (Iopamidol 370 mg/ml, Bayer, Berlin, Germany; 100 ml) and saline chaser (20 ml) were injected at a rate of 2 ml/s using an automatic dual injector (Stellant DualFlow; Nihon Medrad, Osaka, Japan) to maintain efficient myocardial perfusion. Last, 1 min after contrast medium infusion, stress image acquisition was initiated with prospective electrocardiogram (ECG) gating for the narrow phase 75% RR interval under a single breath-hold without the time delay. The patient’s standard ECG, vital signs, and general condition were continuously monitored during the stress protocol. Mean radiation dose was 3.6±0.4 mSv.

Transmural Perfusion Gradient on MPCT
The 16 LV segment model was used, which was modified from a standard 17 LV segment model except for the apical portion.\(^1\) Using 3 representative cardiac short-axis images (basal, mid-ventricular and apical), a rectangular parallelepiped region of interest (ROI; transmural myocardial thickness×5 mm [ROI width along short axial arc]×3 mm [thickness along LV long axis]) was drawn in each LV segment. Using linear regression analysis, a slope was automatically calculated by dividing the difference between subendocardial and epicardial attenuation by wall thickness in the ROI using available software (Image J). The slope was identified as positive when subendocardial attenuation was lower than epicardial attenuation (Figure 2). The slope defined the transmural perfusion gradient (TMPG; Hounsfield units [HU]/mm) and was used as an estimate of myocardial ischemia on the stress image.

\[
\text{TMPG} = \frac{\text{(epicardial attenuation – subendocardial attenuation)}}{\text{LV wall thickness}}
\]

The 16 LV segments were categorized as the left anterior descending artery (LAD: segments 1, 2, 7, 8, 13, 14), the left circumflex artery (LCX: segments 5, 6, 11, 12, 16) and the right coronary artery (RCA; segments 3, 4, 9, 10, 15), and summed TMPG was calculated in each vessel territory.

Stress/Rest Thallium-201 MPS
Stress and rest thallium-201 MPS was performed according to the American College of Cardiology/American Heart Association/American Society of Nuclear Cardiology guidelines for the clinical use of cardiac radionuclide imaging.\(^1\) Pharmacological stress was induced using the ATP-loading (0.16 mg·kg\(^{-1}\)·min\(^{-1}\), 5 min) as described by Miyagawa et al.\(^1\) The ATP-stress tests were carefully performed without concomitant anti-anginal medication and/or caffeine intake for at least 24 h before the examination. The patient’s condition during the stress protocol was also carefully monitored during the ATP-stress MPCT. Three minutes after the continuous infu-
Injection of ATP, 111 MBq thallium-201 (Nihon Medi-Physics and FUJIFILM RI Pharma, Tokyo, Japan) was injected i.v. and flushed with saline. Stress image and rest image were acquired 10 min after the ATP-stress test and 4 h after the stress image, respectively, using a 3-headed SPECT system (GCA 9300; Toshiba, Tokyo, Japan). Tomographic reconstruction was performed using a standard filtered back-projection technique with a ramp filter to produce a transaxial tomogram. No scatter or attenuation correction was applied. From these trans-axial tomograms, the long axis of the left ventricle was identified and oblique-angled tomograms were generated (i.e., vertical long-axis, short-axis and horizontal long-axis tomograms).

The MPS images were visually and independently analyzed by 2 experienced radiologists. The slices were displayed sequentially to assess the myocardial perfusion in each LV segment.13 A score system was used to quantify the severity of ischemia: MPS score 0, normal uptake; 1, mild hypoperfusion; 2, moderate hypoperfusion; 3, severe hypoperfu-

Table 1. Patient Characteristics, n (%)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>17</td>
</tr>
<tr>
<td>Age (years)</td>
<td>69.6±6.9</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>12/5</td>
</tr>
<tr>
<td>Body mass index</td>
<td>23.1±2.9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (88)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10 (59)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>14 (82)</td>
</tr>
<tr>
<td>Smoking</td>
<td>8 (47)</td>
</tr>
<tr>
<td>Coronary calcium score (range)</td>
<td>1,274 (31–3,514)</td>
</tr>
<tr>
<td>No. patients with</td>
<td></td>
</tr>
<tr>
<td>Single-vessel disease</td>
<td>4 (24)</td>
</tr>
<tr>
<td>Double-vessel disease</td>
<td>7 (41)</td>
</tr>
<tr>
<td>Triple-vessel disease</td>
<td>6 (35)</td>
</tr>
<tr>
<td>No. stenotic vessels</td>
<td>36</td>
</tr>
<tr>
<td>Prevalence of diseased vessels</td>
<td>38/51 (71)</td>
</tr>
</tbody>
</table>

Figure 2. Calculation for the transmural perfusion gradient (TMPG). Using Image J, Osirix for Mac, the average computed tomography value is automatically plotted at a continuous depth from the endocardial to epicardial surface in the rectangular region of interest of each left ventricular segment. The slope is calculated to express TMPG. The slope is positive when the subendocardial attenuation is lower than the endocardial attenuation. HU, Hounsfield units.
Figure 3. Relation between the transmural perfusion gradient (TMPG) and myocardial perfusion scintigraphy (MPS) stress score per (A) segment, (B) territory and (C) patient. Severities of TMPG and summed TMPG were significantly greater with increases of MPS stress score per (A) segment, (B) territory and (C) patient. On segment base analysis, although this correlation occurred at MPS stress scores 0–3, there was no significant difference in TMPG between segments with MPS stress scores 3 and 4. HU, Hounsfield units.
Circulation Journal Vol.75, August 2011

Semi-Quantification of Stress Myocardial Perfusion CT

CAG images were obtained using 5-Fr catheters. The angiograms were saved to CD-ROM and interpreted by 2 cardiologists with >10 years’ clinical experience blinded to any other results. Identification of the coronary tree was based on a standard 15 coronary segment model. Quantitative angiographic analysis was performed using the most severe, well-defined lesion in each segment, using a previously described digital caliper method. Significant stenosis was defined as a reduction in diameter >70%. In the case of multiple lesions in a given segment, the segment was classified by the worst lesion. In the case of multiple abnormal segments per artery, the vessel was classified by the worst segment. In the present study, coronary arteries were also analyzed according to the 3 vessel territories (LAD, LCX and RCA) as well as the aforementioned form. Stenosis of the left main trunk (>50% stenosis) was classified as double-vessel disease (LAD and LCX).

 Statistical Analysis

Data are given as mean±SD (median and range) as appropriate according to the distribution of the data. Intra- and inter-observer concordance for the reproducibility of TMPG was calculated using the Cohen k-value.

TMPG for each level of MPS score was analyzed using Kruskal–Wallis test and Steel–Dwass test among the range of 5 MPS scores (from 0 to 4) per segment, respectively. Pearson’s test was used to analyze the correlation between summed TMPG and the summed MPS score per vessel territory and per patient.

Summed TMPG and MPS stress score in the 3 main coronary territories were compared between with and without significant coronary stenosis using the Mann–Whitney test. Cutoffs for summed TMPG and MPS stress score were defined using an area under the curve for detecting significant coronary stenosis, and sensitivity, specificity, positive and negative predictive value were evaluated, respectively. P<0.05 was considered statistically significant.

Results

All 17 patients underwent ATP-stress MPCT and MPS without major complication. With regard to adverse side-effects, hot flush (n=4), headache (n=3), palpitation (n=8) and chest pain (n=3) disappeared soon after the termination of the ATP infusion. Mean examination time was 15±6 min. Invasive CAG was also performed. Baseline characteristics are given in Table 1. Six patients had the left main disease (2-vessel disease). In total, the number of patients with single-, double- and triple-vessel disease was 4, 7 and 6, respectively. There were 36 diseased vessels in 51 vessel territories.

TMPG was not calculated for 20 segments in 6 patients due to motion artifact. A total of 252 segments was analyzed. Intra- and inter-observer concordance for the reproducibility of TMPG was 0.96 and 0.81, respectively. We concluded that these reliabilities were satisfactory (k>0.70, in each). There were 84 segments with MPS score 0 on MPS, 77 segments with score 1, 64 segments with score 2, 24 segments with score 3, and 3 segments with score 4, respectively.

TMPG and MPS Score

The median TMPG (range) per segment vs. stress score 0, 1, 2, 3 and 4 was –0.1 HU/mm (–7.4–12.3), 3.8 HU/mm (–5.2–19.9), 7.6 HU/mm (–3.5–16.8), 12.8 HU/mm (1.9–48.7), and 19.8 HU/mm (16.3–27.8), respectively. There was a significant difference in TMPG among the 5 MPS score groups (P<0.05; Figure 3A). Post-hoc analysis showed that the severity of TMPG was significantly greater as MPS score increased from 0 to 3 and there was no significant difference in TMPG between segments with stress scores 3 and 4.

In the assessment of the severity of myocardial ischemia, summed TMPG correlated well with summed MPS stress per territory (P<0.05; Figure 3B) and per patient (P<0.05; Figure 3C).

Figure 4. On both (A) summed transmural perfusion gradient (TMPG) and (B) summed myocardial perfusion scintigraphy (MPS) stress score, there were significant differences with regard to presence or absence of coronary artery stenosis (P<0.05). With regard to the distribution of data, (A) summed TMPG was better than (B) MPS stress score for detecting significant coronary artery stenosis. CAG, coronary angiography; HU, Hounsfield units.
CAG detected 36 significant stenotic vessels in 51 vessel territories. On territory-based analysis, summed TMPG with and without significant coronary stenosis was 32.3 HU/mm (–1.9–90.9) and 14.5 HU/mm (–5.6–38.4), respectively (P<0.05; Figure 4A), and summed MPS stress score with and without significant coronary stenosis was 6 (1–17) and 4 (1–13), respectively (P<0.05; Figure 4B).

Using area under the curve, cut-offs for summed TMPG and MPS were calculated as 16.9 HU/mm and 4.5, and the
diagnostic accuracy of detecting significant coronary stenotic vessel was evaluated (Table 2). As the proportion of diseased vessels increased, summed TMPG performed better than summed MPS stress score.

**Discussion**

The present study evaluated a semi-quantification of myocardial perfusion abnormalities using ATP-stress MPCT in patients with CAD.

The present data showed that (1) TMPG had a positive significant correlation with MPS severity per segment; and (2) a significant positive correlation with the summed MPS stress score per territory and patient. Theoretically, very severe ischemia corresponds to an MPS score of 0. In all the enrolled patients, the LV segments with thallium-201 uptake score 4 on the stress image, showed some redistribution on the late image; that is, ischemic but viable. ECG and echocardiography also showed some viable myocardium without complete scar formation. We think that the high spatial resolution of CT could describe contrast enhancement of the outer layer in the epicardial myocardium and could be used to evaluate small transmural gradient CT attenuation. Stress MPS is the most commonly used functional imaging modality in CAD assessment, given its robust prognostic value. The present data suggest that TMPG and summed TMPG are on a par with MPS and summed MPS as regards evaluation of the severity of myocardial ischemia and the stratification of high risk of heart event. We used a small ROI because this is simple and easy to assess. Therefore, in the present study, use of TMPG in a small ROI may have overestimated the gradient compared with a large ROI or a whole segment. But we believe that there was minimal overestimation of the TMPG using a small ROI and it can be used as representative of the whole segment.

For detecting coronary artery stenosis, the present data showed that summed TMPG performed well in comparison with MPS when there was a higher proportion of diseased vessels. The sensitivity of SPECT was low (64%) in the present study, but we performed the ATP-stress tests carefully, ensuring that there was no anti-anginal medication and/or caffeine intake at least 24h before the test. There are several possible reasons for the low sensitivity. First, the proportion of multi-vessel disease was dominant (76%). Second, the assessment was based not on per-patient analysis but on per-territory analysis, using only stress score. Last, “balanced ischemia” might have been missed on SPECT perfusion assessment. In patients with multi-vessel disease, it is more important to assess the extent of the diseased area for revascularization therapy. Because MPCT has higher spatial resolution and provides anatomical information on coronary arteries, it is useful in differential diagnosis of the culprit coronary stenotic segment and artery.

With the use of prospective ECG gating, less invasive CT CAG has rapidly become widespread due to its clinical usefulness in some patients and situations. But when significant or intermediate coronary stenosis is detected, the number of patients requiring invasive CAG for final diagnosis or functional assessment on stress SPECT and/or magnetic resonance imaging has increased. The present stress MPCT can be used as an alternative functional test in the assessment of CAD.

It is important to maintain image quality and objectivity of assessment in stress MPCT. As for the former, contrast enhancement of myocardium in myocardial perfusion depends on the injection protocol of contrast medium, scan timing, coronary stenosis and the stress test. Stress images in the present study were collected in the myocardial phase after the arterial phase, while contrast enhancement was maintained using slow infusion of contrast medium. As for the latter, most stress MPCT have been evaluated using visual interpretation, and George et al reported on a semi-quantitative method using the ratio of endocardial to epicardial attenuation. The ratio was a physiological investigation item to assess the progression of myocardial ischemia, and we evaluated this on preliminary data. The preliminary data showed that there was a correlation between the ratio and MPS stress score per segment, but that per-territory and per-patient analysis did not produce favorable results. Small scale range (0.5–1.6) and/or overlapping interpretation between the presence and absence of stenotic vessels (MPS stress score) in the ratio seems to be the reason. The present data showed that TMPG was a more objective and comprehensible investigation item for evaluating the severity of myocardial ischemia (Figure 5).

The present study had several limitations. The number of patients was low, and non-selected patients with a higher prevalence CAD were enrolled. Myocardial infarction, one of the exclusion criteria in the present study, was defined based not on magnetic resonance imaging but on history. Therefore minor previous infarction may be missed. Further study is needed to address these points. The injection protocol for the contrast medium for myocardial enhancement was not standardized, in that it was not performed strictly according to body weight and cardiac function. The specific image filter for reduction of beam hardening artifact was not used. Temporal resolution and coverage of this 64-slice CT was not sufficient for assessment of whole heart dynamic myocardial perfusion. Myocardial perfusion-dedicated stress image was not suitable for assessment of coronary artery stenosis. Using the present injection protocol of contrast medium and CT scanning parameters, the LV cavity and myocardium were contrast enhanced homogeneously, and stable assessment was performed using the static image without bias. This suggests that more patients would be able to benefit from, and more facilities would be able to use, this procedure.

**Conclusion**

We propose TMPG as an alternative investigation item to MPS stress score in the semi-quantitative assessment of the transmural extent of ATP-stress-induced myocardial perfusion abnormalities, in patients with CAD.

**Acknowledgment**

This research was supported in part by Grants-in-Aid for scientific research from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

**References**


