Diagnostic Accuracy of Endocardial-to-Epicardial Myocardial Blood Flow Ratio for the Detection of Significant Coronary Artery Disease With Dynamic Myocardial Perfusion Dual-Source Computed Tomography

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Background: Previous dynamic stress computed tomography perfusion (CTP) studies used absolute myocardial blood flow (MBF in mL/100 g/min) as a threshold to discriminate flow-limiting coronary artery disease (CAD), but absolute MBF can be vary because of multiple factors. The aim of this study was to compare the diagnostic performance of absolute MBF and the transmural perfusion ratio (TPR) for the detection of flow-limiting CAD, and to clarify the influence of CT delayed enhancement (CTDE) on the diagnostic performance of CTP.

Methods and Results: We retrospectively enrolled 51 patients who underwent dual-source CTP and invasive coronary angiography (ICA). TPR was defined as the endocardial MBF of a specific segment divided by the mean of the epicardial MBF of all segments. Flow-limiting CAD was defined as luminal diameter stenosis >90% on ICA or a lesion with fractional flow reserve ≤0.8. Segmental presence and absence of myocardial scar was determined by CTDE. The area under the receiver-operating characteristics curve (AUC) of TPR was significantly greater than that of MBF for the detection of flow-limiting CAD (0.833 vs. 0.711, P=0.0273). Myocardial DE was present in 27 of the 51 patients and in 34 of 143 territories. When only territories containing DE were considered, the AUC of TPR decreased to 0.733.

Conclusions: TPR calculated from absolute MBF demonstrated higher diagnostic performance for the discrimination of flow-limiting CAD when compared with absolute MBF itself.

Key Words: Coronary artery disease; Dual-source computed tomography; Myocardial infarction; Myocardial ischemia; Myocardial perfusion imaging
Circulation Journal Vol.81, October 2017

Figure 1. Study flow chart. Of the 355 consecutive patients in the myocardial CTP registry, 51 were enrolled in the analysis. Flow-limiting CAD was found in 67 of 153 (43.8%) territories. CABG, coronary artery graft surgery; CAD, coronary artery disease; CTP, computed tomography perfusion; FFR, fractional flow reserve; ICA, invasive coronary angiography; OMI, old myocardial infarction; pts, patients; ves, vessel territories.

Hospital, we identified a total of 355 patients who had undergone a comprehensive cardiac CT study by dual-source CT (SOMATOM Definition Flash; Siemens Healthcare) consisting of adenosine-stress dynamic CTP, rest CCTA and CT delayed enhancement (CTDE) between March 2012 and August 2015. The comprehensive CT protocol was indicated for patients between 45 and 85 years of age who were referred for comprehensive CT protocol was indicated for patients with known or suspected CAD. Patients with experienced revascularization therapy or change in medi-

CT Data Acquisition and Reconstruction
During a 3-min administration of adenosine (Adenoscan; Daiichi-Sankyo, Tokyo, Japan) at 0.14 mg/kg/min, dynamic myocardial CTP was initiated with injection of 40 mL of iopamidol with an iodine concentration of 370 mgI/mL at a flow rate of 5 mL/s. Dynamic datasets were acquired for 30 s using ECG-triggered axial scan mode with alternating table position “shuttle modes scan” with a Z-axis coverage of 73 mm. On completion of the imaging, adenosine administration was discontinued. ECG, blood pressure, and arterial oxygen saturation were monitored throughout the procedure.

Figure S1

CT Perfusion and CTDE Data Evaluation
The dynamic CTP data were analyzed with commercially available perfusion software (Syngo VPCT body, Siemens Healthcare). As has been previously described, MBF was estimated using a dedicated parametric deconvolution technique based on a 2-compartment model of the intravascular and extravascular spaces to fit the time attenuation curves. The algorithm then generated a MBF map with 3-mm thickness and 1-mm increments by applying the maximum slope approach onto the model curve that was fit for every voxel. The MBF map was analyzed using in-house software written on MATLAB (MathWorks, Natick, MA, USA) by 2 independent observers (Figure S1). Endocardial and epicardial borders of the left ventricular myocardium were manually traced on short-axis slices and then the subendocardial MBF and subepicardial MBF in each of the 16 segments, excluding the apical segment of the American College of Cardiology/American Heart Association 17-segment model, were calculated automatically.

To estimate the transmural distribution of perfusion abnormalities, the transmural perfusion ratio (TPR) was calculated as the subendocardial MBF of a specific segment divided by the mean subepicardial MBF of all 16 segments. Minimum MBF of subendocardial segments and minimum TPR were used for analysis.

By using multiplanar image stacks aligned with the short-axis and long-axis of the left ventricle (5-mm thickness, 5-mm increment, window width/window level=200/100), CTDE images were analyzed visually to determine the presence and absence of hyperenhancement suggestive of infarct scar within each segment of the 16 segments by the consensus of 2 observers who were unaware of the CTP, CCTA and ICA results.

CCTA images were reviewed to confirm the correct assignment of the myocardial segment to the coronary artery territories using previously described methods. The myocardial segment was reassigned in 7 of the 51 patients according to coronary artery anatomy.

ICA and FFR
ICA images were analyzed visually on multiple projections by the consensus of 2 experienced cardiologists who were unaware of the CT results. Segments with a diameter <1.5 mm were excluded from analysis. Critical lesions (≥90% diameter narrowing) were classified as hemodynamically significant stenosis, while mild lesions (<30% diameter nar-
Statistical Analysis
Continuous variables are presented as mean±standard deviation if normally distributed. Categorical variables are displayed as frequency (percentage). Distribution of the continuous variables was assessed using the Shapiro-Wilk test. Differences within groups were compared using the paired Student t-test for normally distributed variables, or the Mann-Whitney signed rank test for independent samples and non-parametric variables. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and 95% confidence intervals (CI) were calculated to predict the ability of each index to identify hemodynamically significant stenoses on a per-vessel (left anterior descending coronary artery [LAD], left circumflex coronary artery [LCx], right coronary artery [RCA]) basis.

Figure 2. An 80-year-old man with exertional angina pectoris. (A) On the myocardial blood flow (MBF) map, a slight perfusion abnormality can be seen in the anteroseptal wall-left anterior descending artery (LAD) territory. The corresponding MBF is 83.4 mL/min/100g (arrowheads), which indicates no ischemia. (B) Computed tomography delayed enhancement demonstrates no myocardial scar, but the transmural perfusion ratio of 0.78 indicates ischemia in the LAD territory. (C) Invasive coronary angiography and fractional flow reserve (FFR=0.78) reveal flow-limiting coronary artery disease in the LAD (arrowhead).
Optimal cutoff values for MBF and TPR were calculated as the thresholds maximizing the Youden index J, where J=sensitivity + specificity - 1. Sensitivity and specificity were calculated for the cutoff values. Intraobserver and interobserver variabilities were compared using the intraclass correlation coefficient for absolute agreement. A two-sided value of P<0.05 was considered to represent statistical significance. All analyses were performed with the MedCalc (version 13.2.2 MedCalc Software, Mariakerke, Belgium).

Results

Baseline Characteristics

Patient characteristics are summarized in Table 1. The comprehensive CT protocol and ICA were successfully done without major adverse events. No patients and no vessel territories were excluded because of CT image quality. A total of 7 patients (13.7%) and 13 vessels (8.5%) had prior stent implantation for stable angina pectoris. There was no patient with a left ventricular wall thickness >13 mm on echocardiography.

ICA and FFR Findings

On ICA, 46 patients (90.2%) had >30% stenosis in at least 1 coronary artery. On a territory basis, 58 territories (37.9%) had critical lesions, 31 territories (20.3%) had moderately severe lesions, and 64 territories (41.8%) had angiographically mild lesions. Of the 31 territories with moderate lesions, FFR results were not available for 11 territories (11/31, 35.5%), which were excluded from the analysis. The remaining 20 territories were successfully interrogated, demonstrating a FFR ≤ 0.80 in 9 territories (9/20, 45.0%). Thus, data from 142 territories (46 LAD, 47 LCX and 49 RCA) were available for comparison and were included in the analysis. A total of 67 territories (67/142, 47.2%, [29 LAD, 22 LCX and 16 RCA]) in 39 patients (39/51, 76.5%) were identified as territories with flow-limiting CAD (Figure 1).

CT and MBF Results

Table 2 demonstrates the CT scan parameters. The mean heart rate significantly increased from 62.5±10.6 beats/min at baseline to 70.3±12.4 beats/min with adenosine administration (P<0.0001). The mean systolic blood pressure significantly decreased from 141.3±24.5 mmHg at baseline to 124.4±22.1 mmHg with adenosine administration, while the diastolic blood pressure significantly decreased from 71.8±12.3 mmHg to 64.4±14.1 mmHg (P<0.0001 and P<0.0001). The mean MBF of all myocardial segments, all subepicardial myocardium, and all subendocardial myocardium on dynamic stress perfusion CT was 98.1±34.6 mL/100 mL/min (range, 41.2–173.6 mL/100 mL/min), 99.8±34.6 mL/100 mL/min (range, 41.1–175.4 mL/100 mL/min) and 97.1±35.0 mL/100 mL/min (range, 39.1–172.1 mL/100 mL/min), respectively. Representative images are provided in Figure 2.

Diagnostic Performance of MBF Indices

At the territory level, both MBF and TPR were significantly different between those with flow-limiting CAD and those without (73.5±26.5 mL/100 g/min vs. 98.6±36.0 mL/100 g/min, P<0.0001, and 0.811±0.136 vs. 0.966±0.094, P<0.0001, respectively). On ROC curve analysis, MBF had an AUC of 0.711 (95% CI, 0.629–0.801) and TPR had a significantly greater AUC of 0.833 (95%
Diagnostic Accuracy of Relative MBF by Dynamic CTP

When only those containing DE were considered, the AUC of TPR for detecting flow-limiting coronary stenosis was 0.733 (95% CI, 0.554–0.870), with a sensitivity, specificity, PPV and NPV of 88.0% (22/25), 33.3% (3/9), 78.5% (22/28) and 50.0% (3/6), respectively. Exclusion of territories containing DE improved the AUC of TPR from 0.833 to 0.838 (95% CI, 0.756–0.901), but the effect was not statistically significant (P=0.930) (Figure 4).

Discussion

The major findings of this study were: (1) TPR calculated from absolute MBF yielded higher diagnostic performance for discriminating flow-limiting CAD when compared with absolute MBF itself, and (2) there was a high prevalence of myocardial scar detected by CTDE in patients who underwent comprehensive cardiac CT and subsequent ICA after excluding subjects with a history of myocardial infarction.

There are a number of pathophysiological and methodological factors that can affect absolute MBF in the vasodilator-induced hyperemic state,11 which may explain the wide range of optimal MBF cutoff values to detect ischemia among previous studies.6–10 Because it is well established that the endocardial layer is more susceptible to ischemia and that perfusion of epicardial layers is relatively spared, even in the presence of severe coronary stenosis, one can assume that the relative flow index focussing on the difference between the endocardium and epicardium accurately reflects stenosis severity better than absolute thresholds.17 Indeed, the TPR of absolute MBF, a ratio of endocardial MBF and epicardial MBF, improved the accuracy of stress dynamic CT for the detection of flow-limiting CAD in our study.

George et al25 were the first to describe the utility of transmural differences in the attenuation CT density in the subendocardial and subepicardial layers of the left ventricle during adenosine stress. They used TPR derived from static CTP (assessment of myocardial perfusion obtained from a single data sample) and demonstrated that TPR can predict myocardial perfusion abnormalities in the setting...
of obstructive atherosclerosis in comparison with combined quantitative coronary angiography and single-photon emission computed tomography. However, the CT density of the myocardium on static CT perfusion imaging is highly dependent on the contrast material bolus profile as well as on data acquisition timing. A previous cardiac magnetic resonance study analyzed the transmural gradient in myocardial contrast uptake as signal intensity using dynamic magnetic resonance perfusion. That study indicated that the transmural gradient of the signal intensity in the left ventricular myocardium can be affected by the timing of contrast material administration and that it varies over time. The same might be equally true with regard to the transmural differences in the attenuation CT density, while the TPR of the absolute MBF might be less affected by acquisition timing issues. Superior diagnostic performance of the CT-derived relative MBF value has been demonstrated for the detection of significant coronary artery stenosis when compared with absolute MBF values. Kono et al demonstrated that the AUC of the relative MBF value was significantly greater than that of the absolute MBF value (0.87 and 0.75, respectively). Their AUCs were comparable with our current results. However, their relative MBF values were not TPR, rather, they were ratios of the absolute MBF divided by the highest remote MBF value, which may be strongly affected by the selection of regions of interest.

Analysis of the prevalence of myocardial DE in candidates for CTP is a unique feature of the current study. We found a high prevalence of myocardial DE of 41.2% in all subjects and of 34.1% in subjects without stent implantation. In this study, all DE lesions involved the subendocardium in a coronary distribution, which is typical of myocardial infarction and 73% of those myocardial DE were associated with a flow-limited epicardial coronary artery. We anticipated a deterioration in the accuracy of CTP as a result of the high prevalence of myocardial DE because myocardial scar or infarction is likely to show reduced MBF regardless of the presence or absence of flow-limiting CAD. In reality, myocardial DE had only a small effect on the diagnostic performance of CTP in the territories without previous stent implantation because the presence of myocardial DE is almost always associated with both reduced TPR and significant stenosis in the epicardial coronary artery.

The presence of myocardial DE is probably more clinically problematic in patients with prior stent implantation, because the myocardial DE in per-stent-implanted vessels was as high as 46% in our study and because all of these DE lesions demonstrated reduced MBF regardless of the presence or absence of in-stent restenosis, as exemplified in Figure 5. Our finding explains the extremely low PPV of CTP for the detection of in-stent restenosis as reported by Rief et al. For CTP to be truly useful in the evaluation of in-stent restenosis, differentiation between ischemia and infarction is necessary. The comprehensive CT study protocol in this study can provide discrimination of myocardial ischemia and infarction. Further study is needed to evaluate the utility of comprehensive CT study for diagnosing in-stent restenosis.

**Study Limitations**

Our study had several. First, it was a single-center study with a small sample size. Second, patients with an intermediate or high probability of CAD were evaluated, so selection bias could have had some effect on the results. Third, not all vessels were interrogated with FFR. FFR evaluation was not performed in vessels with <30% diameter narrowing, as angiographically normal, or in >90% diameter narrowing as significant stenosis. Although that was in agreement with generally accepted clinical standards, the effect of coronary collateral circulation on myocardial ischemia was not considered. Fourth, combining CTCA with CTP will increase the ionizing radiation dose as well as the contrast medium volume. Fifth, CTDE was performed for the detection of myocardial scar, but late gadolinium enhancement cardiac magnetic resonance, which is widely accepted as the standard noninvasive imaging technique for detecting myocardial scar, was not performed.

**Conclusions**

TPR obtained from quantitative stress dynamic dual-source CT perfusion demonstrated higher diagnostic performance for discriminating flow-limiting CAD when compared with absolute MBF. There was a high prevalence of myocardial DE detected by CTDE in patients who had undergone comprehensive cardiac CT and subsequent ICA but had no history of myocardial infarction.

**Conflict of Interest Statement**

Hajime Sakuma received a research grant from Siemens Healthcare K.K. and Bayer Yakuhin, Ltd.

**References**

Circulation Journal Vol.81, October 2017


30. Supplementary Files

Supplementary File 1

Figure S1. MBF map analysis using in-house software written in MATLAB.

Please find supplementary file(s):