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A statistically significant correlation was observed between the severity of anatomic stenosis and coronary flow reserve in experimental animals. A similar correlation in human coronary artery disease (CAD) was shown using positron emission tomography (PET) and pharmacologic vasodilator stress. The present study tested whether the concept of relative myocardial perfusion reserve (MPR) might be superior to absolute MPR in correlating coronary stenosis determined by quantitative coronary arteriography in patients with single vessel CAD using [13N]ammonia and PET. The study group comprised 21 patients (62±10 years old; 15 men, 6 women) with normal left ventricular function who underwent angioplasty for isolated left anterior descending coronary artery stenosis. Absolute MPR, the ratio of dipyridamole-induced hyperemic blood flow to baseline blood flow by [13N]ammonia PET, and relative MPR, the ratio of MPR in regions supplied by stenosed coronary arteries to MPR in remote regions, were measured before and 3 months after angioplasty. The percent diameter stenosis was also quantified on coronary arteriograms just before the angioplasty and again at 3 months after. The study found that absolute MPR (r=0.755; p<0.0001) and relative MPR (r=0.814; p<0.0001) were inversely and nonlinearly correlated with the percent stenosis on angiography. The fitting curve of the correlation between relative MPR and coronary stenosis on angiography was identical to that observed in animal models. Therefore, relative MPR measured by [13N]ammonia PET more accurately and specifically describes stenosis severity in patients with CAD compared with absolute MPR, probably because of its independence from hemodynamic variations and the effects of coronary risk factors. (Jpn Circ J 2001; 65: 23 – 27)

Key Words: Coronary stenosis; Positron emission tomography; Relative myocardial perfusion reserve; Single-vessel coronary artery disease

| Table 1 Clinical and Angiographic Baseline Characteristics (n=21) |
|-----------------|----------------|
| Age (years)     | 62±10          |
| Sex (M/F)       | 15/6           |
| Hypertension (%)| 10 (48)        |
| Diabetes mellitus| 4 (19)        |
| History of smoking (%)| 9 (43)   |
| Hypercholesterolemia (%)| 11 (52) |
artery was the left anterior descending (LAD) artery in all patients. Patients with the clinical conditions of hypertension, diabetes mellitus or hypercholesterolemia (total cholesterol >220 mg/dl) associated with impaired MPR were not excluded from the study. Ten patients had a history of hypertension, but no evidence of ventricular hypertrophy on 2-dimension echocardiography. Baseline characteristics are shown in Table 1.

**Study Protocol**

Coronary angioplasty was performed in all 21 patients; 13 patients underwent balloon angioplasty and 8 had coronary stenting. Thirteen patients underwent coronary angiography to evaluate coronary restenosis 3 months after the angioplasty. Cineangiograms obtained before coronary angioplasty and at the time of follow-up recatheterization were analyzed by quantitative angiographic measurement, as described later. PET scanning with measurement of the myocardial blood flow (MBF) and MPR was performed both before and 3 months after angioplasty. All the participants refrained from consuming caffeine-containing food or beverages for at least 24 h before the study, and did not take any medication for at least 12 h before the study. The study protocol was approved by the PET safety committee of Chiba University School of Medicine. Written informed consent was obtained from all patients.

**Positron Emission Tomography**

PET images were obtained with a SET-130W PET scanner (Shimadzu Co, Kyoto, Japan), which can obtain 3 slices simultaneously with a slice thickness of 16.5 mm and has a spatial resolution of 10.5 mm at full width at maximum (FWHM). Effective in-plane resolution was 12.8 mm FWHM after a smoothing filter was used.

MBF was quantified at baseline and during dipyridamole-induced hyperemia using [13N]ammonia and dynamic PET imaging. A 20-min transmission scan was acquired for correction of photon attenuation. Subsequently, 333–370 MBq of [13N]ammonia was infused into the left antecubital vein over a period of 15–20 s. Dynamic data acquisition was started simultaneously with the injection of the tracer; 16 frames were acquired over 270 s (15 frames of 10 s and 1 frame of 120 s). Then, 50–60 min later, 0.56 mg/kg of dipyridamole was infused over 4 min for determining absolute MPR defined as the ratio of hyperemic to baseline MBF. [13N]ammonia was infused 2 min later, and dynamic data was acquired in each sequence. Reconstruction was performed without ECG gating. All images were corrected for physical decay of the tracer. Relative MPR was defined as the ratio of MPR in regions supplied by stenosed coronary arteries to MPR in remote regions.

Heart rate (HR), arterial blood pressure, and 12-lead ECG were recorded at the time of tracer injection of the baseline study and every minute during and after dipyridamole infusion, with continuous ECG monitoring. HR and arterial blood pressure obtained at the time of each tracer injection were used to calculate the rate–pressure product as an index of cardiac work.

**Quantitative of MBF**

The method used for the quantification of MBF has been described previously. In brief, to determine the myocardial activity curves, 18–24 regions of interest (ROIs), each with an area of 0.36 cm², were drawn on the left ventricular myocardium at the midventricular level. ROIs were drawn on the last image of uptake and then projected to the early dynamic images. The ROIs were divided into 6 segments (posteroseptal, anteroseptal, anterior, anterolateral, midlateral, and posterolateral regions). All patients had LAD artery disease, and thus the anterior and septal regions were designated as stenosis-related regions, and the mid-lateral and posterolateral regions as remote. Arterial input function was obtained from the ROI in the center of the left atrial cavity. The observed myocardial activity was corrected using the recovery coefficient of the myocardium (partial volume effect) and the spillover fraction from blood pool activity to the myocardium (Sm). We used the constant values of 0.63 and 0.18, respectively, assuming that the left ventricular wall thickness was 1.0 cm. MBF was quantified from the arterial tissue time activity curves using the previously validated Simple Flow Model as follows:

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F = \frac{Cm(t)}{E \times g \times \int_{0}^{t} Ca(x) dx}
\]

where F is myocardial blood flow, E the myocardial extraction fraction of the tracer, \(Cm(t)\) myocardial activity, Ca(x) arterial input function, and g myocardial density (1.05 g/ml). The myocardial activity data were used for myocardial uptake at 90 s after the intravenous injection, and the arterial input function data were used to integrate the first 90 s.

**Quantitative Angiographic Measurement**

At least 2 cineangiograms, in orthogonal projections, were obtained before coronary angioplasty and repeated at the time of follow-up recatheterization in the same projections. Intracoronary nitroglycerin at 0.1–3 mg was administered to achieve maximal coronary vasodilatation. Two independent specialists without knowledge of the clinical and PET data analyzed the cinefilms. Matched views and frames were selected for offline quantitative analysis. A computer-assisted analysis system was used. Automatic edge detection of the luminal dimensions (MLD and reference diameter) and videodensitometric analysis were performed by use of a guiding catheter filled with contrast as a scaling factor.
Relative Myocardial Perfusion Reserve and Stenosis Severity

Statistical Analysis
All values were expressed as mean ± SD. Hemodynamic and MBF results before and after dipyridamole were compared with paired Student’s t test. Hemodynamic and MBF results before angioplasty and at the follow-up study (after 3 months) were compared using Student’s t test for paired or unpaired data as appropriate. A regression curve was calculated between percent diameter stenosis and hyperemic MBF, MPR, relative MPR and minimal vascular resistance. A p value <0.05 was considered statistically significant.

Results
Hemodynamics Findings
Table 2 summarizes the hemodynamics findings at rest and after dipyridamole before angioplasty and at the time of the follow-up study. After dipyridamole, patients demonstrated a significant increase in HR and rate-pressure product, whereas no significant changes were observed in systolic, diastolic and mean aortic blood pressure. No significant difference was found between the hemodynamics parameters before angioplasty and at the time of the follow-up study.

Changes in Stenosis Severity on Coronary Arteriograms
Before angioplasty, the percent diameter stenosis was 82±7%, and it improved to 37±21% (p<0.0001 vs before angioplasty) at the time of the follow-up study. Before angioplasty, the minimal luminal diameter was 0.50±0.23 mm, improving to 1.67±0.62 mm (p<0.0001 vs before angioplasty) at the time of the follow-up study.

Changes in MBF and MPR
Before angioplasty, there was no significant difference between basal MBF in regions supplied by stenosed arteries and remote regions (0.86±0.24 and 0.90±0.26, p=NS). Three months after angioplasty, there was also no difference between basal MBF in the angioplasty regions and remote regions (0.76±0.18 and 0.76±0.19, p=NS) (Fig 1).

The dipyridamole-induced increase in MBF in regions supplied by stenosed arteries before angioplasty was lower than that in remote regions (1.17±0.46 and 2.03±0.63, p<0.0001). At 3 months after angioplasty, the MBF response to dipyridamole was similar in the angioplasty and remote regions (1.91±0.66 and 2.00±0.78, p=NS) (Fig 1).

Before angioplasty, MPR was significantly lower in regions supplied by stenosed arteries than in the remote regions (0.76±0.18 and 0.76±0.19, p=NS) (Fig 2).

The dipyridamole-induced increase in MPR in regions supplied by stenosed arteries before angioplasty was lower than that in remote regions (1.17±0.46 and 2.03±0.63, p<0.0001). At 3 months after angioplasty, the MPR response to dipyridamole was similar in the angioplasty and remote regions (1.91±0.66 and 2.00±0.78, p=NS) (Fig 1).

Changes in MPR and MPR
Before angioplasty, MPR was significantly lower in regions supplied by stenosed arteries than in the remote regions (0.76±0.18 and 0.76±0.19, p=NS) (Fig 3).

Relative MPR before angioplasty was 0.60±0.15, and
improved to 0.96±0.17 (p<0.0001 vs before angioplasty) 3 months after angioplasty (Fig 3).

**Correlation Between MBF and Coronary Stenosis Severity**

Hyperemic MBF was linearly related to the percent diameter stenosis on coronary arteriography (y=2.388–0.015x; r=0.638; p<0.0001; Fig 4A).

**Correlation Between Absolute MPR and Coronary Stenosis Severity**

Absolute MPR was significantly correlated with the percent diameter stenosis on coronary arteriography (r=0.755; p<0.0001; Fig 4B).

**Correlation Between Relative MPR and Coronary Stenosis Severity**

Relative MPR was significantly correlated with the percent diameter stenosis on coronary arteriography (r=0.814; p<0.0001; Fig 4C). As well, the shape of the fitting curve was identical to that observed in animal models.

**Correlation Between Minimal Coronary Vascular Resistance and Coronary Stenosis Severity**

To relate the hyperemic blood flow to one of its major determinants, the coronary driving pressure, mean aortic blood pressure was divided by hyperemic blood flow, and an index of minimal coronary resistance was obtained. A significant correlation was observed between coronary vascular resistance and the percent diameter stenosis on angiography (r=0.571; p=0.0022; Fig 4D).

**Discussion**

The present study demonstrates that the absolute and relative MPR measured by [13N]ammonia PET were each inversely and nonlinearly correlated with stenosis on angiography. In particular, the correlation between relative MPR and percent stenosis was superior to that of absolute MPR, and their fitting curve was virtually identical to that of previously published data in animal models. There is considerable variability in the correlation between absolute MPR and percent stenosis. Two major factors may be involved, the first being the differences in the responsiveness of individual subjects to pharmacologic vasodilatation and in the hemodynamic state at baseline in case of patients with hypertension, as previously discussed. The second is the microcirculatory impairment of the myocardial bed. For example, in patients with coronary risk factors such as diabetes mellitus or hyperlipidemia, MPR is reduced not only in the myocardium supplied by normal coronary arteries but also in the myocardium supplied by stenosed arteries. Relative MPR theoretically nullifies the influence of variables and describes the stenosis severity independent of them. This may contribute to the superior correlation with the percent stenosis and the virtually identical fitting curve compared with those using absolute MPR. To our knowledge, this is the first report to show the advantage of relative MPR in clinical settings using PET.

We chose patients with single-vessel disease, because patients with 3-vessel disease are not appropriate for relative estimates. Relative MPR cannot be determined in patients with 3-vessel disease having no reference vessel, as Di...
Carli et al reported: Therefore, absolute and relative MPR together provide a more complete description of physiologic stenosis severity than either does alone.

In addition, we also chose patients who underwent angioplasty, and we measured MPRs and stenosis severity both before and 3 months after the procedure, which gave a better correlation than would be found in routine clinical settings that include patients with moderate coronary stenosis.

Arteriographic factors also may have contributed to the variability in the correlation. Unlike the controlled and idealized coronary stenosis in an experimental setting, single human coronary stenoses reveal remarkably greater morphologic complexities such as eccentricity, variable lengths, and irregular surfaces. These features may not be fully accounted for by assumptions underlying model-based estimates of stenosis severity.

The concept of relative flow reserve is one of the topics in laboratory coronary physiological measurement that is being transferred to clinical practice as relative coronary velocity reserve (CVR)\(^{21,22}\). Better correlation of relative CVR than absolute CVR with percent coronary stenosis was shown by Baumgart et al\(^2\), which concords with our results. However, their technique needs pharmacological stress at least twice for the reference and target coronary arteries and, moreover, was an invasive technique using Doppler wire. PET scans at rest and single pharmacological stress enable measurement of relative MPR to be done noninvasively and, therefore, our method is ideal for evaluating the functional significance of stenosis.

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