Correlation between Myocardial Blood Flow and Fasting Glucose Metabolism in Ischemic Heart Disease

Quantitative Assessment by Nitrogen-13 Ammonia and Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography

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SUMMARY

Ischemic myocardium avidly incorporates fluorine-18 fluorodeoxyglucose (F-18 FDG) in the fasting state, in contrast to the relative absence of F-18 FDG uptake in normal myocardium with sufficient blood flow in the fasting state. Although many studies have attempted to use F-18 FDG uptake to discriminate ischemic but viable myocardium from scarred myocardium, little is known clinically about the correlation between blood flow and F-18 FDG uptake in ischemic myocardium. We studied the critical level of blood flow that causes avid F-18 FDG uptake in myocardium in 9 patients. All patients had angiographically proven ischemic heart disease but no diabetes. Regional myocardial blood flow (RMBF) was measured quantitatively by positron emission tomography (PET) using nitrogen-13 ammonia in the resting state, in which the normal value was 80.2 ± 13.0 ml/min/100 cm³. The F-18 FDG uptake in myocardium was assessed with the differential uptake ratio (DUR) scale. We constructed circumferential profiles of radioactivity uptake in myocardium for each study, and chose 780 sections of myocardium in which the relation between the two factors could be analyzed. In moderately ischemic to normal myocardium with RMBF of 50 to 90 ml/min/100 cm³, RMBF and F-18 FDG uptake were negatively correlated (r = −0.44, p < 0.01). When RMBF was 50 to 60 ml/min/100 cm³ (n = 121), the peak DUR value of F-18 FDG uptake was 4.0 ± 2.0. The two factors were not correlated when RMBF was less than 50 ml/min/100 cm³ or 90 ml/min/100 cm³ or higher. Our results suggest that RMBF and F-18 FDG uptake values as measured with PET may provide valuable information on the possible benefit of intervention in ischemic heart disease. (Jpn Heart J 1998; 39: 275–285)
Key words: Myocardial blood flow, Glucose metabolism, Ischemic heart disease, Positron emission tomography

During ischemia, energy production shifts from the oxidation of free fatty acids to that of glucose. Under normal conditions, glycolysis (glucose utilization) results predominantly in CO₂ production with minimal lactate generation. However, during ischemia, lactate production is increased relative to CO₂ production; glucose may produce up to 70% of the total energy production during ischemia. Furthermore, necrotic myocardium due to severe ischemic damage is unable to produce energy.¹

Assessment of myocardial viability by positron emission tomography (PET) imaging involves comparison of regional myocardial perfusion with regional glucose utilization.³ Myocardial perfusion can be visualized and quantified with flow tracers such as nitrogen-13 (N-13) ammonia, rubidium-82, and oxygen-15 water.³⁻⁶ Regional myocardial glucose utilization can be visualized with fluorine-18 fluorodeoxyglucose (F-18 FDG).⁷⁻¹¹ Rates of myocardial F-18 FDG uptake, which reflect myocardial glucose utilization, are proportional to tissue consumption of exogenous glucose. Experimental studies have demonstrated that glucose utilization is enhanced in segments that are hypoperfused and ischemic but viable.¹² However, little is known clinically about the correlation between blood flow and F-18 FDG uptake in ischemic myocardium.

The aim of the present study was to evaluate the correlation between regional myocardial blood flow (RMBF) and regional myocardial glucose metabolism as assessed with F-18 FDG uptake in patients with ischemic heart disease (IHD).

**Methods**

**Subjects:** The 16 subjects were 9 patients (5 men and 4 women; mean age, 58 ± 8 years) with recent IHD (acute myocardial infarction in 7 and unstable angina pectoris in 2, <1 month after onset) and left ventricular dysfunction and 7 healthy volunteers (all men; mean age, 39 ± 13 years). Patients who had diabetes mellitus or had undergone emergency interventions were excluded from the study. Patients underwent coronary angiography and N-13 ammonia and F-18 FDG PET while healthy volunteers underwent only N-13 ammonia PET. Written informed consent was obtained from all subjects.

**Coronary angiography:** Coronary angiography was performed with the Judkins technique within 1 week before PET. The site and severity of coronary artery stenosis were graded according to the classification of the American Heart Association.¹³ Significant IHD was defined as a lumen diameter stenosis of 75%
or more in at least one of the three major coronary arteries. Collateral vessels were graded on the basis of collateral filling as follows: 0 = none, 1 = filling of side branches only, 2 = partial filling of the epicardial segment, and 3 = complete filling of the epicardial segment. Cardiac output was measured by the thermodilution method using a Swan-Ganz catheter.

**PET:** After patients had fasted overnight, PET studies were performed with a whole-body PET scanner (Headtome IV, Shimadzu Corp., Kyoto, Japan) at Nakano National Chest Hospital. The spatial resolution for static images at the center of the field of view was adjusted to 6 mm with a Butterfield filter. A compact cyclotron (Japan Steel Works, Tokyo, Japan) was used for production of N-13 ammonia (half-life, 10 minutes) and F-18 FDG (half-life, 110 minutes). Before and after PET studies, blood was sampled to measure fasting plasma glucose, free fatty acids, and insulin.

In each study, a transmission scan was performed with 2 mCi of a germanium-68 external source for 5 minutes to confirm the position of the patient's heart and to correct the radiation attenuation in subsequent emission scans. Each study was aided by marking three points on the patient's skin and carefully aligning the landmarks with reference to the light beam of the scanner. While the patient lay at rest on a couch in the PET gantry tunnel, 10 to 20 mCi of N-13 ammonia was injected intravenously. Immediately after injection of N-13 ammonia, blood was sampled from the radial artery at a constant rate of 10 mL/min for 2 minutes. After the blood sample was thoroughly mixed, 1 mL was used to measure radioactivity with a decay correction. Five minutes after injection of N-13 ammonia, an emission scan was performed for 10 minutes. The F-18 FDG study was performed after the N-13 ammonia study had been performed for 30 minutes. While lying in the same position, 2 to 7 mCi of F-18 FDG was injected intravenously. Immediately after injection of F-18 FDG, blood was sampled as before. The blood sample was thoroughly mixed and 0.5 mL used to measure radioactivity with a decay correction. The patient was repositioned within the PET scanner with reference to the three landmarks for a glucose metabolic scan, which was performed for 10 minutes from approximately 40 minutes after injection of F-18 FDG.

**Analysis of myocardial images:** Acquisition of myocardial images was synchronized with the QRS complex on a 12-lead electrocardiogram (Siemens, Erlangen, Germany). The average R-R interval was divided into five time frames. In each time frame, transaxial PET images of five slices were obtained in 13-mm increments from the base to the apex of the left ventricle. The lowest of the five slices was positioned at the upper surface of the right diaphragm in each transmission scan. Of the five slices of the first time frame, which represented left ventricular end diastole, several slices that clearly showed myocardium
Figure 1. The patient was a 57-year-old man with acute anterior wall myocardial infarction. Coronary angiography revealed 100% occlusion of the proximal left anterior descending coronary artery (segment 6). A: Blood flow is represented by N-13 ammonia and glucose metabolism by F-18 FDG. The arrows indicate markedly reduced RMBF with preserved F-18 FDG uptake (blood flow-metabolism mismatch) in anterior areas. B: Circumferential profile analysis of N-13 ammonia and F-18 FDG images presented in the second slices from the left. The thin line represents RMBF and the broken line represents F-18 FDG uptake. The RMBF is low and F-18 FDG uptake is high in anterior areas.
with reduced blood flow but preserved glucose metabolism (blood flow-metabolism mismatch) were chosen (Figure 1A). In each slice, RMBF and myocardial F-18 FDG uptake were measured in 60 sections with circumferential profile analysis (Figure 1B).

Quantification of RMBF and myocardial F-18 FDG uptake: The RMBF of every section \( n = 780 \) was calculated with the formula of Hara et al.\(^{16}\):

\[
\text{RMBF} = \left( \frac{Q}{E \times \int_0^2 \text{Ca}(t) \, dt} \right) \times 100,
\]

where \( Q \) (counts/sec [cps]/cm\(^3\)) is the radioactivity of each section, \( \int_0^2 \text{Ca}(t) \, dt \) (cps ⋅ min/ml) is the integration of radioactivity in the arterial blood withdrawn at a constant rate for 2 minutes, and \( E \) is the first-pass extraction fraction, for which 0.82 was used in our study. Eighty-two percent of arterial N-13 ammonia is trapped in myocardium on the first pass through the coronary microcirculation.\(^{17}\) The calculated value corresponds to RMBF in ml/min per 100 cm\(^3\) of tissue.\(^{15}\)

Myocardial F-18 FDG uptake was assessed quantitatively with the differential uptake ratio (DUR) scale, which was obtained from mean counts per pixel data calibrated by the injection dose (mCi), body weight (kg), and PET-well coefficient factor according to the study of Kubota et al.\(^{18}\) The DUR was defined as (pixel count/pixel volume)/(injected RI activity/body weight) × coefficient factor (cps/cm\(^3\)).

Statistical analysis: Data are expressed as mean ± SD. Comparisons between healthy volunteers and patients with IHD were made by performing the unpaired Student’s \( t \)-test for continuous variables and the chi-square test for discrete variables. The analysis of variance was used to examine differences among the patient subgroups divided by RMBF. Correlations between RMBF and myocardial F-18 FDG uptake were determined using regression analysis. A \( p \)-value < 0.05 was considered to indicate statistical significance.

Results

Coronary artery disease and cardiac output: Of the 9 patients with IHD, 4 (45%) had single-vessel disease, 3 (33%) had double-vessel disease, and 2 (22%) had triple-vessel disease. Visible collateral vessels (grade 1 to 3) were present in 3 (33%) of the patients with multivessel disease. Mean cardiac output was significantly lower in patients with IHD than in healthy volunteers (4.52 ± 1.25 vs. 6.08 ± 0.84 l/min, \( p < 0.001 \)).

Plasma glucose, free fatty acids, and insulin: Before PET studies, mean fasting plasma glucose was normal (98.0 ± 4.7 mg/dl; normal range, 60 to 110 mg/dl), mean free fatty acids were higher than normal (1.44 ± 1.04 mEq/l; normal range, 0.14 to 0.85 mEq/l), and mean insulin was normal (10.6 ± 4.1 µU/ml; normal, ≤ 17 µU/ml) in patients with IHD. After PET studies, mean
fasting plasma glucose was normal (97.1 ± 5.5 mg/dl), mean free fatty acids were higher than normal (1.73 ± 1.00 mEq/l), and mean insulin was normal (7.9 ± 3.8 μU/ml) in patients with IHD.

**RMBF and myocardial FDG uptake:** In healthy volunteers, the mean RMBF was 80.2 ± 13.0 ml/min/100 cm³ in the resting state. Figure 2 shows a scatterplot of the relation between RMBF and myocardial F-18 FDG uptake in all sections.
(n = 780) of patients with IHD. The RMBF was 21.7 to 105.2 ml/min/100 cm³ and the mean 63.7 ± 20.3 ml/min/100 cm³. The F-18 FDG uptake was 0.9 to 8.2 DURs and the mean 3.0 ± 1.5 DURs. The RMBF and F-18 FDG uptake were negatively correlated (r = −0.37, p < 0.01). The F-18 FDG uptake was less than 4.0 DURs in most sections in which RMBF was 80 ml/min/100 cm³ or higher, which was regarded as normal, or less than 50 ml/min/100 cm³, which was more than 2 SD below the normal value. However, F-18 FDG uptake was 4.0 DURs or higher in most sections in which RMBF was 50 to 80 ml/min/100 cm³. Maximal F-18 FDG uptake was 8.2 DURs in a section with RMBF of 55.9 ml/min/100 cm³. Figure 3 shows the changes in F-18 FDG uptake with RMBF. When RMBF was 50 to 90 ml/min/100 cm³ (n = 508), the mean RMBF was 69.8 ± 11.1 ml/min/100 cm³ and the mean F-18 FDG uptake 3.0 ± 1.6 DURs. The RMBF and F-18 FDG uptake were negatively correlated (r = −0.44, p < 0.01). When RMBF was 50 to 60 ml/min/100 cm³ (n = 121), the mean F-18 FDG uptake was 4.0 ± 2.0 DURs and was significantly higher than at other RMBF levels (p < 0.01, p < 0.05). However, RMBF and F-18 FDG uptake were not correlated when RMBF was 90 ml/min/100 cm³ or higher or less than 50 ml/min/100 cm³. When RMBF was 90 ml/min/100 cm³ or higher (n = 73), the mean RMBF was 95.9 ± 4.7 ml/min/100 cm³ and the mean F-18 FDG uptake 2.4 ± 0.5 DURs. When RMBF was less than 50 ml/min/100 cm³ (n = 199), the mean RMBF was 36.3 ± 8.0 ml/min/100 cm³ and the mean F-18 FDG uptake 3.3 ± 1.5 DURs.

**DISCUSSION**

By virtue of its ability to assess myocardial perfusion and glucose metabolism with N-13 ammonia and F-18 FDG, PET is widely regarded as the most accurate technique for detection of ischemic but viable myocardium. After patients with recent IHD have fasted, viable myocardium takes up F-18 FDG whereas normal or necrotic myocardium does not. Three basic patterns of blood flow and glucose metabolic activity can be demonstrated. First, there may be a match between blood flow and metabolic activity with homogeneous myocardial distribution of each tracer. Second, RMBF may be decreased while glucose utilization in the same area is normal or increased relative to normally perfused myocardium or to regions with reduced RMBF. This pattern of blood flow-metabolism mismatch is the PET scintigraphic signature of myocardial viability in the presence of left ventricular dysfunction. Third, RMBF and glucose utilization may be concordantly decreased. This pattern is the marker of myocardial scarring or irreversible damage. However, to our knowledge, this study is the first attempt to assess the correlation between RMBF and myocardial F-18 FDG
uptake by quantitative measurements with PET.

Myocardium in which RMBF was 90 ml/min/100 cm³ or higher, which was regarded as normal, had F-18 FDG uptake of 2.4 ± 0.5 DURs. Myocardium with RMBF of 50 to 90 ml/min/100 cm³, which was regarded as moderately ischemic to normal, had F-18 FDG uptake of 3.0 ± 1.6 DURs. Energy production is thought to shift from the oxidation of free fatty acids (beta oxidation) to that of glucose (anaerobic glycolysis) in myocardium with this range of RMBF. In particular, myocardium with RMBF of 50 to 60 ml/min/100 cm³ had F-18 FDG uptake of 4.0 ± 2.0 DURs and had the highest glucose metabolism. In some cases, F-18 FDG uptake reached 8.0 to 8.2 DURs in this RMBF range. Gibbs has reported that exogenous glucose uptake in myocardium during ischemia can increase to almost three times that under normal conditions.20)

Myocardial F-18 FDG uptake decreased when RMBF was less than 50 ml/min/100 cm³, which was regarded as severely ischemic. In this range of RMBF, myocardial viability has been widely investigated and the myocardium has been identified as viable, nonviable, or scarred. Gewirtz et al.21) reported that RMBF less than 25 ml/min/100 g predicts myocardial scarring and RMBF higher than 39 ml/min/100 g suggests viable myocardium on the basis of wall motion analysis. Our previous report22) suggested that RMBF may improve after intervention in infarcted regions or regions of severe coronary artery disease in which RMBF is at least 30 ml/min/100 g. Our present study suggests that RMBF of about 50 ml/min/100 cm³ indicates the most favorable response to intervention.

Limitations: There were several potential limitations in measurements of RMBF and myocardial F-18 FDG uptake. First, the factors that influence the measured RMBF value are described. The RMBF changes to some degree with age.23) Healthy volunteers were slightly younger than patients with IHD. However, RMBF in normal sections of myocardium in patients did not differ significantly from that of healthy volunteers. The effect of age was thought to be minor in this study. Our assumption of the fixed value of 0.82 as the extraction rate of nitrogen-13 ammonia in myocardium was based on the observation of Schelbert et al.17) in canine hearts; a similar treatment of data was made in our previous study.16) The extraction rate is almost constant, regardless of an increase in coronary flow within the physiological range of 44 to 200 ml/min/100 g. When the coronary flow falls below 44 ml/min/100 g, particularly in severely ischemic myocardium, the extraction rate may decrease. Second, the factors that influence the measured F-18 FDG uptake value are described. Myocardial F-18 FDG uptake is known to differ with dietary condition.1) In the fasting state, as was used in this study, the F-18 FDG uptake is increased in ischemic myocardium but is suppressed in normal myocardium. As a result, ischemic myocardium can be distinguished from normal myocardium on metabolic imaging.9,24) In the quanti-
tative assessment of myocardial F-18 FDG uptake, the regional myocardial glucose utilization rate (moles of glucose/min per g of tissue) according to Patlak's method is generally accepted for dynamic imaging. However, only static imaging is performed in most PET centers so that the number of routine clinical studies can be increased. The simplified method with the DUR scale on static imaging used in this study might be suitable for clinical studies and valuable for comparing myocardial F-18 FDG uptake with RMBF. Third, myocardial perfusion and metabolic imaging with PET is subject to the partial-volume effect. As in our previous studies, the electrocardiographic gated-mode scan was used in this study to minimize the partial-volume effect caused by left ventricular wall motion. However, its use could not completely eliminate the effect of left ventricular wall motion, since radioactivity in the myocardium at systole was always slightly higher than that at diastole in our previous study. When the myocardial wall becomes thin in an infarcted area, measured RMBF may be lower than actual RMBF. Comparisons of RMBF and myocardial F-18 FDG uptake among patients have not presented serious problems clinically, although measurements of RMBF and myocardial F-18 FDG uptake have been performed in all patients under the same conditions.

Conclusions: Our observations suggest that RMBF of 90 ml/min/100 cm$^3$ or higher may indicate normal myocardium and RMBF of less than 50 ml/min/100 cm$^3$ may indicate severely ischemic myocardium, which is nevertheless viable, nonviable, or scarred. Glucose metabolism may increase with decreased blood flow in moderately ischemic to normal myocardium with RMBF of 50 to 90 ml/min/100 cm$^3$ and may be highest in ischemic myocardium with RMBF of 50 to 60 ml/min/100 cm$^3$. The RMBF and myocardial F-18 FDG uptake values as measured with PET provide valuable information on the possible benefit of intervention in IHD.

ACKNOWLEDGMENT

We gratefully thank Toshihiko Hara, MD, Director of Division of Nuclear Radiology, International Medical Center of Japan, for his generous support throughout the study.

REFERENCES


