DETERMINATION OF REGIONAL MYOCARDIAL BLOOD FLOW WITH ^{13}N -AMMONIA POSITRON EMISSION TOMOGRAPHY DURING LOW-GRADE EXERCISE FOR EVALUATING CORONARY ARTERY STENOSIS

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We measured regional myocardial blood flow (RMBF) by positron emission tomography (PET) with ^{13}N -ammonia at rest and during low-grade exercise using a bicycle ergometer fixed at 25 watts for 6.5 min. The ischemic area with severe coronary artery stenosis was evaluated in terms of quantitative RMBF. The study was performed in 46 subjects consisting of 19 patients with old myocardial infarction, 20 with effort angina pectoris, and 7 normal individuals. RMBF was calculated using the radioactivity in myocardial tissue measured by PET and the radioactivity in arterial blood. The PET data were compared with coronary arteriographic findings and ECG findings. When the analysis was restricted to the anterior wall of the myocardium, it was found that exercise caused RMBF to increase by 44.9% ($n=28$) in normal area, to increase by 23.3% ($n=37$) in severely stenotic area (stenosis $\geq 90\%$), and to decrease by 17.4% ($n=20$) in infarcted area. When we considered only the infarcted area of the entire heart, exercise caused RMBF to decrease by 26.6% ($n=30$) in the area of angiographically positive collaterals, and to increase by 0.8% ($n=31$) in the area of negative collaterals. Thus, we were able to quantitate the degree of ischemia in myocardium that was associated with severe coronary artery stenosis. By application of low-grade exercise, RMBF in normal myocardium increased, while RMBF in myocardium perfused by collaterals decreased.

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MYOCARDIAL blood flow is commonly evaluated with thallium-201 using a gamma-camera. Positron emission computed tomography (PET) corrects for the depth-related attenuation of sensitivity, and

also provides superior spatial resolution. PET allows tissue blood flow and metabolism to be measured quantitatively. Evaluation of regional myocardial blood flow (RMBF) by PET using ^{13}N -ammonia as a tracer is useful for determining the location of coronary ischemia in heart disease^{1–5}. However, RMBF is usually evaluated qualitatively by visual inspection, and can not be

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Fig. 1. PET images of 3 slices and heart schemes corresponding to the level of each slice. Schematic drawings of PET images on the right side illustrate the wall boundary of the left ventricle myocardium. LV: left ventricle. LAD: left anterior descending artery. CX: left circumflex artery. RCA: right coronary artery.

considered an objective and quantitative evaluation. We performed PET examinations in patients with coronary artery disease at rest and during exercise using ^{13}N -ammonia, and measured RMBF by PET, by visualizing the infarcted area and the area of severe coronary artery stenosis. The degree of ischemia was quantitated using the image data.

SUBJECTS AND METHODS

Patient

A total of 46 patients (36 males and 10 females) were studied. Of these, 19 had old myocardial infarction (OMI), 20 had effort angina pectoris (angina), and 7 were normal volunteers. The ages were 58.7 ± 12.3 (mean $\pm$ S.D) years for OMI, 62.9 ± 10.8 for angina, and 42.4 ± 12.4 for the normal controls. OMI was diagnosed on the basis of clinical findings, abnormal Q wave on ECG, and previous elevation of serum enzymes. The infarct-related vessel was defined as the stenotic coronary artery with more than 75% stenosis and the cause of the reduction in wall motion. PET study was performed

about 1 month after the occurrence of myocardial infarction. Thirteen subjects underwent the test only at rest, and 33 underwent the test both at rest and during exercise. Informed consent was obtained from all patients.

PET Study

RMBF was measured with ^{13}N -ammonia (half-life of ^{13}N = 10 min) as the tracer, using a HEADTOME IV PET machine (Shimadzu Co.).⁶ The spatial resolution for static images at the center of the field of view was adjusted to 6 mm using a Butterfield filter. The exercise test was conducted in the supine position using a bicycle ergometer (Monark Co.) at a fixed level of 25 watts for a total duration of 6.5 min.

RMBF was measured by PET at rest and during exercise. During the rest scan, the patient lay on a couch in the PET gantry tunnel, and the transmission scan was taken for 5 min using 2 mCi of a ^{68}Ge external source. The transmission scan data were used to correct the radiation attenuation in the emission scan data and also to confirm the position of the patient's heart. We then administered

Fig.2. PET images at rest and during exercise in a normal subject. The various areas of the myocardium are shown on the abscissa, and RMBF (ml/min/100 cm³) for each myocardial area is shown on the ordinate.

10–20 mCi of ^{13}N -ammonia by intravenous injection to the patient in the supine position. Immediately after injection of the tracer, arterial blood was sampled for 2 min at a constant rate of 10 ml/min. After thorough mixing of the blood sample, 1 ml was taken to measure radioactivity with a decay correction. The emission PET scan began 5 min after injection of the tracer, and continued for 10 min. After about 20 min, the couch was removed from the scanning position, and the patient was instructed to exercise on a bicycle ergometer in the supine position, with an exercise level of 25 watts for 5 min.

^{13}N -ammonia (10–20 mCi) was then injected intravenously, and the patient continued to exercise for another 1.5 min. Arterial blood was again withdrawn for 2 min at a constant rate after injection of the tracer. The patient was placed in the correct position for the next emission scan. The second emission data were collected as before. All of the emission data were automatically decay-corrected in a computer and stored in memory.

PET Imaging

Myocardial images with gated ECG were

Fig.3. PET images at rest and during exercise in a case of old myocardial infarction. The infarcted area is in the antero-septal wall. Myocardial infarction was diagnosed by coronary arteriography, cardiac ventriculography, ECG, and clinical findings. Coronary arteriography showed that segment 6 of the left anterior descending artery was completely obstructed. PET images at rest and during exercise are shown on the left. The various areas of myocardium are shown on the abscissa, and RMBF (ml/min/100 cm³) for each myocardial area is shown on the ordinate.

obtained by synchronizing the patient's R wave with the opening of the gate. The average R-R interval was divided into 5 time-frames. Data were collected from the first 4 time-frames. PET images of 5 slices were taken in 13-mm steps from the base of the left ventricle to the apex. Twenty images were obtained from 4 time-frames of 5 slices. PET images of the first time-frame, which

represented the end-diastolic phase of the left ventricle, were chosen for quantitative analysis of RMBF. Even if the myocardial wall contained a clinically infarcted area, the shape of this area was visualized in the CRT screen by intensifying the uptake rate. Each image was divided clockwise into 16 points (or 8) over 360°. The 0° point was taken as the position of the crevice of the left ven-

M. K. 58yrs. M Angina Seg 2 99% stenosis

Fig.4. RMBF at rest and during exercise in a case of angina pectoris. Coronary arteriography showed that segment 2 of the right coronary artery was 99% stenotic. The various areas of myocardium are shown on the abscissa, and RMBF (ml/min/100 cm³) for each myocardial area is shown on the ordinate.

tricular wall (the position of the mitral valves). Thus, the myocardium was divided into 16 or 8 sectors, and each sector was allotted to an ROI (region of interest). The radioactivity of each ROI was then measured.

Quantitative Measurement of RMBF

The radioactivity of each ROI was presented as Q (cps/cm³). $\int_0^2 \text{Ca}(t)dt$ (cps · min/ml) refers to the integration of radioactivity in the arterial blood withdrawn at a constant rate for 2 min. RMBF of each ROI was

calculated according to the equation of Hara et al⁷:

$$\text{RMBF} = \left\{ \frac{Q}{[E (\text{Extraction}) \cdot \int_0^2 \text{Ca}(t)dt]} \right\} \times 100$$
, where E represents “extraction fraction”, for which 0.82 was used in our study. The calculated value corresponds to the value (ml/min/100 cm³) in 100 cm³ of tissue. According to Schelbert et al,⁸ 82% of arterial ^{13}N -ammonia is trapped in myocardium.

Analysis of PET Image

Typical PET images of a normal myocardium are presented in Fig. 1. The schematic

Fig. 5. At rest, RMBF (ml/min/100 cm³) of three different disease states: A. infarcted area; B. severely stenotic area with stenosis of more than 90% located in a non-infarcted wall; C. normal area. Data represent the mean and standard deviation of RMBF at rest for 46 subjects.

drawings of the PET images on the right side illustrate the areas which correspond to the anterior, septal, lateral and inferior walls of the left ventricle at the level of each slice. These three images were chosen from PET images of 5 slices taken in the end-diastolic phase, and were used to measure RMBF. Sixteen ROIs were allotted on the myocardium, and the Q value of each ROI was measured. RMBF of the anterior, septal, lateral, and inferior walls was calculated by averaging the ROI data within each wall. The septal wall extended from 90° to 135°, the anterior wall from 157.5° to 202.5°, the lateral wall from 257.5° to 292.5°, and the inferior wall from 315° to 347.5°.

Coronary Arteriography

Coronary arteriography was performed within 2 weeks before the PET study. The position of coronary artery stenosis was referenced to the 15 coronary artery segments designated by the AHA classification for coronary arteriography. We expressed the extent of coronary artery stenosis as 100%, 99%, 90%, 75%, and 50%. If there was multiple stenosis in a single artery, the segment of coronary artery with the greatest degree of stenosis was considered responsible for the disease.

Data Analysis

RMBF was measured quantitatively by PET at rest and during exercise, and compared with the findings of coronary arteriography. Data were expressed as the mean $\pm$ standard deviation. Statistical analysis was performed using the unpaired Student's t-test, and a p-value of less than 0.05 was considered statistically significant.

RESULTS

Coronary Arteriography

Of the 19 patients with OMI, 18 had single vessel-related infarction, and 1 had 2 vessel-related infarction. In the 46 subjects, 138 coronary vessels were studied. Of these, 62 vessels were normal, 20 were related to infarction, and 56 vessels were stenotic but not related to the myocardial infarction. The latter group of vessels included 4 with 100% stenosis, 13 with 99% stenosis, 24 with 90% stenosis, 9 with 75% stenosis, and 6 with 50% stenosis.

Case Presentation

Fig. 2 shows typical PET images and RMBF of 16 ROIs on the myocardium of a normal subject. The RMBF at rest was approximately 75 ml/min/100 cm³ in every area. The RMBF during exercise was about 130 ml/min/100 cm³, i.e., about 70% greater than the RMBF at rest.

Fig. 3 shows the image of a heart with OMI in which coronary arteriography showed a complete obstruction of segment 6. The antero-septal wall, an infarcted area in this case, showed low RMBF both at rest and during exercise. At the infarcted anterior wall, RMBF changed with exercise differently in each slice; 2% decrease in slice 1,

Fig. 6. At exercise, RMBF (ml/min/100 cm³) of three different disease states: A. infarcted area; B. severely stenotic area with stenosis of more than 90% located in a non-infarcted wall; C. normal area. Data represent the mean and standard deviation of RMBF during exercise for 33 subjects.

8.9% increase in slice 2, and 12.3% increase in slice 3. In 3 slices, the change in the infarcted areas was smaller than that in normal areas. In normal areas, RMBF increased by more than 30%.

Fig. 4 shows the RMBF of a case with angina pectoris in which coronary arteriography showed 99% stenosis of segment 2. In the inferior wall, a severely stenotic area in this case, RMBF changed with exercise differently in different slices; 6.8% decrease in slice 1, 9.7% increase in slice 2. In 3 slices, the change in RMBF in severely stenotic areas was smaller than that in normal areas. In normal areas, RMBF increased by 24.5%.

RMBF in an Ischemic Area

Fig. 5 shows the difference in RMBF between disease states at rest; i.e., OMI, stenosis of more than 90%, and normal. RMBF was examined in 138 areas, from anterior, septal and lateral walls, of 46 cases consisting of both ischemic heart disease and normal controls. In the inferior wall, a total of 92 areas were examined from 2-slice images of 46 cases. The analysis was made for the following 3 disease states: A. infarcted area; B. severely stenotic area with stenosis of more than 90% located in a non-infarcted area; and C. normal area. In the anterior wall, RMBF was 43.1 ± 20.0 ml/min/100 cm³ in infarcted area (n=29), 73.9 ± 19.3 in severely stenotic area (n=59), and 77.1 ± 18.4 in normal area (n=38). The RMBF of infarcted area was significantly lower than the RMBFs of severely stenotic area ($p < 0.001$) and normal area ($p < 0.001$). Similar results were obtained in the septal, lateral, and inferior walls. In the inferior wall, the RMBF of severely stenotic area was also significantly lower than that of normal area ($p < 0.001$).

Fig. 6 shows the RMBF of normal and abnormal areas during exercise in all 33 cases. In the anterior wall, the RMBF was 37.9 ± 24.7 ml/min/100 cm³ in infarcted area (n=20), 89.8 ± 27.6 in severely stenotic area (n=37), and 110.8 ± 30.3 in normal area (n=29). The RMBF of infarcted area was significantly lower than that of severely stenotic area ($p < 0.001$), and that of severely stenotic area was significantly lower than that of normal area ($p < 0.01$). Similar results were obtained in the septal and lateral walls. In the inferior wall, RMBF was 45.7 ± 24.6 ml/min/100 cm³ in infarcted area (n=12), 50.6 ± 31.5 in severely stenotic area (n=9), and 92.2 ± 29.4 in normal area (n=32). The RMBF of infarcted area and severely stenotic area were significantly lower than that of normal area (each $p < 0.001$), but there was no significant difference in RMBF between infarcted area and severely stenotic area.

Double products were $13,374.5 \pm 3,772$ (maximum systolic pressure 145.3 ± 29.5 mmHg $\times$ maximum heart rate 91.7 ± 13.9 beats/min) for OMI cases, $14,942 \pm 3,698$ ($179.0 \pm 18.9 \times 82.7 \pm 13.8$) for angina cases, and $24,776 \pm 9,571$ ($215.8 \pm 71.6 \times 113.6 \pm$

Fig. 7. Change in RMBF induced by exercise (%) for three different disease states: A. infarcted area; B. severely stenotic area with stenosis of more than 90% located in a non-infarcted wall; C. normal area. Data represent the mean and standard deviation of the change in RMBF for 33 subjects.

11.7) for normal cases. There was no significant difference in the double product between OMI and angina cases. Normal cases had significantly higher double products than the other cases ($p < 0.001$).

Regarding normal area that was distant from infarcted area in the OMI and angina cases, RMBF during exercise in this remote area was 100.2 ± 25.5 in the anterior wall ($n = 12$), 112.8 ± 29.4 in the septal wall ($n = 12$), 96.2 ± 20.6 in the lateral wall ($n = 31$), and 84.2 ± 25.0 in the inferior wall ($n = 21$). All of these values were lower than that of normal myocardium. The RMBF of severely stenotic area was significantly lower than that of this remote with exercise ($p < 0.05$ in the septal wall, $p < 0.01$ in the lateral and inferior walls, but and $p = \text{NS}$ in the anterior wall).

Change in RMBF Induced by Exercise

Fig. 7 shows the change in RMBF of nor-

mal and abnormal areas during exercise in all 33 cases. In the anterior wall, RMBF significantly decreased by $17.4 \pm 29.3\%$ ($p < 0.001$) in infarcted area ($n = 20$), increased by $23.2 \pm 37.0\%$ in severely stenotic area ($n = 37$), and increased by $44.9 \pm 22.8\%$ in normal area ($n = 28$). The increase in RMBF in severely stenotic area was significantly less than that in normal area ($p < 0.001$). Similar results were observed in the septal and lateral walls. In the inferior wall, RMBF increased slightly in infarcted area, but significantly decreased in severely stenotic area ($p < 0.001$). There was a significant difference in the percent change between each of the disease states in each wall ($p < 0.001$).

Regarding remote area in the OMI and angina cases, the exercise-induced increase in RMBF was $36.0 \pm 17.3\%$ in the anterior wall ($n = 12$), $32.3 \pm 17.1\%$ in the septal wall ($n = 12$), $30.8 \pm 22.0\%$ in the lateral wall

($n=31$), and $15.9 \pm 25.7\%$ in the inferior wall ($n=20$). All of these values were lower than that in normal myocardium of normal cases. In the diseased heart, the increase in severely stenotic area was less than that in the surrounding remote area ($p < 0.001$).

When the analysis was restricted to infarcted area, RMBF decreased by $26.6 \pm 32.4\%$ in the area of angiographically positive collaterals ($n=30$), and increased by $0.8 \pm 31.2\%$ in the area of negative collaterals ($n=31$).

Throughout the entire 6.5 min of the 25-watt exercise test, none of the patients developed angina pectoris, which is in sharp contrast to the use of dipyridamole loading, where reportedly one half of the patients with angiographic collaterals developed chest pain during the test?

DISCUSSION

Ever since PET measurement of coronary flow using ^{13}N -ammonia was initiated by Schelbert et al,¹⁰ great strides have been made in the study of RMBF.^{8,11,12} RMBF as measured by PET is not greatly affected by spatial attenuation, as is encountered in imaging with SPECT.^{13,14} The superior spatial resolution and quantitiveness of PET enable a more accurate clinical diagnosis of myocardial ischemia.

The radioactive tracers ^{82}Rb ,^{11,15,16} ^{13}N -ammonia,^{8-10,17} and H_2^{15}O ,^{12,18} are used to measure RMBF. ^{13}N -Ammonia is widely preferred due to its ease of clinical use.^{1-5,19} About 82% of ^{13}N -ammonia in the coronary arterial blood is trapped in myocardial tissue during first-pass circulation.⁸ Ammonia is chemically converted to glutamine in the myocardium, which persists in the tissue, and this forms the basis of RMBF measurement using ^{13}N -ammonia.¹⁰ We assumed that ^{13}N -ammonia in arterial blood is trapped by myocardium at a constant rate of 82%, and that the rate at which the tracer is extracted by myocardium both at rest and during exercise is equally 0.82.

The normal coronary blood flow, as calculated from the difference in arterial-venous oxygen concentration by the method of Binak et al²⁰ and Messer et al,²¹ was almost equal to the RMBF value of normal myocardium measured by our method.

The diagnosis of ischemic myocardium by PET has been extended by Damer et al,¹ Gould et al²² and Schelbert et al² using dipyridamole, and by Yonekura et al³ using ergometer exercise. The RMBFs in these studies were presented only qualitatively, and evaluated in relative grades. In contrast, the RMBFs given by our method are presented as numerical and absolute values.

The exercise test, even at a submaximal level, requires careful performance in patients with severe coronary artery stenosis. We developed a low-grade exercise stress test which used a fixed workload, and have encountered no accidents or complications.

We observed a paradoxical phenomenon in the infarcted myocardium. When the anterior wall was considered, RMBF increased by 44.9% during exercise in normal area, by 23.2% in severely stenotic area, but actually decreased in infarcted area by 17.4%. These contra-directional changes in RMBF induced by exercise, between normal-hypoperfusion area and infarcted area, were noteworthy. The decrease in RMBF in infarcted area may be interpreted as the result of coronary steal. Coronary steal is conventionally defined as a fall in absolute coronary perfusion of collateralized myocardium after coronary arteriolar vasodilation, usually after intravenous dipyridamole.^{9,23} So far, there has been no report of a human study on the steal phenomenon induced by exercise. The high sensitivity and quantitiveness of our method for measuring RMBF may have disclosed a minute decrease in RMBF in infarcted area, in which RMBF is already low at the resting state, merely by applying a mild workload. This steal phenomenon was particularly obvious in the area of angiographically positive collaterals: RMBF decreased by 26.6% in the area of angiographically positive collaterals ($n=30$), and increased by 0.8% in the area of negative collaterals ($n=31$).

The concept of coronary flow reserve has been used as a measure of the severity of stenosis.²⁴ It depends on the effectiveness of a vasodilatory stimulus to maximally increase coronary flow, and can be measured by administration of a very large dose of dipyridamole. Thus, the extent of the increase in RMBF induced by low-grade exercise is not equivalent to coronary flow reserve. Howev-

er, in cases in which dipyridamole administration may increase RMBF, low-grade exercise may also increase RMBF, and vice versa.

Fig. 7 shows that low-grade exercise caused a decrease in RMBF in the ischemic inferior wall (with more than 90% stenosis), but not in other ischemic walls. The inferior wall is located parallel to the tomographic plane. Therefore, it is rather difficult to image the inferior wall at the middle of its thickness. Thus, the result shown in Fig. 7 may not be entirely accurate with regard to the inferior wall.

Concerning the extraction rate of ^{13}N -ammonia by myocardium, Schelbert et al^{8,10} observed in dogs that the value was almost constant, regardless of an increase in coronary blood flow within the physiological range of 44 to 200 ml/min/100 g. When coronary blood flow rose over 200 ml/min/100 g, extraction decreased. A large rise in coronary blood flow should occur at an extremely high or maximum level of exercise. Since our examination used a low-grade exercise at 25 watts for 6.5 min, the extraction rate may not have changed significantly during exercise. With exercise, the RMBF of normal area was approximately 110 ml/min/100 cm³, which is certainly less than 200. In the study by Laarman et al,²⁵ in which a low-grade exercise stress test was performed at a fixed level of 30 watts for 3 min with a bicycle ergometer after injection of dipyridamole, thallium perfusion scintigraphy accurately delineated ischemic areas. Our subjects underwent low-grade exercise using a bicycle ergometer at 25 watts for 6.5 min, and achieved a double product that averaged about 16,000. It was possible to visualize and identify infarcted area and area with severe coronary stenosis under these conditions. If the level of exercise stress is further increased to a point which we did not dare to use in this study, one may be able to visualize the area of stenosis with higher contrast at the sacrifice of quantitiveness (due to a non-linear decrease in extraction).

Our assumption of the fixed value of 0.82 as the extraction rate is based on the observations of Schelbert et al⁸ in canine heart. Strict criticism and refinement of this value should be accomplished by a test in human heart. In 6 healthy subjects, we obser-

ved a slight discrepancy between the extent of the increase in RMBF and the extent of the increase in cardiac output, measured simultaneously, when exercise (25 watts $\times$ 6.5 min) was employed; i.e., the increase in RMBF in the anterior wall was $51.4 \pm 23.9\%$ and the increase in cardiac output was $64.4 \pm 30.8\%$. This observation suggests a slight decrease in ^{13}N -ammonia extraction even at our mild condition of exercise. However, deviation from our assumption (i.e., an extraction rate of 0.82) might not impose a serious problem clinically, because our method of calculation merely renders a change in RMBF smaller than actual. Even under this condition, we were able to determine the diseased state of the heart.

Finally, several comments are required concerning the limitations of our method.

In PET imaging, a partial volume effect of the PET image influences the RMBF value²⁶⁻²⁸. We used ECG-synchronized gating to minimize the partial volume effect caused by wall motion of the myocardium. However, this procedure was not sufficient to completely eliminate the effect of wall motion, since the radioactivity in the myocardium at systole was always slightly higher than that at diastole ($11.2 \pm 18.4\%$ increase at rest, $14.5 \pm 13.9\%$ increase during exercise in normal cases). On the other hand, discrimination of the ischemic portion of the heart was easier with the diastolic image. Our method of quantitation is a compromise between numerical objectivity and visual distinction. This drawback was minimized by a comparative analysis of the rest image and the exercise image. When the myocardial wall is thinner at the infarcted area, the measured RMBF value may be lower than the actual RMBF, even with an ECG-synchronized scan.

The positioning of the patient at the rest scan should be exactly the same as that at the exercise scan. We marked 3 points on the patient's body while the patient was laid supine, so as maintain the same positioning before and after exercise. We confirmed that the error caused by re-positioning before and after bed motion was negligible. The heart moves vertically due to movement of the diaphragm during respiration. This may be yet another cause of the partial volume effect.

Bergmann et al²⁹ and Rauchi et al³⁰ suggested that the extraction of ¹³N-ammonia could be influenced by ammonia metabolism; anaerobic metabolism would be accelerated in the ischemic region during myocardial ischemia. The extraction rate in ischemic myocardium has not been well studied, and requires further investigation.

In summary, we were able to quantitate the degree of ischemia in myocardium that was associated with severe coronary artery stenosis. By application of low-grade exercise, RMBF in normal myocardium increased, while that in myocardium perfused by collaterals decreased.

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