Clinical Studies

Relation between Cardiac Index and Regional Myocardial Blood Flow in the Non-infarcted Wall Using PET with $^{13}$NH$_3$ in Healed Myocardial Infarction

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SUMMARY

It is not clear whether there is any relationship between cardiac output and myocardial blood flow in the infarcted heart. We measured regional myocardial blood flow (RMBF) quantitatively by positron emission tomography (PET) with $^{13}$N-ammonia at rest in 18 patients with prior myocardial infarction. RMBF was calculated using the radioactivity in myocardial tissue measured by PET and the radioactivity of arterial blood. Cardiac output was determined by the dilution method using $^{13}$NH$_3$ as an indicator, and the relation between cardiac output and RMBF was evaluated at the same time during PET study. There was a good linear correlation between cardiac index (C.I.) and mean RMBF in non-infarcted myocardium ($r = 0.45$, $p < 0.05$), and non-infarcted size ($r = 0.74$, $p < 0.01$). There was an even better linear correlation between C.I. and $\Sigma$RMBF (representing the product of mean RMBF and non-infarcted size) as follows: $y = 0.016x + 1.94$, $r = 0.76$ ($p < 0.001$). It was indicated that the value of C.I. may be related to RMBF of non-infarcted myocardium and its size (Jpn Heart J 36: 283–292, 1995).

Key words: Regional myocardial blood flow (RMBF) Positron emission tomography (PET) Cardiac index (C.I.).

PHYSIOLOGICAL evidence of left ventricular dysfunction is shown by the decrease in cardiac index and ejection fraction, and myocardial infarct patients with these findings have a worse prognosis than those without.1-3) In myocardial infarction, previous studies have described a linear correlation between ejection fraction of the left ventricle and infarct size4) or the decrease in regional myocardial blood flow (RMBF) at the site of reduced wall motion.5)

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Cardiac output is not always related to infarct size or regional wall motion in the infarct-related area. There has been little consideration of RMBF and the size of the non-infarcted wall for evaluation of cardiac output. Therefore, we measured RMBF quantitatively by PET using $^{13}$N-ammonia, which was used to measure cardiac output by the dilution method simultaneously, and the relation between RMBF and cardiac output was evaluated at the same time during the PET study.

**Materials and Methods**

**Study patients:** Eighteen patients (15 males and 3 females) who had a history of myocardial infarction with a duration of more than one month after onset without interventions were studied. The mean age was $59.4 \pm 12.1$ years. Myocardial infarction was diagnosed on the basis of clinical findings, the presence of abnormal Q waves on electrocardiography (ECG), and elevation of serum enzymes. Patients who had undergone both PET and cardiac catheterization within 1 month, were included. Informed consent was obtained from all patients.

**Cardiac catheterization:** Left ventriculography, coronary arteriography, and measurement of cardiac output were performed during cardiac catheterization. Left ventriculography (LVG) was performed in the 30-degree right anterior oblique (RAO) and 60-degree left anterior oblique (LAO) projections, based on AHA criteria. Cardiac wall motion was measured in 15 patients by the LVG ASC system (Ver. 3.1) according to Sheehan$^6$), which normalized the measured data automatically. The measured value was then converted into units of normal standard deviations (SD) from the normal mean for motion at each chord derived from 100 subjects without coronary artery disease from Showa University Fujigaoka Hospital. Coronary arteriography was performed according to the Judkins method.$^7$ The position of coronary artery stenosis was designated by the American Heart Association classification for coronary arteriography.$^8$ The extent of coronary artery stenosis was expressed as 100%, 99%, 90%, 75%, or 50%. The infarct-related vessel was defined as the coronary artery with a greater than 75% stenosis. The cardiac output was measured by thermodilution through the right ventricle and pulmonary artery using a Swan-Ganz catheter.$^9$

**Positron emission tomography:** RMBF was measured with $^{13}$N-ammonia (half-life of $^{13}$N, 10 minutes) as the tracer, using a HEADTOME IV positron emission tomography machine (Shimadzu Co.) according to our previously reported method.$^{10}$ A brief explanation follows. The spatial resolution for a static image at the center of the field of view was adjusted to 6 mm using a Butterworth filter. Regional myocardial blood flow was measured by positron emission tomography at rest. During the rest scan the patient lay on a couch in the gantry tunnel, and the transmission scan was taken for 5 minutes 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. Next, 10–20 mCi of $^{13}$N-ammonia were administered by intravenous injection with the patient in the supine position. Immediately after injection of the tracer, arterial blood was sampled for 2 minutes at a constant rate of 10 ml/min. After thorough mixing of the blood sample, 1 ml of blood was taken to measure radioactivity with decay correction. Five minutes following injection of the tracer, the emission scan was started and continued for 10 minutes. All of the emission data were automatically decay-corrected in a computer and stored in the memory.

**Analysis of the myocardial images:** Myocardial PET images with gated ECG were 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. Myocardial images of five 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. Of five slices, 3 images of the first time

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**Figure 1.** PET images of 3 slices and heart schematics corresponding to the level of each slice. Schematic drawings of PET images on the right side illustrates the wall boundary of the left ventricular myocardium. Myocardial area illustrated correspond to the anterior, septal, lateral and inferior walls of the left ventricle at the level of each slice.
frame, which represented the end-diastolic phase of the left ventricle, were chosen for quantitative analysis of regional myocardial blood flow (Figure 1). Each image was divided clockwise into 60 points over 360°. Each sector of 60 points, choosing the zero point as the position of the crevice of the LV wall, was allotted to a region of interest.

**Quantitative measurement of regional myocardial blood flow:** The radioactivity of each region of interest, presented as $Q_\text{(cps/cm}^3\text{)} \cdot \int_0^t \frac{C_\text{a}(t)\text{dt}}{\text{(cps min/ml)}}$, refers to the integration of radioactivity in the arterial blood withdrawn at a constant rate for 2 minutes. Regional myocardial blood flow of each region of interest was calculated according to the equation of Hara et al: $\text{Regional myocardial blood flow} = \{ \frac{Q}{[\text{E(Extraction)} \cdot \int_0^t \text{C}_\text{a}(t)\text{dt}]} \} \times 100$, 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, 82% of arterial $^{13}$N-ammonia is trapped in the myocardium.

**Measurement of cardiac output using radioactivity with $^{13}$NH$_3$:** From the analogy of the indicator dilution method, the intravenously injected $^{13}$NH$_3$ served also for measurement of cardiac output, in which $^{13}$NH$_3$ was considered as an indicator added to the circulation. The advantage of utilizing $^{13}$NH$_3$ as an...
indicator in place of ordinary dyes such as indocyanine green is that the recirculation of $^{13}$NH$_3$ is almost negligible for the first 2 min after injection as the result of the rapid disappearance of $^{13}$NH$_3$ in the systemic circulation, making the extrapolation of the blood curve to a single circulation curve unnecessary. Cardiac output was calculated according to the equation of Hara et al: Cardiac output ($I/min) = I(^{13}NH_3)/\int_0^{\infty} Ca(t)dt$, where $I(^{13}NH_3)$ represents the total injected dose of $^{13}$NH$_3$, decay-corrected to time zero. The value of $I(^{13}NH_3)$ was calculated from the radioactivity with decay correction of non-injected $^{13}$NH$_3$, at 10 minutes (half-life) after injection of the tracer.

In order to verify the reliability of the value of cardiac output measured by radioactivity, it was compared with that obtained by thermodilution using a Swan-Ganz catheter during cardiac catheterization. In 58 patients, simultaneous measurement by both methods was performed in 8 patients, in 4 patients at rest, in 3 patients following administration of 0.1 mg/kg of isosorbide dinitrate i.v., and in 1 patient following exercise on a bicycle ergometer in the supine position, with an exercise level of 25 watts for 5 min. In the other 50 patients, the two measurements were performed within 1 month. Cardiac index was measured from body weight in each patient.

Measurement of non-infarcted size and mean RMBF of non-infarcted region: RMBF of myocardium in each slice was represented by a circumferential profile curve. The non-infarcted regions were defined as circumferential profile points, in which RMBF was more than 50 ml/min/100 cm$^3$ ($\geq 50$). The non-infarcted size was defined by the ratio of non-infarcted points summed up in 3 slices to total myocardial points. Mean RMBF of non-infarcted regions was shown by the average RMBF of the total non-infarcted points. $\Sigma$RMBF which was a product of mean RMBF and the size of the non-infarcted region as shown in Figure 2, was compared with cardiac index (C.I.).

Evaluation of regional wall motion and RMBF: Score of regional wall motion was the average of the chord data (SD) from the anterobasal, anterolateral, apical, posterobasal, septal, and posterolateral walls. Each slice obtained by PET was divided into anterior, septal, lateral, and inferior walls, and RMBF was calculated by averaging the ROI data of each wall, and was compared with regional wall motion of LVG assessed by centerline methods. The reference point of the regional walls of the PET image and the LVG cinefilm was determined according to the recent report of Yamashita et al.

Statistical analysis: The RMBF value and regional wall motion score were expressed as means $\pm$ 1 SD. Statistical analysis was linear correlation and Student’s paired t-test was used to compare variables. A $p$-value of less than 0.05 was considered statistically significant.
RESULTS

Correlation of cardiac index by the thermodilution method and the $^{13}$NH$_3$ dilution method: Cardiac index (C.I.) measured by the thermodilution method using a Swan-Ganz catheter and dilution method of $^{13}$NH$_3$ simultaneously in 8 patients was $2.95 \pm 0.30$ and $2.73 \pm 0.20$ (l/min/m$^2$) respectively, and there was a close correlation between them ($n = 8$, $r = 0.94$, $p < 0.001$). The C.I. of 50 patients in whom C.I. was measured by the two methods within 1 month were $2.86 \pm 0.50$ and $2.90 \pm 0.40$ (l/min/m$^2$), respectively and a good linear correlation was observed; $y = 0.54x + 1.30$, $r = 0.38$, $p < 0.01$ (Figure 3).

Correlation between cardiac index and non-infarcted size, mean RMBF, and $\Sigma$RMBF: In 18 patients, mean RMBF was $74.0 \pm 13.0$ ml/min/100 cm$^3$, total infarcted size was $0.80 \pm 0.15$, and cardiac index measured by radioactivity was $2.90 \pm 0.38$ l/min/m$^2$ (range 2.20 to 3.71). There was a good linear correlation between C.I. and non-infarcted size ($r = 0.45$, $p < 0.05$), or mean RMBF of the non-infarcted region ($r = 0.74$, $p < 0.01$). $\Sigma$RMBF (product of mean RMBF and size of non-infarcted region) was $60.0 \pm 18.0$, and a better linear correlation between C.I. and $\Sigma$RMBF was observed; $y = 0.016x + 1.94$, $r = 0.76$, $p < 0.001$ (Figure 4).

Correlation between RMBF and regional wall motion: In fifteen patients,
Figure 4. Correlation between cardiac index by the $^{13}$NH$_3$ dilution method as an indicator and non-infarcted size (upper left), or mean RMBF of non-infarcted region (upper right), or $\Sigma$RMBF (lower left). The product of mean RMBF and non-infarcted size is represented as $\Sigma$RMBF. The slope and correlation coefficient ($r$) are shown.

Figure 5. Correlation between score of regional wall motion and RMBF in this wall. Score of regional wall motion was obtained by averaging the chord data (SD) within each wall using the centerline method from left ventriculography. RMBF was measured with $^{13}$NH$_3$ using PET. Correlation coefficient ($r$) is shown.
wall motion by LVG was assessed using the centerline method, and the wall motion score was compared with RMBF in each regional wall measured by PET as shown in Figure 5. There was no correlation between them ($n = 82, r = 0.18$).

**DISCUSSION**

Cardiac function after myocardial infarction is an important factor to determine the patient's prognosis. The relation between impairment of left ventricular function and infarct size has been studied, and recent development of nuclear imaging techniques have made it possible to compare the RMBF and cardiac function. However, there have not been any reports on the simultaneous measurement of RMBF of infarcted or non-infarcted myocardium with cardiac output in clinical cases. We developed a method to measure the cardiac output using radioactivity in arterial blood simultaneously with the measurement of RMBF by PET using $^{13}$NH$_3$ in the infarcted heart.

Previous studies have shown that the cardiac function of the infarcted heart might depend not only on infarct size, but also on some other factors such as hypertrophy of the non-infarcted myocardium. Therefore we examined the relation between cardiac output and RMBF of non-infarcted myocardium. In our previous study, there was no correlation between total myocardial blood flow which included the RMBF of the infarcted region and C.I. in the case of myocardial infarction. In this study, there was a good linear correlation between C.I. and non-infarcted size ($r = 0.45, p < 0.05$), or mean RMBF of the non-infarcted region ($r = 0.74, p < 0.01$), and a better linear correlation between C.I. and $\Sigma$RMBF (product of mean RMBF and size of non-infarcted region) ($r = 0.76, p < 0.001$). These results indicate that the cardiac function of the infarcted heart might depend on the RMBF in the non-infarcted region and its size.

Tamaki et al reported that regional perfusion on PET and wall motion were relatively preserved in the infarcted region. However, in our results, there was no significant correlation between local wall motions and RMBF in each wall. One of the causes may be the comparison of heterogeneous walls in our study; we did not distinguish between different vascular distributions (left anterior descending artery, left circumflex artery vs right coronary artery). However, the standardization of wall motion with the centerline method allows comparison of the motion of different regions of the ventricle.

Our study has several limitations. First, the infarct-related regions were defined as regions with RMBF of less than 50 ml/min/100 cm$^3$. The mean value $\pm 1.96$ SD had previously been chosen as the normal range because it is the criterion used by many clinical laboratories. Second, our assumption of the fixed
value of 0.82 as the extraction rate of $^{13}$N-ammonia by myocardium is based on the observation of Schelbert et al\textsuperscript{12} in canine hearts; a similar treatment of data was made in another recent study\textsuperscript{10}. Concerning the extraction rate, Schelbert et al\textsuperscript{12} observed that the value was almost constant in dogs, regardless of an increase in coronary blood flow within the physiological range of 44 to 200 ml/min/100 g. When coronary blood flow falls below 44, the extraction may increase. It is possible that, because myocardial blood flow in the infarcted region is low, we overemphasized the decrease in myocardial blood flow in relation to the actual decrease. Third, a partial volume effect of the myocardial perfusion imaging on positron emission tomography influences the RMBF value\textsuperscript{23}. 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 eliminate the partial volume effect caused by wall motion; the radioactivity in the myocardium at systole was always slightly higher than that at diastole.

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