A New Strategy for the Assessment of Viable Myocardium and Regional Myocardial Blood Flow Using $^{15}$O-Water and Dynamic Positron Emission Tomography

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Background. We have developed a new measure of myocardial viability, the water-perfusable tissue index (PTI), which is calculated from transmission, $^{15}$O, and $^3$H$_2^{18}$O positron emission tomography (PET) data sets. It is defined as the proportion of the total anatomical tissue within a given region of interest (ROI) that is capable of rapidly exchanging water and has units g (perfusable tissue)/g (total anatomical tissue). The aim of this study was to assess the prognostic value of PTI in predicting improvement in the cleft myocardial wall motion ratio after successful thrombolysis for acute myocardial infarction (AMI) and to measure the myocardial blood flow to the perfusable tissue (MBF$_p$, ml/min/g [perfusable tissue]). Furthermore, PTI was compared with $^{18}$FDG metabolic imaging in patients with old myocardial infarction (OMI).

Methods and Results. PET scans were performed in healthy volunteers (group 1, n=8), patients with OMI (group 2, n=15), and in patients who were successfully thrombolysed after an AMI (group 3, n=11). Systolic wall thickening was measured by two-dimensional echocardiography within 2–4 days of AMI and after 4 months to assess contractile recovery. In the healthy volunteers, MBF$_p$ was 0.95±0.13 ml/min/g (perfusable tissue). PTI in these regions was 1.08±0.07 g (perfusable tissue)/g (total anatomical tissue), which was consistent with all normal myocardium being perfusable by water. In the OMI group, the ratio of the relative $^{18}$FDG activity to the relative MBF$_p$ defect (metabolism-flow ratio) was calculated for each asynergic segment. Regions in which the metabolism–flow ratio was ≥1.20 were considered reversibly injured, whereas those in which the ratio was <1.20 were deemed irreversibly injured. PTI in the former group of regions (n=9) was 0.75±0.14 g (perfusable tissue)/g (total anatomical tissue) and was significantly higher than in irreversibly injured regions (n=6) (0.53±0.12 g [perfusable tissue]/g [total anatomical tissue], p<0.01). Values of MBF$_p$ were similar in these segments. Seven of 12 segments in the AMI patients showed improved systolic wall thickening on follow-up. PTI in these recovery segments was 0.88±0.10 g (perfusable tissue)/g (total anatomical tissue) (p=NS versus control). PTI in the nonrecovery regions was 0.53±0.11 g (perfusable tissue)/g (total anatomical tissue), which was similar to the segments in group 2 in which $^{18}$FDG uptake was absent. MBF$_p$ was similar in both the recovery and nonrecovery segments in the subacute phase.

Conclusions. These data indicate that PTI may be a good prognostic indicator for the recovery of contractile function after successful thrombolysis and show that myocardial viability may be assessed by PET without metabolic imaging. (Circulation 1992;86:167–178)

Key Words • myocardial viability • perfusable tissue index • myocardial blood flow • positron emission tomography

The evolution of tissue necrosis after myocardial infarction is a complex pathophysiological process that is dependent on many factors such as the duration of occlusion,1 residual blood flow,2,3 and myocardial metabolism.4–6 Myocardial infarction in the clinical setting can therefore result in an admixture of both necrotic and injured but viable myocardium. The clinically important tasks are to identify such functionally recoverable myocardium and the residual blood flow to these regions.

A number of radionuclide imaging techniques have emerged for the detection of viable myocardium, in particular, reinjection of $^{201}$TI imaged by using single-photon emission computed tomography7,8 and positron emission tomography (PET).9,10 Schweiger et al11 and Tillisch et al12 identified viable myocardium by demonstrating sustained glucose utilization in hypoperfused asynergic segments using $^{15}$N-ammonia ($^{15}$NH$_3$) and $^{18}$F-2-fluoro-2-deoxyglucose ($^{18}$FDG) to qualitatively assess...
myocardial blood flow (MBF) and residual tissue metabolism, respectively. However, in these reports, quantification of MBF was not performed, and no attempt was made to measure the proportion of viable tissue in the regions of interest (ROIs) defined.

In this study, PET imaging was used to measure absolute MBF and to investigate the use of a quantitative parameter of tissue viability, the water-perfusable tissue index (PTI). This is obtained from the analysis of transmission, blood volume (15O-carbon monoxide: C15O), and MBF (15O-water:H215O) emission data sets. This procedure has the potential advantages that, first, both MBF and tissue viability can be assessed simultaneously using the same tracer and, second, that the need for metabolic imaging may be obviated. To investigate whether this new strategy was accurate in assessing myocardial viability, these measurements were made in three groups of subjects: normal volunteers, patients with old myocardial infarction (OMI), and patients with acute myocardial infarction (AMI) after successful thrombolysis. In the AMI patients, cardiac function was assessed by echocardiography and improvement of contractile function was considered as evidence of tissue viability. In the OMI group, we compared PTI with 18FDG metabolic imaging for detecting tissue viability, as coronary revascularization in these patients was not performed.

Theory

Recently, a method for calculation of MBF using C15O, inhalation and dynamic PET has been reported. Briefly, time–activity curves generated from ROIs placed over the left atrial chamber and left ventricular myocardium were fitted to a single tissue compartment model that is described by Equation 1:

\[ C_{ROI}(t) = \alpha \cdot MBF \cdot C_a(t) \cdot \exp[-(MBF/p+\lambda) \cdot t] + V_a \cdot C_a(t) \]  

where \( C_{ROI}(t) \) equals H215O concentration in the tissue ROI (counts/sec/ml of ROI); \( \alpha \) equals tissue fraction (g of H215O-perfusable tissue/ml of ROI); MBF equals regional myocardial blood flow to the H215O-perfusable tissue (ml/min/g of H215O-perfusable tissue); \( C_a(t) \) equals H215O concentration in the arterial ROI (counts/sec/ml of ROI); \( \otimes \) is the symbol for the operation of convolution; \( p \) is the partition coefficient of water (ml of blood/g of tissue); \( \lambda \) is the decay constant of 15O; and \( V_a \) equals the fraction of arterial blood in the tissue plus spillover from left ventricle (ml of arterial blood/ml of ROI).

This operational equation incorporates two corrections. First, the spillover of activity from the left ventricular chamber into the myocardial ROI because of the limited spatial resolution of the PET scanner was accounted for by the term \( V_a \). Second, the underestimation of myocardial radiotracer concentration caused by cardiac wall motion and the small transmural myocardial thickness relative to the spatial resolution of PET scanners (the so-called partial volume effect), was corrected for by implementation of the concept of tissue fraction (\( \alpha \)), as first proposed by Lida et al. These workers defined tissue fraction as the fractional volume of a given ROI occupied by myocardium that is capable of rapidly exchanging water, i.e., the H215O-perfusable tissue. Tissue fraction is therefore dependent on the ability of the tissue to exchange H215O at a microscopic level in addition to the wall motion and partial volume effects mentioned above. This is derived from information contained within the kinetic H215O data set of the delivery of the tracer to the myocardial ROI and its subsequent clearance. In this study, we have renamed this parameter the water-perfusable tissue fraction (PTF), which has units (g (H215O-perfusable tissue)/ml ROI) (Figure 1). The use of this mode of partial volume correction has implications for the interpretation of the MBF measurement. Using this model, MBF is defined as the blood flow per gram of H215O perfusable tissue, i.e., the tissue defined by PTF, and has units of [ml/
min/g (H$_2$O-perfusable tissue)]. We have used the term MBF$_p$ for the blood flow to the H$_2$O-perfusable tissue (Figure 1).

In addition, we have developed an alternative method of partial volume correction that involves manipulation of the transmission and C$^{15}$O blood pool images. This procedure involves the pixel-by-pixel subtraction of a blood density image from the transmission image after the normalization of the latter for tissue density. This provides a quantitative image of extravascular tissue density with units of [g(extravascular anatomical tissue)/ml ROI]. This method of extravascular tissue density measurement has been previously validated for the lung.13 Phantom studies in our laboratory show that this procedure accurately corrects for the object size-dependent underestimation of tracer concentration over a range of wall thicknesses of 3–27 mm.14 The value of the extravascular tissue density measurement is dependent only on cardiac wall motion and the physical dimensions of the heart wall; therefore, we have used the term anatomical tissue fraction (ATF) to describe this parameter (Figure 1).

In theory, the ratio of PTF/ATF for a given ROI indicates what proportion of the extravascular tissue is perfusable by H$_2$O. We have termed this ratio the perfusable tissue index (PTI), which has units of [g(H$_2$O perfusable tissue)/g(extravascular anatomical tissue)]. We hypothesized that in normal myocardium, this ratio should be unity in that all the myocardium should be perfusable by H$_2$O.

We applied PTI to our measurements of MBF$_p$. The product of MBF$_p$ and PTI gives a measure of the average blood flow to the entire anatomical tissue bounded within the ROI (MBF$_p$) (Figure 1). This parameter would be equivalent to the average MBF measured using the microsphere method and should be contrasted with MBF$_p$, which indicates the blood flow exclusively to the water-perfusable tissue.

**Methods**

**Patient Population and Protocol**

Three groups of subjects were studied: normal volunteers (group 1, n=8), patients with nonreperfused Q wave myocardial infarction (group 2, n=15), and patients with AMI in whom the infarct-related artery was recanalized either spontaneously (n=2) or after successful thrombolytic therapy (n=9) (group 3, n=11). In both patient groups, only subjects with either single or two-vessel disease were included in order to enable reference measurements to be made in myocardium supplied by a normal coronary artery.

Group 1 consisted of eight healthy male volunteers with an average age of 29±5 years (range, 21–36 years). All subjects were free of any symptoms or signs of heart disease and received no medication.

Group 2 comprised 15 patients (14 men and one woman; mean age, 57±9 years, range, 40–68 years) with OMI who did not receive thrombolytic therapy for AMI. All except two subjects in this group had significant Q waves on the ECG. The time interval from the onset of AMI to PET scanning was 5–12 months. Localization of infarction was based on the wall motion abnormality as observed on either an echocardiogram or left ventriculogram and the localization of significant Q waves on a 12-lead ECG (V$_1$–V$_5$ to anterior; I, aVL, V$_6$ to lateral; II, III, aVF to inferior).

Group 3 consisted of 11 patients (10 men and one woman; mean age, 56±10 years, range, 39–75 years) who arrived in the emergency room within 4 hours of onset of severe continuing chest pain. The clinical diagnosis of AMI was made on the basis of typical chest pain and ECG changes. All patients developed significant Q waves (>0.04 seconds) and a rise in cardiac enzymes. After AMI was diagnosed, subjects underwent emergency catheterization according to a protocol approved by the Hammersmith Hospital Research Ethics Committee. Intracoronary administration of streptokinase or tissue plasminogen activator (tPA) recanalized the infarct-related artery in eight of 11 subjects (A2–A8 and A11). In two of the three remaining patients (A9, A10), spontaneous recanalization had occurred at the time of the acute-phase angiogram, but thrombolytic agent was still administered because of the very slow washout of contrast medium from the infarct-related artery. The last patient (A1) underwent spontaneous recanalization after administration of thrombolytic agents failed to achieve vessel patency. In all subjects, follow-up angiograms confirmed successful recanalization of the infarct-related artery 24 hours later.

In all patients, wall motion abnormalities in the risk areas were revealed by two-dimensional echocardiography, which was performed on the same day as the PET scan. In the subacute phase, PET scanning was performed within 4 days of thrombolysis (average, 2±1 days; range, 1–4 days). Follow-up echocardiographic studies were performed 4 months later in all patients to assess the improvement in systolic dysfunction, and a follow-up PET study was performed in six patients. No patient received further revascularization therapy during the follow-up period.

All patients and normal volunteers gave written informed consent to a protocol approved by the Hammersmith Hospital Research Ethics Committee and the Administration of Radioactive Substances Advisory Committee.

**Scanning Procedures**

All PET scans were performed using an ECAT 931-08/12 scanner (CTI/Siemens Inc., Knoxville, Tenn.), which consists of eight rings of bismuth germanate crystal detectors. This scanner enables 15 planes of data to be acquired in a field of view of 10.5 cm, thus allowing the whole heart to be imaged. All emission and transmission sinograms were reconstructed with a Hanning filter with a cut-off frequency of 0.5 of maximum. This resulted in a spatial resolution of 8.4±0.7 mm full width at half maximum (FWHM) for the emission data and 7.7±0.7 mm FWHM for the transmission data14 at the center of the field of view with a slice thickness of 6 mm. Further details on the physical performance of this scanner have been reported elsewhere.15

All subjects were fasting for at least 6 hours before PET scanning. In the case of the OMI patients, all medication was stopped 48 hours before the PET scan. All subjects lay supine on the scanner bed. The optimal imaging position was determined by a 5-minute rectilinear scan after exposure of an external germanium-68 ($^{68}$Ge) ring source. A 20-minute transmission scan was
then performed by exposure of the same external ring source. These data were used to correct subsequent emission scans for tissue attenuation of 511 keV annihilation gamma photons. After the transmission scan, the blood pool was imaged by inhalation of $^{15}$O-labeled carbon monoxide ($^{15}$O, $t_{1/2}=2.05$ minutes), which labels erythrocytes by the formation of carboxyhemoglobin. $^{15}$O was administered for 4 minutes at a radioactive concentration of 3 MBq/ml and at a flow rate of 500 ml/min. A 6-minute, single-frame emission acquisition was initiated 1 minute after the end of $^{15}$O inhalation. Venous blood samples were taken every minute during the scan, and the $^{15}$O concentration in whole blood was measured using a NaI well counter cross-calibrated with the scanner.

After a 15-minute period to allow for decay of $^{15}$O radioactivity to background levels, MBF was measured using a previously validated protocol. Briefly, $^{15}$O gas, which is converted in the lung to $^{15}$O-labeled water ($H_2^{15}O$) was inhaled for a period of 3.5 minutes (4 MBq/ml at a flow rate of 500 ml/min). A 25-frame dynamic PET scan was started 30 seconds before the start of $^{15}$O delivery, thus enabling a measurement of residual background activity, and lasted for a total of 7 minutes.

Metabolic imaging was performed in all of the OMI patients and during the acute phase in two of 11 group 3 subjects (A1, A2) using $[^{18}F]-2$-fluoro-2-deoxyglucose ($^{18}$FDG, $t_{1/2}=110$ minutes) after an oral load of 75 g of glucose given 90 minutes before the administration of $^{18}$FDG to standardize study conditions. $^{18}$FDG (185 MBq) was infused intravenously over 2 minutes, and a single 10-minute data acquisition was performed 55 minutes after the end of tracer administration. An $^{18}$FDG scan was also performed in one of the AMI patients (A1) during the follow-up PET study.

**Data Analysis**

All sinograms were corrected for tissue attenuation and reconstructed on a MicroVax II computer (Digital Equipment Corp., Marlboro, Mass.) using dedicated array processors and standard reconstruction algorithms. Images were transferred to SUN 3/60 workstations (Sun Microsystems, Mountain View, Calif.) for further analysis. Image manipulations and data handling were performed using the ANALYZE (Mayo Foundation, Rochester, Minn.) and PRO-MATLAB (The MathWorks Inc., South Natick, Mass.) software packages.

A blood volume image ($V_b$) was calculated using the $^{15}$O emission data. The raw image was divided by the product of the average of the blood radioactivity concentration (counts/sec/g of whole blood) measured from the venous blood samples and the density of whole blood (1.06 g/ml). These images were also corrected to account for the decay of $^{15}$O during the 6-minute acquisition period. The resultant quantitative images of blood volume have units of milliliters of blood per image volume element. These images were used to position two to four ROIs in the left atrial chamber with a recovery greater than 90% of the true tracer concentration. These ROIs were then projected onto the dynamic $^{15}$O-water data set to generate time–activity curves for each ROI. The average of these curves was used as arterial input function for calculation of MBF.

Images of extravascular tissue density were created by subtracting images of blood density ($V_b\times1.06$) from the corresponding transmission images after conversion of the latter to tissue density (1.06 x transmission/counts on transmission image from a left ventricular ROI). This method has been described and validated previously for the lung and more recently for the heart. Myocardial tissue ROIs with an average size of 2.8±0.8 cm$^3$ were positioned in four myocardial segments (anterior, lateral, inferior, and septal) on these transaxial images as illustrated in Figure 2. Values of ATF (see "Theory" and Figure 1) for each tissue ROI were determined from these images and have units of grams of total anatomical tissue per milliliter of ROI.

To ensure that minimal patient movement had occurred during the study, the position of these tissue ROIs was checked on integrated $H_2^{15}O$ images that were obtained by subtracting the blood volume from the sum of scans recorded after the end of $^{15}$O inhalation as reported previously. These ROIs were then projected onto the dynamic $H_2^{15}O$ data set to generate myocardial tissue time–activity curves for the different regions of the heart wall. The arterial and tissue time–activity curves for $H_2^{15}O$ were then fitted to a single tissue compartment model to produce values of MBF, (milliliters per minute per gram of perfusable tissue) and perfusable tissue fraction (PTF, grams of perfusable tissue per milliliter of ROI) for each myocardial segment (see "Theory" and Figure 1). Consequently, PFI for each myocardial region was calculated by taking the ratio of PTF/ATF. The PET images used for this analysis are illustrated in Figure 3.

The tissue ROIs described above were also projected onto the $^{18}$FDG images, and in each individual, the mean pixel counts for all segments supplied by normal uninvolved coronary arteries and normal wall motion were calculated. In each subject, the $^{18}$FDG pixel counts in the tissue ROIs positioned in the asynergic regions were expressed as a proportion of the counts in the corresponding control regions, thus providing a relative value of $^{18}$FDG uptake in the infarcted zone. The $^{18}$FDG data were normalized to blood flow according to previously reported criteria. The relative $^{18}$FDG uptake in the asynergic regions was normalized to the relative defect in MBF, as follows.
Yamamoto et al Tissue Viability and MBF by $H_2^{15}O$ and PET

**Figure 3.** Serial transaxial positron emission tomography images from a normal volunteer showing anatomical tissue fraction (top), blood volume (middle), and $H_2^{15}O$ (bottom).

Metabolism–flow ratio =
\[
\frac{(\text{FDG counts in asynergic zone/ FDG counts in control region})}{(\text{MBF}_p \text{ in asynergic zone/ MBF}_p \text{ in control region})}
\]

Relative metabolism–flow ratios $\geq 1.2$ were considered to represent regions containing functionally recoverable myocardium, whereas regions in which this ratio was $<1.2$ were considered to represent irreversibly injured tissue.\(^{18}\)

**Echocardiography**

Echocardiography was performed using Toshiba SSH 65A and 160A ultrasound equipment and a 3.75-MHz transducer. Imaging was performed according to a standardized protocol.\(^{19}\) A computer analyzer (Nova-Microsonics) was used to measure the myocardial wall thickness in segments of the anterior, lateral, inferior, and septal wall from parasternal short-axis views.\(^{20}\) These segments were assigned to equivalent regions defined on the PET images. The percentage systolic wall thickening was calculated as follows.

\[
\% \text{ Systolic wall thickening} = \frac{\left\{ \text{Th(ES)} - \text{Th(ED)} \right\}}{\text{Th(ED)}} \times 100
\]

where Th(ES) equals end-systolic wall thickness and Th(ED) equals end-diastolic wall thickness.

All echocardiographic analyses were performed by an investigator who was blinded to the results of the PET studies. ROIs drawn on the transaxial PET images were matched with the regions on the short-axis echo images by using anatomical landmarks such as the papillary muscles and the junction of the right ventricular wall to the left ventricular wall for guidance.

**Statistics**

All data are represented as mean±SD. For comparison of two data sets, a paired or unpaired Student's $t$ test was performed. A value of $p<0.05$ was considered significant. Comparison of multiple data sets was performed using ANOVA, and specific differences were identified by a Student's $t$ test corrected for multiple comparisons with the Bonferroni inequality adjustment.\(^{21}\)

**Results**

**Normal Volunteers**

All subjects tolerated the scanning procedures well. The PET data from the normal volunteer subjects are summarized in Table 1. MBF\(_p\) was homogeneously distributed in all parts of the left ventricular myocardium and had a mean value of $0.95\pm 0.13 \text{ ml/min/(g of perfusible tissue)}$ ($p=\text{NS by ANOVA}$). There was a significant regional difference in the value of PTF ($p<0.05$ by ANOVA), with the value in the septum being higher than those in the other heart regions (Figure 4). However, individual comparison of the septal values of PTF with those in the anterior, lateral, and
TABLE 1. Summary of Positron Emission Tomography Data for Normal Volunteers

<table>
<thead>
<tr>
<th>Region</th>
<th>MBF&lt;sub&gt;p&lt;/sub&gt;</th>
<th>PTF</th>
<th>V&lt;sub&gt;a&lt;/sub&gt;</th>
<th>ATF</th>
<th>PTI</th>
<th>MBF&lt;sub&gt;f&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior (n=8)</td>
<td>0.98±0.15</td>
<td>0.70±0.05</td>
<td>0.15±0.05</td>
<td>0.68±0.04</td>
<td>1.03±0.07</td>
<td>1.01±0.17</td>
</tr>
<tr>
<td>Lateral (n=8)</td>
<td>0.95±0.14</td>
<td>0.67±0.02</td>
<td>0.19±0.09</td>
<td>0.66±0.03</td>
<td>1.02±0.05</td>
<td>0.97±0.15</td>
</tr>
<tr>
<td>Inferior (n=8)</td>
<td>0.95±0.15</td>
<td>0.69±0.03</td>
<td>0.17±0.06</td>
<td>0.67±0.05</td>
<td>1.04±0.08</td>
<td>0.99±0.18</td>
</tr>
<tr>
<td>Septum (n=8)</td>
<td>0.93±0.18</td>
<td>0.77±0.11</td>
<td>0.17±0.10</td>
<td>0.63±0.04</td>
<td>1.23±0.07*</td>
<td>1.15±0.32</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>0.95±0.13</td>
<td>0.71±0.03</td>
<td>0.17±0.05</td>
<td>0.66±0.02</td>
<td>1.08±0.07</td>
<td>1.03±0.18</td>
</tr>
</tbody>
</table>

MBF<sub>p</sub>, myocardial blood flow to the 15O-water perfusable tissue (ml/min/[g of perfusable tissue]); PTF, 15O-water perfusable tissue fraction (g [perfusable tissue]/ml region of interest, ROI); V<sub>a</sub>, anatomical tissue fraction (g [total anatomical tissue]/ml ROI); PTI, 15O-water perfusable tissue index (g [perfusable tissue]/g [total anatomical tissue]); MBF<sub>f</sub>, myocardial blood flow to the total anatomical tissue (ml/min/g [total anatomical tissue]).

*p<0.017 vs. anterior and lateral walls.

Inferior walls did not reach statistical significance. The mean value for PTI for all regions was 1.08±0.07 g (perfusable tissue)/g (total anatomical tissue). A significant regional difference in the value of PTI was observed (p=0.001 by ANOVA). The value in the septum was significantly higher than in the anterior (p=0.016) and lateral walls (p=0.004) (Figure 5). There were no significant regional differences in the values of V<sub>a</sub>, ATF, and MBF<sub>f</sub>.

**OMI Patients (Group 2)**

PET data for the OMI group are summarized in Table 2. Of the 15 patients studied in this group, six patients had relative metabolism–flow ratios <1.20 in the areas showing wall motion abnormalities on the echocardiogram, whereas in the other nine patients, the ratio was ≥1.20. In the former group, there was no significant difference in the levels of MBF<sub>p</sub> when the infarcted and corresponding control regions were compared (0.64±0.23 versus 0.97±0.25 ml/min/[g of perfus-
able tissue], p=NS). Values of MBF<sub>p</sub> in the asynergic regions with metabolism–flow ratios ≥1.20 were significantly lower than in the corresponding remote control regions (0.51±0.16 versus 1.09±0.23 ml/min/[g of perfus-
able tissue], p<0.001). As illustrated in Figure 6, there was no significant difference between the MBF<sub>p</sub> values in regions where the metabolism–flow ratio was ≥1.20 and in those where it was not (0.64±0.23 versus 0.51±0.16 ml/min/[g of perfus-
able tissue], p=NS). Values of PTI in asynergic regions where the flow–metabol-
ism ratio was ≥1.20 were significantly higher than in those where the ratio was <1.20 (0.75±0.14 versus

![Figure 4](http://circ.ahajournals.org/lookup/doi/10.1161/01.CIR.86.1.70#fig4)

**Figure 4.** Bar graphs showing regional differences in 15O-
water perfusable tissue fraction (PTF) and anatomical tissue
fraction (ATF) in normal volunteers (group 1). Ant, anterior; lat, lateral; inf, inferior; sep, septal.

![Figure 5](http://circ.ahajournals.org/lookup/doi/10.1161/01.CIR.86.1.70#fig5)

**Figure 5.** Bar graphs showing regional differences in blood flow to the 15O-water perfusable tissue (MBF<sub>p</sub>), 15O-water perfusable tissue index (PTI), and average blood flow to perfusable and nonperfusable tissue (MBF<sub>f</sub>) in normal vol-
unteers (group 1). *p<0.017 vs. anterior (ant) and lateral (lat). Inf, inferior; sep, septal.
2. AMI Patients

The PET data for this group of patients are summarized in Table 4. Analysis of the data acquired in the subacute phase by ANOVA showed that there were significant differences in the values of MBF_p (p=0.02), PTF (p<0.001), and PTI (p<0.001) (Figure 7) between the recovery, nonrecovery, and remote control regions. MBF_p in both the recovery and nonrecovery segments were both reduced relative to their respective remote control segments (p=0.009 and p=0.004, respectively). However, MBF_p in the recovery and nonrecovery regions was similar at this time (Figure 7). The difference in PTI between groups was solely attributable to the values of this parameter being significantly lower in the nonrecovery group relative to the recovery and remote control segments. PTI in the recovery and remote control segments were not significantly different (Figure 7).

Repeat PET studies were performed at the time of follow-up echocardiography in five subjects. MBF_p in the recovery regions was higher than in the subacute phase, but this did not reach statistical significance. There was no change in the value of PTI between the two PET studies. Similarly, the results from the PET study in the subacute and follow-up phases for the nonrecovery regions were similar.

Two patients (A1 and A2) were studied with 18F-DG in the subacute phase after an oral glucose load. Residual 18F-DG uptake was demonstrated in asyneric segments, and both regions had improved contractile function at the time of the follow-up echocardiography. PTI in these regions was close to unity.

Discussion

In this study, we have reported the preliminary findings of a new method for simultaneously detecting viable myocardium and measuring the blood flow to
In normal myocardium, we hypothesized that the value of PTI should be unity, as all the myocardium should have been perfusable by H$_2^{15}$O. This was found to be the case in all (apart from septal) myocardial segments in normal volunteers and in the remote control segments in both patient groups. In the septum, PTI was significantly higher than in the other left ventricular ROIs resulting from the spillover of activity from the right ventricular chamber into septal tissue ROIs caused by the limited spatial resolution of the PET scanner. The concentration of H$_2^{15}$O in the right ventricular chamber is equivalent to that in venous blood, which is the same as in tissue, as H$_2^{15}$O is a freely diffusible tracer. Therefore, the spillover from the right ventricular chamber is considered by the model as an additional tissue component, hence, the overestimation of PTI.

**AMI Patients**

We found that in successfully thrombolysed AMI patients (group 3), systolic wall thickening improved in seven of 12 affected segments. In the subacute phase, PTI in the recovery segments was well preserved and not significantly different from the remote control segments. We performed an additional $^{18}$FDG scan in two of these patients and observed a positive uptake. In the nonrecovery regions, PTI was significantly decreased compared with the recovery segments and was similar to that found in segments without $^{18}$FDG uptake in the OMI patients. PTI for a given ROI was defined as the fraction of the anatomical tissue that was perfusable by H$_2^{15}$O. Our data indicate that only those segments with a preserved PTI (i.e., >0.7) recovered contractile function. We performed repeat PET scans on six of the 11 patients at the time of the follow-up echocardiography and showed that in the recovery segments, PTI was similar to that measured in the subacute phase. In the recovery regions, PTI was lower than in the control segments, but this did not reach statistical significance. This suggests the presence of some tissue damage in these regions as a result of the acute ischemic insult. No improvement in PTI was observed in segments in which contractile function remained depressed. These data suggest that at least 70% of the myocardium should be perfusable by water to enable improvement of contractile function.

In the subacute phase, MBF$_p$ was reduced to a similar extent in both the recovery and the nonrecovery segments relative to the remote control segments. The diminished values of MBF$_p$ in the recovery segments in the subacute phase can be explained by the decreased myocardial metabolic demand as a result of the reduced wall thickening at this time. However, MBF$_p$ was not a good predictor of recovery of myocardial contractile function, as there was no significant difference between the values in the recovery and the nonrecovery segments. At follow-up, MBF$_p$ in the recovery segments was greater than at the subacute phase because of the improvement in myocardial contractility. In the nonrecovery segments, no increase in MBF$_p$ was observed.

**Comparison With $^{18}$FDG**

The presence of residual metabolism in infarcted segments has been documented previously by Tillisch et al.$^{10}$ who showed $^{18}$FDG uptake in 15 of 28 asynergic myocardial segments in patients with Q wave myocardial infarction...
TABLE 3. Angiographic Profiles of Successfully Thrombolysed Acute Myocardial Infarction Patients (Group 3)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)/Sex</th>
<th>Infarction site</th>
<th>Responsible lesion</th>
<th>Stenosis (%) Before</th>
<th>After</th>
<th>24 Hours</th>
<th>Collaterals</th>
<th>Interval from onset of AMI to recanalization (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>60/M</td>
<td>Anterior</td>
<td>LAD (seg 7)</td>
<td>100</td>
<td>100</td>
<td>70</td>
<td>+</td>
<td>4-28</td>
</tr>
<tr>
<td>A2</td>
<td>47/M</td>
<td>Anterior</td>
<td>LAD (seg 6)</td>
<td>100</td>
<td>75</td>
<td>75</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>A3</td>
<td>75/M</td>
<td>Anterior</td>
<td>LAD (seg 7)</td>
<td>100</td>
<td>90</td>
<td>90</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>A4</td>
<td>58/M</td>
<td>Anterior</td>
<td>LAD (seg 7)</td>
<td>100</td>
<td>99</td>
<td>90</td>
<td>+</td>
<td>1.8</td>
</tr>
<tr>
<td>A5</td>
<td>54/F</td>
<td>Inferior</td>
<td>RCA (seg 1)</td>
<td>100</td>
<td>75</td>
<td>75</td>
<td>-</td>
<td>4.8</td>
</tr>
<tr>
<td>A6</td>
<td>48/M</td>
<td>Inferior</td>
<td>LCx (seg 13)</td>
<td>100</td>
<td>99</td>
<td>50</td>
<td>-</td>
<td>5.7</td>
</tr>
<tr>
<td>A7</td>
<td>39/M</td>
<td>Anterolateral</td>
<td>LAD (seg 6)</td>
<td>100</td>
<td>25</td>
<td>25</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>A8</td>
<td>55/M</td>
<td>Inferior</td>
<td>RCA (seg 2)</td>
<td>100</td>
<td>90</td>
<td>75</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>A9</td>
<td>70/M</td>
<td>Anterior</td>
<td>LAD (seg 8)</td>
<td>75</td>
<td>50</td>
<td>50</td>
<td>-</td>
<td>...</td>
</tr>
<tr>
<td>A10</td>
<td>48/M</td>
<td>Anterior</td>
<td>LAD (seg 6)</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>-</td>
<td>...</td>
</tr>
<tr>
<td>A11</td>
<td>61/M</td>
<td>Inferior</td>
<td>LCx (seg 11)</td>
<td>100</td>
<td>99</td>
<td>90</td>
<td>-</td>
<td>4.3</td>
</tr>
</tbody>
</table>

AMI, acute myocardial infarction; LAD, left anterior descending coronary artery; RCA, right coronary artery; LCx, left circumflex artery; seg, segment.

dial infarction. This study showed that in asynergic regions that had both a relatively reduced blood flow and a relatively preserved or enhanced \(^{18}\)FDG uptake ("mismatch"), revascularization improved contractile function. These workers also showed that in regions that were both hypoperfused and had a depressed \(^{18}\)FDG uptake ("match"), revascularization did not improve the regional wall motion abnormality. These data provided the basis for the terms "PET viable" and "PET necrotic." Similar findings were subsequently reported in patients after AMI.\(^9\)

Of the 15 subjects with OMI (group 2) investigated in the present study, nine patients had asynergic regions in which the metabolism–flow ratio was \(\geq 1.20\), whereas in the remaining six patients, this ratio was found to be \(<1.20\). The threshold value of 1.20 for the metabolism–flow ratio has recently been suggested to distinguish reversibly from irreversibly injured tissue.\(^8\) This approach is similar to the original methods used for assessing myocardial viability from metabolism and perfusion PET images.\(^8\)-\(^10\) There was no significant difference in the values of \(MBF_p\) between the reversibly and irreversibly injured tissue defined above. These findings further demonstrate the inadequacy of perfusion measurement alone to discriminate viable from nonviable myocardium. This distinction was detected by measurement of PTI, which was significantly higher in asynergic regions that were deemed reversibly injured on the basis of having metabolism–flow ratios \(\geq 1.20\).

Although recent studies have demonstrated the presence of \(^{18}\)FDG uptake in reperfused myocardium showing a wide degree of histologically defined transmural necrosis,\(^23\)-\(^24\) there is considerable evidence that preserved \(^{18}\)FDG uptake augurs an improvement in contractile function upon successful reperfusion.\(^9\)-\(^10\),\(^25\)-\(^28\) In our study, there was agreement between the PTI data and the metabolism–flow ratio for identifying reversibly from irreversibly injured myocardium. Ideally, a direct comparison of \(^{18}\)FDG uptake, PTI, and wall motion recovery should have been performed. However, this was not performed in the interest of minimizing the scanning duration for patients in an unstable condition. In the two AMI patients in whom we were able to perform metabolic imaging, concordance was observed between PTI, \(^{18}\)FDG uptake, and improvement in systolic function.

PTI measures the proportion of the anatomically defined myocardium that is functionally exchanging water and provides quantitative information regarding the proportion of viable tissue within a given ROI. Our observation that PTI in irreversibly injured myocardial regions was not zero suggests the presence of residual tissue that was capable of rapidly exchanging water. This was probably due to there being an admixture of both perfusable and nonperfusable tissue in the region supplied by the infarct-related artery. The reduced values of PTI in both the irreversibly injured asynergic segments in the OMI group and the nonrecovery areas in the AMI patients were entirely due to a reduction in PTF. This suggests that the necrotic myocardium is not capable of exchanging water rapidly. Therefore, we suggest that only myocardium that is capable of doing so, i.e., where PTI is preserved \((>0.7)\), has the potential for some recovery of contractile function. We speculate that the main physiological determinant of PTF may be the density of open capillaries and/or the degree of myocardial fibrosis, but further experiments in animals will be required to confirm such a hypothesis.

**Critique of the Methodology**

The method that we have reported on assessing myocardial viability is mainly dependent on the measurement of PTF and ATF. A more detailed comparison of both methods has been reported,\(^29\) but a brief consideration of both methods would be appropriate.

Measurement of PTF was first introduced by Lida et al\(^12\) to correct for the underestimation of myocardial radiotracer concentration caused by the partial volume effect in H\(_2\)\(^{15}\)O studies. This parameter is dependent not only on the physical dimensions of the heart wall and cardiac motion but also on its functional ability to exchange water rapidly. The efficacy of this mode of partial volume correction in H\(_2\)\(^{15}\)O studies for measurement of MBF has recently been shown in our laboratory.\(^11\) However, the measurement of PTF is limited in the septum because of the spillover from the right ventricular chamber, as explained above. This may be overcome by changing the protocol for administration of
Table 4. Positron Emission Tomography and Two-dimensional Echocardiography Data for Successfully Thrombolysed Acute Myocardial Infarction Patients (Group 3)

<table>
<thead>
<tr>
<th>Subcutaneous phase</th>
<th>Follow-up phase</th>
<th>Subcutaneous phase PET data</th>
<th>Follow-up phase PET data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>Region</td>
<td>%WT</td>
<td>Th(ED)</td>
</tr>
<tr>
<td>A1</td>
<td>Anterior</td>
<td>10 0</td>
<td>10 30</td>
</tr>
<tr>
<td>A2</td>
<td>Anterior</td>
<td>8 0</td>
<td>9 40</td>
</tr>
<tr>
<td>A3</td>
<td>Anterior</td>
<td>9 0</td>
<td>10 24</td>
</tr>
<tr>
<td>A4</td>
<td>Anterior</td>
<td>11 11</td>
<td>10 33</td>
</tr>
<tr>
<td>A5</td>
<td>Inferior</td>
<td>7 14</td>
<td>8 50</td>
</tr>
<tr>
<td>A6</td>
<td>Inferior</td>
<td>8 0</td>
<td>8 64</td>
</tr>
<tr>
<td>A7</td>
<td>Lateral</td>
<td>10 0</td>
<td>9 21</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>9 37†</td>
<td>0.68*</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td>1 1 5</td>
<td>0.18*</td>
</tr>
</tbody>
</table>

For recovery segments:

- **H<sub>2</sub>O to slow intravenous infusion of the tracer rather than inhalation of C<sup>15</sup>O<sub>2</sub>**

  An alternative approach to partial volume correction is the measurement of ATF, as first developed by Rhodes et al<sup>13</sup> for the lung, which is dependent solely on the physical characteristics of the heart wall. This method has recently been validated by using a cardiac phantom to accurately correct for underestimations in tracer concentration caused by wall thickness over the range of 3-27 mm.<sup>15</sup> Further phantom experiments have suggested that this method provides adequate correction for the underestimation of tissue tracer concentration that occurs as a result of cardiac wall motion, provided that the spatial resolution of emission and transmission data sets is similar.<sup>16</sup> Studies in a greyhound have confirmed that when this correction is used, 18FDG activity measured by the scanner is almost identical to that measured in a NaI well counter cross-calibrated with the scanner.<sup>17</sup> These data show the validity and accuracy of this mode of partial volume correction. In some instances, though, the value of ATF may be underestimated in the anterior region because of spillover from the chest wall.

**PTI** is calculated by taking the ratio of PTF to ATF for a given ROI. This measurement is independent of partial volume effects and ROI size and provides a quantitative measurement of the proportion of the myocardium, which is functionally exchanging water.
FIGURE 7. *Bar graphs show the differences in blood flow to the 18O-water perfusable tissue (MBFp), 13O-water perfusable tissue index (PTI), and average blood flow to perfusable and nonperfusable tissue (MBF) between recovery, nonrecovery, and remote control segments in the thrombolysed acute myocardial infarction patients (group 3). *p<0.017 vs. remote control; †p<0.017 vs. nonrecovery; p=NS vs. remote control.

We have shown a relation between PTI, 18FDG uptake, and contractile function in the heart. In our study, recovery of contractile function was associated with a PTI value >0.7. Although these data are very encouraging, a prospective blinded study incorporating a larger study population would be required to corroborate our initial findings.

Our method is based on the hypothesis that only viable myocardium exchanges water rapidly. Therefore, in theory, PTI will differentiate both stunned and hibernating myocytes from necrotic ones in regions of myocardial infarction. Our data further suggest that at least 70% of the myocardium within the infarcted zone needs to be viable to enable contractile recovery. Animal studies will be required to further investigate the physiological basis of the PTI measurement and its ability to accurately differentiate viable from necrotic tissue. Although normal myocytes cannot be distinguished from stunned or hibernating cells on the basis of PTI alone, our method additionally provides simultaneous quantitative measurements of MBFp. The combination of MBFp measurements and PTI should enable distinction of normal from hibernating myocardium because of the latter having a reduced blood flow by definition.

In the AMI patients, PTI has an apparent 100% sensitivity in distinguishing recoverable and irreversibly damaged tissue. Although these findings should be confirmed in a larger study group, this represents a particularly attractive feature of using PTI for assessing myocardial viability. Indeed, an identical threshold value of PTI for predicting improved regional wall motion after coronary revascularization has also been observed. To our knowledge, systematic studies designed specifically to assess the degree of transmural histologically defined necrosis that limits improvement in regional wall motion after revascularization have not been performed. Previous studies have investigated the degree of transmural necrosis that correlates with the severity of wall motion abnormalities identified by using a number of techniques. These studies indicated a direct relation between the extent of transmural necrosis and the severity of the wall motion abnormality. In one study, a weak but statistically significant correlation between the severity of the preoperative wall motion abnormality and subsequent postrevascularization improvement in regional wall motion was observed. Thus, although a relation between the degree of transmural myocardial necrosis and postreperfusion improvement in myocardial contractility can be surmised, the precise details of this relation remain to be elucidated.

There are several practical advantages to this method of assessing tissue viability. First, the entire study can be performed in less than 1 hour. This decreases the chance of patient movement occurring during the study and has the logistical advantage of increasing patient throughput. Second, the lack of requirement for 18FDG in this method decreases the total scanning duration, the radiation dose to the patient, and the cost of the procedure. The advent of relatively inexpensive equipment dedicated to the production of tracers labeled with 18O should make this method more amenable to clinical centers.

Conclusions

In summary, we have evaluated a new parameter, PTI, for assessing myocardial viability by performing studies in OMI patients and AMI patients after the administration of thrombolytic agents. In the latter group, improvement in cardiac wall motion was used as evidence of myocardial viability. However, in the OMI patients, the previously reported 18FDG method was used as evidence of tissue viability, as revascularization was not performed.

We have shown that in the OMI patients, PTI in infarcted segments considered viable (on the basis of the preserved 18FDG uptake relative to the level of myocardial perfusion) was significantly higher than in those segments in which there was a concomitant reduction of both 18FDG uptake and perfusion. In the group of patients who were successfully thrombolysed after AMI, we showed that contractile recovery only occurred in segments in which PTI was >0.7. These data suggest that at least 70% of the tissue within a given ROI should be perfusable by water to enable improvement of contractile function. Although further studies in experimental animals and in a larger group of patients would be required to confirm our initial findings, these data suggest that PTI is a good prognostic indicator of improvement in contractile function, and that myocardial...
dial viability may be assessed by PET without metabolic imaging.

Acknowledgments

The authors would like to thank Grahame Lewington for technical assistance, the staff of the MRC Cyclotron Unit for radioisotope and tracer production, and Dr. Paolo Camici for valuable suggestions.

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_Circulation_. 1992;86:167-178
doi: 10.1161/01.CIR.86.1.167

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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