Regional myocardial and organ blood flow after myocardial infarction: application of the microsphere principle in man


ABSTRACT A physiologic means of measuring the distribution of cardiac output and regional myocardial blood flow has been developed that uses human albumin microspheres labeled with carbon-11 ($^{11}C$) and external detection with positron emission tomography. Ten patients with previous myocardial infarction were studied to investigate the level of blood flow in normal and infarcted segments of the heart. After diagnostic catheterization, 4 to 6 mCi of $^{11}C$ on 2 to 3 million sterile microspheres (15 to 20 μm) were mixed and injected into the apex of the left ventricle during timed withdrawal of arterial blood to obtain reference flow values. Regional activity in brain, heart, lungs, liver, spleen, and kidneys was measured tomographically. Blood flow was calculated based on the relationship between total activity in a reference flow and tissue activity in tomograms of each organ (ml/min/100 g). No adverse effects were noted after injection of the microspheres. Successive myocardial tomograms showed no loss of activity. There were no significant differences in flow values in matched regions of paired organs. Mean cerebral flow was 52.4 ± 10.0 ml/min/100 g in the frontal lobes, 54.4 ± 8.8 in the temporal lobes, 67.6 ± 8.2 in the occipital lobes, and 53.0 ± 9.4 in the basal ganglia. Flow was 16.0 ± 8.4 ml/min/100 g (range 0 to 40.0) in the center of infarcted myocardium and 82.0 ± 32.0 in the remote segments. This method meets most of the demands for use of microspheres to measure tissue blood flow. The wide range of flow values in infarcted myocardium may be a function of infarct size, spatial resolution, or pathologic evidence of islands of viable tissue. Patients with angina had high flow values in the infarcted segment, whereas those with heart failure had significantly lower values. Surviving myocardium in the region of the infarct may need to be considered if patients complain of angina, particularly when treatment is aimed at preserving ventricular function.


BLOOD FLOW can be assessed based on distribution of cardiac output, perfusion of organs, and regional flow within organs. All these measurements represent physiologic requirements essential for tissue function. Although many of the demands for measuring these different aspects of flow are met by the traditional use of microspheres, this experimental approach is destructive in that tissue activity must be measured by blood sampling and well counting. With new radiochemical techniques, a stable bond can be formed between carbon-11 ($^{11}C$) (t½ = 20.3 min) and biodegradable human albumin microspheres. These can be injected in vivo, and the tissue concentration can be determined by means of positron emission tomography. Finally, experiments have shown an excellent correlation with reference measures of flow, introducing an invasive but nondestructive approach employing microspheres that can be adapted for use in patients.

This report describes the use of $^{11}C$-labeled microspheres and positron emission tomography to measure the distribution of cardiac output and regional organ flow in patients with past myocardial infarction. Residual flow in infarcted segments of the heart were...
examined in two groups of patients who also suffered from angina and heart failure.

Methods

Ten patients (nine men and one woman, ages 42 to 68 years) were selected for study because of the following clinical characteristics: (1) previous myocardial infarction confirmed by symptoms, diagnostic changes on the electrocardiogram (Q waves), and plasma creatine activity, (2) cardiac enlargement on chest roentgenogram (cardiothoracic ratio above 50%), and (3) performance of diagnostic cardiac catheterization because of post-infarction angina or the possibility of a left ventricular aneurysm that might be resected. Patients 1, 3, 5, 7, 9, and 10 underwent catheterization because of angina and patients 2, 4, 5, and 8 because of the possibility of aneurysm.

Patient evaluation consisted of a history, physical examination, chest roentgenogram, and a 12-lead electrocardiogram. The reasons for and the nature and dangers of cardiac catheterization were explained, and informed consent was obtained before each study. Separately, the reasons for and the nature and dangers of measuring organ blood flow with labeled microspheres were explained as a research procedure and again informed consent was obtained. On the basis of the previous use of microspheres in humans, experimental work, and dosimetry, permission to administer up to 6 mCi of $^{11}$C on sterile biodegradable albumin microspheres (2 to 3 million) was obtained from the hospital ethics committees and those government agencies controlling the administration of isotopes to patients.

Preparation of $^{11}$C-labeled microspheres. $^{[11]}$C-carbon dioxide was produced by a cyclotron, reduced by lithium aluminum hydride in ether, and used to produce $^{[11]}$C-iodomethane. Sterile human serum albumin microspheres (particle size 15 μm, CIS Sorin Catalogue No. TCK-5-S) were suspended with the $^{[11]}$C-iodomethane in 0.9% w/v saline and filtered (Millex G.S. Filter, pore size = 0.22 μm, Millipore Corp.) to remove activity of the unbound fractions. The microspheres were then resuspended and 0.1% w/v polysorbate 80 (Tween 80) was added. Further information about preparation and yield have been published previously.

Activities of 1.3 GBq (35 mCi) were prepared and passed independent tests for sterility and pyrogenicity (SafePham Ltd., London, UK). Microscopic examination of the microspheres showed that they increased in size to a mean diameter of 18 μm.

Protocol in patients. Under sterile conditions a No. 8F sheath with a nonreturn valve was positioned in the right femoral artery by percutaneous puncture. By this route, selective coronary arteriography was performed with Judkins catheters and left ventriculography was carried out with a No. 7 pigtail catheter. If the patient was free of symptoms after 15 to 30 min, the pigtail catheter was flushed with heparinized saline and replaced in the apex of the left ventricle.

A 60 cm Portex tube was attached to the side arm of the sheath to withdraw blood from the femoral artery. The end of the tubing was connected to a heparinized and tared syringe mounted in a Harvard pump set to withdraw 13.8 ml/min for 60 to 120 sec. Two to 5 ml of sterile normal saline containing 2 to 3 million microspheres (2 to 6 mCi of $^{11}$C) was mixed mechanically and injected with a 5 ml flush into the apex of the left ventricle 2 to 3 sec after the start of the timed withdrawal. The injection of microspheres and the flush were started coincident with appearance of the T wave on the electrocardiogram in an attempt to inject the majority of the microspheres during diastole.

Before and after the injection, any new symptoms or physical signs were noted. Heart rate, electrocardiographic changes, and left ventricular pressure were also recorded. A stopwatch was started with the arterial withdrawal and the injection. After 5 min the pigtail catheter was removed and the sheath was covered with a sterile dressing. The patient was transported to a facility for emission computed tomography and positioned supine on a cushioned bed. This transport could be completed in 15 to 20 min, after which the femoral artery sheath was removed and hemostasis was achieved by compression. Symptoms, heart rate, arm cuff blood pressure, and a 12-lead electrocardiogram were monitored during the rest of the study.

Analysis of blood samples. The syringe with arterial blood was weighed and agitated. Three blood samples (1 ml aliquots) were placed in tared tubes and weighed. The activity was counted twice in a calibrated well counter and decay was corrected back to the time of injection. The well counter is calibrated weekly with a known activity that was also used to calibrate the tomographic device, equating counts per milliliter per second in the well counter with counts per pixel per second. The cross-calibration varied by less than 5% over 1 week so that activity in the reference arterial sample could be converted from counts per milliliter per minute to counts per pixel per minute. This total activity was divided by the known withdrawal rate into the syringe to obtain the reference flow rate.

Free activity of $^{11}$C in blood. Venous blood samples (1 ml each) were taken 30, 60, and 90 min after injection of the microspheres. These were heparinized, weighed, and well counted to assess the quantity of free $^{11}$C in the blood.

Positron emission tomography. Each patient was positioned within an array of detectors arranged to collect coincidence photons arising from positron annihilation (EG and G Ortec ECAT II Positron Scanner). This device records multiple projections from twin 511 keV photons rejecting random events squash scan with a spatial resolution of 17 mm at full-width half-maximum with a slice thickness of 19 mm. A separate and measured ring source of germanium-68, positioned between the subject and the detectors, was used to record transmission data for attenuation correction at each tomographic level. Ungated emission tomograms were collected with correction for decay of $^{11}$C during each 300 sec scan.

Tomograms were collected at the following transaxial levels: (1) through the brain at 4.5 cm above the orbitomeatal line, (2) through the heart at four levels 1.5 cm apart, (3) through the liver and spleen, and (4) through both kidneys.

Each tomographic level was marked on the skin by means of a laser source aligned with the detectors, which permitted transaxial registration for transmission scans and echocardiography.

Two hours after injection of the microspheres, less than 100 counts/sec were registered over the chest and head by the array of detectors linked to a scalar counter. The same detectors and scalar counters registered more than 15,000 counts/sec with the germanium-68 transmission ring source in position. In these circumstances, 300 sec transmission tomograms were recorded at the same levels as those described above. Each level was marked on the patient’s skin and matched to a laser source in line with the detectors noting longitudinal, lateral, and rotational orientation.

Data analysis in calculating regional flow in organs. The emission tomograms were reconstructed by the appropriate transmission correction and decay corrected to the time of injection. The reconstruction variables provided the dimension of each pixel, and data were displayed as images within a 100 × 100 matrix of pixels.

Regional activity in tomograms of internal organs was calculated by enclosing large anatomic regions of interest. In each region the mean of nine peak pixel values was used. In the brain, these regions enclosed the frontal cortex, temporal cortex, oc-
Activity of the $^{11}$C-labeled microspheres in each region of interest was calculated from equation 1:

$$C_m = \frac{C_{mo}}{k \times g} \quad (1)$$

where $C_{mo}$ is the measured activity in the region of interest, $k$ is the calibration factor used to normalize tissue activity concentrations measured by positron emission tomography to the well-counter background, and $g$ is the specific gravity of the tissues. No attempt was made to correct for underestimation due to the partial volume effect, since each anatomic region of interest was greater than 3 cm$^3$. Blood flow in each region (RBF) was then calculated from equation 2:

$$RBF = \frac{Fa \cdot C_{m} \cdot 100 \text{ ml/min/100 g}}{C_b} \quad (2)$$

where $Fa$ is the withdrawal rate of arterial blood (ml/min), $C_m$ is the activity in each tomographic region, and $C_b$ is the total activity in the arterial sample (counts/min). Regional myocardial blood flow. The tomograms of the heart were reconstructed and decay corrected to the time of injection. The linear dimension of each pixel was 1.30 mm. Two investigators were given the printed matrix of pixel values and asked (1) to identify the myocardium by enclosing all values that were 50% or more of the peak value, (2) to identify large (1.37 cm$^2$) anatomic regions of interest enclosing the posterior wall, free wall, anterior wall, interventricular septum, and cavity of the left ventricle, (3) to calculate a mean in the region enclosing the evidence of myocardial infarction with the nine lowest values in the center of the affected area to minimize the difference of activity from adjacent regions, and (4) to calculate a mean in the nine highest values in each of the remaining noninfarcted regions. These values were corrected for partial volume effect by means of echocardiography, as outlined below. It was decided that if any difference between the two investigators’ results was greater than 5%, a third, independent calculation was done; however, the differences were all less than 5%.

**Echocardiography.** During tomography, the laser source and the ink markings indicated the four transaxial levels on the chest representing the levels of scanning. Two-dimensional echocardiographic images were performed within 24 hr of the procedure at a time when the patient was supine. A high-resolution, phased-array system with a 3.3 MHz transducer (General Electric Pass C IGE Ca) was used to record images on videotape. This device has a spatial resolution of less than 2 mm. Echocardiographic images of the left ventricle were obtained by angulating the transducer in a transaxial position on each of the four levels marked on the chest at the time of positron emission tomography. At each level, one systolic and one diastolic frame were selected according to the electrocardiogram. A mean of three values for wall thickness was calculated from the posterior, free, and anterior walls of the left ventricle and the interventricular septum. The echocardiogram provided an anatomic slice with the same landmarks seen in tomography (i.e., mitral orifice, posterior wall, free wall, anterior wall, and interventricular septum). The wall motion abnormality in the infarcted area was identified for measurement and corresponded with the regional infarction seen in the tomograms. A mean of three measurements of wall thickness was calculated (diastolic value $\times 2 +$ systolic value, divided by 3) in each region of interest. This was used to correct the myocardial counts for the partial volume effect.

The true activity of $^{11}$C-labeled microspheres in each region of interest ($C_m$) was calculated from equation 3:

$$C_m = \frac{C_{mo}}{k \times RC \times g} \quad (3)$$

where $C_{mo}$ is the decay-corrected activity measured during tomography, $k$ is the calibration factor that normalizes tissue activity measured by tomography to the well counter, $RC$ is the recovery coefficient, which corrects for underestimation of true activity measured during tomography because of small object size, and $g$ represents the specific gravity of myocardium. These methods of correction have been examined and validated in detail previously. Regional myocardial blood flow was calculated with equation 2.

**Correlation between infarction and flow.** The coronary arteriograms, ventriculograms, and echocardiograms were each interpreted by two experienced operators who had not interpreted the positron emission tomograms.

**Statistical analysis.** Flow data are expressed as means ± SD. Flow in similar regions from paired or symmetric organs (brain hemispheres, lungs, and kidneys) were compared with paired $t$ tests.

After each study, symptoms, physical signs, and a 12-lead electrocardiogram were recorded before and for 12 hr after the patient was returned to the ward. Patients were evaluated again as outpatients 3 to 5 months after the procedure.

**Results**

The clinical characteristics of the patients are listed in table 1. Myocardial infarctions occurred 7 months to 8 years before this study. All the left ventricular angiograms demonstrated regional wall motion abnormalities. Six of the patients presented with angina pectoris (table 1).

During and after the injection of microspheres, none of the patients complained of any symptoms nor were there any changes in heart rate, blood pressure, electrocardiographic features, or left ventricular end-dias tonic pressure. A complete examination of the central nervous system, fundi, urine, renal function, and peripheral circulation was performed before and after the procedure. No changes were noted.

**Reference blood samples.** The 1 ml blood samples were each well counted twice with less than 2.0% variation and 5000 to 20000 counts/sec/ml, thus providing excellent counting statistics. The 1 ml venous samples drawn at 30, 60, and 90 min after injection all had less than 10 counts/sec/ml, equivalent to 0.5% of the peak activity in the left ventricular myocardium recorded by positron emission tomography. There was no progressive increase in activity of $^{11}$C in the venous blood. The timed withdrawal of blood from the femoral arterial sheath may have been technically unsatisfactory in patient 4. Nevertheless, calculations were made to show regional differences in myocardial blood flow and to show the uniform distribution of micro-
Patient data

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)/sex</th>
<th>Angina</th>
<th>LV angiogram</th>
<th>Coronary arteries</th>
<th>Collaterals</th>
<th>Tomography (site of infarction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50/M</td>
<td>F</td>
<td>AMSI</td>
<td>↑</td>
<td>70% LAD</td>
<td>100% Anterior and inferior</td>
</tr>
<tr>
<td>2</td>
<td>64/M</td>
<td>F</td>
<td>AMI</td>
<td>↑</td>
<td>70% LCX</td>
<td>100% Anterior and inferior</td>
</tr>
<tr>
<td>3</td>
<td>64/M</td>
<td>O</td>
<td>AMI</td>
<td>↑ Anterior</td>
<td>100% LAD</td>
<td>RCA to LAD Anterior and inferior</td>
</tr>
<tr>
<td>4</td>
<td>68/M</td>
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<td>AMI</td>
<td>Anterior</td>
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<td>50% LCX Apical</td>
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<tr>
<td>5</td>
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<td>F</td>
<td>AMI</td>
<td>↑ Anterior</td>
<td>100% LAD</td>
<td>100% LCX Apical</td>
</tr>
<tr>
<td>6</td>
<td>42/M</td>
<td></td>
<td>ALMI</td>
<td>↑ Anterior</td>
<td>70% LAD</td>
<td>70% LCX Apical and lateral</td>
</tr>
<tr>
<td>7</td>
<td>60/M</td>
<td>F</td>
<td>AMSI</td>
<td>↑ Apical</td>
<td>100% LAD</td>
<td>100% LAD Apical and inferior</td>
</tr>
<tr>
<td>8</td>
<td>59/M</td>
<td>F</td>
<td>AMI</td>
<td>↑ Apical</td>
<td>100% LAD</td>
<td>70% LAD Anterior and apex</td>
</tr>
<tr>
<td>9</td>
<td>49/M</td>
<td>F</td>
<td>AMI</td>
<td>↑ Apical inferior</td>
<td>75% LAD</td>
<td>100% LAD LCX Apical and inferior</td>
</tr>
<tr>
<td>10</td>
<td>59/M</td>
<td></td>
<td>AMI</td>
<td>↑ Apical</td>
<td>100% LAD</td>
<td>75% LAD Apical and inferior</td>
</tr>
</tbody>
</table>

O = occasional; F = frequent; ↑ = increased; LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery; AMI = anterior myocardial infarction; ASMI = anteroseptal myocardial infarction; ALMI = anterolateral myocardial infarction; IMI = inferior myocardial infarction.

spheres with no significant differences in flow in matched regions of paired organs.

**Positron tomography**

**Brain.** After the administration of 4 to 6 mCi of $^{11}$C-labeled microspheres, 300 sec scans of the brain yielded 150,000 to 300,000 coincidence events (counts). Figures 1 and 2 clearly show that the regional distribution of activity and flow in the frontal, temporal and occipital lobes are symmetrical in the two hemispheres. Flow values for each region of the brain are shown in table 2 and confirm this symmetry.

**Myocardium.** Tomograms of the myocardium yielded a total of 100,000 to 400,000 counts and 1800 to 2500 counts/pixel (range) in all the segments outside the region of infarction, providing excellent statistics. There were 200 to 900 counts/pixel (range) in the infarcted segments. The mean ratio of peak counts per pixel in the left ventricular myocardium to counts in the left ventricular cavity was 16.0 ± 3.4:1 with the same-sized region of interest. The four myocardial tomograms in each case were recorded over 20 min, and there was no evidence of a fall in the peak myocardial activity during this period after values were decay corrected to the time of injection. Figure 1 shows regional myocardial activity and flow in a patient with anterior infarction and no cardiomegaly; there is a small area of abnormal perfusion. Figure 2 shows evidence of extensive anteroseptal myocardial infarction in another patient. These figures show that although there was negligible activity in the blood and lungs, caudal tomograms revealed splenic activity adjacent to the myocardium. Although cross-contamination can introduce errors in quantitation, measurements of flow in these segments of myocardium were not significantly different from values in the other more cephalad and noninfarcted regions after decay and partial volume correction. Figure 3 shows the values obtained from the remote myocardium and from the center of the infarcted segment.

**Regional myocardial blood flow.** Regional myocardial flow in areas remote from the infarct ranged from 30 to 150 ml/min/100 g (82.0 ± 32.0). Although there were significant differences among patients, within each patient the difference between the highest and lowest values for flow in these remote regions was 6.0 ± 4.1% (mean ± 1 SD, range 1.5% to 11.0%). Patients 3, 4, 5, 9, and 10 all had remote noninfarcted myocardial segments supplied by coronary arteries with different degrees of disease (table 1). Within each of these patients, flow in noninfarcted regions supplied by vessels showing 50%, 70%, or 100% stenosis with collaterals were compared and no significant differences were found (i.e., values were within the range given above [1.5% to 11.0%]). The value for flow in
the center of the infarcted segment was more than 2 SDs below the mean values for the four remote segments in all the patients. Flow in the center of the infarcted segment was 16.0 ± 8.4 ml/min/100 g (range 0 to 40) for all 10 patients. However, infarct flow in patients with a left ventricular end-diastolic pressure of 20 mm Hg or more was 11.20 ± 9.0 ml/min/100 g. However, when the left ventricular end-diastolic pressure was less than 20 mm Hg, flow was 30.0 ± 10.2 ml/min/100 g (p < .01). There was consistent agreement among the electrocardiogram, left ventricular angiogram, echocardiogram, and tomographic evidence of regional myocardial infarction. Figure 3 shows that those patients who also complained of angina pectoris had the highest values for flow in the infarcted segment. Figure 4 shows regional myocardial flow in two patients: patient 6 had no angina but had cardiomegaly and heart failure, and patient 9 had angina but no cardiomegaly or heart failure.

**Tomography of the lungs, liver, spleen, and kidneys.** Flow was 1.4 ± 0.5 ml/min/100 g in the right lung and 1.6 ± 0.8 ml/min/100 g in the left lung, showing no significant difference between these two values. Peak flow values for the spleen were 141 ± 77.0 ml/min/100 g and those for the liver were 39 ± 14.0. Flow was 163 ± 84 ml/min/100 g in the right kidney and 166 ± 81 in the left kidney (NS).

**Organ dosimetry.** Each millicurie of 11C-labeled microspheres injected was equivalent to a whole-body dose of 23 mR, with 64.1 mR to the brain, 86.2 mR to the heart, and 366.0 mR to the kidneys.

**Discussion**

Regional tissue blood flow is a critical determinant of function in health and disease. In this study, a reference technique using microspheres has been adapted to measure absolute regional flow within internal organs in human beings.1 With the use of labeled microspheres, simultaneous measurements could be made of regional flow in the brain, lungs, heart, liver, spleen, and kidneys. The patients in this study presented with past myocardial infarction, and a detailed examination of regional flow in the heart showed a wide range of values in the infarcted segment. Relatively high flow values in the affected area were noted in patients who presented with angina but no evidence of heart failure, whereas these values were lowest in those who presented with no angina but with cardiomegaly and heart failure.

**Use of labeled microspheres to measure blood flow.** In
the last decade the practice of using microspheres to measure tissue blood flow has developed as a reference technique. Ideally, microspheres should be 7 to 15 μm in diameter, with the radionuclide securely bound to them throughout the period of the measurement. The microspheres must be thoroughly mixed in an afferent chamber and distributed according to cardiac output; flow can be calculated only if the quantity (i.e., activity) of microspheres can be measured in each tissue and in a reference blood sample. This study deals with the adaptations necessary to allow this method to be used for examining organ flow and regional abnormalities in patients with myocardial infarction.

Limitations of microsphere technique in patients. Intravascular administration of large particles (diameter greater than 100 μm) can lead to severe disturbance of cardiac function. However, other investigators have shown in both experimental and clinical studies that up to 0.5 mg/kg particles ranging from 10 to 60 μm in diameter can be injected into the coronary circulation without detectable harmful effects. The same results were reported by Zolle et al., who pointed out that only a minute proportion of the capillary bed is embolized. In qualitative clinical studies, labeled macroaggregates and microspheres have been used to assess perfusion in the brain, liver, and atherosclerotic limb vessels with no complications. Schelbert et al. concluded that there is little risk of harmful effects if the number and size of the particles are controlled.

The biodegradable albumin microspheres used in this study were 15 to 20 μm in size and these are known to be degraded within 6 to 12 hr after administration. The size and number were chosen to comply with previous studies that described no harmful effects in patients when assessing perfusion. At the time

**TABLE 2**

Regional cerebral blood flow (ml/100 ml/min, n = 9)

<table>
<thead>
<tr>
<th>Region</th>
<th>Right hemisphere</th>
<th>Left hemisphere</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal</td>
<td>52.0 ± 9.7</td>
<td>52.7 ± 10.4</td>
</tr>
<tr>
<td>Temporal</td>
<td>55.8 ± 7.3</td>
<td>53.0 ± 10.30</td>
</tr>
<tr>
<td>Occipital</td>
<td>67.0 ± 8.2</td>
<td>68.2 ± 8.3</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>54.0 ± 9.40</td>
<td>51.8 ± 9.40</td>
</tr>
</tbody>
</table>
of injection, none of the patients complained of any symptoms and there were no changes in heart rate, blood pressure, electrocardiographic features, or ventricular pressures. Hours after the study there were no changes in symptoms, retinal vessels, or results of urinalysis or blood chemistry, or in examination of the central nervous system. There was no evidence that healthy myocardium had been jeopardized or affected in any way.

In experimental studies the left atrium was found to be more suitable than the left ventricle or aortic root as a mixing chamber for delivery of microspheres.\textsuperscript{2, 10, 25} Although the left atrium is not easily available at cardiac catheterization, the left ventricle is usually entered. The labeled microspheres in this study were suspended and injected into the apex of the left ventricle, and multiple scans of symmetrical or paired organs, such as the cerebral hemispheres, lungs, and kidneys showed no signs of regional inequalities during flow measurements. Within the macroscopic resolution of positron emission tomography (1.7 cm full-width, half-maximum), no evidence of unequal mixing of the tracer could be detected. The left ventricular injection of microspheres will provide a measure of bronchial artery flow per unit of intact lung tissue. The low and symmetric values of flow in right and left lungs in this study provide further evidence that recirculation is not significant and mixing is adequate.

As in Wilson’s experimental work,\textsuperscript{4} this study showed a high and fixed ratio of activity between myocardium and blood. Nevertheless, there must have been some contamination of low-activity regions from areas of high activity and flow. We examined only the center of the infarcted segment to minimize this spill-over. It is also true that we could not separate endocardial from epicardial events or rule out some overestimation of flow in infarcted regions.

Wilson et al.\textsuperscript{4} have shown a secure bond between \textsuperscript{11}C and albumin microspheres in vitro and in vivo. In this study, there was no significant activity in the blood, stable activity in the tissues, and a high ratio of activity between the left ventricular myocardium and blood. A systematic comparison in dogs in the experiments by Wilson et al. demonstrated a high correlation between measurements of regional myocardial blood flow when using \textsuperscript{11}C microspheres and carbonized reference microspheres.\textsuperscript{4} When using the microsphere technique in patients, we find that (1) the radiolabel is securely bound to the microspheres, (2) the procedure produces no adverse effects, and (3) mixing of the microspheres appears to be uniform in paired organs. Some of the additional technical demands to be met in measuring regional myocardial blood flow are discussed below.

In this study, 15 to 25 min were required (i.e., one half-life of \textsuperscript{11}C) to transport the patient to the scanning device; however, adequate statistics were obtained in scans of all the organs. The decreased flow and therefore decreased activity in the infarcted segments resulted in weaker but adequate statistics in these regions.

Regional blood flow in organs. For years cerebral blood flow has been measured by a variety of different techniques, most of which demand a long steady state and present problems of spatial resolution, partition coefficient, recirculation, and nonlinearity.\textsuperscript{26-28} Raichle et al.\textsuperscript{29} have recently introduced a means of measuring cerebral blood flow using intravenous labeled water (H\textsubscript{2}\textsuperscript{18}O) and positron emission tomography. This adaptation of the Fick principle also requires an arterial puncture for quantitation and must take into account the possibility of underestimation as flow increases resulting from the limited permeability of the brain to water.\textsuperscript{29} Nevertheless, it is certainly more convenient, could provide multiple estimates, and does not require

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**FIGURE 3.** These data show the wide range of values for flow (ml/min/100 g) in segments of the myocardium remote from the infarcted area. Flow in the center of the infarcted myocardium also shows a range of values that overlap with those in the normal areas and include values that have been associated with viable myocardium. The wide range and high values in infarcted segments suggest the presence of viable myocardium within the infarcted area. In patients presenting with previous infarction and angina pectoris, flow values were relatively high in the center of the infarction (O). In contrast, in patients with large hearts and left ventricular end-diastolic pressures (EDP) exceeding 20 mm Hg, values were lower in the infarcted segment (X).
cardiac catheterization. Use of $^{11}$C-labeled microspheres is not dependent on permeability, surface area, or metabolic derangement. The values of cerebral flow recorded for adults in our study are in close agreement with the values published by others.\textsuperscript{28}

**Blood flow in lungs, kidneys, liver, and spleen.** Inert gas clearance, the mean transit time of vascular tracers and complexed technetium-99 have all been used to assess renal perfusion.\textsuperscript{30} These also suffer the problems of partition coefficient and lack of physiologic units.

Clearance techniques and indicator dilution methods have been used to measure total flow in the kidney, liver, and spleen, but these require the same assumptions that accompany the use of diffusible tracers and in addition regional localization is limited.\textsuperscript{30-32} Systemic microspheres will measure hepatic artery flow in the liver, which has a dual circulation. Nevertheless, this may be of value in assessing the kidneys in patients with hypertension and heart failure, with cirrhosis, and with hepatic neoplasms that usually derive their nutrient supply from the hepatic artery.\textsuperscript{32}

**Blood flow in the myocardium.** Coronary sinus thermodilution and washout of xenon-133 can be used but are associated with limited regional localization and, for xenon-133, the disadvantages of planar imaging.\textsuperscript{33, 34}

Intravenous administration of cations (thallium-201 and rubidium-82) provides a measure of uptake (flow \times extraction) and is widely used to detect ischemia in patients with anginal chest pain.\textsuperscript{35-37} However, a specific flow measurement cannot be made in man, since the gamma camera cannot recover the true tissue activity of the tracer in each region of the heart. In contrast, positron emission tomography uses attenuation correction and tomograph reconstruction in two or three dimensions and is calibrated to a known source of activity.\textsuperscript{7} Goldstein et al.\textsuperscript{38} have described the use of an intravenous bolus of rubidium-82 with fast scanning to measure the vascular and myocardial transit of this cation.\textsuperscript{38} In experiments, uptake, flow, and extraction are assessed separately by means of an independent intravascular tracer. Many factors apart from flow can affect the extraction of rubidium, so that this technique requires independent measurements of flow and extraction when applied to human beings. Measurements of regional myocardial uptake of nitrogen-13–labeled ammonia by Shah et al.\textsuperscript{6} clearly provided a measure of regional myocardial perfusion. Nevertheless, this signal can be affected by changes in extraction and metabolic disturbances.\textsuperscript{39} Bergman et al.\textsuperscript{40} have used intravenous labeled water (H$_2$O) with positron emission tomography to measure the regional myocardial concentration and transit of the tracer. Although attrac-
tive, this method may be hindered by the propagation of errors during the necessary subtraction of intravascular activity and nonlinear response at high flow. Nevertheless, these are all important recent advances that will be explored with regard to their individual advantages and limitations.

Microspheres, which are totally extracted and free of a metabolic component,\textsuperscript{2, 41} have been used for years for the qualitative assessment of regional perfusion in patients.\textsuperscript{42-49} Nevertheless, this technique had to be adapted to examine the human heart. First, Wisenberg et al.\textsuperscript{5} studied the effects of gating the acquisition of emission tomograms when using germanium-68–labeled microspheres to measure regional myocardial blood flow. The best correlation with reference flow was obtained with diastolic gating of the emission data ($r = .99$); however, ungated measurements as used in this study also showed a high correlation with reference measures of flow ($r = .98$). Wisenberg’s results also supported Hoffman’s phantom studies\textsuperscript{7} indicating the need for correction owing to underestimation of myocardial activity due to object size (the partial volume effect).\textsuperscript{5} Again, these studies demonstrated that if partial volume correction is performed using postmortem wall thickness, diastolic echocardiographic wall thickness, or mean diastolic and systolic wall thickness based on echocardiograms (as used in this study), the correlation with reference measures of flow is still high ($r = .99$, .98, and .96, respectively).

In this study in patients we used ungated scans to assemble all the available counts and to obtain the best statistics during tomography, since the half-life of $^{14}$C is 20.3 min. In addition, echocardiography was used to calculate mean diastolic and systolic wall thickness to correct for the partial volume effect. Ungated emission data and even postmortem estimates of wall thickness have both been used successfully in recent quantitative studies.\textsuperscript{4-7} The analysis of flow in the noninfarcted segments in this study showed a narrow range of variability (6.0 ± 4.1%), supporting the previously published results with ungated scans and mean values from echocardiography for partial volume correction. Finally, errors may have been introduced by recording the transmission scans 2 hr later, although chest markers, a constant position, and a light marker aligned to the detectors were all used to minimize this effect.

**Regional myocardial blood flow in infarction.** This study showed a wide range of values for flow in the infarcted segment, possibly because of variations in infarct size and limited spatial resolution with spillover of activity between regions. It is also possible that the wider range of values for flow in the center of the infarct represent-ed variable amounts of surviving myocardium.\textsuperscript{50} Interestingly, the values for flow in the noninfarcted segments at rest were not affected by the state of the vessel (50% or 70% stenosis) even if it was occluded and replaced by collaterals. In such patients the size of a myocardial infarct, residual dysfunction, and/or angina pectoris are important determinants of mortality and morbidity. Dwyer et al.\textsuperscript{51} have demonstrated in patients a wide range of values for flow in infarcted segments of myocardium by xenon washout. This study with microspheres and positron emission tomography also supports those findings with a wide range and high values of flow that could be due to survival of myocardium in the affected segment. Residual flow months after infarction could also be determined by the extent of scar tissue, recanalization, and finally development of collaterals.

The patients with cardiomegaly and heart failure showed the most severe reductions in flow, probably representing more homogeneous transmural infarction. In contrast, the patients with angina pectoris but no heart failure had the highest values of flow in abnormal but inhomogeneous infarcts. When planning therapy, therefore, it may be important to identify these patient subsets, consider the surviving myocardium as a possible source of ischemia and angina, and preserve this jeopardized tissue.

This technique with $^{14}$C-labeled microspheres to measure regional myocardial blood flow at the time of cardiac catheterization appears to be safe and could be used to assess the distribution of cardiac output, cerebral blood flow, and flow within internal organs. The conditions governing the use of microspheres to measure flow have been adapted for clinical use. Disadvantages of this technique are that it is invasive, requires the injection of short-lived nuclides, and must be performed at cardiac catheterization. However, it is a specific measure of regional blood flow in human beings and could be used to answer pathophysiologic questions, validate less invasive but more available methods, or evaluate the short-term effects of new treatments on flow. These flow data could also provide an essential basis for interpreting the signal from tracers delivered by flow but involved in myocardial metabolism.

This group of patients with myocardial infarction showed a wide range of values of flow in the affected segment, suggesting that quantities of viable tissue might survive within the infarcted myocardium. Such a possibility may need to be considered if the areas are involved in the maintenance of heart size and ventricular function after infarction. In assessing patients with
anginal chest pain, previously infarcted segments of the left ventricle should not be ignored as a source of symptoms.

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Circulation. 1986;73:433-443
doi: 10.1161/01.CIR.73.3.433

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

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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