Residual Coronary Reserve Despite Decreased Resting Blood Flow in Patients With Critical Coronary Lesions

A Study by Technetium-99m Human Albumin Microsphere Myocardial Scintigraphy

Oberdan Parodi, MD; Gianmario Sambuceti, MD; Alberto Roghi, MD; Roberto Testa, MD; Eugenio Inglese, MD; Salvatore Pirelli, MD; Franco Spinelli, MD; Luigi Campolo, MD; and Antonio L'Abbate, MD

Background. Experimental data demonstrate the persistence of a transmural vasodilator reserve in the face of depressed resting myocardial perfusion. The present study was designed to determine whether resting myocardial hyperperfusion indicates exhausted coronary reserve (CR).

Methods and Results. Fifteen patients with stable angina, isolated left anterior descending coronary artery (LAD) stenosis, and no previous myocardial infarction were evaluated by means of 99mTc human albumin microsphere scintigraphy. Regional myocardial perfusion and CR were assessed at baseline and after LAD papaverine (10–12 mg) by means of two microsphere injections in the left ventricle and compared with five normal subjects. Two 300-second scans were obtained with a mobile gamma camera positioned in the 70° left anterior oblique projection; actual microsphere distribution after papaverine was obtained by image subtraction. The two arterial input functions (basal and papaverine) were measured from the first-pass time–activity curves and validated with the reference arterial sample technique. From the comparison of circumferential profile analysis between patients and normal subjects, nine patients (group IA) showed perfusion defects at rest (reduction of percent radioactivity below 2 SD of normal subjects) in the LAD territory, and the other six (group IB) showed homogeneous perfusion. CR (papaverine/resting perfusion) was 3.8±0.2 and 1.51±0.27 in normal subjects and in ischemic patients, respectively (p<0.01). Despite resting hyperperfusion, group IA showed a papaverine-recruitable CR similar to that of group IB (1.57±0.33 and 1.43±0.16, respectively, p=NS).

Conclusions. In patients with stable angina pectoris, isolated LAD stenosis, and no previous myocardial infarction, microsphere scintigraphy disclosed a high incidence of resting perfusion defects; in those patients, a residual CR was observed despite decreased resting blood flow. (Circulation 1993;87:330–344)

Key Words • myocardial blood flow • radioisotopes • papaverine • ischemia

Measurement of coronary flow reserve has been pointed out as a valuable tool to define the functional severity of a coronary lesion.1–3 In the presence of critical stenosis, the ability of coronary blood flow to increase in response to vasodilating stimuli is blunted; further reduction in luminal area may eventually cause reduction in resting perfusion.1,4

In the clinical setting, most of the methods used to evaluate coronary flow reserve, such as Doppler-tip catheters5–7 and digital subtraction angiography,8,9 are based on the measurement of relative changes in coronary blood flow before (baseline flow) and after maximal vasodilation. Despite the recognized validity of these approaches, the lack of absolute flow quantification does not allow flow measurements before vasodilation, i.e., the denominator of coronary reserve calculation, which is known to vary with changes in hemodynamics and metabolic state of the heart. In addition, the inability to take into account collateral perfusion as well as the mass of perfused territory prevents correct assessment of the nutrient flow to myocardial regions supplied by the stenosed vessel.2

In clinical practice, it is generally accepted that the ability to increase coronary flow implies a normal perfusion at rest, although experimental data demonstrate the persistence of a transmural vasodilator reserve in the face of depressed resting perfusion.4,10–12 Although patients with coronary artery disease may show hypoperfused segments basally in the absence of myocardial infarction,13,14 no information is available on the presence and extent of vasodilator capacity in these areas. Techniques able to accurately assess regional...
myocardial perfusion at rest and during maximal vasodilation can clarify this aspect.

Quantification of regional myocardial blood flow and assessment of coronary flow reserve are feasible today with positron emission tomography. Regional distribution of either $^{18}$O-labeled water$^{15}$ or $[^{15}N]$ammonia$^{16}$ reflects myocardial perfusion in absolute terms, although technical problems and biological characteristics intrinsic to these tracers limit the accuracy of these measurements.

Application of microsphere technique in humans in association with positron emission tomography represents, at the moment, the most suitable approach to quantitatively assess regional myocardial blood flow.$^{17,18}$ Disadvantages of this technique are its invasiveness and the short half-life of radionuclides, which prevents easy connection between the catheterization laboratory and the scanning device. Furthermore, the reference arterial blood sampling, mandatory for quantification and comparison among different injected doses performed in different flow conditions, is not feasible in the tomography room.

$^{99m}$Tc-labeled human albumin microspheres have been safely used in humans with conventional gamma camera only for qualitative assessment of myocardial perfusion.$^{19,20}$ In fact, because of the intrinsic limitation of gamma-camera capabilities, the injected dose and the cardiac output cannot be measured with the same efficiency by which the myocardial uptake is counted.

Therefore, we developed a method that could allow measurement of regional coronary flow reserve with microsphere scintigraphy in the catheterization laboratory.

Purposes of this study were 1) to develop and validate a method able to measure, in the catheterization room, changes in myocardial perfusion using $^{99m}$Tc-labeled human albumin microspheres and a gamma detector imaging device and 2) to determine whether reductions in regional myocardial perfusion at rest can occur in humans before pharmacological reserve is exhausted.

**Methods**

**Patients**

The study population consisted of 20 patients referred to our institution either for indication of coronary revascularization by percutaneous transluminal coronary angioplasty (15 patients, group 1) or for evaluation of chest pain atypical for angina pectoris (five patients, group 2).

Group 1 patients (14 men, one woman; age, 55±7 years; range, 42–67 years) were selected for the study because of the following characteristics: 1) isolated, proximal left anterior descending coronary artery stenosis, 2) stable angina pectoris associated with objective signs of myocardial ischemia on effort or during dipyrindamole echocardiography test, 3) no clinical or ECG evidence of previous myocardial infarction, 4) no history of hypertension or left ventricular hypertrophy (septal or posterior wall ≤12 mm at echocardiography), 5) no conduction abnormalities, and 6) exclusion of other cardiac disorders.

Group 1 patients agreed to undergo percutaneous transluminal coronary angioplasty on the basis of the clinical and angiographic findings. The exercise ECG stress test was positive (ST segment depression ≥1.5 mm 0.08 second after the J-point) in 14 of 15 patients at the mean rate–pressure product of 20,395±6,671. The “high-dose” dipyrindamole echocardiography test$^{21}$ (0.84 mg/kg over 10 minutes) disclosed new dysynergies in seven of the 11 patients evaluated by this approach.

Six of the 11 patients had a normal basal echocardiogram, and five patients showed resting hypokinesis in the anteropapal segments.

Therapy with β-blockers (three patients) was discontinued at least 3 days before the study. All patients were on calcium entry blockers (nifedipine, 30–50 mg daily) the day before the procedure.

Group 2 patients with a chest pain syndrome (five men 51±2 years old; range, 47–53 years) were eligible for the study because of the negativity of the exercise stress test, normal regional and global left ventricular function, and angiographically normal coronary arteriograms. No subject had other cardiac disorders, arterial hypertension, lung disease, history of alcoholism, or cerebrovascular disease. None were under medical therapy.

With all patients, the nature of the study and the reason for using radiolabeled human albumin microspheres were explained; all patients were studied after informed consent was obtained; the study protocol was approved by the Institutional Review Board of the Niguarda Hospital.

**Microsphere Preparation**

The kits were provided in lyophilized sterile pyrogen-free vials containing 4,000,000 human albumin microspheres (Sferotec S, Sorin, Saluggia, Italy) to be diluted with 3 ml of saline containing 1.1–2.2 GBq (30–60 mCi) of $^{99m}$Tc-pertechnetate; after microsphere labeling, the vial was continuously shaken by means of a rotating mixer to prevent the occurrence of particle aggregation. For each lot, the distribution of the diameters was checked: 95% of the particles showed a diameter between 12 and 20 µm, and none were >50 µm. For each vial, the radiochemical purity of the tracer was checked, resulting in a bound fraction >98%.

**Coronary Angiography and Left Ventriculography**

Standard coronary angiography in multiple views was performed according to the Judkins technique. All patients were pretreated with oral aspirin (50–100 mg/day), intravenous heparin (10,000 units at the beginning of the procedure), and intracoronary nitroglycerin (120 µg). No patient received atropine before the study. If the stenosis was not well defined by standard views, supplementary “ad hoc” views were obtained. In any case, once the “best view” was established, an orthogonal view was performed. Coronary stenoses were measured by means of a semiquantitative method (caliper) by two independent observers evaluating the best projection and the orthogonal projection. Results were expressed as percent of the ratio between stenotic and normal portions of the vessels. Nine patients showed concentric lesions, and six showed eccentric lesions.

Left ventricular function was evaluated by monoplane contrast ventriculography (30° right anterior oblique view) in all patients. Regional wall motion was estimated by a quantitative computerized approach described elsewhere.$^{22}$ Briefly, the longitudinal axis of the left ventricle was divided into 10 sectors defining 20 slices (10 along the anterior and 10 along the inferopos-
terior walls). The percent systolic reduction in the area of each of these slices was calculated; values < 2 SD from the mean reference values of a control population were considered abnormal.

**Study Protocol**

At the end of coronary angiography, a 7F sheath was positioned in the left femoral artery and a 6F pigtail catheter was advanced into the left ventricle and placed in the apex. A 50-cm Vigon tube (1 ml) was connected to the side arm of the sheath to withdraw arterial blood by a peristaltic pump (P-1, Pharmacia, Sweden). Thereafter, through an 8F guide catheter advanced via the right femoral artery sheath into the left coronary artery, a 3F angioplasty catheter was introduced into the left anterior descending coronary artery 1 cm proximal to the stenosis in group 1 patients. In group 2, a 3F infusion catheter was placed 2 cm below the origin of the left anterior descending coronary artery. When catheters were in place, a small-field (20-cm) mobile gamma camera (Aper 210M, Elscint, Israel) was positioned over the patient’s chest, using the 70° left anterior oblique projection. This projection allows good separation between the anterior and the posteriorinferior segments of the left ventricle, because the two areas are viewed tangentially and are well separated by the left ventricular cavity.

The pigtail catheter was then filled with 0.6 ml of sterile saline containing approximately 0.8 million microspheres labeled with 259 MBq (7 mCi) of $^{99m}$Tc$	ext{per-}$technetate. The arterial blood sampling was started 15 seconds before tracer injection by switching on the peristaltic pump set to withdraw at 6 ml/min for 3 minutes. All blood (18 ml) was collected into a 20-ml heparinized syringe connected to the peristaltic pump by a silicon tube. Furthermore, a 15-second dynamic acquisition with the gamma camera was started (framing rate, 25 frames per second; matrix size, 32×32; zooming factor, 1; energy peak, 140 keV; energy window ±10%) a few seconds before the pigtail catheter was vigorously flushed with 5 ml of normal saline. Three minutes after tracer injection, a “static” acquisition lasting 300 seconds began (matrix size, 128×128; zooming factor, 1); a minimum of 400,000 counts was always collected in the whole field of view.

Tubes used for blood sampling were carefully washed, and the pigtail catheter was again filled with 0.8 ml of sterile saline containing approximately 1 million microspheres labeled with 333 MBq (9 mCi) of $^{99m}$Tc$	ext{per-}$technetate. Immediately after, a bolus of 10–12 mg of papaverine (5–6 ml) was injected into the left anterior descending coronary artery, and the whole procedure was repeated, injecting the microspheres into the left ventricular cavity 30 seconds after the end of papaverine injection.

Heart rate, three precordial ECG leads, and left ventricular pressure were recorded throughout all procedures. During the study, movements of the patient were carefully avoided to ensure the geometric constancy of radioactivity measurements. Furthermore, venous blood samples were taken during the acquisition to assess the amount of free $^{99m}$Tc in the blood. The entire procedure usually lasted no more than 40 minutes.

A schematic representation of the study protocol is depicted in Figure 1.

**Analysis of the Input Function**

Generally, quantification of blood flow with perfusion tracers implies measurement of the radioactivity concentrations in the arterial blood. Although correct measurements of radioactivity concentrations in blood with a planar imaging device are difficult to achieve, it is possible to calculate the ratio between the two input functions by measuring the activity in a constant volume, provided that the constancy of the geometric relation between the structures under study and the detector is maintained. This ratio can then be used for the calibration of two different tracer injections in two different conditions.

The theoretical and mathematical bases for the input function calculation are extensively explained in the “Appendix.” Briefly, because of their diameter (12–20 μm), microspheres are trapped in each tissue before the capillary network. The amount of labeled microspheres (myocardial uptake, Mup) that arrive and then are trapped in the myocardium is

$$Mup = CBF \times MCa \times t$$  \hspace{1cm} (1)

where CBF is myocardial blood flow and MCa is the microsphere concentration in the arterial blood during time t.

A planar imaging device such as the mobile gamma camera does not allow measurement of the tracer concentration in the blood; instead, it is possible to measure the radioactivity (and then the amount of microspheres) in a district of unknown dimensions. If one looks at a constant volume, positioning a region of interest at the edge of the thoracic aorta, changes in the radioactivity detected can be considered representative of changes in the radioactivity concentration. Despite the variability of aortic size in different patients, it seems correct to assume that its diameter will not change in the same patient in a period of a few minutes; accordingly, the curve of radioactivity (Maa) in such a region can be considered to be linearly related to the curve of the radioactivity concentration by a factor K that remains constant in the same patient in a short period of time and depends on the aortic diameter and the thoracic attenuation of each patient. Then

$$CBF = \frac{Mup}{KMAa \times t}$$  \hspace{1cm} (2)

Using a bolus injection, Equation 2 must be rewritten as

$$CBF = \frac{Mup}{\int_0^t MAa(t) \times dt}$$  \hspace{1cm} (3)

where Aa is the radioactivity (counts per second) detected under the region of interest in the aorta.

Although CBF cannot be quantified, the percent changes of these variables can be measured; in fact, in the case of double tracer injection,

$$\frac{CBF_2}{CBF_1} = \frac{\int_0^t MAa_2(t) \times dt}{\int_0^t MAa_1(t) \times dt}$$  \hspace{1cm} (4)
To calculate the ratio between the two input functions, a rectangular region of interest was drawn at the edge of the thoracic aorta after all frames were grouped, the alignment of this region in the second injection was checked, and the background was subtracted using the first 3 seconds of the acquisition as a mask. The computer was asked to plot the time–activity curve under this region from the original sequence of frames for both microsphere injections, the peak of radioactivity was identified, and the experimental points were fitted by a gamma-variate function by the least-squares method from the appearance of the radioactivity up to 0.6–1 second after the peak; with these limits, the fit was always excellent ($\chi^2$ value, 0.07±0.04). Then the ratio between the two input functions was calculated as the ratio between the integral of the gamma-variate function of each time–activity curve (Figure 2). To verify the reliability of this approach, the ratio of the two input functions was checked against the ratio between the radioactivity of the two arterial blood samples collected at the time of tracer injection.

A reference arterial blood sample was placed in vials (2 ml each) and counted in a well counter. After correction for radioactivity decay, the ratio between the two input functions (papaverine/basal) was calculated.

**Calculation of Regional Blood Flow Changes**

Because microspheres labeled with the same radioisotope were used in both injections, the two static images were subtracted to visualize the blood flow distribution in the second condition according to the formula true image 2 equals raw image 2 minus image 1.

The epicardial left ventricular borders were manually outlined on both frames, and the distribution of radioactivity in the myocardial wall was plotted in “circumferential profiles” according to previously described methods; briefly, the centroid of the left ventricle was automatically identified, and 60 radii were explored clockwise through 360°, starting ~180° apart from the apex, corresponding to the posterobasal segment. Sectors (36°) corresponding to the valvular planes were not considered. The computer was asked to identify the maximal activity in five consecutive pixels for each radius and to plot this value against its position. The two histograms were then smoothed by the running average method and divided for the respective input function value to calibrate for the differences in the injected dose and the cardiac output. The reliability of this procedure was checked by calculating the reproducibility of two measures of myocardial perfusion in the absence of changes in myocardial blood flow. To this purpose, three additional patients who underwent coronary angiography because of suspected coronary artery disease were studied by two consecutive injections of radioactive microspheres performed in resting conditions.

The effect of papaverine was characterized as 1) mean value of coronary reserve (calculated as the ratio between the areas of the histogram after papaverine and at control); 2) the maximal coronary reserve (maximal ratio between flow after papaverine and control flow); 3) site and extension of vasodilation; 4) site of maximal drug effect; and 5) mean and maximal changes in total coronary resistance (calculated as the ratio of papaverine to basal mean arterial pressure divided by the mean or maximal coronary flow reserve, respectively).
Evaluation of Resting Myocardial Perfusion

With such an approach, no absolute measurement of resting myocardial blood flow can be performed. Nevertheless, regional reduction of perfusion can be identified by the presence of abnormal inhomogeneities of radioactivity. To evaluate the presence of resting perfusion defects, the circumferential profiles obtained in all patients were expressed in percent values of the maximum, then a normalcy histogram and its SD were obtained from the five normal subjects of group 2. The profiles were divided clockwise into 20 (18°) sectors. Sectors 2–10 and 11–19 were assigned to the distribution territory of circumflex/right coronary artery and left anterior descending coronary artery, respectively. Sectors 1 and 20 (valvular planes) were not considered. The profiles of group 1 patients were then analyzed: a percent activity below the normalcy values minus 2 SD was considered abnormal, according to the standard protocol used for quantitative analysis of thallium scans.23

Statistical Analysis

Data are expressed as mean±SD. Fitting of the primary curve by the gamma-variate function was assessed by $\chi^2$ analysis. Comparison among the input functions calculated by the reference sample technique and by the gamma-camera primary curves was performed by measuring the standard error of estimate (SEE). Intergroup comparison of mean and maximal increase of myocardial blood flow during papaverine was evaluated by two-way ANOVA. Differences were considered significant at $p<0.05$.

Results

Clinical and Hemodynamic Findings

No patient experienced side effects during or after the injection of labeled microspheres in control conditions. The continuous ECG and hemodynamic monitoring did not show changes in heart rate, ST segment, or left ventricular systolic and end-diastolic pressures. During papaverine injection, two patients complained of chest pain, and eight showed transient T wave inversion (all in group 1). A prolonged QT interval during papaverine with respect to baseline values (430±60 versus 370±20 msec, respectively; $p<0.01$) was observed in 11 of 15 patients of group 1. No patient

<table>
<thead>
<tr>
<th>Group 1, normal subjects (n=5)</th>
<th>Group 2, LAD stenosis (n=15)</th>
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<tr>
<td>Heart rate (bpm)</td>
<td>LVSP (mm Hg)</td>
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<tr>
<td>Basal</td>
<td>Pap</td>
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<td>72±5</td>
<td>72±6</td>
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<td>71±12</td>
<td>71±14</td>
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LAD, left anterior descending coronary artery; bpm, beats per minute; LVSP, left ventricular systolic pressure; LVEDP, left ventricular end-diastolic pressure; LVEF, basal left ventricular ejection fraction; Pap, papaverine.
developed arrhythmias during intracoronary drug administration. Heart rate and left ventricular systolic and end-diastolic pressures were not significantly different between the two groups and did not show significant changes during papaverine injection. Basal left ventricular ejection fraction was not significantly different between the two groups (Table 1). In group 1, anterior or apical hypokinesis was detected in eight patients by the quantitative angiographic analysis.

**Assessment of Validity of the Method**

**Input function.** The reliability of the input function ratio, calculated from the gamma-camera primary curves, was evaluated by comparison with the "gold standard" reference arterial sample technique. A total of 46 tracer injections were performed, which provided 23 points for the statistical evaluation. The ratio between the two input functions calculated from the time–activity curves agreed with the ratio obtained by means of the arterial samples, showing an SEE of 9%.

From each of the 2-ml vials of the arterial samples, >200,000 counts · min⁻¹ · ml⁻¹ were always collected. The venous samples always showed negligible radioactivity (<3,000 counts · min⁻¹ · ml⁻¹).

**Reproducibility.** The reproducibility of perfusion measurements (i.e., microsphere arterial input function and myocardial uptake) were evaluated in the three patients in whom microspheres were injected twice in control conditions. The rate–pressure products as well as the mean transit time (see "Appendix") of the microspheres in the aorta were superimposed during the two injections. Analysis of 150 image points in the three patients showed a linear relation between the two acquisitions in the evaluation of regional perfusion distribution (Figure 3); the SEE was 6%.

**Regional Myocardial Perfusion at Rest**

According to the normalcy distribution of regional myocardial blood flow at rest assessed in group 2 (Table 2), six patients of group 1 showed homogeneous perfusion (group 1A), whereas the other nine showed a significant reduction of the radioactivity values in the anteroseptal walls (group 1B). In group 1B, the mean extension of the perfusion defects at rest was 144±52°.

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**Table 2.** Circumferential Profiles of Blood Flow Distribution in Five Normal Subjects: Percent Distribution

<table>
<thead>
<tr>
<th>Sector</th>
<th>Case No.</th>
<th>Percent Distribution %</th>
<th>Mean</th>
<th>SD</th>
<th>CV (%)</th>
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<td>20</td>
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<td>CV (%)</td>
<td>5</td>
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CV, coefficient of variation. Sectors 2–9 represent inferoposterior wall; sectors 10–19 apical and anterior segments.
the mean severity, evaluated as the ratio between the mean percent activity of the hypoperfused areas and the mean percent activity minus 2 SD of the same areas in normal subjects was 0.83±0.8. Two defects were located at the apical segment, four at the anterior wall, and three at the anterior and apical walls. Thus, according to the distribution of regional myocardial blood flow in control group 2, 60% of patients with stenosis of the left anterior descending coronary artery undergoing coronary angioplasty without clinical and ECG evidence of previous myocardial infarction showed perfusion defects by microsphere scintigraphy in resting conditions.

Regional wall motion at contrast ventriculography was abnormal in two of six and six of nine patients of groups 1A and 1B, respectively. Hypoperfused segments showed a significantly lower wall motion index than normoperfused segments (56±18% versus 66±21%; p<0.01). Echocardiography (11 patients) and left ventriculography agreed in all but one patient, who showed localized apical hypokinesia at angiography and normal function at echocardiographic evaluation. All five patients with resting wall motion abnormalities at echocardiography had perfusion defects in the anterolateral walls. The hemodynamic findings in subgroups 1A and 1B are reported in Table 3.

Coronary Reserve

In control group 2, the mean and maximal increases of myocardial blood flow during papaverine were 3.2±0.3 and 3.8±0.2 units, respectively. The horizontal extension of increased flow was 175±22°, and the location of peak flow was at 270±15°, i.e., in the midproximal portion of the anterior wall (Figure 4). Mean and maximal coronary resistance were reduced to 29±20% and 25±2% of control value, respectively.

In patients of group 1, the values of mean and maximal coronary reserve were 1.28±0.13 (p<0.0001 versus group 2) and 1.51±0.27 units (p<0.0001 versus group 2), respectively. The horizontal extension of the papaverine effect was 147±45° (p=NS versus group 2), and the location of the peak flow was markedly variable. Mean and maximal coronary resistance were reduced to 78±11% and 67±13% of control, respectively.

Relation Between Resting Perfusion and Regional Coronary Reserve

In all nine patients of group 1B who showed perfusion defects at rest in the territory of the left anterior descending coronary artery, papaverine induced an increase in myocardial blood flow to the hypoperfused region (maximal coronary reserve, 1.57±0.31 units). The mean and maximal coronary reserve were similar in the two subgroups 1A and 1B (1.24±0.13 versus 1.30±0.13, p=NS and 1.44±0.16 versus 1.57±0.31, p=NS, respectively). Mean and maximal reduction in total coronary resistance were not statistically different in the two subgroups (80±12% versus 77±11%, p=NS and 70±12% versus 65±15%, p=NS, respectively). Furthermore, the horizontal extension of the increased blood flow during papaverine was also similar (155±50° versus 141±61°, p=NS). Resting myocardial perfusion and coronary reserve in subgroups 1A and 1B are depicted in Table 4. Figures 5 and 6 show two typical examples of microsphere scintigraphy at rest and after papaverine in one patient with resting regional hypoperfusion defect and in one with normal perfusion.

Perfusion of the Normally Supplied Regions at Rest and During Papaverine

In all patients and in control subjects, the highest myocardial radioactivity at rest was observed in the inferior and posterior walls. In particular, the highest counts were collected in the region of the posterior papillary muscle. In all cases, the 70° left anterior
oblique projection used in this study allowed a good spatial separation between the inferior wall and the subdiaphragmatic radioactivity. In the postpapaverine images, the radioactivity of the posteroinferior walls was quantitatively similar to that obtained in control conditions, demonstrating the reliability of the approach and the absence of a spillover effect of papaverine in the territories not supplied by the left anterior descending coronary artery.

**Discussion**

Our results indicate that, in patients with stable angina pectoris and critical coronary stenosis, regional myocardial perfusion at rest is reduced in 60% of cases,

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**TABLE 4. Coronary Reserve and Resting Perfusion in the 15 Patients With LAD Stenosis**

<table>
<thead>
<tr>
<th>Patient</th>
<th>CR Pap basal flow Mean</th>
<th>Max</th>
<th>%ΔCRI Mean</th>
<th>Max</th>
<th>Vasodilated sectors (degrees)</th>
<th>Site of max vasodilation (degrees)</th>
<th>% LAD coronary narrowing</th>
<th>Resting perfusion defect</th>
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<td>80±12</td>
<td>70±12</td>
<td>155±50</td>
<td>265±40</td>
<td>78±9</td>
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LAD, left anterior descending coronary artery; CR, coronary reserve; %ΔCRI, percent decrease in total coronary resistance after papaverine; max, maximum; pap, papaverine.
despite the persistence of papaverine-recruitable vasodilator reserve. The coronary flow reserve, measured by the microsphere technique proposed in this study, was similarly impaired in patients with or without reduced perfusion in the myocardial territory supplied by the left anterior descending coronary artery.

These findings confirm the experimental evidence of a persistent coronary flow reserve in the face of functionally depressed perfusion at rest.10-12

Thus, the presence of vasodilator reserve in hypoperfused areas at rest and the similar magnitude of decrement in resistance distally to the critical stenosis, irrespective of presence or absence of resting perfusion abnormalities, suggest that other mechanisms besides the severity of stenosis affect coronary resistance and cause a reduction in resting flow despite the presence of recruitable flow reserve.

Pathophysiological Implications

Several clinical studies have reported reduced levels of resting myocardial perfusion distal to severe coronary stenoses in the absence of subjective or objective evidence of either acute myocardial ischemia or necrosis.13,14,23 Local reductions in thallium exchange not associated with clinical evidence of myocardial ischemia and presumably representing hypoperfusion of viable myocardium have been reported by several groups.26,27 These authors showed that a transient defect in thallium uptake may occur in the regions supplied by severely stenotic artery despite the presence of viable myocardium, as demonstrated by the normalization of scintigraphic pattern late after injection26 and after revascularization.27 The present findings are consistent with the concept of a chronic reduction in resting flow at reduced coronary pressure, with flow and oxygen supply being able to increase moderately during periods of increasing demand. Arani et al13 demonstrated a reduction in coronary flow per unit weight under resting conditions in collateral-dependent myocardium of patients with occlusion of the left anterior descending coronary artery by the helium desaturation technique. Nichols et al14 using the 133Xe clearance technique, showed that regional myocardial blood flow distal to a stenotic lesion was reduced at control in all eight patients with minimum area of stenosis <0.8 mm².

These clinical works were not addressed to the evaluation of coronary reserve in areas with reduced resting flow; our study confirms the experimental data4,10-12 and extends the findings obtained to humans with critical coronary lesions.

Note, however, that despite the evidence of a persistent vasodilation in the nine patients with anterior wall hypoperfusion in resting conditions, coronary reserve was markedly (maximal increase in flow, 57%) and consistently (SD from the mean, 33%) impaired in all patients. This finding indicates that the method correctly assessed the functional severity of coronary stenosis in a selected group of patients with stable angina pectoris who underwent coronary angioplasty because of moderately low threshold of ischemia during exercise and/or positive dipyridamole echocardiography test.

The spatial resolution of the technique used in our study did not allow definition of transmural compartmentalization of coronary flow reserve, i.e., the occurrence of epicardial or transmural vasodilation. This phenomenon has been described by Gallagher et al,28 who created a left circumflex stenosis able to abolish the reactive hyperemia while maintaining the resting flow at prestenosis level and documented no increase in the endocardial
flow associated with an increase in the epicardial perfusion during dipyridamole infusion.

However, the decline in the poststenotic pressure consequent to the increased flow after vasodilation could result in apparent inability of flow to increase in the endocardial layers despite a residual endocardial reserve. This hypothesis seems to be confirmed by the findings in animal experiments with coronary perfusion at a constant pressure. Using this experimental model, Canty and Klocke\textsuperscript{10} and Aversano and Becker\textsuperscript{11} showed that regional myocardial blood flow significantly decreased transmurally, despite a residual vasodilating capability both in the subendocardial and epicardial layers. These findings suggest that a residual vasodilating capability, although probably greater in the subepicardium than in the subendocardium, might be preserved transmurally.

The mechanisms underlying a chronic reduction in coronary flow in the presence of a vasodilator reserve are not yet understood. Reduced regional myocardial contractility without concomitant regional myocardial ischemia has been experimentally and clinically documented\textsuperscript{13,28}; moreover, a normalization of the metabolic pattern associated with persistent wall motion abnormality has been demonstrated during prolonged flow reduction.\textsuperscript{29} Accordingly, a possible explanation of this phenomenon might be a downregulation of oxygen demand by a myocardium supplied by a severely stenotic vessel.\textsuperscript{30}

"Chronic" hibernating myocardium or recurrent stunning in critically perfused segments may, in turn, result in reduced resting blood flow; in fact, impaired left ventricular contractility lowers myocardial metabolic needs and resets blood flow to lower levels.\textsuperscript{31}

In the acute experimental model, Aversano and Becker\textsuperscript{11} showed a residual coronary reserve in the face of reduced resting myocardial perfusion and contractility, indicating the presence of active ischemia. In our study, wall motion and perfusion data were sequentially collected during the cardiac catheterization procedure using comparable projections (30° right anterior oblique and 70° left anterior oblique view, respectively). Six of the nine patients with resting hypoperfusion in the anteropapillary segments showed hypokinesis in the corresponding regions. Since an experimental model of "chronic" hibernation is still lacking, it cannot be stated whether reductions in both perfusion and contractility were associated with the metabolic fingerprints of active ischemia or to a downregulation of normal metabolic activity.

The findings of the present study indicate that in patients without previous myocardial infarction who are candidates for coronary angioplasty because of severe flow-limiting coronary lesions, hibernating myocardium can frequently be observed and microsphere scintigraphy is able to detect resting perfusion abnormalities.

Moreover, the observation of a residual vasodilating capability in hypoperfused dysfunctional areas indicates that hibernating myocardium still preserves coronary vascular tone.

Potential Methodological Problems

The data presented in this report demonstrate the feasibility of estimating myocardial perfusion reserve in humans by means of \textsuperscript{99m}Tc-labeled human albumin microspheres and a simple conceptual approach to the measurement of the time–activity curves in the aortic arc.

This method does not allow absolute measurement of myocardial blood flow, inasmuch as the factor $K$, which
correlates the integral of radioactivity concentration with the integral of total radioactivity, is unknown and depends on both the aortic volume sampled and the thoracic attenuation in each patient. Nevertheless, the assumption that this factor does not change in the time interval of a few minutes throughout the study seems reliable and is supported by the close agreement with the gold standard sampling reference technique.34

The method proposed in this study makes possible the calculation of changes in regional myocardial perfusion occurring after any stimulus. The simultaneous evaluation of coronary reserve in territories supplied by normal and stenotic vessels allows calculation of relative flow reserve,32 i.e., the maximal flow in the stenotic artery normalized by maximal flow in the normal artery. This normalization makes the measurement of coronary reserve independent of physiological variables unrelated to the stenosis geometry (such as aortic pressure, heart rate, metabolic demand, etc.) that are known to affect the magnitude of this parameter.32

In addition, the imaging approach more accurately describes the presence and location of perfusion defects and the inhomogeneity of coronary flow reserve within the region supplied by the same vessel. As a matter of fact, obvious differences in coronary reserve in the territory supplied by the left anterior descending coronary artery were observed in most of the patients studied, providing further support to the existence of mechanisms (local?) other than the stenosis that may affect resting perfusion and vasodilator capacity. Our study does not provide information on the site of vasodilation induced by papaverine. On the basis of previous reports,39 it is evident that papaverine does not induce changes in epicardial artery cross-sectional area and that its major effect is at the microcirculation level.

In the present study, we were aware of the partial volume effect, which can cause underestimation of regional tracer concentrations in the presence of wall motion abnormalities.34 In fact, dyssynergy induced by subendocardial ischemia consequent to papaverine administration might underestimate, according to the partial volume effect, the extent of coronary reserve. However, this problem should not have affected our measurements, because 1) no patient showed abnormal increase of left ventricular end-diastolic pressure during papaverine injection; 2) ECG abnormalities never lasted more than 1 minute, the T wave inversion (never ST segment depression) probably reflecting the electrophysiological rather than the ischemic effect of papaverine; 3) the static acquisition started 3 minutes later, when all the monitored parameters were completely at baseline; and 4) no significant differences in coronary reserve between patients with or without T wave inversion during papaverine injection were found.

Another potential methodological problem deals with the magnitude of background count subtraction in papaverine images, which might have affected quantification of the "true" postpapaverine count rates. The average ratio of myocardial activity between papaverine and control images was about 2.5:1. This magnitude of background should have ensured a statistically correct subtraction of the two images, mostly in the territory supplied by the left anterior descending coronary artery. Actually, a high background should have caused underestimation, not overestimation, of the coronary reserve.

Furthermore, the goodness of the method seems demonstrated by the reproducibility of our measurements in the three additional patients in whom microspheres were injected twice in control conditions and by the constancy of radioactivity in the inferior wall in the postpapaverine images with respect to the control conditions.

Comparison With Other Methods

With the attempt to assess the maximal vasodilator capacity in humans, Doppler flow velocity5–7 and digital subtraction angiography8,9 have been proposed and clinically applied. In particular, intracoronary Doppler technique, associated with either intracoronary adenosine or papaverine administration,15 offers the advantage of arterial selectivity and a high temporal resolution; moreover, it has been validated more extensively than any other method now in use and represents a reliable tool to assess the physiological impact of a coronary stenosis. However, these selective methods characterize native but not total flow (native plus collateral flow); furthermore, the inability of Doppler technique to appreciate differences between territories in the prevasodilation flow and to take into account physiological variables affecting coronary reserve may represent important limitations in the assessment of maximal flow capacity and could explain the reason for the large spectrum of coronary reserve values observed in ischemic patients undergoing coronary angioplasty.36

The microsphere imaging approach overcomes these limitations, but radioactive particles need to be repeatedly injected into the left ventricle to measure coronary flow reserve; as a consequence, no monitoring capability at high temporal resolution is available.

The ideal tool to overcome these problems and, in general, to measure the ability of the myocardium to increase its perfusion should be represented, in theory, by positron emission tomography, inasmuch as this approach couples the ability to precisely measure tissue tracer concentrations with the attractiveness of a non-invasive approach.15,16,37,38 Unfortunately, this goal is still to be achieved in clinical practice because of concerns about the cost effectiveness of this expensive technique and the potential competition with other imaging technologies in the cardiology field.

Measurement of regional perfusion reserve by use of [18O]H2O and positron emission tomography has been performed by Walsh et al.,38 who evaluated the dipyridamole effect in poststenotic areas of seven ischemic patients undergoing coronary angioplasty. No patient of their series showed resting hyperperfusion; unexpectedly, the level of resting flow in the jeopardized territory was higher than that observed in control areas or in the myocardium of normal subjects in six of the seven patients. Nevertheless, the values of perfusion reserve were comparable to those obtained in our population.

Limitations of the Study

As already mentioned, the invasiveness, the limited number of measurements achievable, and the lack of absolute flow quantification represent the major limitations of the method proposed in this study. Radioactive particles injected into the systemic circulation have been demonstrated to be safe up to 3 million to 4 million
microspheres\textsuperscript{18,20,24}; therefore, a split-dose approach may permit three or four evaluations of myocardial perfusion at different flow conditions: this appears to be the sampling limit of the microsphere technique. Furthermore, a mobile gamma camera is necessary in the catheterization laboratory to ensure correct subtraction among images obtained by different microsphere injections. Application of this method should be directed toward the study of physiology and pathophysiology of coronary circulation in humans, a goal that appears feasible in a clinical environment (the catheterization laboratory) in which hemodynamics, coronary angiography, and flow data can be collected simultaneously.

Finally, although they were carefully selected, we cannot exclude in some of our patients the presence of subendocardial necrosis or patchy fibrosis that might have impaired resting blood flow and the response to vasodilators. Eight patients showed mild hypokinesis of the anterior or apical segments at contrast ventriculography. Whether wall motion abnormalities would always be the consequence of hibernation or of silent nontransmural infarction cannot be solved with the available data.

Clinical Implications

First, this study indicates that the microsphere approach for basic study of coronary circulation in the cardiac catheterization laboratory is feasible and safe; it provides regional information on coronary blood flow and reserve not available with Doppler-tip catheters, digital subtraction angiography, or coronary sinus thermodilution. The problem of safety of this technique is relevant. In our institute, we had direct experience with more than 300 patients studied with the microspheres injected into the left ventricle. These studies included patients with acute or recent myocardial infarction, transient ischemia, or dilated cardiomyopathy; no adverse reactions related to the systemic effect of these particles were observed in any. Selwyn et al\textsuperscript{18} showed by positron emission tomography that, after left ventricular injection of human albumin microspheres in patients with previous myocardial infarction, brain and kidney perfusion was homogeneous and urine and blood parameters were unaffected. Perfusion brain scans have been performed in more than 290 patients with neurological disorders\textsuperscript{39-44} evaluated after intracarotid injection of \textsuperscript{99m}Tc human albumin microspheres (particle size, 5–30 μm). No untoward neurological or systemic effects were observed in all studies. Only Verhas et al\textsuperscript{42} reported a 7% morbidity among patients with brain infarct; this value was not different from that observed during arteriography alone (8.5%). Burdine et al\textsuperscript{45} performed histological studies in dogs after carotid and renal artery injection of human albumin microspheres (up to 10 times our injected dose). The authors did not observe ischemic, hemorrhagic, or necrotic lesions; granuloma or focal gliosis, which were not attributed to the direct or indirect effect of microspheres, were described in two of the 17 dogs with intracarotid tracer injection. The paper provided no description of the methodology used for the histological examination and no clear information on neurological damage (microfoci of recent hemorrhage) that occurred in four of the 28 control dogs in which microspheres were injected into a forelimb vein. Briz-Kanafani and Lagos-Costantino\textsuperscript{46} were able to evaluate histologically the brains of 12 patients with cerebrovascular disorders who died during the month in which \textsuperscript{131}I–albumin macroaggregates were injected into the carotid artery for diagnostic brain scanning. Microscopic studies of the brain did not reveal any pericapillary lesion that could be attributed to the intravascular injection of the macroaggregates.

Therefore, the amount of clinical data collected in this field and the available histological evaluations adequately exclude the possibility that the central nervous system might potentially be damaged after microvascular occlusion by microspheres. This point appears satisfied especially when small microspheres (10–20 μm in diameter), carefully checked, are chosen.

The second point is dealing with the evidence of frequent perfusion defects at rest in patients with critical coronary stenosis and no previous myocardial infarction (nine of 15 patients, or 60%), which raises questions about the conventional interpretation of myocardial scintigrams.

\textsuperscript{99m}Tc-hexakis(2-methoxy-2-isobutyl isonitrite), or sestamibi, recently proposed for clinical use,\textsuperscript{46} is a liquid deposit flow tracer that behaves, to some extent, like microspheres. Like microspheres, it is rapidly cleared from blood and presents a negligible myocardial washout. We found a high incidence of sestamibi perfusion defects at rest in 42 of the 81 patients (52%) with coronary artery disease and no previous myocardial infarction enrolled in a multicenter study\textsuperscript{47}; this identified a subset of patients with more severe impairment of coronary flow reserve assessed by dipyridamole echocardiography test.\textsuperscript{48} Our findings suggest that resting hypoperfusion at microsphere scintigraphy does not imply the presence of necrotic tissue; therefore, fixed perfusion defects assessed by sestamibi scintigraphy in patients with severe coronary lesions should be explained cautiously. The evidence of residual coronary reserve in hypoperfused segments at rest, as assessed by quantitative methods (such as positron emission tomography),\textsuperscript{49} might support diagnosis of viable myocardium in these areas.

Finally, the evidence of a "chronic" reduction in resting blood flow in the face of residual pharmacological vasodilator reserve indicates that reductions in regional myocardial perfusion cannot always be taken to indicate exhaustion of vasodilation in the distal vasculature. Mechanisms independent of the severity of coronary stenosis underlying this behavior in patients with ischemic heart disease remain to be elucidated.

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Appendix

The mathematical basis for blood flow measurements with microspheres was documented by Sapirstein\textsuperscript{50} in 1956. The Sapirstein principle states that

\[ D/CO = Mup/CBF \]  

(5)
where D is the injected dose, CO the cardiac output, Mup the myocardial uptake, and CBF the coronary blood flow.

In the 1970s, Heymann and coworkers proposed a simplified method for measuring blood flow with radiolabeled microspheres by using an arterial sampling as an artificial "parallel" organ, applying the same mathematical formulation:

\[ \frac{d}{dt} = Mup/CBF \]  

(6)

where d represents the collected activity by sampling arterial flow at the constant flow f. The accuracy and reliability of this method have been mathematically and experimentally validated, and to this day it is almost generally used for CBF measurement in the experimental setting.

According to the Hamilton principle, the CO can be calculated with a tracer that disappears from the intravascular space by the formula

\[ CO = TBV/MTT \]  

(7)

where TBV represents the total blood volume and MTT the mean transit time of the tracer in a district of the intravascular volume.

Assuming that TBV does not change during double tracer injection in the absence of hemorrhage or massive liquid infusion in the time interval of a few minutes (in this study it was 5–10 minutes), the changes in CO can be calculated from Equation 7:

\[ \frac{CO}{CO_0} = \frac{MTT_1}{MTT_2} \]  

(8)

If Equation 8 holds, then the changes in the CBF can be measured from Equation 5:

\[ CBF = COMup/D \]  

(9)

then

\[ \frac{CBF_2}{CBF_1} = \frac{Mup_2}{Mup_1} \times \frac{D_1}{D_2} \times \frac{CO_0}{CO_1} \]  

(10)

or

\[ \frac{CBF_2}{CBF_1} = \frac{Mup_2}{Mup_1} \times \frac{D_1}{D_2} \times \frac{CO_0}{CO_1} \]  

(11)

Thus, according to Equation 8,

\[ \frac{CBF_2}{CBF_1} = \frac{Mup_2}{Mup_1} \times \frac{D_1}{D_2} \times \frac{MTT_1}{MTT_2} \]  

(12)

Applying the classic Stewart formulation, MTT can be measured by gamma-variate fitting of the experimental time–activity curve obtained with a gamma camera on any constant volume of arterial tree after the bolus injection of microspheres in the left ventricle:

\[ MTT = \frac{\sum a(t) \cdot t}{\sum a(t)} \]  

(13)

where \( a(t) \) is the arterial activity at each time t; then Equation 12 can be rewritten

\[ \frac{CBF_2}{CBF_1} = \frac{Mup_2}{Mup_1} \times \frac{D_1}{D_2} \times \frac{\sum a_2(t) \cdot t}{\sum a_1(t)} \]  

(14)

Regional Mup can be easily calculated by means of a static acquisition with the same imaging device; by contrast, the measurement of actually injected D is not practically feasible by this approach.

To overcome this practical limitation, another theoretical approach was used, based on the law of conservation of mass, a principle used in the past by Kety in the measurement of cerebral blood flow from the washout curve of inert gases.

Because of their entrapment before the capillary network, the amount of microspheres (and then of radioactivity) taken up by the myocardium is

\[ Mup = CBF \times Ca \times t \]  

(15)

where Ca is the arterial concentration of labeled microspheres in the time t. Inasmuch as we used a bolus injection, Equation 15 must be rewritten

\[ Mup = CBF \int_0^t Ca(t) dt \]  

(16)

or

\[ CBF = \frac{Mup}{\int_0^t Ca(t) dt} \]  

(17)

This method does not imply the problematic measurement of the actual injected dose but presents two problems:

1) With a planar imaging device such as the mobile gamma camera, it is not possible to measure the radioactivity (and then microsphere) concentration in the arterial blood; instead it is allowable to measure the amount of radioactivity present in each time t in a district of unknown dimensions.

Assuming that the descending aorta does not change in diameter in the few minutes throughout the study, and maintaining the same geometry between the patient and the detector, the changes in radioactivity detected in a fixed region of interest can be considered linearly correlated with the changes in the radioactivity concentration by a factor K that remains constant throughout the study. Then

\[ CBF = \frac{Mup}{\int_0^t MAa(t) dt} \]  

(18)

where MAa is the radioactivity measured in the fixed region of interest in the descending aorta at each time t.

Such a formulation does not allow any measurement of blood flow, but it renders possible the calculation of changes in such a parameter; in fact, in the case of double tracer injection,

\[ \frac{CBF_2}{CBF_1} = \frac{Mup_2}{Mup_1} \times \frac{D_1}{D_2} \times \frac{\int_0^t MAa_2(t) dt}{\int_0^t MAa_1(t) dt} \]  

(19)

The integral \( \int_0^t MAa(t) dt \) is calculated by fitting the experimental data of activity in a region of the descending aorta obtained with a dynamic acquisition with a gamma-variate function and calculating its integral.

2) The second problem arises from the passage of the tracer first through the catheter then in the aorta under the same region of interest. To measure only the aortic arterial radioactivity without contamination by the catheter phase, it is necessary to plot the curve in an aortic region where the two compartments can be temporally separated, such as the edge of the descending thoracic aorta. A satisfactory temporal separation of the two curves was always obtained with this approach in the 46 input functions collected in this study.

Equation 19 seems quite similar to the more "classic" Equation 14; as a matter of fact, in such a formulation, the problematic measure of the actually injected dose does not
appear, owing to the different basic assumption: Whereas with the first approach we assume the constancy of total blood volume, with this method we must assume that the diameter of the descending aorta does not change in the few minutes of the study.

The reliability of this method was checked with the use of the gold standard reference Heymann24 technique: the ratio between the activities collected from the femoral arterial cannula setting the pump at a constant flow of 6 ml/min during the two microsphere injections was compared with the ratio between the two input functions; the SELL calculated from the regression analysis of the 23 points of this study was 9%. Although the Heymann procedure could be used in the evaluation of blood flow changes, the possibility of measuring the ratio between the two input functions by external counting allows a more practical study protocol in the catheterization room.

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