Myocardial Blood Flow Distribution in Patients With Ischemic Heart Disease or Dilated Cardiomyopathy Undergoing Heart Transplantation

Oberdan Parodi, MD; Renata De Maria, MD; Luigi Oltrona, MD; Roberto Testa, MD; Gianmario Sambuceti, MD; Alberto Roghi, MD; Mario Merli, MD; Luisella Belingheri; Roberto Accinni, ChD; Franco Spinelli, MD; Alessandro Pellegrini, MD; and Giorgio Baroldi, MD

Background. The present investigation was designed to obtain an absolute measurement of myocardial blood flow and of its transmural distribution in ischemic heart disease and idiopathic dilated cardiomyopathy and to provide a reference standard for cardiac imaging in nuclear cardiology.

Methods and Results. Regional myocardial blood flow and its transmural distribution were estimated by the reference microsphere method in eight patients with idiopathic dilated cardiomyopathy (n=4) or ischemic heart disease (n=4) during heart transplant procedure. Before aortic clamping, 99mTc-labeled human albumin microspheres were injected into the left atrium while arterial blood was sampled from the aorta at a constant rate. No complications were observed during or after the procedure. From the excised heart, myocardial slices for gamma camera imaging and well counting analysis were obtained. Myocardial blood flow was assessed by a well counter, correlated with the extent of fibrosis expressed as collagen per total tissue proteins obtained from 4-hydroxyproline and glycine as determined by high-performance liquid chromatography. Microsphere distribution, as seen by gamma camera images in a different slice, was correlated with the extent of fibrosis assessed by histological analysis of the same myocardial specimen. Mean transmural myocardial blood flow was 0.49±0.17 and 0.38±0.15 mL·min⁻¹·g⁻¹ in idiopathic dilated cardiomyopathy and ischemic heart disease, respectively (P<.01). Endocardial-to-epicardial flow ratio was lower in ischemic heart disease than in idiopathic dilated cardiomyopathy patients (0.99±0.33 versus 1.16±0.30, P<.05). Mean myocardial fibrosis was 9±6% in idiopathic dilated cardiomyopathy and 25±28% in ischemic heart disease. In both groups, no correlation was found between myocardial blood flow values and the extent of fibrosis. In ischemic heart disease, regional myocardial blood flow was not significantly affected by the severity of coronary stenosis (≤70% or >70%) either in the endocardium (0.44±0.24 versus 0.36±0.16 mL·min⁻¹·g⁻¹, P=NS) or in the epicardium (0.50±0.33 versus 0.38±0.33 mL·min⁻¹·g⁻¹, P=NS). By gamma camera imaging, transmural microsphere distribution appeared more homogeneous in idiopathic dilated cardiomyopathy than in ischemic heart disease (mean coefficient variation, 18% and 27%, respectively; P<.02); the severity of perfusion impairment did not correlate with the extent of fibrosis evaluated by histological criteria.

Conclusions. Heart transplant surgery offers a valuable model to assess absolute myocardial perfusion in human heart failure. Myocardial blood flow is markedly depressed in failing hearts of both ischemic heart disease and idiopathic dilated cardiomyopathy patients; a different transmural myocardial blood flow distribution is observed in ischemic heart disease than in idiopathic dilated cardiomyopathy, with prevalent endocardial perfusion in the latter but not the former condition. In patients with end-stage heart failure, myocardial blood flow appears to be similarly impaired in fibrotic and viable regions. Mechanisms other than myocardial fibrosis and coronary lesions appear to operate in determining myocardial blood flow impairment in heart failure. (Circulation 1993;88:509-522)

KEY WORDS • blood flow • myocardium • microspheres • heart disease • transplantation

Although numerous experimental and clinical studies have attempted to investigate and quantitate myocardial blood flow in human pathology, absolute measurement of perfusion and, in particular, its distribution within the myocardial layers remains an ambitious goal in clinical cardiology.
Imaging of the heart by means of nuclear techniques appears, at the moment, to be the most reliable method of assessing regional myocardial blood flow in cardiac disorders.

Inert gas washout techniques, such as $^{133}$Xe or hydrogen desaturation,\(^1\)\(^-\)\(^6\) and positron emission tomography (PET) in conjunction with positron-emitting flow tracers\(^7\)\(^-\)\(^8\) have been used to assess myocardial blood flow distribution in absolute terms. However, these techniques have limited capability in the assessment of regional tracer localization and are hampered by the intrinsic limitations of flow tracers used to measure blood flow distribution.

The most accurate measurement of regional myocardial blood flow can be achieved clinically with PET and $^{11}$C- or $^{68}$Ga-labeled human albumin microspheres.\(^9\)\(^-\)\(^11\) Application of the microsphere principle with PET in patients with previous myocardial infarction provided important pathophysiological information on regional myocardial blood flow in the necrotic and remote segments.\(^11\) However, the limited spatial resolution of the available instrumentation prevents the assessment of flow heterogeneity within the different cardiac walls. Furthermore, regional wall motion abnormalities or wall thinning in infarcted areas might produce obvious underestimates of myocardial activity and of the related myocardial blood flow values because of the partial volume effect.\(^12\)

Microspheres are totally extracted from circulation, and their tissue deposition is not dependent on metabolic condition. This flow tracer, labeled with $^{99m}$Tc, has been used extensively in patients since the 1970s, and its safety, when injected into the coronary circulation or the left ventricle,\(^13\)\(^-\)\(^18\) has been proved in hundreds of evaluated patients.

In the present study, our goal was to quantitate regional myocardial blood flow in the left and right ventricles and to evaluate the transmural distribution of blood flow in patients with advanced ischemic heart disease or idiopathic dilated cardiomyopathy.

To this purpose, the regional myocardial blood flow of patients with cardiac failure caused by ischemic heart disease or idiopathic dilated cardiomyopathy who were undergoing orthotopic heart transplantation was quantitated by the microsphere technique during the surgical procedure. This clinical model allows direct assay by well counter of tissue tracer radioactivity distribution within the heart as well as comparison among myocardial blood flow, histology, and biochemical markers of myocardial viability (noncollagen proteins) and fibrosis (collagen proteins) in the same specimen. Moreover, tissue tracer content was assessed by a gamma camera imaging device; this approach permits better visualization of the myocardial blood flow spatial distribution with respect to the well counter data and to obtain a more precise estimate of the perfusion defect extension in the entire myocardial slice.

Although in the past decade differentiation between idiopathic dilated cardiomyopathy and ischemic heart disease has been attempted with nuclear imaging techniques,\(^19\)\(^-\)\(^22\) the reliability of these methods is not clearly demonstrated. Gamma camera analysis of perfusion distribution in explanted hearts may provide new insights into the interpretation and differentiation of the two conditions through a scintigraphic approach.

In adopting this clinical model, regional myocardial blood flow and its transmural distribution were assessed not only regarding the composition of myocardial tissue (ie, normal, viable, fibrotic) but also as to flow behavior in a specific pathology (ie, idiopathic dilated cardiomyopathy) in a manner that is not reproducible in the experimental setting.

**Methods**

**Selection and Characterization of Patients**

Eight patients who underwent orthotopic heart transplantation for end-stage heart failure at the Cardiac Surgery Division of our institution between November 1990 and May 1991 are the subjects of this report. There were seven men and one woman (mean age, 43.7±16 years; range, 19 to 61 years). Four patients had idiopathic dilated cardiomyopathy as diagnosed from the finding of a dilated, hypocontractile left and/or right ventricle in the absence of other forms of cardiac disease. Four patients had chronic ischemic heart disease as documented either by a history of previous myocardial infarction or by the evidence of a more-than-50% luminal reduction in at least one major coronary artery branch at coronary angiography.

Clinical characteristics and preoperative treatment of all patients are shown in Table 1. Laboratory data were obtained a mean of 6.5±5 months before surgery (range, 1 to 13 months).

All patients showed severe impairment of ventricular function; mean cardiac index was 1.9±0.2 L·min$^{-1}$·m$^{-2}$, mean left ventricular ejection fraction was 0.23±0.06, mean pulmonary wedge pressure was 21±7 mm Hg, mean pulmonary artery pressure was 28±9 mm Hg, and mean pulmonary vascular resistance was 3.9±1.4 Wood units. Hemodynamic impairment was similar in idiopathic dilated cardiomyopathy and ischemic heart disease.

For all patients, the nature of the study and the reason for injecting radiolabeled human albumin microspheres were explained; all patients were studied after an informed consent was obtained. The study protocol was approved by the local Ethics Committee for Human Research.

**Microsphere Preparation**

The kits were provided in lyophilized sterile pyrogen-free vials containing 4 million human albumin microspheres (Sferotec S, Sorin, Saluggia, Italy) to be diluted with 3 mL of saline containing 259 MBq (7 mCi) of $^{99m}$Tc-pertechnetate; radioactive microspheres were shaken continuously by means of a rotating mixer to prevent particle aggregation. For each lot, the diameter distribution was checked; 95% of the particles had a diameter between 12 and 20 μm (mean size, 14 μm), and none were more than 50 μm. For each vial, the radiochemical purity of the tracer was checked, resulting in a bound fraction of more than 98%. The absorbed radiation dose to the heart with particles labeled with $^{99m}$Tc is based on an estimated absorbed fraction of 0.1 and heart volume according to MIRD.\(^23\) The dose of $^{99m}$Tc microspheres based on an effective half-life of 3.6 hours is approximately 570 mrad per mCi. The biological half-life of human albumin microspheres is 9 hours.
**Table 1. Clinical and Hemodynamic Findings in Eight Patients With Heart Failure Who Were Undergoing Transplantation**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (y)</th>
<th>Diagnosis</th>
<th>Clinical history</th>
<th>ECG</th>
<th>EF (%)</th>
<th>CI (L·min⁻¹·m⁻²)</th>
<th>PVRI (WU)</th>
<th>mPAP (mm Hg)</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>T.P.</td>
<td>37</td>
<td>IDC</td>
<td>Recent-onset heart failure</td>
<td>LVH</td>
<td>24</td>
<td>1.68</td>
<td>4.37</td>
<td>22</td>
<td>Digoxin, furosemide, captopril</td>
</tr>
<tr>
<td>L.A.</td>
<td>24</td>
<td>IDC</td>
<td>Low-output syndrome</td>
<td>LAH</td>
<td>27</td>
<td>2.08</td>
<td>5.77</td>
<td>42</td>
<td>Digoxin, furosemide, enalapril, enoximone</td>
</tr>
<tr>
<td>D.M.</td>
<td>19</td>
<td>IDC</td>
<td>Progressive heart failure</td>
<td>LAH</td>
<td>17</td>
<td>2.11</td>
<td>1.42</td>
<td>20</td>
<td>Digoxin, furosemide, enalapril, ibopamine</td>
</tr>
<tr>
<td>B.L.</td>
<td>61</td>
<td>IDC</td>
<td>Progressive heart failure</td>
<td>LBBB</td>
<td>17</td>
<td>1.62</td>
<td>4.91</td>
<td>20</td>
<td>Digoxin, furosemide, captopril, amiodarone</td>
</tr>
<tr>
<td>S.G.</td>
<td>56</td>
<td>IHD</td>
<td>Anterior MI and lateral MI</td>
<td>Anterior and inferior Q</td>
<td>20</td>
<td>2.14</td>
<td>4.67</td>
<td>34</td>
<td>Furosemide, captopril, nitrates, amiodarone, mexiletine</td>
</tr>
<tr>
<td>R.G.</td>
<td>60</td>
<td>IHD</td>
<td>Anterior MI</td>
<td>LAH, anterior Q</td>
<td>35</td>
<td>2.05</td>
<td>2.43</td>
<td>22</td>
<td>Digoxin, furosemide, captopril, nitrates</td>
</tr>
<tr>
<td>C.M.</td>
<td>40</td>
<td>IHD</td>
<td>Anterior MI</td>
<td>LAH, anterior Q</td>
<td>23</td>
<td>1.75</td>
<td>4.57</td>
<td>32</td>
<td>Digoxin, furosemide, captopril, amiodarone</td>
</tr>
<tr>
<td>P.L.</td>
<td>53</td>
<td>IHD</td>
<td>Progressive heart failure</td>
<td>LBBB</td>
<td>26</td>
<td>1.80</td>
<td>2.77</td>
<td>37</td>
<td>Digoxin, furosemide, captopril, amiodarone, enoximone</td>
</tr>
</tbody>
</table>

EF indicates left ventricular ejection fraction; CI, cardiac index; PVRI, pulmonary vascular resistance index in Wood units; mPAP, mean pulmonary artery pressure; IDC, idiopathic dilated cardiomyopathy; IHD, ischemic heart disease; MI, myocardial infarction; LVH, left ventricular hypertrophy; LBBB, left bundle branch block; and LAH, left anterior hemiblock.

**Study Protocol**

All patients were premedicated with 0.005 mg/kg im scopolamine and 0.1 mg/kg oral diazepam; anesthesia was induced with 0.5 mg/kg iv diazepam or 2 to 3 mg/kg thiopentone plus 0.005 mg/kg fentanyl and maintained with 0.01 mg·kg⁻¹·h⁻¹ fentanyl plus diazepam (total dose, 1 mg/kg). Muscle relaxation was obtained with 0.1 mg/kg pancuronium bromide. Patients were ventilated with oxygen and air to maintain PaO₂ at 100 to 150 mm Hg and PaCO₂ at 30 to 35 mm Hg.

Medial sternotomy was performed with suspension of the heart in a pericardial cradle. The ascending aorta was cannulated with a 3F polyethylene catheter connected to an heparinized 50-cm Vigon tube (1 mL) for withdrawal of microsphere reference sample by means of a peristaltic pump (P-1 Pharmacia, Sweden). A flared 3F polyethylene tube was placed in the left atrial appendage for the injection of radiolabeled microspheres. Two milliliters of sterile normal saline containing 2.5 to 3 million microspheres labeled with 185 MBq (5 mCi) of ⁹⁹ᵐTc-pertechnetate was injected into the atrial tube and then flushed with heparinized saline. Arterial blood sampling was started 10 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 syringe connected to the peristaltic pump by a silicon tube. The entire procedure usually lasted no more than 10 minutes.

Heart rate, limb, and V₁ leads of the ECG, arterial blood pressure by a left radial artery cannula, right atrial pressure by a central venous cannula, and nasopharyngeal temperature were monitored continuously throughout the procedure. Before harvesting, the heart was arrested using a standard cold (4°C) hyperkalemic crystalloid solution infused through the ascending aorta.

**Postexcision Evaluation**

After completion of the surgical protocol, the heart was excised according to the Shumway technique and transported to our laboratory near to the operating room. Less than 5 minutes elapsed between explantation and arrival in the laboratory.

The heart, free of the atria according to the surgical procedure adopted, was weighed and inspected for the presence of gross abnormalities; the main branches of the coronary arteries were sequentially cross sectioned at 3-mm intervals to detect critical stenosis. Any segment with a luminal reduction and at least one normal segment was excised for histological processing.

The heart subsequently was divided from base to apex into four or five slices of equal thickness; for this purpose, a steel grade with 1-cm septa separated by 2-mm openings was mounted over a cage furnished with a small hydraulic lifter that was able to hold the fresh heart firmly against the grade. Regular 1-cm-thick slices thus were obtained with a very sharp knife introduced into the grade openings.

On each slice, the presence and distribution of grossly evident fibrotic scar were noted. Wall thickness was measured from endocardium to epicardium of the anterior, lateral, and posterior walls of both ventricles and the interventricular septum, at the basal and apical levels.

Three adjacent slices were selected and used in the following manner. The middle slice was used to determine regional myocardial blood flow and biochemical assay, the upper (basal) slice was used to image tracer distribution with a gamma scintillation camera and, subsequently, for histology, and the lower (apical) slice was assigned to histological analysis.

**Determination of Regional Myocardial Blood Flow**

The middle slice was divided into nine transmural wedges, eight from the left ventricle and one from the right ventricle, and further subdivided into epicardial (outer half) and endocardial (inner half) wedges. These segments then were divided into two parts, one for well counter determination and one for biochemical analysis. Thus, a total of 18 segments corresponding to the

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anterior, lateral, posterior, and septal walls of the left ventricle and the free wall of the right ventricle were evaluated.

Each wedge was placed into one vial to be weighed (average weight, 1.3 g; range, 0.8 to 1.8 g) and then counted. Counting of myocardial radioactive segments and microsphere reference blood samples was performed within 12 hours from tracer injection using a calibrated well counter with an energy window of 130 to 170 keV, and decay was corrected back to the time of injection. Regional myocardial blood flow was determined by the method of Heymann and colleagues.35

**Assessment of Fibrosis by Biochemistry**

The 18 segments obtained from the middle slice were used for quantitative determination of fibrosis measured by a method described elsewhere.36 Briefly, percent fibrosis of cardiac tissue samples was calculated as the ratio between collagen and total proteins, the latter expressed as collagen and noncollagen proteins as measured as 4-hydroxyproline and glycine, respectively, by high-performance liquid chromatography.

Five hundred milligrams of each tissue sample was frozen in liquid nitrogen and homogenated in a Mikro Dimembrator II (B. Braun, Melsungen, FRG). After addition of 3 mL of HCl 8 mol/L containing 0.3 mmol/L n-methyltaurine to 50 mg of homogenate, the samples were hydrolysed for 16 hours at 95°C in glass-stoppered tubes at a constant temperature.

The hydrolyses were derivatized in a carbonate buffer (0.5 mol/L, pH 9) with 4-dimethylamino-azobenzol-4'-sulfonyl-chloride (0.6 mmol/L) in 40% acetone in glass-stoppered tubes. The tubes were heated at 70°C for 10 minutes in a water bath.

After derivatization, the samples were diluted with 500 μL of mobile phase composed of a 28% acetonitrile and 72% 10 mmol/L citric acid–disodium hydrogen (pH 3) phosphate buffer, and a 20-μL portion was chromatographed to quantify 4-hydroxyproline and glycine concentration.

Isocratic elution was carried out in reversed-phase high-performance liquid chromatography; the flow rate was 1.5 mL/min at 60°C of mobile phase. The elution profile was read at 471 nmol in a UV detector.

To evaluate noncollagen protein concentration, the glycine value relative to collagen was subtracted from total acid hydrolysat glycine value, the latter reflecting total protein content of the sample. The following equations:

Noncollagen proteins (μg/mL) =
[glycine – (2.38 4-hydroxyproline + 1.23)]384.9 – 181

Collagen proteins (μg/mL) =
107.026 4-hydroxyproline – 54.803

allowed quantification of both collagen and noncollagen proteins from a single chromatogram, expressing 4-hydroxyproline and glycine concentration in nanograms in 20 μL of injected volume.

A high correlation with classic colorimetric protein assay was observed using myosin as a standard reference. The linearity and reproducibility of the method were tested; the linear calibration curve gave an r value for 4-hydroxyproline and glycine of .99 (P<.01). The intrasample and intersample mean coefficients of variation (CVs) were 1.8% and 7.3%, respectively. The minimum detectable amounts (sensitivity) of 4-hydroxyproline and glycine were 40 and 45 fmol/μL, corresponding to 104 and 67.5 pg, respectively (signal-to-noise ratio, 10:1 at 0.005 AUFS). The accuracy of the method was 99% and 96% for 4-hydroxyproline and glycine, respectively.

**Gamma Camera Imaging Analysis**

The upper slice was photographed, covered with plastic wrap, and placed under a gamma scintillation camera (Apex 210 M, Elscint, Israel) using a high-resolution, low-energy, parallel-hole collimator (spatial resolution at full-width half-maximum, 7 mm) with a 20% window centered around the 140-keV photopeak of 99mTc. The image was recorded using a 256x256 matrix (pixel size, 0.86x0.86 mm), usually collecting more than 100,000 counts in 3600 seconds. The microsphere reference sample syringe was imaged in the same way and subsequently subdivided into 2-mL aliquots for well counter determination, while the slice was stored in 10% buffered formalin. For quantitative estimate of regional myocardial blood flow, the background was subtracted from both myocardial and blood images. The total blood counts were corrected for physical decay considering the interval between the blood and myocardial midscan times and divided by blood-sampling rate to obtain the calibration factor. The myocardial image was processed according to the following algorithm. Epicardial and endocardial borders were identified automatically by the isocontour profiles, whereas the epicardial boundary was outlined manually; the center of the left ventricle was recognized automatically as the center of gravity of the epicardial profile. Thereafter, the computer was asked to identify the fraction of 16 angular sectors (22.5° each) corresponding to the myocardial wall. The counts of each region were divided for the corresponding area (in cm²) and expressed as counts per milliliter of myocardium assuming a constant slice thickness of 1 cm. The values then were divided by tissue density (1.08 g/mL) and normalized for the calibration factor to obtain the flow per unit mass.

**Histological Analysis**

The upper slice (after gamma camera imaging) and the lower slice were divided into 11 whole wall blocks (eight of the left and three of the right ventricle) and processed for histology. Each histological slice of left ventricle was further subdivided into inner-half (endocardial) and outer-half (epicardial) layers for precise correlation with myocardial blood flow values.

Coronary arterial and myocardial samples were fixed in 10% buffered formalin, embedded in paraffin, and routinely stained with hematoxylin and eosin. Percent luminal reduction of main coronary arteries was calculated by averaging major and minor diameters of the residual lumen measured on the histological slide and referred to the average diameter of normal vessels.37 The total area of each myocardial slide was measured with an image analysis system (Vidas, Zeiss, Oberkuchen, FRG); the slide image was digitized, and the total area in pixels was calculated and converted to square millimeters through a calibration procedure using a reference system. By the same image analysis, the percentage of myocardial fibrosis
TABLE 2. Pathological Findings in the Eight Excised Hearts

<table>
<thead>
<tr>
<th>Patient</th>
<th>Heart weight (g)</th>
<th>Heart/body weight (%)</th>
<th>Diagnosis</th>
<th>Gross pathology</th>
<th>Mean LV wall thickness</th>
<th>Mean RV wall thickness</th>
<th>Coronary arteries</th>
</tr>
</thead>
<tbody>
<tr>
<td>T.P.</td>
<td>300</td>
<td>0.51</td>
<td>IDC</td>
<td>Mild RV and LV dilatation</td>
<td>11</td>
<td>3</td>
<td>Normal</td>
</tr>
<tr>
<td>L.A.</td>
<td>280</td>
<td>0.54</td>
<td>IDC</td>
<td>Severe RV and mild LV dilatation</td>
<td>10</td>
<td>3.5</td>
<td>Normal</td>
</tr>
<tr>
<td>D.M.</td>
<td>600</td>
<td>0.95</td>
<td>IDC</td>
<td>Severe LV dilatation</td>
<td>15.2</td>
<td>5</td>
<td>Normal</td>
</tr>
<tr>
<td>B.L.</td>
<td>580</td>
<td>0.88</td>
<td>IDC</td>
<td>Severe LV dilatation, mural thrombi</td>
<td>13.4</td>
<td>4</td>
<td>Normal</td>
</tr>
<tr>
<td>S.G.</td>
<td>420</td>
<td>0.66</td>
<td>IHD</td>
<td>Apex, inferior third anterior wall, septum, midlateral wall fibrosis</td>
<td>11.4</td>
<td>7</td>
<td>LAD, 95%; LCx, 70%; RC, 60%</td>
</tr>
<tr>
<td>R.G.</td>
<td>350</td>
<td>0.48</td>
<td>IHD</td>
<td>Apex, inferior third anterior wall, septum fibrosis</td>
<td>10.6</td>
<td>3.5</td>
<td>LAD, 80%; LCx, 70%; RC, 70%</td>
</tr>
<tr>
<td>C.M.</td>
<td>550</td>
<td>0.78</td>
<td>IHD</td>
<td>Apex, inferior third anterior wall, septum, midlateral wall fibrosis</td>
<td>8</td>
<td>6</td>
<td>LAD, 50%; RC, 20%; others, patent</td>
</tr>
<tr>
<td>P.L.</td>
<td>450</td>
<td>0.62</td>
<td>IHD</td>
<td>Apex, anterior lateral wall subendocardial fibrosis</td>
<td>9.8</td>
<td>8</td>
<td>LM, 75%; LAD, 100%; LCx, 70%; RC, 60%</td>
</tr>
</tbody>
</table>

LV indicates left ventricle; RV, right ventricle; IDC, idiopathic dilated cardiomyopathy; IHD, ischemic heart disease; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; RC, right coronary artery; and LM, left main.

in regard to the total examined area was calculated on histological slides stained with AFOG for connective tissue. In this evaluation, fibrous thickening of the endocardium was excluded. In the present study, no other morphological changes, apart from myocardial fibrosis, were considered.

Statistical Analysis

Continuous data are expressed as mean±1 SD values. Where appropriate, Student’s t test for paired or unpaired data or one-way ANOVA and post hoc Scheffe’s test were used to assess statistically significant differences. Myocardial blood flows were correlated to clinical, histological, and biochemical indices by linear regression analysis. A value of P<.05 was considered significant.

Results

Mean systolic and diastolic arterial pressures and heart rate at the time of microsphere injection during the surgical procedure were 97±18 mm Hg, 58±13 mm Hg, and 78±16 beats per minute, respectively. Mean rate-pressure product was 7617±2253.

Neither hemodynamic changes nor new ECG abnormalities were observed during and after microsphere injection.

Seven patients had a good clinical recovery at 1-month follow-up; one ischemic heart disease patient (S.G.) died 30 days after heart transplantation because of graft failure.

Pathological Findings

The main pathological findings confirmed the clinical diagnosis in all patients (Table 2).

Idiopathic dilated cardiomyopathy. At gross examination, the four idiopathic dilated cardiomyopathy patients presented with dilatation of the cardiac chambers and hypertrophy. The heart weight, exclusive of the atria, ranged from 280 to 600 g (mean weight, 440±173 g). The left and right ventricular wall thicknesses measured from 10 to 15.2 mm (mean, 12.4±2 mm) and 3 to 5 mm (mean, 3.8±0.7 mm), respectively. All patients had normal coronary arteries.

No gross evidence of myocardial fibrosis was observed. Histologically, fibrosis ranged from 0% to 10% (mean, 1.7±2.6%) in the inner half of the left ventricular wall and from 0% to 13% (mean, 1.6±2.9%) of the total area examined in the outer half (P=NS). In all four of the hearts, the fibrosis was intermyocellular or microfocal, mainly in the subendocardial layer.

Ischemic heart disease. Similarly, in the ischemic heart disease patients, there were dilatation of the cardiac cavities and hypertrophy of the heart (mean weight, 442±83 g; range, 350 to 550 g).

The mean left and right ventricular wall thicknesses were 9.9±1 mm (range, 8 to 11.4 mm) and 6.1±1.8 mm (range, 3.5 to 8 mm), respectively. All patients except one had multiple severe coronary stenoses. In all patients except one (P.L.), extensive substitute fibrosis replacing previous infarcted myocardium was seen grossly.

On the histological section, the percent of fibrosis with regard to the total examined area ranged from 0% to 70% (mean, 22.2±20%) in the inner left ventricular wall and from 0% to 70% (mean, 12.6±17%) in the outer wall (P<.05) (Fig 1). Both endocardial and epicardial values of percent fibrosis were significantly higher in the ischemic heart disease than in the idiopathic dilated cardiomyopathy patients (P<.0001).

Biochemical Fibrosis

Idiopathic dilated cardiomyopathy. Mean percent fibrosis assessed at biochemistry was 9.07±6.12%; mean endocardial and epicardial percent fibrosis was 8±4.3% (range, 0% to 29%) and 10±7.5% (range, 0% to 23%), respectively (P=NS).

Ischemic heart disease. As expected, higher mean values of percent myocardial fibrosis (24.9±28%) were observed in the ischemic patients with regard to idiopathic dilated cardiomyopathy (P<.01). Mean endocardial percent fibrosis (29.6±32%; range, 2% to 99%) was significantly higher than epicardial fibrosis (20±23%;
range, 1% to 93%) \( (P<.05) \). Both endocardial and epicardial values of percent fibrosis were higher in ischemic heart disease than idiopathic dilated cardiomyopathy patients \( (P<.0001) \).

Myocardial Blood Flow Distribution

Idiopathic dilated cardiomyopathy. Mean left ventricular transmural flow was 0.49±0.17 mL·min\(^{-1}\)·g\(^{-1}\); no significant difference in transmural flow among the anterior, lateral, posterior, and septal walls was found, although myocardial blood flow of the posterior wall appeared to be lower than that of other regions.

The mean endocardial flow of the left ventricle was significantly higher than the epicardial flow \( (0.53±0.20 \text{ vs } 0.45±0.17 \text{ mL·min}^{-1}\cdot \text{g}^{-1}); \ P<.002 \). The mean endocardial-to-epicardial flow ratio was more than 1 in the four left ventricular regions \( \text{mean ratio, } 1.16±0.30 \).

Mean right ventricular transmural flow was 0.36±0.19 mL·min\(^{-1}\)·g\(^{-1}\); the mean right and left ventricular blood flows were not significantly different.

Ischemic heart disease. Mean left ventricular transmural flow was 0.38±0.15 mL·min\(^{-1}\)·g\(^{-1}\); significant differences in transmural and epicardial flows among anterior versus posterior and septal walls were found \( (P<.05) \). Mean left ventricular endocardial and epicardial flows were not significantly different \( (0.37±0.15 \text{ vs } 0.40±0.19 \text{ mL·min}^{-1}\cdot \text{g}^{-1}); \ P=NS \); the mean endocardial-to-epicardial flow ratio was less than 1 in three of the four territories \( (0.99±0.33) \).

The mean right ventricular transmural flow was 0.56±0.33 mL·min\(^{-1}\)·g\(^{-1}\); this value was not significantly different from the mean left ventricular transmural flow.

Myocardial blood flow distribution in idiopathic dilated cardiomyopathy and ischemic heart disease patients is represented in Fig 2.

When mean myocardial blood flows of idiopathic dilated cardiomyopathy and ischemic heart disease patients were compared, differences in myocardial blood flow values and transmural distribution were observed: mean endocardial and transmural flows were significantly higher in idiopathic dilated cardiomyopathy than in ischemic heart disease patients \( (P<.01) \), whereas epicardial flows were similar. Mean left ventricular endocardial-to-epicardial flow ratio was statistically different in the two groups \( (1.16±0.30 \text{ in idiopathic dilated cardiomyopathy versus } 0.99±0.33 \text{ in ischemic heart disease, } P<.05) \).

Mean myocardial blood flow in the left and right ventricles and its regional distribution with statistical differences between idiopathic dilated cardiomyopathy and ischemic heart disease patients are depicted in Table 3.

Correlation Between Myocardial Blood Flow and Biochemical Fibrosis

Idiopathic dilated cardiomyopathy. When myocardial blood flow was compared with the extent of fibrosis assessed in the same specimen by biochemical analysis, no correlation was found \( (P<.03) \).

Ischemic heart disease. As overall results, no relation between myocardial blood flow values and the relative percent fibrosis was observed \( (P<.03) \). To evaluate differences in myocardial blood flow between areas with or without obvious scar, areas with more or less than 10% of fibrosis were separated arbitrarily and compared: flow values were 0.38±0.18 versus 0.35±0.11 mL·min\(^{-1}\)·g\(^{-1}\) for the endocardium and 0.46±0.23 versus 0.34±0.13 mL·min\(^{-1}\)·g\(^{-1}\) for the epicardium, respectively. These differences were not significant. Furthermore, the endocardial-to-epicardial flow ratios were not significantly different in areas with endocardial fibrosis of more or less than 10%.

When only areas with less-than-10% fibrosis were considered (territories with absent or mild fibrosis), flow values were not significantly different between regions supplied by a critically or noncritically stenosed coronary vessel: 0.42±0.24 versus 0.34±0.13 mL·min\(^{-1}\)·g\(^{-1}\) for the epicardium and 0.40±0.17 versus 0.34±0.11 mL·min\(^{-1}\)·g\(^{-1}\) for the endocardium, respectively.

Gamma Camera Imaging

Gamma camera imaging of the proximal (basal) myocardial slice allowed a more continuous spatial evaluation of myocardial blood flow distribution and a more straight correspondence with conventional perfusion images than that provided by the wall counter data \( (P<.03) \). Mean left ventricular transmural flow, as evaluated by applying the Heymann approach to the scintigraphic imaging, was similarly impaired in idiopathic dilated cardiomyopathy and ischemic heart disease patients.
Fig 2. Plots of myocardial blood flow (MBF) distribution by well counter determination. Flow values (mL·min⁻¹·g⁻¹) in the eight endocardial (left) and eight epicardial (right) wedges of the left ventricle in idiopathic dilated cardiomyopathy (IDC, top) and ischemic heart disease (IHD, bottom) patients are plotted. Segments 1-2, 3-4, 5-6, and 7-8 indicate anterior, lateral, posterior, and septal left ventricular wall, respectively.

(0.44±0.18 versus 0.40±0.02 mL·min⁻¹·g⁻¹, P=NS) (Fig 5). In agreement with the well counter findings, the mean endocardial-to-epicardial flow ratio was higher in idiopathic dilated cardiomyopathy (1.04±0.11) than in ischemic heart disease (0.81±0.24) (P<.05).

Within each patient, transmural blood flow was relatively more homogeneous in the idiopathic dilated cardiomyopathy than in ischemic heart disease patients (Fig 5), with the exception of one idiopathic dilated cardiomyopathy patient (L.A.) who showed marked perfusion defects in the posterolateral wall. The heterogeneities among the different myocardial walls, evaluated by the CV of myocardial blood flow values in idiopathic dilated cardiomyopathy and ischemic heart disease, were 18% and 27% for transmural flow, 19% and 51% for endocardial flow, and 21% and 41% for epicardial flow, respectively (P<.02).

When the extent of fibrosis by histological criteria was related to the severity of flow impairment assessed in the same territory by gamma camera analysis, no correlation could be demonstrated in either idiopathic dilated cardiomyopathy or ischemic heart disease patients.

Correlation Between Myocardial Blood Flow and Coronary Stenosis

The four ischemic heart disease patients had nine of the myocardial regions listed in Table 3 supplied by a normal or not critically stenosed (lumen reduction, 0.6±0.4, 1.0±0.1, 0.8±0.1) and critically stenosed (lumen reduction, 0.2±0.2, 0.1±0.0, 0.0±0.0) coronary arteries.

<table>
<thead>
<tr>
<th>Location</th>
<th>Idiopathic dilated cardiomyopathy (n=4)</th>
<th>Ischemic heart disease (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Endocardium</td>
<td>Transmural</td>
</tr>
<tr>
<td>Anterior wall</td>
<td>0.50±0.14</td>
<td>0.56±0.24</td>
</tr>
<tr>
<td>Lateral wall</td>
<td>0.44±0.22</td>
<td>0.59±0.17</td>
</tr>
<tr>
<td>Posterior wall</td>
<td>0.38±0.14*</td>
<td>0.41±0.16</td>
</tr>
<tr>
<td>Septum</td>
<td>0.49±0.16</td>
<td>0.56±0.22</td>
</tr>
<tr>
<td>Mean left ventricle</td>
<td>0.45±0.17</td>
<td>0.53±0.20†</td>
</tr>
<tr>
<td>Right ventricle</td>
<td>0.32±0.09</td>
<td>0.44±0.28</td>
</tr>
</tbody>
</table>

Endo/epi indicates endocardial-to-epicardial flow ratio.

*P<.05, †P<.01 vs ischemic heart disease.
FIG 3. Plots of correlation between the extent of fibrosis (% Fibrosis) assessed by biochemical analysis and the corresponding myocardial blood flow (MBF) values in idiopathic dilated cardiomyopathy and ischemic heart disease patients. • and ○ indicate the endocardial and epicardial wedges in which flow and fibrosis were assessed, respectively.

≤70% coronary artery and 11 regions perfused by a critically stenosed (>70%) vessel. The latter territories showed lower, although not significantly reduced, flows in the endocardium (0.36±0.16 versus 0.44±0.24 mL·min⁻¹·g⁻¹ and epicardium (0.38±0.21 versus 0.50±0.27 mL·min⁻¹·g⁻¹); the endocardial-to-epicardial flow ratio was 1.02±0.40 versus 0.94±0.28 in territories supplied by ≤70% or >70% stenosed vessels, respectively (P=NS).

Interestingly, one patient (C.M.) with single left anterior descending coronary artery disease (50% coronary lumen reduction) and prior anteroseptal infarction showed comparable values of transmural myocardial blood flow in the posterior (0.43 mL·min⁻¹·g⁻¹) and anteroseptal (0.42 mL·min⁻¹·g⁻¹) walls.

Correlation With Clinical Findings
To assess whether interpatient clinical differences might explain variations of myocardial blood flow, systolic, diastolic, and mean arterial pressures; heart rate; rate-pressure product; age; heart weight; left ventricular ejection fraction; cardiac index; pulmonary vascular resistance; and pulmonary artery and wedge pressures were correlated with myocardial blood flow values. Flow

FIG 4. Gamma camera imaging of microsphere distribution in myocardial slice of one patient with dilated cardiomyopathy (top) and in one with postischemic cardiopathy (bottom). From the original image (upper left), the epicardial and endocardial borders were automatically identified by the isocontour profiles, whereas the epiendocardial boundary was manually outlined; the center of the left ventricle was automatically recognized as the center of gravity of the epicardial profile (upper right). Thereafter, the computer was asked to identify automatically the fraction of 16 angular sectors (22.5° each) corresponding to the myocardial wall. The values of epicardial, transmural, and endocardial blood flow for each sector are depicted in the histogram. Arrows indicate the areas with lowest flow located in the anterior and septal walls. ANT, LAT, POST, and SEPT indicate anterior, lateral, posterior, and septal walls.
to the inner wall showed a significant inverse relation only with patient age \( r=1, P<.04 \). Heart weight showed a significant inverse relation only with mean left ventricular endocardial-to-epicardial flow ratio \( r^2=.95, P=.02 \) in idiopathic dilated cardiomyopathy but not in ischemic heart disease patients.

No other correlation between myocardial blood flow values and the clinical variables was found.

One patient (B.L.) with idiopathic dilated cardiomyopathy and left bundle branch block showed septal blood flow similar to that measured in the left ventricular free wall (0.39 and 0.33 mL \( \cdot \) min\(^{-1} \cdot \) g\(^{-1} \), respectively).

**Discussion**

This study is the first that quantitatively assessed regional myocardial blood flow and its transmural distribution in patients with idiopathic dilated cardiomyopathy or ischemic heart disease who were undergoing cardiac transplantation.

The major finding of the present study is that in advanced idiopathic dilated cardiomyopathy and ischemic heart disease, a similar impairment in regional myocardial blood flow is present, despite the markedly lower degree of fibrosis and lack of flow-limiting stenosis in idiopathic dilated cardiomyopathy patients. However, a different behavior in transmural myocardial blood flow distribution was observed in the two conditions. In fact, the endocardium was better perfused than the epicardium in cardiomyopathic patients, with a significant gradient present in all left ventricular walls of each patient. Conversely, the endocardial and epicardial flows were not significantly different in ischemic patients, with a trend toward a better epicardial perfusion (endocardial-to-epicardial flow ratio of <1).

Moreover, in our study population, no correlation between the degree of myocardial blood flow impairment and the extent of myocardial fibrosis, assessed both biochemically and histologically, was found. This indicates that in patients with severe left ventricular dysfunction who are undergoing heart transplantation, myocardial fibrosis was not the main determinant of globally depressed myocardial perfusion.

**Myocardial Blood Flow Distribution in Ischemic and Cardiomyopathic Patients**

Systematic reductions in resting myocardial blood flow in idiopathic dilated cardiomyopathy and ischemic heart disease have been reported in literature since the late 1960s. Early studies using helium desaturation technique provided evidence that myocardial blood flow was more heterogeneous than normal in coronary patients.28 Cannon and colleagues3 first described reductions in myocardial perfusion throughout the ventricles of patients with discrete coronary vascular lesions. The same laboratory3 and Klocke and colleagues2 used inert gas techniques to measure average flow per unit weight in patients with angiographically proven advanced coronary artery disease. The average perfusion rate in patients with multivessel disease was 0.45±0.09 mL \( \cdot \) min\(^{-1} \cdot \) g\(^{-1} \), whereas it was 0.57±0.11 mL \( \cdot \) min\(^{-1} \cdot \) g\(^{-1} \) in patients with variable coronary artery disease involvement.2 Both studies found significantly lower myocardial blood flow values in ischemic heart disease patients than in normal individuals, who showed an average myocardial blood flow of 0.61±0.07 and 0.70±0.13 mL \( \cdot \) min\(^{-1} \cdot \) g\(^{-1} \) in the two studies, respectively.

These data confirmed and expanded previous findings of depressed total coronary perfusion as assessed with radioactive potassium or rubidium in patients with advanced coronary artery disease.29,30 Data from Cannon and colleagues3 also showed that regional perfusion rates were reduced in areas supplied by normal or not significantly stenosed vessels. These findings suggested to these authors that the reduced resting myocardial blood flow per unit mass was appropriate for reduced oxygen demands of the diseased ventricle.

The same investigators, using regional clearance rates of \(^{133}\text{Xe} \) and precordial counting, assessed the relation between resting myocardial blood flow and the hemodynamic determinants of myocardial oxygen consumption.31 They found that myocardial blood flow per unit mass was...
significantly reduced in patients with multivessel disease compared with normal subjects with normal coronary arteries (0.48±0.11 versus 0.67±0.12 mL·min⁻¹·g⁻¹). The reduction in myocardial blood flow observed in ischemic heart disease at rest was related to lower levels of hemodynamic variables that determine myocardial oxygen consumption. Lowering of peak left ventricle wall stress appeared to be the most important feature for reduced levels of resting myocardial blood flow in multivessel disease. These patients had systematically increased left ventricle wall thickness and mass, which could explain lower levels of wall stress and reduced myocardial blood flow than in the control population. Arani and colleagues quantified myocardial blood flow per unit weight in collateral-dependent myocardium in patients with complete occlusion of the proximal left anterior descending coronary artery by hydrogen-helium curves. They found a reduced myocardial blood flow per unit weight in collateral-dependent myocardium (average, 0.38±0.08 mL·min⁻¹·g⁻¹). In addition to the inability of collateralized myocardium to maintain a normal myocardial blood flow, the authors recognized a possible role of reduced myocardial contractility or patchy fibrosis as an explanation for reduced myocardial blood flow values.

The inotropic state is important as a determinant of myocardial oxygen consumption in the chronically depressed heart. Henry and colleagues first reported that decreased myocardial oxygen requirements in patients with ventricular dysfunction were associated with decreased myocardial blood flow, as estimated by helium washout curves. This study included angiographic assessment of inotropic state based on mean left ventricular circumferential fiber shortening velocity and the value at peak tension. Patients with depressed shortening velocities showed reduced myocardial blood flow and reduced myocardial oxygen consumption. Shortening velocities correlated significantly with myocardial oxygen consumption.

In the present study, no correlation among myocardial blood flow values, clinical characteristics, and the hemodynamic determinants of oxygen consumption assessed during the surgical procedure was found. Although contractile state could not be assessed directly in our study, it is likely that reduction of myocardial blood flow in our patients was related to the depressed contractile state.

All studies with inert gas washout techniques have limitations related to technical and anatomic problems. Cardiac motion and geometry, transmural heterogeneity of myocardial blood flow, and scar and infarction may represent sources of error in the evaluation of regional myocardial blood flow. A systematic underestimation of normal resting myocardial blood flow values in these previous studies appears to be present when flow values are compared with those recently obtained by PET. Quantitation by ¹³N ammonia and PET attained in our laboratory in normal subjects provided mean rest myocardial blood flow values of 0.95±0.23 mL·min⁻¹·g⁻¹, which are comparable with those obtained by Bergmann and colleagues using ¹⁵O-labeled water (0.90±0.22 mL·min⁻¹·g⁻¹). Although PET provides more accurate measurements of regional myocardial blood flow than inert gas techniques, a significant limitation of all of these methods is their inability to distinguish epicardial from endocardial blood flow.

In the present study, the transmural myocardial blood flow distribution was assessed by the microsphere technique, which represents the gold standard for quantitation of regional myocardial blood flow.

Measurements of myocardial blood flow in end-stage congestive heart failure demonstrated a severe impairment of total and regional flows in both idiopathic dilated cardiomyopathy and ischemic heart disease. The mean transmural blood flow of the left ventricle was markedly depressed in the two groups of patients. Despite the severe degree of flow reductions, the most striking finding of our study was a different behavior of transmural flow distribution in the two conditions.

It is well known from experimental research that the subendocardium of the left ventricle is more susceptible to ischemia than the subepicardium. The nonuniform distribution of myocardial blood flow has been attributed to the higher extravascular resistance in the innermost regions of the wall with respect to the superficial layers; this myocardial tissue pressure may impede blood flow to the endocardium during diastole when coronary autoregulation is abolished as in presence of critical coronary stenosis. Kjekshus studied the effect of diastolic ventricular pressure augmentation on regional myocardial blood flow distribution in dog experiments either with unrestricted coronary supply or with abolished coronary flow autoregulation. He found that in presence of the autoregulatory mechanism, transmural flow distribution was independent of gradient in tissue pressure. Flow was distributed uniformly across the left ventricle, with a relatively larger increase to the inner half of the wall during increased ventricular preload. This implies active regulation of the coronary vascular tone, which compensates for the transmural gradient in the extravascular component of coronary resistance. Conversely, when the coronary bed was fully dilated by coronary occlusion, the flow distribution was directly dependent on gradients in myocardial tissue pressure, with a marked decrease in endocardial-to-epicardial flow ratio.

In agreement with experimentally preserved coronary autoregulation and increased ventricular diastolic pressure, our patients with idiopathic dilated cardiomyopathy and heart failure showed that the "physiological" pattern of myocardial blood flow distribution with the subendocardial flow significantly higher than the subepicardial (mean flow ratio, 1.16±0.30). By contrast, ischemic patients showed a flow proportionately more reduced to the deep layers of the myocardial wall than to the superficial ones (endocardial-to-epicardial flow ratio, 0.99±0.33), regardless of the presence and extent of myocardial fibrosis. Nevertheless, both idiopathic dilated cardiomyopathy and ischemic heart disease showed a marked impairment of myocardial blood flow (0.49±0.17 and 0.38±0.15 in idiopathic dilated cardiomyopathy and ischemic heart disease, respectively). At this low flow level, an abolishment of coronary autoregulation mechanism should be expected, with concomitant reduction of endocardial-to-epicardial flow ratio in the presence of elevated diastolic intramyocardial pressures. This behavior was not observed in idiopathic dilated cardiomyopathy patients, suggesting a maintenance of vascular tone with preservation of the
physiological flow distribution. In contrast with the postulated pathophysiology of small-vessel disease in idiopathic dilated cardiomyopathy,\textsuperscript{45-47} our observation indicates the persistence of microcirculatory function in the face of marked coronary flow reduction. In these circumstances, an abnormal down-resetting of myocardial blood flow (with preservation of physiological transmural flow distribution) consequent to decreased myocardial metabolic demand of damaged myocytes could be hypothesized.

Whether the different pattern of transmural myocardial blood flow distribution in idiopathic dilated cardiomyopathy and ischemic heart disease could depend on differing transmural oxygen requirements (related to differences in wall stress and/or sarcomere length) cannot be determined from our data.

Additional information gained from our results is that the right and left ventricular flows were not significantly different in both conditions. However, right ventricular flows had a tendency to be lower than left ventricular flows in idiopathic dilated cardiomyopathy and higher than the left in ischemic heart disease, suggesting a more pronounced involvement of the right ventricular structures in dilated cardiomyopathy than in ischemic heart disease and a maintenance of the physiological gradient between left and right ventricular flow in the latter condition.

**Cardiac Imaging in Idiopathic Dilated Cardiomyopathy and Ischemic Heart Disease**

Myocardial perfusion imaging has been advocated as a useful technique to differentiate ischemic from dilated cardiomyopathy.\textsuperscript{48} Despite conflicting results on this issue using \textsuperscript{201}TI scintigraphy,\textsuperscript{19,20} PET demonstrates that idiopathic dilated cardiomyopathy exhibits more homogeneous perfusion and metabolism than ischemic heart disease.\textsuperscript{21,22,48} The presence of regional defects in idiopathic dilated cardiomyopathy has been interpreted as technical artifacts caused by limited spatial resolution of the instrumentation and partial volume effect.\textsuperscript{49} In our study, gamma camera imaging of the excised hearts showed larger transmural myocardial blood flow homogeneity in ischemic than in cardiomyopathic patients (mean CV of transmural flow, 27\% and 18\%, respectively), which is in agreement with the in vivo scintigraphic findings. However, the regional distribution of transmural flow in idiopathic dilated cardiomyopathy was more heterogeneous than that observed by the microsphere technique\textsuperscript{49} in normal subjects (mean CV, 18\% versus 5\% in idiopathic dilated cardiomyopathy and normal subjects, respectively); analogous homogeneity of microsphere distribution was observed by Cobb and colleagues\textsuperscript{50} in anesthetized control dogs. Nevertheless, one of the four idiopathic dilated cardiomyopathy patients exhibited severe regional perfusion defects, which cannot be explained by technical artifacts or differences in regional wall thickness, indicating that actual perfusion abnormalities in localized areas of the left ventricle also can occur in patients with idiopathic dilated cardiomyopathy. The scintigraphic imaging obtained in the excised hearts confirms that the pattern of myocardial blood flow distribution is more homogeneous in idiopathic dilated cardiomyopathy than in ischemic heart disease, although severe regional perfusion defects also may occur in the former condition.

In addition, microsphere distribution in the endocardial and epicardial segments separated by drawing of regions of interest showed further heterogeneity with respect to the transmural values in ischemic heart disease but not in idiopathic dilated cardiomyopathy patients. Our study indicates that the availability of imaging techniques with better spatial resolution to distinguish endocardial from epicardial perfusion would better differentiate the two clinical conditions.

**Correlation Between Myocardial Blood Flow and Fibrosis**

In our investigation, no correlation was found between the degree of myocardial blood flow impairment and the extent of fibrosis. This was observed by both biochemical and histological analyses, and it occurred in both idiopathic dilated cardiomyopathy and ischemic heart disease patients. In the experimental setting, myocardial blood flow is impaired in infarcted areas more than in the borderzone ischemic segments.\textsuperscript{51} In animal models, the acute coronary occlusion is the main determinant of myocardial damage, and it accounts for spatial differentiation among areas with normal, ischemic viable, and necrotic tissue. However, in ischemic patients with heart failure, it is conceivable that complex and proteiform mechanisms sustain diffuse hypoperfusion in both necrotic and viable areas. In fact, mixture of zones with normal and necrotic cells as well as with viable tissue supplied by critically stenosed vessels are frequently observed in specimens from our explanted hearts (Fig 1). This may justify the similar myocardial blood flow reduction observed in infarcted and remote areas of patients with chronic heart disease. Dwyer and colleagues\textsuperscript{52} demonstrated by \textsuperscript{133}Xe washout technique that patients with previous Q wave anterior myocardial infarction had residual, albeit subnormal, myocardial perfusion rates in necrotic areas. Blood flow in these areas was similar to the mean values obtained in our ischemic heart disease patients (0.40 mL·min\textsuperscript{-1}·g\textsuperscript{-1}) and not significantly different from that of noninfarcted areas supplied by stenotic circumflex artery. Selwyn and colleagues\textsuperscript{53} used human albumin microspheres labeled with \textsuperscript{125}I and PET in patients with previous myocardial infarction and found a wide range of values of flow in infarcted segments with a large overlap with noninfarcted segments. Both studies indicate that a surprisingly large quantity of viable tissue may survive within infarcted regions.

These clinical investigations could not correlate the flow impairment with the extent of myocardial irreversible damage; in the present study, no relation between the percent tissue fibrosis and coronary flow reduction of corresponding areas was found. Our findings indicate that in end-stage ischemic and idiopathic cardiomyopathies, the low perfusion rates are not necessarily determined by the amount of fibrotic myocardium.

**Clinical Implications**

In the clinical setting, several implications arise from measurement of myocardial blood flow in the failing human heart. First, in ischemic heart disease patients, hypoperfusion also is present in myocardial segments not involved by necrotic processes and not supplied by stenotic vessels. In these territories, hypoperfusion and
contractile impairment could be primarily linked to metabolic derangement consequent to chronic fiber straining and tissue hypoxia. This indicates that in advanced ischemic heart disease, depressed hypoperfusion and wall motion of some areas may not depend on underlying coronary lesions or tissue fibrosis. Furthermore, also in cardiomyopathic patients, myocardial blood flow is markedly reduced despite the lack of coronary lesions and less fibrosis than in ischemic patients, as has been shown in previous reports\(^5\) and confirmed in our population. This confirms the presence of low resting perfusion rates in idiopathic dilated cardiomyopathy as also observed noninvasively in cardiomyopathic patients with heart failure\(^4\) and in subclinical stages of this condition by PET.\(^5\) Weiss and colleagues\(^5\) assessed myocardial blood flow with \(^{133}\)Xe while simultaneously measuring the determinants of myocardial oxygen consumption in idiopathic dilated cardiomyopathy patients and in control subjects; left ventricular perfusion per unit mass was significantly reduced at rest in idiopathic dilated cardiomyopathy (0.43 versus 0.63 mL/min \(\cdot\) g \(^{-1}\)). The abnormal myocardial blood flow values found in idiopathic dilated cardiomyopathy significantly correlated with reductions in myocardial performance. Thus, in addition to the impairment of coronary microcirculation postulated for idiopathic dilated cardiomyopathy, functional and structural damage of myocytes may downregulate myocardial blood flow at lower levels, even in the early stages of the disease, to meet the reduced metabolic needs. Quantitation of myocardial blood flow allows early recognition of flow impairment even in the presence of homogeneous distribution of perfusion.\(^5\)

Furthermore, our data confirm that quantitation of regional blood flow may differentiate the relatively homogeneous perfusion pattern of idiopathic dilated cardiomyopathy from the perfusion heterogeneity characteristic of ischemic heart disease;\(^5\) however, severe regional perfusion defects may occur even in idiopathic dilated cardiomyopathy, limiting the value of perfusion techniques alone in differentiating these two clinical entities.

Finally, the excised heart at cardiac transplantation represents a suitable model to test the accuracy of methods that assess myocardial viability in vivo; the ability of imaging approaches, such as \(^{201}\)TI scintigraphy and dobutamine-stress echocardiography, to detect viability can be determined by markers of cellular integrity obtained directly from tissue analysis.

**Study Limitations**

Although our findings give rise to speculation on the different behaviors in myocardial blood flow distribution in ischemic heart disease and idiopathic dilated cardiomyopathy, because of the small size of study sample, definitive conclusion should be cautiously extended to all populations with heart failure.

Furthermore, the altered hemodynamic state associated with anesthesia and surgical stress might have affected absolute myocardial blood flow measurements and transmural flow distribution as well.\(^5\) Cobb and colleagues\(^5\) showed that pentobarbital anesthesia increased epicardial and endocardial flows and decreased the transmural gradient between endocardium and epicardium present during control conditions. In our study, the effect of these variables should have been superimposed on both populations; nevertheless, idiopathic dilated cardiomyopathy patients maintained an obvious gradient between endocardium and epicardium, whereas ischemic heart disease patients showed no gradient or prevalent perfusion to the epicardial layers.

The number of microspheres required for accurate measurement of myocardial blood flow is critical, mostly for portion of organs with low flow. By knowing for each patient the mean myocardial blood flow, cardiac output, amount of injected tracer, and heart weight, we calculated the number of particles as 397\(\pm\)71 per gram of tissue. This number ensures satisfactory, although not perfect, accuracy of myocardial blood flow measurements, with a distribution variability within 10\% of the mean distribution at the 95\% confidence level.\(^25,57\)

A potential problem in obtaining accuracy in calculating myocardial blood flow is related to the labeling stability of human albumin microspheres with radionuclides after tracer injection, once it is trapped into the tissues. In previous studies,\(^11,49\) tracer stability was checked by collecting and measuring venous blood, showing a negligible amount of circulating radioactivity during a prolonged observation period.

Microsphere size and tachycardia also have been shown to alter the correct estimate of myocardial blood flow\(^5\); in the present study, we used microspheres with a mean size of 14 \(\mu\)m, similar to those used by Neill and colleagues\(^5\) and Becker and colleagues.\(^4\) A preferential streaming of microspheres to deep layers was observed in these previous studies compared with myocardial blood flow distribution using microspheres of 7 to 10 \(\mu\)m.\(^5\) The larger size of microspheres used in our study would have overestimated the endocardium-to-epicardium gradient in idiopathic dilated cardiomyopathy without affecting the different patterns of flow distribution observed in the two populations.

Finally, heart rate during microsphere injection was within the physiological range (mean heart rate, 78±16 beats per minute), ruling out a possible effect of this parameter on myocardial blood flow distribution.

**Safety**

The use of particulate tracers into the systemic circulation poses concern for safety, particularly when used in patients with heart failure during a heart transplantation procedure. Previous reports on intracoronary particle injection in dogs and humans\(^13-16,59\) demonstrated the safety of this procedure. Moreover, at our institute, we have had direct experience with more than 300 patients who had microspheres injected into the left ventricle. These studies included patients with acute or recent myocardial infarction or idiopathic dilated cardiomyopathy, and no adverse reaction related to the systemic effect of these particles was observed.\(^16\) Selwyn and colleagues\(^11\) showed by PET in patients with previous myocardial infarction that after injection into the left ventricle of human albumin microspheres, 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\(^60-64\) evaluated after intracoronary injection of \(^{99m}\)Tc human albumin microspheres (particle size, 5 to 30 \(\mu\)m). No untoward neurological or systemic effects were observed in any study. Only Ver-
has and colleagues\textsuperscript{62} reported a 7% morbidity among patients with brain infarct; this value was not different from that observed during arteriography alone (8.5%). Briz-Kanafani and Lagos-Costantino\textsuperscript{65} 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.

In our study, neither hemodynamic changes during microsphere injection nor neurological consequences in the postoperative phase were observed in any patient, confirming the safety of this procedure even in critically ill patients who were undergoing cardiac surgery.

As far as the dosimetry safety is concerned, the injected dose of 5 mCi of \textsuperscript{99m}Tc labeled with microspheres produces a negligible absorbed radiation dose for the patient.

Conclusions

Heart transplant surgery offers a valuable model to assess absolute myocardial perfusion in human heart failure. Myocardial blood flow is markedly depressed in failing hearts of idiopathic dilated cardiomyopathy and ischemic heart disease patients; a transmural flow gradient, with endocardial perfusion higher than the epicardial, is present in idiopathic dilated cardiomyopathy but not in ischemic heart disease. The preferential endocardial perfusion in cardiomyopathic patients, in the face of very low perfusion rates and augmented intramyocardial pressures, suggests that the autoregulatory mechanism in the coronary microcirculation of these patients should still be operating. These findings, together with those observed in ischemic patients, indicate that mechanisms other than coronary lesions, myocardial fibrosis, and microvascular damage appear to operate in determining myocardial blood flow impairment in heart failure.

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References


Myocardial blood flow distribution in patients with ischemic heart disease or dilated cardiomyopathy undergoing heart transplantation. O Parodi, R De Maria, L Oltrona, R Testa, G Sambuceti, A Roghi, M Merli, L Belingheri, R Accinni and F Spinelli

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