Determination of Coronary Flow Reserve by Parametric Imaging

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Nine mongrel dogs were instrumented with electromagnetic flow probes (EMF) to measure coronary blood flow through the left anterior descending (LAD) and left circumflex (LCx) coronary arteries at rest and after maximal coronary vasodilation (1 mg/kg/min adenosine). Relative coronary blood flow was determined by parametric imaging in the left posterior oblique projection using digital subtraction angiography (DSA). Transmural myocardial perfusion of the LAD and LCx beds was determined with tracer-labeled microspheres. Coronary flow reserve (maximal coronary blood flow divided by resting blood flow) was calculated under control conditions and after constriction of the proximal LAD or LCx by a screw occluder. Heart rate decreased significantly from 140 beats/min at rest to 122 beats/min after adenosine (p<0.001) and from 134 (rest) to 120 beats/min (adenosine; p<0.05) after coronary constriction. Peak systolic pressure was kept constant with an aortic constrictor. Left ventricular end-diastolic pressure increased significantly from 18 mm Hg at rest to 23 mm Hg (p<0.05) after coronary constriction. At baseline, coronary flow reserve was 4.2 with DSA, 3.8 with EMF, and 3.7 with microspheres; after coronary constriction, it was 2.6 (DSA), 1.9 (EMF), and 1.5 (microspheres) (all p<0.001 versus baseline). Coronary blood flow showed a good correlation between EMF and microspheres (r=0.87, p<0.001), with a standard error of estimate (SEE) of 0.78 ml/g/min. Coronary flow reserve also showed a good correlation between EMF and microspheres (r=0.82, p<0.001), with an SEE of 0.93. There was a moderate correlation between EMF and DSA (r=0.68, p<0.001), with an SEE of 1.35 (40% of mean coronary flow reserve). The correlation coefficient between microspheres and DSA was 0.54 (p<0.01), with an SEE of 1.46 (39% of mean coronary flow reserve). The mean difference (accuracy) and standard deviation of difference (precision) were 0.2±1.0 between EMF and microspheres, −0.1±1.4 between EMF and DSA, and −0.6±1.7 between microspheres and DSA. We conclude that determination of coronary flow reserve by parametric imaging is associated with large variations that are greater than variations also inherent in the two reference techniques. Parametric imaging allows relatively accurate assessment of coronary flow reserve (small mean difference), but precision is low (large standard deviation of mean differences). This low precision probably is due to the superposition of different cardiac structures in the two-dimensional display of a three-dimensional perfusion zone, potentially inhomogeneous contrast distribution, poor temporal resolution of the once-per-cycle imaging, inadequate displacement of blood by contrast material, and perturbations of flow caused by contrast material. Thus, in this animal model, only changes in coronary flow reserve that are clearly greater than 40% can be expected to be measured correctly with the currently available technique. (Circulation 1990;82:1438–1448)

Coronary arteriography, used in the past as the gold standard for assessing coronary artery disease, determines the severity of a coronary stenosis solely in terms of anatomy. More recently, functional measurements reflecting the physiological significance of stenosed coronary arteries have become available. For example, digital sub-

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traction angiography has been used successfully to determine coronary flow reserve (CFR) in patients with coronary artery disease,1–3 but the requirement for expensive and complex techniques has limited its
clinical application. Intracoronary Doppler flow probes also have been used to measure CFR,6,7 but catheter positioning, changes in coronary luminal diameter, limited access to distal stenoses, and inability to measure flow velocities in different myocardial regions simultaneously have restricted its use for assessing CFR in daily practice. Moreover, this technique measures only epicardial arterial flow reserve, which may not reflect myocardial flow reserve in the presence of collateral recruitment and infarction. Positron emission tomography is another means for evaluating CFR in patients with coronary artery disease,7-9 and trials are underway to determine its suitability in the clinical setting.

The purpose of the present study was to determine the accuracy and reproducibility of a specific digital subtraction angiography method1,2 for measuring relative coronary blood flow and CFR in the experimental animal. We compared results with regional coronary arterial flow reserve measured with electromagnetic flowmeters and myocardial flow reserve measured with tracer-labeled microspheres.

Methods

Animal Preparation

Mongrel dogs were anesthetized with 35 mg/kg pentobarbital i.v. and were intubated and ventilated with a Harvard ventilator pump (Harvard Apparatus, South Natick, Mass.). A left thoracotomy was performed in the fifth intercostal space, and the heart was exposed and supported in a pericardial cradle. The proximal left anterior descending (LAD) and the proximal left circumflex (LCx) coronary arteries were dissected free, and an appropriately sized and calibrated electromagnetic flow probe (Carolina Medical Electronics, King, N.C.) was placed on each vessel. A screw occluder was placed distal to the flow probe either on the LAD (n=2) or LCx (n=4) arteries or both (n=3). Vascular sheaths were introduced into the left and right carotid arteries and the left jugular vein for vascular access. A calibrated 5F micromanometer (Millar Instruments, Houston) was passed into the left ventricle via an apical stab wound and secured with a purse-string suture. A second 5F micromanometer was passed through the right carotid artery sheath into the ascending aorta.

A 7F Amplatz catheter was introduced through the left carotid artery into the ascending aorta and positioned into the ostium of the left coronary artery; care was taken to avoid subselective placement. Six milliliters of a nonionic contrast medium (iohexol, Winthrop-Breon, New York) was injected at a flow rate of 4 ml/sec using a power injector with electrocardiographic gating (Mark IV, Medrad, Pittsburgh). Immediately after intracoronary injection of contrast material, cancellation of the flow signal was observed because of the nonionic nature of the contrast followed by a short hyperemic response that lasted usually up to 30 seconds in the control state (Figure 1). A polyethylene tube was placed in the left atrial appendage for injection of tracer-labeled microspheres; a second catheter was placed in the femoral artery for withdrawal of reference blood samples using a Harvard withdrawal pump. A Blalock clamp was placed around the descending aorta for constriction of the aorta to maintain peak systolic pressure at a constant level during the experiment.

Coronary Blood Flow Measurements

Electromagnetic flow probe. Coronary blood flow through the LAD and LCx arteries (Figure 1) was measured with electromagnetic flowmeters. They were calibrated by timed collection of blood, and the zero reference was checked several times during the experiments by brief occlusion of the coronary artery. Any alterations in waveform suggesting poor placement or instability of the probes prompted repositioning or selection of a probe of different size. Instability due to potential collapse of the vessel within the probe during the hypotension induced during maximal hyperemia was minimized by maintaining aortic pressure with a constrictive Blalock clamp on the aorta. Normalization of coronary blood flow was carried out at the conclusion of the experiment by dividing the electromagnetic flow data by the corresponding muscle mass of the LAD or LCx.10

The perfusion beds of the two arteries were determined by selective intracoronary infusion with 2,3,5-triphenyltetrazolium chloride (Sigma Chemical Co., St. Louis) and Evan's blue (Sigma), respectively. The coronary arteries were cannulated separately and perfused simultaneously with warm isotonic saline. Dye perfusion was performed at 100 mm Hg for 5 minutes to guarantee optimal staining of the two perfusion beds. The perfusion beds were dissected free and weighed. These weights were used to calculate normalized coronary blood flow in milliliters per gram per minute.

Parametric digital angiography. Two images per cardiac cycle (at 50% and 75% of the RR interval) were acquired in the left posterior oblique orientation on a Philips Optimus M200 angiographic system (Philips Nederland, Eindhoven, The Netherlands) that was interfaced directly to a digital radiographic computer (DPS-4100C, ADAC, Milpitas, Calif.). Radiographic parameters were kept constant (peak kV, milliamperes) for each image run. No correction of scatter or veiling glare was undertaken. Logarithmic analog-to-digital conversion was used. The images were stored on a digital disk with a matrix of 512×512×8 bits. All images were processed by mask-mode subtraction, whereby the last image before contrast administration was chosen as the mask. The respirator pump was turned off during the image acquisition to minimize motion artifacts during image subtraction. Five to eight consecutive images were selected as the image subset (only one image per cardiac cycle). A threshold generally less than or equal to 25% of the available grey levels was selected to minimize background noise. Pixel densities exceeding the threshold were used to generate a
functional image. Red was assigned to pixels that had an intensity that surpassed the threshold in the first postinjection cycle, yellow for the second cycle, white for the third, green for the fourth, and so on. A region of interest was defined by two observers in the perfusion area of the LAD and LCx arteries. These regions contained between 500 and 1,500 pixels and were placed carefully to exclude the large and middle-sized coronary arteries, the aortic root, the coronary sinus, and areas that were perfused by both the LAD and LCx arteries. The same pair of regions and the same threshold were used for baseline, hyperemia, and stenosis images.

Mean arrival time (AT) and peak contrast density (CD) were calculated from the regions of interest. The mean AT obtained in cardiac cycle units was converted into seconds by multiplying the units by the true cycle time. Pixels appearing in the first cardiac cycle after contrast administration were assigned an AT of 0.5 cycle, those in the second cycle an AT of 1.5 cycles, and so on. Peak CD was defined as the maximal density achieved during the entire series. From these measurements, a relative coronary flow index (FI) was obtained as: 

\[ \text{FI}_{\text{hyper}} = \frac{\text{CD}_{\text{hyper}} \cdot \text{AT}_{\text{basal}}}{\text{FI}_{\text{basal}} \cdot \text{CD}_{\text{basal}} \cdot \text{AT}_{\text{hyper}}} \]

**Microsphere technique.** Myocardial perfusion was determined with the reference withdrawal technique using commercially available microspheres (15-μm diameter; New England Nuclear, Boston) labeled with \(^{113}\text{Sn}, \, ^{46}\text{Sc}, \, ^{141}\text{Ce}, \, \text{or } ^{85}\text{Sr}.\) For each flow determination, approximately \(3 \times 10^6\) microspheres suspended in 10 ml of 37°C saline was used. The sample was carefully ultrasonicated and vortexed and then injected over 60 seconds through the left atrial line. At the same time, a reference arterial sample was withdrawn from the femoral artery (7.6 ml/min) using a Harvard withdrawal pump. Nine tissue samples were obtained from each perfusion bed (LAD and LCx perfusion areas), and transmural as well as subendocardial, midmyocardial, and subepicardial blood flows were determined. All tissue samples were weighed on a Sartorius digital balance (Goettingen, FRG). Blood samples were hemolyzed with KOH and desiccated at 70°C for 3–5 days. Radioactive counts were determined with a Tracor Model 1185 gamma scintillation counter (Tracor Instruments, Austin, Tex.), and blood flow was calculated as...
Q_m = (c_mQ_t)/c_i, where Q_m is myocardial blood flow (ml/min), c_m is counts in the tissue sample (counts/min), Q_t is withdrawal rate of the reference blood sample (ml/min), and c_i is counts in the reference blood sample (counts/min). Blood flow per gram of tissue was calculated by dividing Q_m by the weight of the tissue sample.10

Study Protocol

Baseline measurements were carried out after instrumentation was completed. Left ventricular pressure, its first derivative (dp/dt), aortic pressure, electromagnetic coronary blood flow of the LAD and LCx arteries, and a standard lead of the electrocardiogram were recorded (Figure 1) on a Gould recorder (model 2800S, Gould Electronics, Cleveland), which was interfaced to an IBM-AT modified for on-line signal digitization at 200 Hz per channel. In each animal, 10 beats were averaged and stored on disk for further analysis. Microspheres then were injected over 60 seconds, and hemodynamic data of 10 cardiac cycles were digitized and averaged during the injection period. After microsphere injection was completed, digital angiography was performed. The respirator pump was turned off during angiography, and only those sequences with good quality coronary angiograms and without premature beats were selected for further analysis.

Hyperemia was induced by infusion through the jugular sheath of 1 mg/kg/min adenosine (Sigma). Adenosine was dissolved in warmed saline and was heated during infusion to prevent precipitation. The infusion rate was considered to cause maximal coronary vasodilation because contrast material injection had no further hyperemic effect during adenosine infusion (Figure 1). Because adenosine caused peripheral vasodilation with a significant drop in aortic pressure, the descending aorta was constricted with a Blalock clamp to maintain peak aortic pressure at a constant level during the experiment.

Coronary stenosis was induced by a screw occluder during adenosine infusion. This occluder was tightened until electromagnetically measured coronary blood flow had fallen to values approximating control flow values before adenosine infusion. After a steady-state pressure was reached, flow data were recorded and stored on disk. Microspheres then were injected and digital angiography was carried out as described previously.12 A second control run in the presence of coronary stenosis was obtained after turning off the adenosine infusion (Figure 1). Aortic constriction usually was released at this stage to keep peak aortic pressure constant. Then pressure and flow data of 10 cardiac cycles were digitized, averaged, and stored on disk. Microsphere injection and digital angiography were performed thereafter. The experiments were concluded by the administration of an overdose of pentobarbital and potassium chloride.

Thirty-four mongrel dogs were studied, but the protocol was completed in only 22 (44 arterial beds). Of these, data from 24 beds were excluded because of changes in electromagnetic blood flow measurements greater than 10% during microsphere injections. In three dogs (six arterial beds), technical difficulties occurred with the withdrawal of a reference sample during microsphere injection; one dog (two arterial beds) was excluded because of a technically inadequate parametric image. Thus, this report is based on 12 arterial beds from nine dogs.

Statistics

Comparisons of hemodynamic variables and flow data at rest and during hyperemia under control conditions and after coronary constriction were performed by a two-way analysis of variance for repeated measures. CFR at rest and after coronary constriction were compared using a Wilcoxon rank sum test. A least-squares linear regression was used to compare the CFR from the three techniques (digital angiography, electromagnetic flow probe, and microspheres). The intercept and slope, the correlation coefficient, and the standard error of estimate (SEE) as well as the mean difference (accuracy) and the standard deviation of the mean difference (precision) were determined for each comparison. Interobserver variability was calculated from the least-squares linear regression analysis of results obtained by two independent observers. Results were considered to be significant at p<0.05. Results in tables are reported as mean±1 SD.

Results

Representative digital angiograms are shown in Figure 2. Functional images are shown at baseline, during adenosine infusion, and after coronary constriction of the LCx artery at rest and during adenosine administration.

Hemodynamics

Table 1 shows standard hemodynamic data taken at rest (baseline), during adenosine infusion, and after coronary constriction at rest and during adenosine infusion. Heart rate decreased significantly during adenosine infusion under baseline conditions and after coronary constriction. Parallel to the decrease in heart rate, left ventricular end-diastolic pressure increased (p<0.001) during adenosine infusion; after coronary constriction, left ventricular end-diastolic pressure increased significantly (p<0.05) when compared with baseline and tended to increase further, but not significantly, after adenosine infusion. Left ventricular peak systolic pressure remained unchanged during the experiment through use of the aortic constrictor. Mean aortic pressure, however, decreased significantly during adenosine infusion because of peripheral vasodilation.

Coronary Flow Measurements

Table 2 shows coronary blood flow data under control conditions and after coronary constriction at rest (baseline) and during adenosine infusion. Coronary blood flow (ml/g/min) increased significantly
during adenosine infusion. Flow data were in the same range (NS) for the electromagnetic flowmeter and microsphere techniques. Absolute coronary blood flow cannot be measured with parametric imaging and, therefore, a coronary Fl (as defined in “Materials and Methods”) is reported for parametric imaging in Table 2. CFR on the average was similar (NS) with all three techniques, ranging from 3.71 (microspheres) to 4.17 (parametric imaging). Coronary constriction was associated with a significant reduction in hyperemic blood flow, but resting coronary flow was not different from baseline. CFR was reduced significantly by all measurement methods after coronary constriction when compared with baseline.

Correlations Between Electromagnetic Flow Probe, Microspheres, and Parametric Imaging

Coronary blood flow. Normalized coronary blood flow (electromagnetic flowmeter) and transmural myocardial blood flow (microspheres) showed a good correlation (Figure 3) ($r=0.87$), with an SEE of 0.78 ml/g/min (36% of mean blood flow). Correlation between coronary Fl (parametric imaging) and transmural blood flow (microspheres) was good (Figure 3), but parametric imaging underestimated high blood flows. When a semilogarithmic plot was used, the correlation coefficient between coronary Fl and the natural logarithm of transmural blood flow was 0.81, with an SEE of 0.32 (40% of the mean blood flow).

Coronary flow reserve. There was a good correlation (Figure 4) between CFR measured with the electromagnetic flowmeter and microspheres ($r=0.82$), with an SEE of 0.93 (28% of the mean CFR). The correlation of CFR determined with parametric imaging and microspheres was only moderate ($r=0.54$), with an SEE of 1.46 (39% of the mean CFR). The correlation of electromagnetically derived CFR and parametric imaging CFR was somewhat better ($r=0.68$) and was associated with an SEE of 1.35 (40% of the mean CFR) (Figure 5).

The angiographic flow reserve parameters (Figure 6) such as contrast density ratio, arrival time ratio, and Fl ratio (CFR) also showed a weak correlation with the CFR estimates based on microsphere-derived data; the correlation coefficient was 0.48 for the contrast density ratio, 0.47 for the arrival time ratio, and 0.54 for the FI ratio.

Accuracy and Precision

Table 3 shows accuracy and precision among the three techniques. Coronary blood flow was significantly less when it was determined by the flowmeter
than by the microsphere technique. The mean difference (accuracy) of coronary blood flow between the electromagnetic flow probe and microspheres was $-0.68$ ml/g/min ($p<0.001$ versus zero) with an SD of difference (precision) of 0.94 ml/g/min. The mean difference in CFR between the electromagnetic flowmeter and parametric imaging measurements was smaller ($-0.10$) than between the flowmeter and microspheres (0.22) or microspheres and parametric imaging ($-0.64$), but none of these was significantly different from zero; that is, both the electromagnetic flowmeter and the parametric images showed good accuracy. The SD of difference or precision for CFR measurements was better between the electromagnetic flowmeter and microsphere measurements (1.0) than between microspheres and parametric imaging (1.7).

**Observer Variability**

There were excellent correlations between the two independent observers for intensity fraction ($r=0.97$), arrival time ($r=0.93$), coronary FI ($r=0.95$), and CFR ($r=0.90$) as assessed by parametric imaging (Figure 7). The SEE for CFR was 20% between observer 1 and 2, the mean difference was 0.34, and the SD of difference was 0.79.

**Discussion**

Estimates of stenosis severity using conventional coronary arteriography are based on anatomic criteria that may not reflect the physiological significance of a coronary stenosis. The effect of diffuse atherosclerosis or eccentric lesions on CFR is difficult to estimate solely from the anatomic informa-

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**Table 1. Hemodynamic Data**

<table>
<thead>
<tr>
<th></th>
<th>Heart rate (beats/min)</th>
<th>LVEDP (mm Hg)</th>
<th>LVSP (mm Hg)</th>
<th>MAP (mm Hg)</th>
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<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
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<tr>
<td>DSA</td>
<td>140±10</td>
<td>18±7</td>
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<tr>
<td>Microspheres</td>
<td>140±11</td>
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<td>Hyperemia</td>
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<tr>
<td>DSA</td>
<td>122±11*</td>
<td>23±9†</td>
<td>145±22</td>
<td>114±21†</td>
</tr>
<tr>
<td>Microspheres</td>
<td>121±12*</td>
<td>21±8</td>
<td>147±19</td>
<td>116±20‡</td>
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<tr>
<td>Stenosis baseline</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>DSA</td>
<td>134±12</td>
<td>21±11</td>
<td>154±19</td>
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<tr>
<td>Microspheres</td>
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<td>156±18</td>
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<tr>
<td>Stenosis hyperemia</td>
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<tr>
<td>DSA</td>
<td>120±13*</td>
<td>25±13</td>
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<tr>
<td>Microspheres</td>
<td>121±13*</td>
<td>24±13</td>
<td>147±29</td>
<td>120±25</td>
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</table>

Data were acquired at rest (baseline), during adenosine infusion (hyperemia), and after coronary constriction at rest (stenosis baseline) and during adenosine infusion (stenosis hyperemia). Data are reported just before acquisition of digital angiograms (DSA) and during microsphere injection. LVEDP, left ventricular end-diastolic pressure; LVSP, left ventricular peak systolic pressure; MAP, mean aortic pressure.

*p<0.001 vs. rest.
†p<0.01 vs. rest.
‡p<0.05 vs. rest.

**Table 2. Coronary Blood Flow Data**

<table>
<thead>
<tr>
<th></th>
<th>EMF (ml/g/min)</th>
<th>Microspheres (ml/g/min)</th>
<th>DSA (sec⁻¹)</th>
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<tr>
<td>Control conditions (n=17)</td>
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<tr>
<td>Baseline</td>
<td>1.08±0.35</td>
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<tr>
<td>Hyperemia</td>
<td>3.90±1.24</td>
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<tr>
<td>CFR</td>
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<td>Coronary stenosis (n=7)</td>
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<tr>
<td>Baseline</td>
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<tr>
<td>Hyperemia</td>
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<tr>
<td>CFR</td>
<td>1.93±0.68†</td>
<td>1.53±0.75†</td>
<td>2.63±0.92†</td>
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Data were acquired from nine dogs under control conditions and after coronary constriction at rest (baseline) and during adenosine infusion (hyperemia). Flow data for electromagnetic flow probe (EMF) are reported during microsphere injection. DSA, digital subtraction angiography (parametric imaging); CFR, coronary flow reserve (hyperemia/rest).

*p<0.001 vs. control conditions.
†p<0.01 vs. control conditions.
tion derived from coronary arteriography. Several attempts have been made to directly quantify CFR in patients with coronary artery disease by gas clearance methods, thermodilution, digital angiography, Doppler flow techniques, positron emission tomography, and newer approaches such as contrast echocardiography, ultrafast computed tomography, and magnetic resonance imaging. Each technique is characterized by certain limitations, and none has been used thus far to assess the functional significance of a coronary stenosis in daily clinical practice.

Use of parametric imaging to assess CFR is conceptually appealing, because the same technique can be used to determine anatomy and the functional significance of a stenosis. Coronary arteriography remains the gold standard for determining the location and severity of coronary artery disease and provides the basic information necessary for performing coronary bypass surgery. Thus, the combination of quantitative coronary arteriography and parametric imaging would seem to have considerable potential for widespread clinical application. There has been, however, some debate on the value and limitations of parametric imaging for assessing CFR. For example, Nishimura et al. observed that videodensitometric measurements of CFR do not accurately reflect CFR measured by microspheres. Accordingly, the purpose of the present study was to carefully reevaluate the accuracy and precision of a specific parametric imaging method for assessing CFR in the experimental animal and to compare this method to two standard techniques, electromagnetic flowmeters and microsphere measurements.

**Coronary Blood Flow and Coronary Flow Reserve**

In the present study, coronary blood flow was examined over a wide range in normal and stenotic conditions both at rest and during hyperemia induced by adenosine. Comparisons were made between parametric imaging, electromagnetic flowmeters, and microspheres under steady-state conditions with minimal changes in the hemodynamic determinants of coronary blood flow (Table 1). Radiographic measurements of coronary FI and CFR were made during the first 1.5–5 seconds of contrast material injection in an effort to minimize the effect of contrast medium on coronary flow.

There was some scatter between the electromagnetic flowmeter and microsphere measurements of absolute flow (Figure 3), with an SEE of 0.8 ml/g/min and an SD of difference of 0.9 ml/g/min. The scatter may be explained, at least in part, by the fact that muscle mass of the perfusion bed of the LAD and LCx arteries had to be determined for normalization of electromagnetic flow data and by the fact that collateral blood flow is not taken into account by the electromagnetic flowmeter. Some scatter also was

<table>
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<th>Table 1</th>
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<th>Normal</th>
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<td>Norm</td>
<td>Stenosis</td>
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<tr>
<td>Stenosis</td>
<td>1.2</td>
<td>0.5</td>
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</table>

**Figure 3.** Correlation between transmural blood flow (microspheres) and normalized coronary blood flow (electromagnetic flow probe [EMF]) (left panel) and coronary flow index (parametric imaging [CMAP]) (right panel). Correlation was fair for both comparisons, with a correlation coefficient of 0.87 and 0.81, respectively. Because large transmural blood flows were underestimated by parametric imaging, a semilogarithmic plot between parametric imaging and microsphere data was chosen. SEE was 0.78 ml/g/min and 0.32 ml/g/min, respectively.

**Figure 4.** Correlation of coronary flow reserve (CFR) between electromagnetic flow probe (EMF probe) and microspheres (left panel) and parametric imaging (CMAP) and microspheres (right panel). Correlation between EMF and microsphere data is clearly better (r=0.82) than between CMAP and microspheres (r=0.54). SEE is 0.93 and 1.46, respectively.
reported between coronary blood flow measurements using the microsphere technique and flow measurements by collection of coronary venous return in dogs and sheep. The comparison of coronary FI (parametric imaging) and microsphere flow data also showed some variations, with an SEE of 0.32. Perhaps most importantly, high coronary blood flows were underestimated by the FI (Figure 3).

CFR estimates based on the electromagnetic flowmeter data paralleled the microsphere-derived data well but tended to underestimate CFR measured with microspheres at higher flow rates. The correlation coefficient was 0.82, with an SEE of 0.93 (Figure 4). The correlation between parametric imaging and microspheres was characterized by greater scatter (Figure 4) with a larger SEE (1.46). The correlation between parametric imaging and electromagnetic flowmeter measurements was slightly better (Figure 5). The correlations clearly are not as strong as those that have been reported previously. The mean difference (accuracy) was, however, good (−0.1), although the SD of difference (precision) was poor (1.4) (Table 3). Interobserver variability, however, was excellent and cannot explain the scatter in measuring CFR by parametric imaging.

Other angiographic flow reserve parameters such as intensity fraction ratio and arrival time ratio were characterized by weaker correlations with the microsphere data (Figure 6) than the ratio of the two. Similarly poor correlations and wide scatter between videodensitometric measurements and microsphere data were reported by Nishimura and coworkers.

Limitations

The limitations of this study relate to three broad areas: the use of radiographic techniques, the unique limitations of the specific parametric imaging modality chosen for study, and the limitations imposed by the model and protocol that were necessary for the successful acquisition of adequate microsphere data and digital angiograms.

In general, some inaccuracy and imprecision results whenever radiographic techniques are used to analyze two-dimensional images of a three-dimensional perfusion bed. In the left posterior oblique projection used in most studies, the area of interest for measuring coronary blood flow represents an integral of different perfusion areas in the posterolateral wall, including subendocardial and subepicardial perfusion zones. Consequently, defining the precise three-dimensional location of the myocardial perfusion zone under investigation is difficult. Additionally, recirculation of contrast through the coronary sinus may cause difficulties with density mea-

**FIGURE 5.** Correlation of coronary flow reserve (CFR) between parametric imaging (CMAP) and electromagnetic flow probe (EMF). The correlation is moderate, with a correlation coefficient of 0.68 and an SEE of 1.35.

**FIGURE 6.** Correlations of coronary flow reserve (CFR) between parametric imaging (CMAP) (ordinate) and microspheres (abscissa). CFR was determined from the intensity fraction ratio (top panel), the arrival time ratio (middle panel), and the ratio of the intensity fraction divided by the arrival time (bottom panel). All three comparisons showed weak correlations.
measurements. Although it has been assumed that the inaccuracies of videodensitometry should cancel each other out when density ratios are calculated (i.e., densities at baseline and hyperemia), this may not always be the case, because the amount of contrast material in the myocardium during hyperemic images is likely to be greater. Furthermore, the spillover can vary from injection to injection depending on absolute coronary blood flow and coronary vascular resistance. These factors will cause differences in the effects of scatter and beam hardening on the density values.

The specific parametric method we used is limited by the temporal imprecision inherent in once-per-cardiac-cycle image analysis of appearance time and density. This factor probably is most important in explaining the systematic underestimation of high flows noted in Figure 3. These errors would tend to cause overestimation of appearance time and underestimation of contrast density. Cusma et al. suggested that improvement in the temporal resolution of the method could be achieved by interpolation methods and that this could simultaneously improve determination of actual appearance time and peak density. Such methods were not used in this study because we set out to examine the methodology originally proposed in an earlier report in which this factor was taken into account only by assigning values of 0.5, 1.5, and 2.5 cycles to the first, second, and third images, etc. The limitation imposed by this factor may be more notable in the current study than in prior studies because maximal flow was sustained by continuous infusion of adenosine and maintenance of perfusion pressure, whereas prior validation attempts used submaximal stimuli such as atrial pacing and graded contrast injections. An underlying prerequisite for this method of parametric CFR imaging is that contrast material must virtually displace blood. The need for this was recognized in prior studies and was explicitly elucidated by Cusma et al. This prerequisite can be approximated, but it is virtually impossible to guarantee it, especially during hyperemic flow, despite the use of maximally tolerable doses of contrast injected rapidly. Although studies with overt streaming and/or subselective contrast injection were omi-

### Table 3. Accuracy and Precision

<table>
<thead>
<tr>
<th></th>
<th>Mean difference</th>
<th>SD</th>
<th>Mean absolute difference</th>
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</thead>
<tbody>
<tr>
<td><strong>Coronary blood flow (n=48)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>EMF vs. microspheres</td>
<td>−0.68*</td>
<td>0.94</td>
<td>0.90±0.73*</td>
</tr>
<tr>
<td><strong>Coronary flow reserve (n=24)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMF vs. microspheres</td>
<td>0.22</td>
<td>1.04</td>
<td>0.71±0.78*</td>
</tr>
<tr>
<td>EMF vs. DSA</td>
<td>−0.10</td>
<td>1.38</td>
<td>1.05±0.88*</td>
</tr>
<tr>
<td>DSA vs. microspheres</td>
<td>−0.64</td>
<td>1.70</td>
<td>1.39±1.14*</td>
</tr>
</tbody>
</table>

Mean differences (accuracy) and standard deviation (SD) of difference (precision) for comparison of coronary blood flow and coronary flow reserve between electromagnetic flow probe (EMF), microspheres, and digital subtraction angiography (DSA). Mean absolute difference values are mean±SD.

*p<0.001 versus zero (paired t test).

**FIGURE 7.** Interobserver variability for intensity fraction (upper left panel), arrival time (upper right panel), flow index (lower left panel), and coronary flow reserve (CFR) (lower right panel) as measured with parametric imaging.
ted from analysis, the possibility of more subtle streaming or preferential flow of contrast into one or the other coronary arteries when contrast was injected into the main stem of the arterial bed could not be completely eliminated. It is possible that this limitation might be overcome by relating the peak density in the myocardial bed to the peak density in the proximal coronary arteries so that the input of contrast and the actual degree of blood displacement achieved by the bolus injection can be taken into account. This approach would require more precise registration of the proximal arteries and avoidance of segments superimposed by reflux into the aortic root to avoid invalidating the intraluminal density values.

The experimental model and protocol we used also presented some unavoidable limitations. The microsphere technique requires a prolonged steady state for injection and collection of samples. This precluded acquisition of the parametric images simultaneously with the microsphere injections. Moreover, the prolonged, systemic infusion of adenosine and the maximal hyperemia of the entire vascular bed may have promoted substantial collateral flow, a factor known to diminish the CFR value. This possibility is supported by the general underestimation of microsphere-determined perfusion by flowmeter measurements. In theory, measurement of contrast density in the myocardium rather than in the arteries should have reduced error due to collateral perfusion. The effects of the contrast agent on red cell morphology and the resultant effects on the rheological characteristics of collateral flow, however, may have led to an underrepresentation of collateral flow by the parametric imaging technique, which always was performed after the microsphere determination of blood flow. In addition, although nonionic contrast was used, such agents can cause a diminution of blood flow that may have caused underestimation of maximal CFR. Capillary solubility, uptake by myocardial cells, extravasation into the extracellular space, and the effect of the high viscosity and osmotic pressure of the dye itself on the small vessels all may influence the densitometric assessment of perfusion. Finally, the variability of microsphere measurements and the regional heterogeneity of CFR measures by microspheres cannot be ignored, although this technique is considered the gold standard for measures of myocardial perfusion.

Comparison to Prior Validation Studies

With these limitations in mind, a more meaningful comparison of this validation study can be made to prior studies. The initial clinical validation of the appearance time concept for measures of flow changes was undertaken using atrial pacing as the hyperemic stimulus and coronary sinus blood flow as the reference measure. Because atrial pacing does not induce maximal hyperemia, CFR estimates probably were not as adversely affected by the factors of high flow and collateralization, which may have played a major role in the present study. On the other hand, the coronary sinus flow measurements cannot be considered a true gold standard for measuring myocardial perfusion. Finally, because the study did not include an analysis of density, the inaccuracies of videodensitometry could not have affected the results.

Subsequently, another validation study was undertaken in dogs, using contrast material as the vasodilating substance. A range of CFR values was created by graded doses of contrast material, whereas in our current study, flow was altered by imposing a stenosis on a fully vasodilated bed. This means that only submaximally dilated states were evaluated in the earlier study and that problems potentially related to high flow and collateralization probably were not critical. Furthermore, in the absence of maximal vasodilation, blood may have been more adequately displaced by contrast material, thereby minimizing the errors of videodensitometry and the errors caused by potentially insufficient contrast injection.

In the study of Cusma et al, electromagnetic flowmeter measurements were used as the only reference standard. A curve interpolation method, discussed above, was used to improve density and temporal resolution. Intracoronary boluses of adenosine were used, and the transient hyperemia that resulted may have minimized difficulties attributable to collateral flow. In addition, contrast doses were injected more rapidly (5–10 ml/sec) than in the current study (4 ml/sec). Thus, methodological differences may explain part of the reason we failed to observe correlations similar to those previously reported.

Nishimura et al undertook a study comparing microsphere-derived blood flow estimates with parametric imaging. Differences from our methods include use of gamma variate curve fitting to construct time-density curves, use of the one-half maximum density value to determine the time parameter, use of interpolation to determine peak density, use of highly disparate stimuli to induce changes in blood flow (intracoronary adenosine and vasopressin, rapid atrial pacing), postprocessing from videotaped images, and inclusion of a paucity of high flow reserve values (only three values greater than 2.0). Nonetheless, the conclusion of Nishimura et al is largely similar to our own; that is, parametric image analysis is reproducible, but the CFR values correlate only moderately well with microsphere-determined CFR ratios.

Clinical Implications

Parametric imaging enables estimation of CFR that correlates with microsphere-derived measure of flow reserve only moderately well over a wide range of values in this animal model. On the average, however, CFR results obtained by parametric imaging were not different from values measured by the electromagnetic flowmeter and microsphere tech-
niques. The specific parametric technique has inherent limitations that lead to imprecision in the measurements. At the present time, only changes of 40% or greater in CFR can be expected to be demonstrated reproducibly with this specific parametric method. Efforts directed at improving the accuracy of both time and density measurements, minimizing the effects induced by contrast material and collateral flow, and avoiding the need for full displacement of blood by contrast material will be required to make the methodology more precise.

References

Key Words • coronary flow reserve • digital subtraction angiography • microspheres • electromagnetic flow measurements
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