Digital subtraction angiographic imaging of coronary flow reserve

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ABSTRACT Recent studies have demonstrated that subjective assessment of the severity of coronary artery stenoses results in poor interobserver concordance and poor correlation with physiologic significance as determined by Doppler measurements of coronary flow reserve. Use of the coronary flow reserve as an integrated measure of the effect of stenosis geometry has been emphasized within the context of quantitative cinemetric analysis. The comparison of two parametric digital subtraction angiographic flow images obtained before and after hyperemic intervention has led to calculation of flow reserve values that correlate well with electromagnetic flowmeter data in dogs. By means of a similar model relating blood flow and image variables, single flow ratio images have been formed. These parametric images provide a two-dimensional display of the ratio of hyperemic flow to baseline flow. Linear temporal interpolation of data from a sequence of cardiac phase-matched subtraction images is used to improve the resolution of the displayed flow ratios. Summation of flow variables measured within the perfusion bed was used to calculate a value for the overall coronary flow reserve and to characterize the significance of isolated lesions in an open-chest canine preparation. A linear regression calculation relating parametric image flow ratio values to electromagnetic flowmeter measurements resulted in a linear fit of $y = 0.96x - 0.19$ with a correlation coefficient of $0.90$. The direct visual representation of flow ratio distribution provided by the parametric imaging method may aid in the interpretation of multiple complex lesions as well as of single lesions.


CORONARY ARTERIOGRAPHY remains the standard method for defining coronary anatomy and assessing coronary atherosclerosis. This method is limited by interobserver variability in the interpretation of angiograms and by poor correlation with postmortem anatomic findings. A third limitation has recently been emphasized as methods to measure coronary flow reserve in humans have been developed. The results of such measurements indicate a general lack of correlation between flow reserve and angiographically measured percent stenosis.

Reduction in coronary flow reserve, which has been proposed as an integrated measure of the physiologic significance of coronary stenosis, had previously been shown to be directly related to percent diameter reduction in an animal preparation of solitary stenosis. However, intraoperative measurement of coronary flow reserve has failed to correlate percent diameter reduction with reduction in flow reserve in humans. Absolute luminal cross-sectional area in proximal left anterior descending arteries and percent area stenosis in patients with single-vessel disease have been reported to correlate moderately well with changes in flow reserve. These findings, however, were in small select patient subgroups and may not be generally applicable.

Because of these major limitations of standard cineangiography, a functional measure of stenosis severity such as measurement of flow reserve obtainable during cardiac catheterization is desirable. This additional clinical data would be complementary to the anatomic data obtained during coronary angiography. The use of digital angiographic techniques provides the potential for obtaining such data by its ability to provide quantitative information in addition to the anatomic information present in the angiogram. Analysis of the temporal and spatial changes in contrast density can be used to...
obtain measurements of physiologic variables such as blood flow and coronary flow reserve.11

The aims of this study include the validation in a single-lesion preparation of coronary stenosis of a parametric flow model and the generation of a single parametric image for direct visual estimation of coronary flow reserve. The ratio of flow variables obtained during hyperemic flow and baseline flow is measured at every location in the myocardium and is encoded as a grey-scale value at the corresponding location in the parametric image, thus providing a direct visual representation of flow reserve. The technique includes the use of an interpolation algorithm to measure contrast arrival time with improved temporal resolution.

Methods

Theory. Coronary reactive hyperemia has been applied in animal preparations as an indicator of coronary vascular reserve. This response to temporary occlusion of the coronary vessels has characteristic effects on contrast pass curves after selective coronary injection of contrast material as illustrated in figure 1. This is a plot of intensity profiles obtained by videodensitometry in the perfusion bed of the left anterior descending coronary artery (LAD) of a dog. The contrast pass curves are shown after injection of contrast into the left coronary artery for resting flow and for hyperemic flow after a 30 sec occlusion of the LAD. The increase in the peak value \( C_{max} \), which theoretically is due to changes in the vascular volume, and the decrease in the time of arrival \( T_{arr} \) when contrast reaches the sampling point are evident. A model for flow that relates these two measured variables to coronary blood flow is described in Appendix 1, where it is demonstrated that, under certain conditions, the coronary blood flow is approximately proportional to a \( \dot{Q} \) parameter defined as:

\[
\dot{Q} = \frac{C_{max}}{T_{arr}}
\]

(1)

Determination of \( \dot{Q} \) for resting flow conditions and for hyperemic flow allows the calculation of the flow ratio value:

\[
R_Q = \left( \frac{C_{max}}{T_{arr}} \right)_{hyp} / \left( \frac{C_{max}}{T_{arr}} \right)_{rest}
\]

(2)

The calculation of \( C_{max} \), \( T_{arr} \), and the \( \dot{Q} \) parameter can be implemented by digital image processing after selective injection by contrast into the coronary artery. The calculated values are then used to determine the flow ratio at every point in the image and an image of these values is produced. If maximal flow is produced, the two-dimensional distribution of \( R_Q \) provides a parametric image of the coronary flow reserve.

Animal preparation. Six mongrel dogs weighing 33 to 45 kg were sedated with morphine sulfate (3 mg/kg) and anesthetized with sodium pentobarbital, endotracheally intubated, and ventilated with a mixture of room air and oxygen to maintain blood gases within the physiologic range. Arterial blood gases were obtained and supplemental oxygen was administered as necessary. A modified left thoracotomy was performed and the heart was suspended in a pericardial cradle. The internal mammary artery was cannulated with polyethylene tubing and aortic pressure was measured with a calibrated Statham P23DB pressure transducer. The LAD and left circumflex coronary artery were dissected in their proximal portions and electromagnetic flow probes of appropriate size were applied. Mechanical zeros were checked frequently during the protocol to compensate for drift. Any visible significant collateral vessels were ligated to reduce the potential error in flow reserve values obtained from parametric images that might arise because of significant collateral flow. Chlorpromazine (0.5 mg/kg) was administered intravenously to prevent spontaneous platelet thrombus formation during the application of stenoses.12 Morphine sulfate was used to maintain heart rate within the 100 to 120 beat/min range. The animals were not paced and any change in heart rate or blood pressure greater than 10% from baseline to hyperemic conditions was reason for exclusion of the image data from the analysis. This ensured that changes in blood flow were due solely to the action of the vasodilating agent and that the parametric imaging result was an accurate measure of flow reserve.

The femoral artery and vein were isolated. The vein was used for the administration of medication and intravenous fluids. A preformed coronary angiographic catheter (brachial preform left 1 bend) was used to engage the left coronary ostia. Ischemia-induced reactive hyperemia was produced with the catheter engaged in the coronary ostia and with its tip in the ascending aorta to ensure that no blunting of reactive hyperemia occurred because of the presence of the coronary catheter. A maximal hyperemic response defined as equal to that produced by a 30 sec coronary occlusion was used to determine the intracoronary dose of adenosine (1 to 3 mg at 0.5 mg/ml concentration) used to induce hyperemia. Electrocardiogram (ECG), aortic blood pressure, and LAD and circumflex flows were recorded on an eight-channel Gould model 481 recorder.

Each animal was positioned under the image intensifier and an optimal projection separating the LAD and circumflex perfusion beds was selected (usually steep left anterior oblique with 10 to 15 degree cranial angulation). The intensifier was operated in the 15 cm mode, resulting in a pixel size of approximately 0.3 mm on a side. Images were obtained after injection by an ECG-triggered power injector of 3 ml of standard contrast material (Renografin-76) at a rate of 6 ml/sec or 5 ml at a rate of 10
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Figure 2. Sequence of cardiac phase-matched subtraction images used to form parametric images. The intensity-time data at each image location are analyzed and the maximum contrast value and the time of arrival at the corresponding heart location are determined.

ml/sec. Images were obtained in the absence of coronary stenoses at baseline and immediately after intracoronary injection of adenosine, allowing for return of coronary blood flow to baseline levels between acquisition of each image sequence. Coronary stenoses of varying severity, as assessed by response to 30 sec coronary occlusion, were applied according to the method of Folts et al., and the imaging sequence was repeated.

Imaging Procedure. Images were acquired with an experimental digital video image processor (DVIP) designed and constructed in our laboratory. The ECG signal was used to synchronize image acquisition and power injection of contrast to the cardiac cycle. The Philips Optimus M200 x-ray generator was operated at a rate of 15 pulses/sec with a pulse duration of 10 msec. The entire image sequence, including one preinjection heart cycle followed by eight to 10 postinjection heart cycles, was logarithmically transformed and stored in $(512)^2 \times 9$ bit format on a real-time digital disk for later processing. The time of injection of the contrast bolus after the R wave varied between 200 and 300 msec, depending on the actual heart rate, but was fixed for a given pair of flow measurements.

Postprocessing. The resulting images from a set of experiments were stored in digital format on a real-time disk from which they were retrieved for analysis. Any sequence of images acquired during a change in heart rate or blood pressure greater than 10% or during presence of ectopy was excluded from analysis. Such changes occurred in fewer than 10% of typical image sequences. After subtraction of a corresponding precontrast mask image, a sequence of eight to 10 images corresponding to the same point in the cardiac cycle (usually end-diastole) was identified as the basic data set (figure 2). From this phase-matched sequence several parametric images were produced by the DVIP and its decision circuitry. This circuitry was used to perform logical and arithmetic operations on every pixel in each image at video rates. In the first step in the analysis, the maximum value of contrast reached during the imaging run was determined for every pixel location and the result was stored in a $C_{max}$ image in the DVIP memory (figure 3). Another memory was used to store a $T_{max}$ image that contained, at every pixel location, the heart cycle when the maximum contrast value was reached.

To arrive at a value for the $\overline{Q}$ parameter at every pixel, a time of arrival of contrast was determined. Sampling of contrast pass information at intervals of one cardiac cycle leads to a limited temporal resolution in values of time of arrival and therefore a discreteness in the final flow ratio values. A linear interpolation algorithm (shown in figure 4) was used to calculate the contrast pass curve values for times between the actual sampled values. This can be expressed for a successive pair of phase matched images:

Acquisition of $C_{max}$ and $T_{max}$

Figure 3. Schematic diagram of the decision circuit used to produce parametric images containing the maximum contrast value $C_{max}$ achieved during a phase-matched sequence and the heart cycle $T_{max}$ in which that value is reached.
The final result is an image that contains, as the value at every pixel, the ratio of flows for the two conditions of flow at that location.

**Time Interpolation**

![Diagram](image)

**FIGURE 4.** Interpolation algorithm used to calculate contrast values during the cardiac cycle. Values measured once every heart cycle are used to determine the contrast values for intermediate points in the cycle.

\[
C_{\text{int}}(x,y) = C(x,y) + k \left( \frac{C_{i+1}(x,y) - C_i(x,y)}{N} \right)
\]

where \( k = 0, 1, \ldots, N - 1 \)

The value of \( i \) ranges through the number of cardiac cycles, and \( N \) is the desired number of interpolated values within a single interval, usually 5. The corresponding time value is:

\[
T_{\text{int}} = T_i + \frac{k}{N} (T_{i+1} - T_i)
\]

where \( \Delta T \) is the length of one cardiac cycle and \( T_i \) is the time of the \( i \)th image after injection. The time of arrival at each pixel \( T_{\text{arr}}(x,y) \) is determined by finding the value of \( T_{\text{int}} \) for which the contrast value reaches half of its peak value:

\[
C_{\text{int}}(T_{\text{arr}},x,y) = 0.5 \ C_{\text{max}}(x,y)
\]

Calculation of a \( T_{\text{arr}} \) image for a sequence of eight phase-matched images with the decision circuit takes 160 frame times (about 5 sec) for five interpolations per cardiac interval.

The \( T_{\text{arr}} \) image is used along with the \( C_{\text{max}} \) image to calculate the value of the \( \dot{Q} \) parameter at every pixel. After analysis of both baseline and hyperemic flow sequences, a final flow ratio image is produced:

\[
R_{\dot{Q}}(x,y) = \frac{\dot{Q}_{\text{hyp}}(x,y)}{\dot{Q}_{\text{rest}}(x,y)}
\]

**Results**

The analysis of experimental image data discussed above results in the production of several parametric images. Examples of \( T_{\text{arr}} \) images generated by the interpolation algorithm are shown in figure 5. These images were generated for hyperemic flow conditions with normal coronary anatomy and after the placement of a circumflex obstruction that reduced the flow reserve in that vessel as measured with flow probes to unity. The qualitative change in the arrival time in the perfusion bed of the circumflex is evident (more brightness indicates a later arrival time). Also shown is a \( T_{\text{arr}} \) image obtained without use of temporal interpolation, thus limited to one sample per cardiac interval. Final flow ratio parametric images are shown in figure 6 for normal anatomy and with a severe stenosis on the circumflex. The intensity at each point in the \( R_{\dot{Q}} \) image is equal to the ratio of \( \dot{Q} \) values calculated for hyperemic flow and resting flow. The change in intensity or flow ratio in the circumflex perfusion bed after placement of a severe stenosis is readily apparent in the parametric images. Images from the corresponding phase-matched image sequences acquired during baseline flow are shown in figure 7. The severe obstruction (approximately 90%) is visible in the standard time-subtraction image.

As is discussed above and in Appendix 1, the ratio of \( \dot{Q} \) parameters in the perfusion bed can be shown to be proportional to the blood flow ratio to the bed. Figure 8, A, is a plot of the parametric image flow ratio values along with values obtained from flow probe measurements of coronary blood flow in six dogs. The coronary flow reserve values measured with electromagnetic flow probes varied over a range of 1.0 to 5.5 due to the use of variable occluders as well as to the variability in flow reserves between animals. The parametric image flow ratios were determined by summing \( \dot{Q} \) values for several regions of interest within a perfusion bed for both resting and hyperemic flows before calculating the overall coronary reserve ratio. As described in Appendix 1, this procedure results in a value for the reserve ratio associated with the lesions of interest that might be expected to be accurate even in the event of uneven distribution of measured flow ratio values, as would occur with the simultaneous presence of stenosed and unstenosed branches distal to a proximal stenosis. Verification of this point will require further study. The regions of interest, which varied in size from 25 to 100 pixels, were chosen to avoid branches of epicardial vessels, and the same regions were used for both flow conditions. The ratio of these sums, which is the final quantitative measure of in-
crease in coronary blood, was determined for 30 sets of flow pairs. Also shown in figure 8, A, is the result of a best linear fit of $y = 0.96x - 0.19$, where $y$ is the flow ratio determined from parametric images and $x$ is the coronary reserve determined by flow probes. Flow ratio values calculated from image sequences obtained with an injection rate of 3 ml/sec are shown in figure 8, B. The underestimation of flow ratio values arises as a result of mixing between contrast and blood, underscoring the need for an adequate injection rate (see Discussion).

The reproducibility of the parametric imaging technique was investigated by performing a series of successive measurements in one dog. After placement of a fixed stenosis on the circumflex branch, eight pairs of baseline-hyperemia image sequences were acquired, using the same dose of intracoronary adenosine to increase flow. The coronary catheter was pulled out and reinserted between each pair of flow measurements. Table 1 shows the results of the flow reserve measurements in the LAD and circumflex artery by flow probe for the series of eight pairs. Also shown are the flow reserve values determined by three observers from the corresponding parametric images produced. Each observer selected four regions of interest in the $\dot{Q}$ images located in the perfusion bed of each artery, and the flow reserve was calculated as described above for each pair. The variability among the three observers is shown in terms of the linear regression relationships between each pair of observers.

Intraobserver variability in the $\dot{Q}$ measurement, a measure of the uniformity of the $\dot{Q}$ values within a bed, is shown in table 2. The standard deviation of the $\dot{Q}$ values was calculated as a percentage of the average for each $\dot{Q}$ image. The average of these variabilities is tabulated for baseline and hyperemic determinations.
FIGURE 6. Parametric flow ratio images. A, Flow ratio image for a normal dog heart. B, Image for the same heart with a severe stenosis placed on the circumflex branch, which reduced the coronary reserve in that vessel to unity.

separately as well as for all 16 $\dot{Q}$ images for each observer.

The high degree of correlation between flow ratio values obtained by the parametric imaging method and actual flow reserve values indicates that, in this animal preparation, parametric images provide an accurate estimate of coronary flow reserve in addition to visualization of the functional effects of a coronary lesion.

Discussion

The limitations in the assessment of coronary stenoses from subjective interpretation of standard coronary cineangiograms are well recognized and have been recently reemphasized.1,9 These include variability in the visual estimation of percent diameter reduction and poor correlation with methods for assessing stenosis severity that measure coronary flow reserve in vivo. Measurements of flow reserve are considered to represent the combined effects of multiple factors that cannot be assessed by standard visual interpretation alone.

The use of intraoperative Doppler velocity probes for the measurement of coronary reserve has been investigated by Harrison et al.9 Catheter systems presently available can be used to measure intracoronary blood flow velocity during diagnostic catheterization or percutaneous coronary angioplasty. This method has the disadvantage of measuring flow velocity rather than absolute blood flow, which may lead to inaccurate values for the flow reserve if significant change occurs in coronary cross-sectional areas between baseline and

FIGURE 7. Phase-matched time subtraction images used to produce the parametric images of figures 6 and 7. A, Time subtraction image acquired during baseline flow in a normal heart. B, Time subtraction image acquired during baseline flow after placement of a severe stenosis on the circumflex artery.
hyperemia. In addition, the use of subselective coronary cannulation may add increased risk during catheterization.

A number of methods have been proposed recently that have in common the derivation of quantitative estimates of coronary flow reserve from angiographic sequences using both standard cine and digital techniques. Prediction of coronary flow reserve through a geometrical analysis of a stenosis based on hydrodynamic principles has been reported by Kirkeeide et al. Calculated values correlated well with measured flow reserve in an animal preparation of a single stenosis, but extension of the method to more complex situations with sequential or branch lesions may be limited.

Several methods incorporating digital angiographic techniques have been used for calculating flow reserve. Initial work by Vogel et al. assumed flow during baseline and hyperemia to be proportional to the inverse of contrast arrival time. This method demonstrated a good linear correlation with measured values of flow reserve but consistently underestimated the actual values. An improved correlation was obtained by the same group when changes in regional vascular volume were accounted for by using mean contrast density as a volume measure. Separate images were obtained for baseline and hyperemia with the arrival time color encoded and the contrast density intensity encoded for each image. Analysis of both images is required to obtain a value for the coronary reserve. An alternative approach, which is an extension of dye dilution techniques to digital angiography, has been investigated by Nissen et al. Such techniques, also used by Foerster et al. to calculate hyperemic ratios, require subselective contrast injection into the coronary vessel of interest, adding increased risk to the catheterization procedure. Vessel misregistration resulting from cardiac motion is more likely to produce errors in such a method compared with our method, which uses digital values measured in the myocardium to calculate the flow reserve. In addition, as required

| TABLE 1 |
| Results of reproducibility and interobserver variability studies in a single lesion parametric imaging method: measurements of coronary flow reserve in eight successive trials |

<table>
<thead>
<tr>
<th>CFR</th>
<th>LAD</th>
<th>Circumflex</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFR (Obs 2)</td>
<td>0.98</td>
<td>CFR (Obs 1) - 0.11</td>
</tr>
<tr>
<td>CFR (Obs 2)</td>
<td>1.17 CFR (Obs 3) - 0.33</td>
<td>r = .97</td>
</tr>
<tr>
<td>CFR (Obs 1)</td>
<td>1.14</td>
<td>CFR (Obs 3) - 0.09</td>
</tr>
</tbody>
</table>

CFR = coronary flow reserve.

| TABLE 2 |
| Intraobserver variability in Q measurement |

<table>
<thead>
<tr>
<th></th>
<th>Observer 1</th>
<th>Observer 2</th>
<th>Observer 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (8 trials)</td>
<td>18 ± 12</td>
<td>14 ± 4</td>
<td>17 ± 6</td>
</tr>
<tr>
<td>Hyperemia (8 trials)</td>
<td>18 ± 6</td>
<td>8 ± 4</td>
<td>16 ± 7</td>
</tr>
<tr>
<td>Overall</td>
<td>18 ± 9</td>
<td>11 ± 5</td>
<td>17 ± 7</td>
</tr>
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aVariability in Q parametric image values in four regions of interest in the LAD perfusion bed expressed as a percentage of the average measured Q variable. The average variability from a total of 16 such determinations is shown for three observers. The independent selection of the regions of interest by each observer is described in the text.
by all dye dilution methods, the ratio of contrast masses that pass the arterial sampling point must be known, thus limiting this technique to evaluation of proximal lesions.

The goal of our work has been to extend digital subtraction angiographic techniques to obtain a single parametric image that can be used to assess qualitatively the functional significance of simple and more complex systems of coronary lesions.

Initial results demonstrate the possibility that such parametric images can also be used to measure the relative values of flow for hyperemic and resting conditions. This provides a means for determining the coronary flow reserve and assessing quantitatively the physiologic significance of coronary stenoses in addition to, and independent of, the standard anatomic image obtained at catheterization. Analysis of parametric images obtained for resting and hyperemic conditions provides values for the ratio of overall coronary blood flow that are in good agreement with values determined by electromagnetic flow probes.

To arrive at accurate and reliable estimates of coronary flow reserve from parametric images obtained with digital subtraction techniques, it is necessary to address a number of factors that limit all angiographic techniques. It is assumed that the contrast medium used as an indicator of blood flow does not itself affect the blood flow. Since the first efforts at measuring blood flow it has been acknowledged that a three-phased response in blood flow takes place after selective injection of ionic contrast media. There is a small increase in flow that occurs during injection, followed by a decrease in flow that lasts up to several seconds and a hyperemic response that peaks at 10 sec after injection. The magnitude of the decrease and the hyperemic response has been shown to depend on the concentration and volume of injected contrast medium. Any transient effect on blood flow during the acquisition of x-ray images introduces error into the determination of flow. It has been reported that the fractional decrease in flow is the same for baseline and hyperemic flow, making it possible to still obtain accurate flow ratios. Figure 9 is a recording of the coronary blood flow measured with an electromagnetic flow probe for baseline and hyperemic flow with an injection rate of 7.5 ml/sec and a bolus of 4.0 ml. Our experience in dogs with a volume of 3 ml of Renografin-76 indicates that the fractional decrease in flow after injection is 10% to 15% less for hyperemic flow in normal vessels. We observed smaller flow decreases for stenosed vessels. To minimize effects on flow, as small a contrast volume as possible is used, which results in good image quality. In addition, use of the leading edge of the contrast pass curve in the determination of arrival time avoids the later hyperemic portion of the flow response. Another advantage of using the front portion of the contrast density curve to determine transit time to the bed is minimization of errors due to effects of background contrast signals as discussed by Bürsch and Heintzen. The use of nonionic contrast medium has been reported to have similar effects on coronary flow because of its high viscosity. Use of such agents, therefore, may not avoid the changes in blood flow and may not improve the accuracy of this technique.

The $Q$ parameter in the flow model described in Appendix 1 includes $C_{max}$ as a measure of regional vascular volume to calculate the change in volume in the distal bed between baseline and hyperemia. The

*Personal communication with G. B. J. Mancini, VA Medical Center, Ann Arbor, MI.
assumed relationship between $C_{max}$ and volume is valid only if the concentration of iodine is the same for both baseline and hyperemic conditions. This requires in turn the use of a sufficiently fast injection rate so that mixing between blood and contrast does not occur. If mixing does occur, then the iodine concentration changes between baseline and hyperemia and no simple relationship exists between $C_{max}$ and vascular volume. This is demonstrated in figure 10, which shows the passage of contrast in the proximal circumflex artery with an injection rate of 3 ml/sec. Since the epicardial vessel volume does not change significantly on this time scale, the ratio of $C_{max}$ values in this case does not reflect volume change. The results of flow ratio calculations for flow pairs with an injection rate of 3 ml/sec are shown in figure 8, B. Because mixing is more likely to occur during hyperemic flow, the result is an underestimation of the flow ratio at high values. Therefore an injection rate of 6 ml/sec was used for five dogs and a rate of 10 ml/sec was used for one dog that had a resting flow of 150 ml/min and a hyperemic flow of 570 ml/min.

The analysis of parametric image data described above requires measurement of $\dot{Q}$ values in the distal bed. This provides an advantage over methods that measure values in the epicardial vessels because of the difficulty in obtaining re-registration of the vessels in the same position in the image between cardiac cycles as well as between baseline and hyperemia. Misregistration can also occur within an image sequence if image acquisition is not synchronized to the cardiac cycle. Soft tissue misregistration artifacts caused by respiratory or other patient motion can occur as well. Use of dual-energy techniques may be found useful in eliminating misregistration caused by such soft-tissue motion that would lead to errors in flow reserve calculations and is presently under investigation in our laboratory.

To provide accurate values for the ratio of hyperemic flow to baseline flow, it is necessary that the experimental procedure itself not induce alterations in the distribution of flow. This would be possible, for example, if placement of the injection catheter led to unequal increase in flow between regions because of nonuniform injection of the vasodilating agent. Catheter-induced aortic valve insufficiency will also lead to errors in the $T_{max}$ image and thus to inaccurate flow ratio values.

**Summary.** We have produced parametric flow ratio images that can be used to calculate the coronary flow reserve in order to determine the functional significance of single stenoses. Such parametric images, which contain the value of the relative increase in coronary blood flow from resting conditions after administration of a vasodilating agent, have been formed by processing digital subtraction images after selective injection of contrast. Encoding of the flow ratio values in the intensity of the parametric image makes it possible to assess regional differences in flow ratio values directly from a single parametric image. In situations where multiple lesions are present, it is expected that the calculated flow ratios will vary with position. In such situations care must be taken in the interpretation of the numerical flow ratios because proximal lesions can alter perfusion pressure above branch lesions, diverting flow to those branches of the distal bed that have the greatest remaining reserve (coronary steal). In the presence of such a complex distribution of lesions, the local flow ratios are no longer simply related to the ratio of the baseline and hyperemic resistance of the regional vascular beds. We propose that the method is still valid for determining overall flow reserve in the presence of multiple and complex lesion distributions. This hypothesis is presently under investigation.

Parametric imaging results from animal studies involving single-vessel lesions demonstrate a potential
for the accurate determination of coronary flow reserve. The parametric imaging technique may be a useful tool that can provide significant physiologic information regarding lesion significance in addition to the anatomic information obtained during standard arteriography.

We acknowledge the assistance of Karen Lund in the preparation of this manuscript and the technical assistance of Steven Smith.

Appendix 1

Derivation of flow model. The formation of parametric flow ratio images requires relating the physiologic variable of coronary blood flow to image-related variables. Measured values of \( C_{\text{max}} \), the maximum contrast value at every image location, and \( T_{\text{arr}} \), the time of contrast arrival at each location, are related to flow through a \( Q \) parameter. The justification for use of the \( Q \) parameter and the underlying assumptions are described in the discussion that follows.

Figure 11 shows schematically the path of blood flow from the injection point at time \( T = 0 \). Flowing from the injection site, the passage of blood proceeds through the epicardial vessel before branching off into regions of the distal bed. The portion of the total blood flow \( Q_i \), that flows into region \( i \) is designated \( Q_i \) and the time at which it arrives in region \( i \) is shown as \( T_i \) (defined as the time required to reach half of peak contrast). The value \( t_i \) is the time of arrival of contrast at the interface between the epicardial vessel and the perfusion volume supplied by \( Q_i \) (denoted as \( V_i \)). The flow into region \( i \), therefore, is given as:

\[
Q_i = f_i Q_a = \frac{V_i}{(T_i - t_i)} \tag{A1}
\]

where \( \sum f_i = 1 \).

The model includes the assumption that, at the time of maximum contrast in region \( i \), the iodine bolus remains undiluted so that the logarithmically processed contrast signal is proportional to the volume of those vessels filled with iodine:

\[
C_{\text{max}}^i = \alpha V_i \tag{A2}
\]

where \( \alpha \) is the constant of proportionality. Substitution of equation A2 in equation A1 results in an expression for the flow \( Q_i \) in terms of variables that can be determined from a digital subtraction angiographic image sequence:

\[
Q_i = \frac{C_{\text{max}}^i}{\alpha (T_i - t_i)} = \frac{k_i}{\alpha} \frac{C_{\text{max}}^i}{T_i} = \frac{k_i}{\alpha} Q_a \tag{A3}
\]

where \( k_i = T_i/(T_i - t_i) \) is the ratio of the observed arrival time to the time spent in the region \( V_i \).

Equation A3 is an expression relating the measured flow variable \( Q_i \) and the regional blood flow \( Q_i^\text{rest} \). This can be rewritten as:

\[
Q_i = k_i Q_a \tag{A4}
\]

where \( k_i' = k_i/\alpha \). In general \( k_i \) and thus \( k_i' \) will vary from one region to another. Since the transit time through the vessel \( t_i \) is relatively short, the variations in \( k_i \) are not large. The requirements on \( k_i \) depend on the particular information that is to be extracted from the model (see below).

The flow reserve in region \( i \) is given by the ratio of regional flow during hyperemia \( Q_i^\text{hyp} \) to that during baseline \( Q_i^\text{rest} \) or:

\[
R_i = \frac{Q_i^\text{hyp}}{Q_i^\text{rest}} \tag{A5}
\]

Expressing \( Q_i^\text{hyp}, Q_i^\text{rest} \) in terms of the measured flow variable results in:

\[
R_i = \frac{k_i^\text{hyp} Q_a^\text{hyp}}{k_i^\text{rest} Q_a^\text{rest}} \tag{A6}
\]

It is evident that, if there is little change in the value of \( k_i \) between baseline and hyperemia, the ratio \( Q_i^\text{hyp}/Q_i^\text{rest} \) provides an accurate measure of the regional flow reserve \( R_i \):

\[
R_i \approx \frac{Q_i^\text{hyp}}{Q_i^\text{rest}} \tag{A7}
\]

In situations where \( k_i^\text{hyp} \) differs significantly from \( k_i^\text{rest} \), such as occurs for high values of flow reserve, then the more accurate expression of equation A6 must be used. Provided that no redistribution occurs between baseline and hyperemia, i.e., \( k_i^\text{hyp} = f_i^\text{hyp} \), then the regional flow reserve \( R_i \), calculated from equation A7 is equal to the overall flow reserve \( R_Q \) since:

\[
R_i = \frac{Q_i^\text{hyp}}{Q_i^\text{rest}} = \frac{f_i^\text{hyp} Q_i^\text{hyp}}{f_i^\text{rest} Q_i^\text{rest}} = \frac{Q_i^\text{hyp}}{Q_i^\text{rest}} \tag{A8}
\]

In the case of redistribution, when a nonuniform distribution of \( R_i \) exists, a flow summation technique may be used to calculate the overall flow reserve \( R_Q \) provided that an additional constraint is placed on the \( k_i \) parameters. The overall flow reserve can be expressed as:

\[
R_Q = \frac{Q_a^\text{hyp}}{Q_a^\text{rest}} = \frac{\Sigma Q_i^\text{hyp}}{\Sigma Q_i^\text{rest}} \tag{A9}
\]

or, using equation A3:

\[
R_Q = \frac{\Sigma k_i^\text{hyp} Q_i^\text{hyp}}{\Sigma k_i^\text{rest} Q_i^\text{rest}} \tag{A10}
\]

relating the overall reserve in terms of measured flow variables \( Q_i \). If it is assumed that, in addition to the previous constraint,
TABLE 3
Variability in measured arrival time within the perfusion bed for rest and hyperemia

<table>
<thead>
<tr>
<th>ROI</th>
<th>k_{rest}</th>
<th>k_{hyp}</th>
<th>k_{rest}</th>
<th>k_{hyp}</th>
<th>k_{rest}</th>
<th>k_{hyp}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.27</td>
<td>1.60</td>
<td>1.33</td>
<td>1.18</td>
<td>1.32</td>
<td>1.53</td>
</tr>
<tr>
<td>2</td>
<td>1.30</td>
<td>1.62</td>
<td>1.30</td>
<td>1.19</td>
<td>1.31</td>
<td>1.38</td>
</tr>
<tr>
<td>3</td>
<td>1.30</td>
<td>1.61</td>
<td>1.33</td>
<td>1.24</td>
<td>1.35</td>
<td>1.48</td>
</tr>
<tr>
<td>4</td>
<td>1.42</td>
<td>1.63</td>
<td>1.35</td>
<td>1.25</td>
<td>1.45</td>
<td>1.60</td>
</tr>
<tr>
<td>5</td>
<td>1.37</td>
<td>1.66</td>
<td>1.35</td>
<td>1.24</td>
<td>1.40</td>
<td>1.47</td>
</tr>
</tbody>
</table>

Calculated values of \( k = T/(T_i - t_i) \), where \( T_i \) is the contrast arrival time measured in the perfusion bed and \( t_i \) is the arrival time measured in the epicardial vessels for five regions of interest (ROI).

\[ k_{hyp} = k_{rest} \]

The values are approximately equal in all regions \( i \), then \( R_Q \) may be approximated by:

\[ R_Q = \frac{1}{S_{hyp}} \sum S_{rest} \] (A11)

Equations A10 and A11 express the relationship between the overall flow reserve and the measured variables \( Q \), during baseline and hyperemia and describe a means for the assessment of the overall reserve \( R_Q \) even in the presence of nonuniform flow reserve such as might be present with a complex lesion distribution.

The assumptions concerning the variables \( k \) have been evaluated by making measurements of the time of arrival values inside \( (t_i) \) and adjacent to \( (T_i) \) an epicardial vessel in several regions. The results of such measurements are shown in table 3 for the case of a dog with relatively high coronary blood flow \( (Q_{rest} = 150 \text{ ml/min}, Q_{hyp} = 570 \text{ ml/min}) \). The values of \( k \) do not vary significantly over regions in the perfusion bed. In this case, however, the changes in \( k \) between baseline and hyperemia were not negligible for normal vessels and intermediate degrees of obstruction. In such cases the parametric flow ratio value calculated from \( T_i \) will underestimate the actual flow ratio by 5% to 15%. This could be avoided by calculating the parametric flow ratio with the value of \( T_i - t_i \) in the denominator of equation A3. The measurements of \( t_i \) demonstrate that the arrival time in the epicardial vessels does not vary significantly and therefore a single value can be subtracted from all points in the \( T_{arr} \) image before producing a \( Q \) image. The value of \( t_i \) was not determined for all the data reported and the \( Q \) parameter was calculated from the total arrival time \( T_i \).

Appendix 2

Effects of scatter and glare on parametric image flow ratio calculations. The effects of radiation scatter and veiling glare on the different stages in the acquisition of a flow ratio parametric image can be understood with the help of a short discussion.

The transmission of x-rays through an attenuating object is expressed ideally by the expression:

\[ I_p(x) = I_0 e^{-\mu x} \] (A12)

relating the x-ray intensity after attenuation by a thickness \( x \) with linear attenuation coefficient \( \mu \). The effects of radiation scatter and veiling glare can be included by including additional terms:

\[ I = I_p + I_o + I_s \] (A13)

At a particular spatial location in the image plane the additional contributions \( I_o + I_s \) can be expressed as

\[ I_o + I_s = \alpha I_p \] (A14)

where \( \alpha \) is the spatially varying scatter (and glare) to primary ratio. Thus the total intensity can be expressed:

\[ I_{tot} = I_p + \alpha I_p \] (A15)

In the presence of iodine contrast media of thickness \( x_i \) and attenuation coefficient \( \mu_i \), the total intensity can be written:

\[ I_{tot} = I_p e^{-\mu_i x_i} + \alpha I_p \] (A16)

Subtraction of the preinjection mask from the contrast image produces the time-subtraction:

\[ D = S' - S = \log(e^{-\mu_i x_i} + \alpha) - \log(1 + \alpha) \] (A18)

This expression is plotted in figure 12 as a function of iodine thickness \( \mu_i x_i \) for different values of the scatter and glare fraction \( \alpha \), including the case of \( \alpha = 0 \). When no scatter is present the difference relation reduces to the familiar case:

\[ D = -\mu x_i \] (A19)

that is, the contrast value in the difference image is proportional to iodine thickness only in the absence of scatter.

Thus the presence of scatter and glare reduces the accuracy of

FIGURE 12. Plot of the relationship between the contrast signal measured in a logarithmically processed time subtraction image and the actual iodine concentration \( \mu x \) for different values of \( \alpha \), the ratio of the scatter and glare contribution to the primary intensity.
determination of absolute iodine thickness, and a number of correction methods have been proposed. When one is concerned only with determinations of relative changes of iodine thick- ness, in particular at the same image location, as we are when determining times of arrival and the relative changes in peak iodine signal, the need for such correction methods is not as great.

We can write expressions for two different iodine thicknesses \( x_2, x_1 \) at the same spatial location, i.e., same \( \alpha \) value, using equation A18:

\[
D_1 = \log(e^{-\mu x_1} + \alpha) - \log(1 + \alpha)
\]
\[
D_2 = \log(e^{-\mu x_2} + \alpha) - \log(1 + \alpha) \tag{A20}
\]

where the subscript 1 has been dropped from \( x \) for simplicity.

The function \( \log(e^{-\mu x} + \alpha) \) can be approximated by a Taylor expansion about the point 1 + \( \alpha \):

\[
\log(e^{-\mu x} + \alpha) = \log(1 + \alpha) - \frac{\mu x}{1 + \alpha} + \ldots \tag{A21}
\]

where we have also made the substitution \( e^{-\mu x} = 1 - \mu x \).

Replacing equation A20 with their respective approximations:

\[
D_1 = \log(1 + \alpha) - \frac{\mu x_1}{1 + \alpha} - \log(1 + \alpha) = -\frac{\mu x_1}{1 + \alpha} \tag{A22}
\]
\[
D_2 = \log(1 + \alpha) - \frac{\mu x_2}{1 + \alpha} - \log(1 + \alpha) = -\frac{\mu x_2}{1 + \alpha}
\]

Comparison of equations A22 and A19 reveals that, for small contrast signals, the effect of scatter and glare is to change the proportionality factor between the log subtraction signal \( D \) and iodine thickness \( x \) by an amount that depends on the fraction \( \alpha \).

Taking the ratio of the two subtraction signals:

\[
\frac{D_2}{D_1} = \frac{\frac{\mu x_2}{1 + \alpha}}{\frac{\mu x_1}{1 + \alpha}} = \frac{x_2}{x_1} \tag{A23}
\]

which is our desired result. Even in the presence of spatially nonuniform scatter and veiling glare, the relative change in iodine thickness at the same location is approximated quite well by the relative change in the image values in logarithmic sub- traction images. Thus we expect the errors in our ratios of \( C_{\text{max}} \) between baseline and hyperemia and in our determination of the time at which contrast reaches half its peak value to be minimal.

**Note:** The relationship between the difference signal \( D \) and iodine thickness (equation A22) also includes a dependence on \( x \), which, if one includes further terms in the expansion (equation A21), is a contribution to the slope of:

\[
\frac{-\mu x \alpha}{2(1 + \alpha)} \tag{A24}
\]

For the values of iodine contrast used in our experiments, this results in an error of about 5% to 10% in each slope and an error of comparable size in the flow ratios.

**References**

Digital subtraction angiographic imaging of coronary flow reserve.
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