Value and limitations of computer analysis of digital subtraction angiography in the assessment of coronary flow reserve

STEVEN E. NISSEN, M.D., JONATHAN L. ELION, M.D., DAVID C. BOOTH, M.D., JOYCE EVANS, and ANTHONY N. DEMARIA, M.D.

ABSTRACT Conventional coronary angiography has significant limitations in quantifying the severity and functional significance of coronary stenoses. However, coronary reactive hyperemia is an excellent physiologic indicator of coronary reserve. Digital subtraction angiography offers the potential to analyze coronary blood flow dynamics quantitatively. Therefore we assessed the accuracy of digital angiographic methods to detect and quantify reductions in coronary flow reserve secondary to stenoses of varying magnitude in an experimental canine preparation. Studies were performed in nine anesthetized open-chest dogs with an electromagnetic flow (EMF) probe and two pneumatic occluders positioned on the left circumflex coronary artery. One occluder served to induce reactive hyperemia by temporary total occlusion, while the other served to produce variable gradations of stenosis. Digital angiography was performed after the subselective injection of contrast under basal conditions and during reactive hyperemia. Time-intensity curves were obtained from digital angiograms for both a coronary and a myocardial region of interest. Measurements included area under the curve, time to peak contrast, and contrast disappearance rate. An index of coronary reserve was computed as the ratio of hyperemic to basal measurements for each of these methods. Coronary blood flow ranged from 6.5 to 142 ml/min, with hyperemic to basal EMF flow ratios of 0.80 to 4.2:1. The index derived from contrast decay rate showed a poor correlation with EMF (r = .34). The correlation between measurements of time to peak myocardial contrast and coronary blood flow was r = .68 (y = .16 x + 0.97). The area under the time-intensity curve from a coronary region of interest showed a close correlation with coronary blood flow (y = 0.91 x + 0.1, r = .86). Thus estimates of coronary reserve by computer analysis of digital subtraction angiograms can yield information regarding the physiologic consequences of coronary stenoses.


CORONARY ARTERIOGRAPHY is the primary modality used to identify and select therapy for patients with coronary artery disease. However, currently available techniques for assessing the magnitude and functional significance of coronary atherosclerotic stenoses by angiography have significant limitations. A variety of imaging problems, including overlapping of vessels and influence of collateral blood flow, have been demonstrated to interfere significantly with the interpretation of coronary angiograms. Angiographic estimates of coronary obstruction may not correspond to subsequent pathologic examination, and significant intraobserver and interobserver differences have been reported in the interpretation of angiograms. Because the severity of a stenosis is conventionally measured as the percent reduction of luminal area, diffuse coronary atherosclerosis with a superimposed discrete lesion may result in an underestimation of the absolute obstruction. Accordingly, even when coronary obstructions are well visualized by angiography, the severity of narrowing may remain uncertain.

Traditional coronary angiography provides little information regarding the physiologic consequences of coronary stenoses. The usual estimate of coronary obstruction, percent luminal narrowing, does not relate in a linear fashion to loss of perfusion or functional reserve. Furthermore, angiographic luminal reduction...
does not always predict the decrease in resting coronary blood flow or maximal coronary reserve capacity that is produced by a lesion. Thus percent stenosis alone may be an unreliable measure of the physiologic consequences of coronary obstruction and an imperfect standard upon which to base therapeutic decisions. In contrast to the limitations inherent in the assessment of percent luminal narrowing, determination of coronary reactive hyperemia has been shown to accurately reflect the physiologic consequences of coronary lesions.

The recent development of digital imaging techniques, specifically digital subtraction angiography, provides a potential method for quantitative analysis of coronary flow dynamics and reserve. Digital techniques convert the video output from an image intensifier into a number of small discrete boxlike compartments referred to as picture elements, or pixels. The brightness of each pixel is then expressed as a numerical value. Accordingly, an analog video image can be converted to a numerical map whose values can be measured or adjusted by standard mathematical methods. Because the brightness of each pixel is determined by the volume of contrast within it, this technique provides a mechanism for the quantitative analysis of coronary blood flow and thereby the assessment of reactive hyperemia.

The objective of this study was to assess the ability of digital angiography to determine the physiologic significance of coronary stenoses produced in a canine preparation of coronary artery disease. Specifically, we sought to validate the accuracy of digital angiographic methods to detect and quantify reductions in coronary flow reserve secondary to stenoses of varying magnitude.

Methods

Animal preparation. Nine conditioned dogs weighing 25 to 30 kg were used in this investigation. The animals were pre-treated with morphine sulfate (3 mg/kg), and anesthesia was induced with α-chloralose and urethane. The animals were mechanically ventilated with room air, a thoracotomy was performed, and the heart was placed in a pericardial sling. The circumflex coronary artery was dissected free of the epicardial surface and an electromagnetic flow (EMF) probe (Zepeda Instruments) was placed on this vessel as proximal as possible. Two Silastic pneumatic occluders were placed distal to the EMF probe, one to create a variable stenosis and the other to produce temporary total occlusion as a stimulus for reactive hyperemia. A right atrial pacemaker was implanted via an epicardial needle electrode and the animal was atrially paced at a rate 10 beats/ min greater than the resting heart rate. The instrumentation of the left circumflex artery is illustrated in figure 1.

A high-quality electrocardiographic signal was obtained with stainless-steel needle electrodes attached to the skin. A micro-manometer-tipped pressure transducer (Millar Instruments) was positioned in the thoracic aorta via a femoral artery cut-down so as to record central arterial pressure. A cut-down was also performed on the right carotid artery, which was isolated and entered with a No. 6F arterial sheath. The coronary electromagnetic flow signal, central arterial pressure, and electrocardiogram were continuously monitored on a multichannel physiologic recorder (Gould Electronics) (figures 2 and 3).

Imaging procedure. A No. 5F catheter (USCI Lehman) was customized by heat molding and inserted into the right carotid artery sheath. Under fluoroscopic guidance, the left circumflex coronary artery was subselectively cannulated. The catheter was attached to an electrocardiogram-gated pressure injector (Angiomat 3000, Liebel-Flarsheim), which was used to perform wave- or trigger power injection of radiographic dye (Renograin-76, Squibb) during digital fluoroscopy. The quantity of contrast injected was adjusted until the maximum dose was determined that did not result in reflux of contrast into the left anterior descending coronary artery, and varied from 1 to 1.5 ml/sec for 2 sec. Fluoroscopic coronary images were obtained at 24 mA and 70 to 100 kV, adjusted to produce images that utilized the full dynamic range of the computer while avoiding saturation. A customized look-up table was used to linearize the exponential relationship between radiographic attenuation and contrast concentration (Beer-Lambert Law) and included a logarithmic transformation. At the termination of each experiment a calibrated step-wedge was imaged under identical conditions to those used in coronary imaging. Since the levels of the step-wedge were uniform in thickness, the gray values of the step-wedge image could be used to confirm that the contrast-density relationship was linear (figure 4).

The fluoroscopic images underwent real-time analog-to-digital conversion into a 256 × 256 pixel matrix, which was 8 bits deep and thus capable of displaying 256 shades of gray. Digital fluoroscopic images were acquired at 30 frames/sec by a prototype digital imaging system (Registrex 1000, Advanced Technology Laboratories). Mask-mode subtraction was performed after modification by the logarithmic look-up table. A 4.5 inch field of view was used, thus producing approximately 2 pixels/mm. All images were stored on the computer hard disk in digital format for subsequent transfer to a dedicated image analysis computer (MIPRON I, Kontron Electronic, Canton, MA).

Experimental protocol. Once satisfactory images were produced and a stable catheter position obtained, collection of data commenced. Control recordings of central arterial pressure, circumflex coronary artery flow, and the electrocardiogram were...
obtained. An electrocardiogram-triggered coronary power injection of the predetermined volume of contrast was performed under basal conditions and the images were digitally subtracted and stored. One of the two pneumatic occluders was then fully inflated to totally obstruct coronary blood flow for 15 sec. After release of occlusion, a prompt hyperemic response was observed on the electromagnetic flow tracing. During the initial 10 sec period of the hyperemic response, a second coronary injection was performed with the identical quantity of dye and flow rate. The images obtained during hyperemia were also digitally subtracted and stored on the computer hard disk. A representative sequence of end-diastolic images is shown in figure 5.

Subsequently, a partial coronary stenosis was produced by inflating the second pneumatic occluder positioned on the circumflex coronary artery. The severity of the stenosis was adjusted to produce variable degrees of reduction in the hyperemic response. Stenoses varied in severity by this criteria from minimal (<25% reduction) to severe (>75% reduction), and included lesions that produced a decrease in resting EMF coronary flow as well as those that did not. Two sequences of images were obtained for each level of stenosis, the first under basal conditions and the second under conditions of maximal hyperemia induced by a 15 sec total occlusion. Thus, for each animal, control and hyperemic image sequences were obtained at several levels of stenosis, which varied from no impairment in coronary reserve to complete ablation of the hyperemic response (figures 2 and 3).

EMF analysis. The EMF signal was recorded on a strip-chart recorder equipped with an event marker to signal the injection of radiographic contrast at the beginning of each sequence. A consistent reduction (always less than 50%) in the EMF signal was observed during the transit of contrast dye during each injection (figures 2 and 3). Work in our laboratory and by others has indicated that this reduction in signal is not an artifact related to the electromagnetic properties of radiographic contrast but likely represents a true fall in coronary flow.10, 11 Thus no comparable reduction of the EMF signal was observed when radiographic contrast was injected into a constant flow model in vitro comprised of rubber tubing and saline. The effects of contrast on coronary flow represented a potentially confounding variable that could be eliminated by beat-by-beat evaluation of the EMF tracing. Accordingly, for the purposes of this investigation, mean coronary blood flow was measured by planimetry of the EMF tracing throughout the cardiac cycle over the time frame corresponding to acquisition of the imaging sequence. In this fashion, the same beats were examined by both the EMF method and the image analysis algorithms. To further evaluate the impact of contrast agent on coronary flow, a separate analysis was performed in which the EMF flow for both the basal and hyperemic sequences was defined as the mean flow immediate-
ly before contrast injection rather than during contrast passage.

For each stenosis, both EMF and angiographic data were analyzed by constructing an index of coronary reserve consisting of a ratio between basal and hyperemic measurements. With regard to EMF, an index of coronary reserve was calculated as the ratio of mean flow during hyperemia divided by mean flow under basal conditions. At the termination of each experiment the EMF probe was calibrated by placing it on the animal’s femoral artery and comparing the signal obtained at several flow rates to actual volumetric flow measured by stopwatch and graduated cylinder. In each case, the validation procedure confirmed that flow measurements were accurate.

**Image analysis.** Analysis of the digital coronary angiograms was performed by transferring the gated sequences of images to an array processor image analysis computer. The images were entered into the computer and displayed on a standard video monitor, and end-diastolic frames were selected interactively. A custom-designed computer program allowed the operator to select a region of interest (ROI), and the summated intensity value for pixels within each sample region was computed. Each sample area was rectangular in shape and could be varied in size from 3 to 512 pixels by the operator. Initially, three regions of interest were identified by the operator: ROI 1 was positioned over the proximal left circumflex coronary artery, ROI 2 was positioned outside the vessel just adjacent to ROI 1, and ROI 3 was positioned over the myocardium perfused at the termination of the experiment.

**FIGURE 4.** Technique for linearization of the contrast-brightness relationship. A standardized step-wedge was imaged for each animal and the resulting gray values plotted. The closed circles represent the data before logarithmic transformation while the open circles represent the adjusted gray values.

**FIGURE 5.** Sequential end-diastolic frames of a digital subtraction coronary angiogram obtained from a representative experiment in this study. The EMF probe obscures the coronary vessel just proximal to a stenosis induced by inflation of the occluder. Panels E and F demonstrate prominent myocardial opacification.
of the left circumflex coronary artery (figure 1). Subsequently, a separate analysis of the myocardium was carried out analogous to previous work by others in which an average measurement of appearance time for multiple pixels was performed.\textsuperscript{10, 11} For this analysis, eight interactively selected regions of interest were positioned along the course of the circumflex coronary artery over the myocardium perfused by this vessel.

Intensity-time curves for these regions of interest were produced by plotting summed brightness vs time. Several sets of intensity-time curves were computed for each injection. In one family of curves, the summed intensity values for ROI 1 minus the summed gray values for the background (ROI 2) was plotted (figure 6). The subtraction of values from ROI 2 served as a method to correct for the contribution of myocardial opacification to the summed gray values for the coronary region of interest. A second family of curves was created that used the single myocardial region of interest (ROI 3). These curves represented the summed pixel values for ROI 3 minus the value obtained from the first end-diastolic frame of each study for this same region (figure 7). Thus these latter curves reflect the incremental changes in intensity for the myocardial region of interest referable to the first cardiac cycle. Finally, a series of similar curves was generated for the eight myocardial regions of interest positioned adjacent to the circumflex artery.

Data analysis. For each pair of injections, the mean planimetered electromagnetic coronary blood flow under hyperemic conditions was divided by the mean flow under basal conditions to obtain an index of coronary reserve capacity.

In addition, a similar index of coronary reserve was constructed as the ratio of electromagnetic coronary flow during hyperemia before contrast injection hyperemia divided by flow under basal conditions. The intensity-time curves obtained from the digital images were analyzed in a comparable fashion. Thus, for the coronary region of interest, an index of coronary reserve was calculated as the ratio of the area under the time-intensity curve obtained during hyperemia divided by the area under the basal curve but expressed as an inverse to be comparable to values by EMF (figure 6). For the myocardial region of interest, two measurements were analyzed: the time to peak myocardial opacification and the myocardial contrast disappearance rate (figure 7). Time-to-peak myocardial contrast was defined as the time in seconds between the beginning of contrast injection and the maximal opacification of the single myocardial region of interest. The measurement of time-to-peak opacification was also computed from the curves of eight distinct regions of interest distributed throughout the perfusion bed of the circumflex. The individual values for these eight regions were then averaged to obtain a mean appearance time.

Contrast disappearance rate was measured only for the single myocardial region of interest (ROI 3) and was calculated as the time from peak myocardial opacification to decay to one-half of the maximal summed intensity. Indexes of coronary reserve were then calculated as the ratio of basal to hyperemic measurements.

Statistical analysis. The ratio of hyperemic to basal electromagnetic coronary flow represented actual coronary reserve capacity and was compared by linear regression analysis with the ratio derived from the area of the intensity-time curves for the coronary region of interest. Similarly, the ratio of hyperemic to basal values for the time-to-peak contrast and disappearance rate of contrast derived from the myocardial region of interest was compared by linear regression analysis to the ratio obtained by electromagnetic flow meter. A correlation coefficient and the regression line were calculated for each of the comparisons.

FIGURE 6. Representative intensity-time curves for a proximal circumflex coronary region of interest. The top panel illustrates the curves obtained in the absence of coronary stenosis, showing a marked decrease in the area under the curve for the hyperemic image (open circles) and the basal image (closed circles). The bottom panel shows similar curves obtained under basal and hyperemic conditions in the presence of a severe coronary stenosis.

FIGURE 7. Intensity-time curves obtained from the myocardial region of interest under basal and hyperemic conditions. In the top panel, the time to peak contrast density is shorter under hyperemic conditions in the absence of a stenosis. In the bottom panel, the shortening of the contrast appearance time is absent during hyperemia in the presence of a severe coronary stenosis. All four curves show similar contrast decay rate.
Results

We performed 76 coronary injections for 38 stenoses in which resting coronary blood flow measurements varied from 6.5 to 142 ml/min by EMF probe. The range of values for the ratio of hyperemic to basal coronary flow by EMF for these injections was 0.8:1 to 4.2:1. Thus coronary stenoses with a broad spectrum of physiologic significance were evaluated. The flowmeter tracings from a representative pair of injections are illustrated in figures 2 and 3. Figure 2 illustrates an injection under basal conditions (panel A) and during hyperemia (panel B) in the absence of stenosis and shows a marked postocclusion hyperemic response. Figure 3 shows the tracings obtained during the severe coronary stenosis and illustrates a nearly complete blunting of the hyperemic response normally present after a 15 sec coronary occlusion. For all nine dogs, heart rate varied from 88 to 126 beats/min but was held constant in each animal by atrial pacing.

For the simple myocardial region of interest, ratios derived from the time-to-peak myocardial opacification during hyperemic and basal states exhibited a smaller range than those derived from EMF in the presence of these graded stenoses, ranging from a low of 0.95:1 to a high of 1.8:1 (figure 8). Thus the magnitude of differences between basal and hyperemic values for the time-to-peak myocardial opacification was considerably smaller for this type of curve analysis than for that of EMF measurements. When linear regression analysis was performed, the ratios derived from the time-to-peak opacification for the myocardial region of interest correlated moderately with the EMF ratio ($r = .68$). The slope of the regression line was small ($y = 0.16 x + 0.97$), reflecting the lesser ratios computed by this method of image analysis compared with EMF (figure 8). The correlation of hyperemic to basal ratios of time-to-peak myocardial opacification with EMF was not improved by averaging of appearance time for eight regions of interest in the circumflex perfusion bed ($r = .60$, $y = 0.15 x + 1.01$).

The results of analysis for measurements of the contrast disappearance rate for the simple myocardial region of interest (ROI 3) and EMF flow are displayed in figure 9. The ratio of basal to hyperemic values for contrast decay rate varied from 0.6 to 2.0:1 for this method of curve analysis. Accordingly, contrast decay ratios also failed to achieve a range comparable to EMF. When the ratio of basal to hyperemic flow derived from the contrast decay rate was compared with EMF ratios, the correlation was poor ($r = .34$). Thus the contrast disappearance rate for a myocardial region of interest was not closely related to the extent of hyperemia in this animal preparation of coronary artery disease.

With the coronary region of interest, the ratio of the area under the intensity-time curve during hyperemic and basal periods yielded values that varied from 0.9:1 to 4.5:1. Thus the ratios of area measurements derived from the background-corrected coronary curves (ROI 1 − ROI 2) were similar in magnitude to those obtained by EMF (figure 10). Linear regression analysis performed for the ratios derived from the angiographic
To validate digital angiographic methods in this study, we developed an experimental preparation that enabled accurate quantitation of maximal coronary flow reserve and allowed control of multiple potential variables. Application of EMF measurements provided a precise and continuous record of coronary flow, while total vessel occlusion produced maximal coronary reactive hyperemia. The animals were atrially paced to prevent changes in heart rate during imaging that might interfere with comparison of pairs of measurements. A very small catheter (No. 5F) was used to prevent obstruction by the catheter from influencing maximal coronary hyperemia. This smaller catheter is suitable for digital angiography because the improved contrast sensitivity of the method requires less radiographic dye. The absence of encroachment upon flow by the catheter was confirmed by obtaining a comparable increase in hyperemic flow before and after cannulation of the circumflex artery. Subselective catheter placement was used so that the effects of contrast run-off in the left anterior descending coronary artery would not interfere with circumflex measurements. An electrocardiogram-gated power injector enabled exact and reproducible quantities of contrast to be injected in the same phase of the cardiac cycle at precise flow rates.

Several approaches to computer analysis of digital subtraction angiograms are feasible. Each type of analysis is based on inherent theoretical assumptions and practical limitations. In this investigation we assessed three methods proposed for evaluation of coronary reserve from digital angiography: an index of myocardial contrast appearance time,\(^\text{10, 11}\) the disappearance rate of myocardial contrast,\(^\text{12}\) and the area under the time-intensity curve obtained from the coronary vessel.\(^\text{13}\)

Although we also planned to examine the area under the time intensity curve from a myocardial region of interest, recording a complete curve would have required continuous imaging for greater than 20 sec, a capacity not present with existing equipment.

Measurement of myocardial contrast appearance time has been proposed as an accurate and reproducible technique for the assessment of coronary flow reserve.\(^\text{10, 11}\) This method is based on the assumption that coronary flow velocity will increase under conditions of reactive hyperemia, thus resulting in a more rapid transit of dye from the site of injection to the myocardial capillaries. Theoretically, a physiologically significant coronary stenosis would blunt this increase in velocity and therefore would be detectable as a delay in myocardial contrast appearance time. In this study we used time to maximal myocardial opacifica-

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**Figure 10.** Results of linear regression analysis comparing coronary reserve measured by the EMF probe to that obtained by the integral of the coronary intensity-time curve. A close correlation was observed with a slope of the regression line near unity. The range of values is similar for both techniques.

and EMF probe measurements demonstrated a close relationship with a correlation coefficient of \(r = .86\) and a slope, near unity, of \(y = 0.91x + 0.1\).

The correlations between EMF ratios and all three methods of image analysis were similar when EMF was taken as the mean flow before contrast injection rather than during passage of contrast. For the time-to-peak, contrast-decay, and intensity-time integral methods, correlation was \(r = .88\), \(r = .38\), and \(r = .67\), respectively. Thus angiographic measurements derived from the integral of intensity-time curves for the coronary region of interest provided a good method by which to quantify coronary flow reserve and correlated closely with EMF ratios determined from flow either before or during contrast injection.

**Discussion**

Conventional angiography has significant limitations in assessing the severity of reduction of coronary cross-sectional area and provides virtually no information regarding the physiologic significance of coronary stenoses. However, coronary reactive hyperemia has been demonstrated to be an excellent physiologic descriptor of coronary reserve.\(^\text{6}\) The recent development of digital angiography offers the potential for a readily accessible, quantitative approach to the assessment of coronary flow reserve. The results of this study establish the ability of digital angiographic techniques to quantitate reactive hyperemia during coronary angiography and thereby to evaluate the physiologic consequences of a coronary obstruction.
tion as the appearance time, rather than the time between injection and the recording of any threshold of intensity. The maximal ratio of hyperemic to basal values for the time to peak myocardial contrast was only 1.8:1, and only a moderate correlation \((r = .68)\) was observed with the ratio of hyperemic to basal coronary flow measured by an EMF probe. This correlation was not improved by calculating the average appearance time for eight regions of interest distributed throughout the circumflex perfusion bed \((r = .60)\). Thus, in this preparation, time to peak myocardial contrast was not sufficiently sensitive to separate various degrees of impairment of coronary reserve produced by graded stenoses.

The explanation for the failure of peak myocardial contrast appearance time to more closely reflect impaired coronary flow reserve in this study is uncertain and may be related to the interaction of several complex factors. A major limitation of this measurement is the temporal resolution of densitometric analysis of digital angiography. Since intensity is constantly changing during systole and diastole, analysis is feasible only if the myocardial region of interest is assessed during the same phase of each successive cardiac cycle. Thus the sampling rate for appearance time is realistically limited to one data point for each cardiac cycle. Averaging of appearance times for multiple regions of interest permits calculation of values that are intermediate in terms of cardiac cycle, but in this experiment did not demonstrate a closer correlation to EMF ratios.

One potential explanation for the failure of appearance time to predict flow reserve relates to the theory underlying analysis of appearance time. Velocity of flow increases in large epicardial coronary vessels during postschematic hyperemia, since there is a greater volume of flow through a relatively constant cross-sectional area. However, this increase in velocity is produced primarily by the augmented cross-sectional area of the dilated resistance vessels at the arteriolar level. Accordingly, if myocardial opacification is caused by appearance of contrast in the capillary bed, a lesser augmentation of velocity in the dilated arterioles than in the larger vessels may result in a blunting of the net velocity increase. Another factor that may influence the correlation between appearance time and EMF coronary reserve is that the capacitance effect produced by the coronary vascular tree may be greater than appreciated. Finally, since both increased coronary perfusion pressure and flow cause changes in the geometry of the ventricular wall, appearance time or any other density measurements in a myocardial region of interest will reflect not only coronary flow but also volume and density changes in the underlying myocardium. The limitations of the contrast appearance approach in dogs under these highly controlled circumstances is also likely to pertain to the clinical analysis of human coronary disease.

Another measurement performed from the time-intensity curves was the rate of disappearance of contrast from the myocardial region of interest during basal and hyperemic conditions. The ratio of contrast decay rate was compared with the ratio of hyperemic flow to basal for the EMF probe. This method of analysis assumes that, under conditions of hyperemia, the disappearance rate of contrast from the myocardium will be increased. Presumably, this increase in contrast washout rate under hyperemic conditions would be attenuated in the presence of physiologically significant stenosis. This method of analysis yielded a poor correlation with EMF reserve \((r = .34)\).

The failure of measurements of myocardial contrast disappearance rate to discern graded impairment of coronary flow reserve was not entirely surprising. Radiographic contrast is not inert but is capable of inducing an intense hyperemic response (figure 2). Thus attempts to measure contrast decay rate under any conditions are influenced by the presence of contrast medium itself, thereby augmenting the decay rate even in the absence of induced hyperemia. The flow conditions during myocardial washout are strongly influenced by contrast-induced hyperemia during the myocardial perfusion phase. This augmentation in flow reaches maximum and subsequently declines during myocardial opacification. Although the precise temporal relationship between myocardial and coronary flow is unknown, based on this observation it is likely that myocardial washout takes place in a “non-steady-state” condition. Accordingly, the decay curves observed in this investigation did not conform to the exponential model expected for a constant flow system. Thus mathematical curve fitting did not reveal a consistent pattern to the decay curve shape. Thus with conventional ionic contrast agents, this method of analysis does not appear to be satisfactory for assessment of coronary flow reserve, although it may be feasible with nonionic agents.

Another method for analysis of digital angiograms is based on the principles of indicator dilution techniques. In this case, the indicator is radiographic contrast medium. There are several assumptions inherent in the application of indicator dilution analysis to contrast angiography. First, the brightness of an individual pixel in the image must be proportional to the quantity.
of contrast present. Since the behavior of x-ray attenuation is exponential rather than linear, this requires a logarithmic correction on a pixel-by-pixel basis. These requirements were satisfied in the current experiment by applying a logarithmic look-up table to the coronary images. The accuracy of this correction was further confirmed by imaging a calibrated step-wedge for each animal (figure 4). A second requirement for using radiographic contrast in a dye dilution analysis is that all of the contrast medium must pass through the vessel to be analyzed. This requirement was satisfied by adjusting the dose of contrast administered until there was good opacification of the coronary artery but no reflux of contrast into the left anterior descending artery or the aortic root. A third requirement is that there be complete mixing of the contrast agent with blood in the analyzed vessel. The accuracy of this assumption in the current experiment could not be validated, but a region of analysis was placed sufficiently downstream so that maximal mixing could occur. It should be pointed out that this requirement is less important when serial studies are being performed in the same animal under identical conditions.

One final methodologic problem was the assumption that contrast injected in the coronary vessel was the sole source of opacification within the region of interest during the period of analysis. Because injection of contrast in the vessel ultimately results in myocardial opacification, the assumption that all contrast in the coronary region of interest reflected coronary opacification was not correct. In this investigation, therefore, we subtracted from the coronary region of interest the summed density for a region of identical size overlying the adjacent myocardium (ROI 2, figure 1).

Measurement of the area under the contrast time-intensity curve for the coronary region of interest showed a close correlation with EMF ratios. The magnitude of the maximal basal to hyperemic flow ratio calculated by this type of indicator dilution analysis (4.5:1) was comparable to that obtained by EMF probes (4.2:1). Furthermore, the correlation coefficient between the ratio of basal to hyperemic flow by area measurement and the EMF probe was \( r = .86 \) and the regression equation was close to the line of identity. Thus this method of analysis seems promising in evaluation of coronary flow reserve in man. There are several significant advantages to estimation of physiologic reserve by analysis of area under a curve derived from a coronary region of interest. Since the transit time is short, an imaging sequence of only 6 to 8 sec is required rather than 15 sec for analysis of myocardial contrast appearance and disappearance. Thus, if applied in a clinical setting, a shorter duration of motion-free imaging would be required with shorter periods of breath holding. Furthermore, since the measurement is derived from multiple points in time, the effect of artifact in a single frame is minimized. The area under a time-intensity curve can be described adequately even with low temporal resolution during image acquisition. Moreover, the method is insensitive to the geometry of the vessel at the region of interest because the volume of the sample area cancels in computation of reserve ratio as long as the region is the same for each pair of images.

Several practical factors require consideration with regard to the clinical application of digital angiography to the assessment of coronary flow. Digital subtraction requires precise registration of images over many cardiac cycles and therefore may be unsuitable in patients with atrial fibrillation or other arrhythmias. In addition, significant respiratory motion artifacts will render digital subtraction angiography impractical, although computer techniques for reregistration of images are under development. Reliable methods for induction of reactive hyperemia will need to be used in patients, although several promising techniques are under investigation, including stimulation of hyperemia with dipyridamole, adenosine, or contrast dye itself. Furthermore, although coronary reactive hyperemia measures flow reserve, this method cannot detect myocardial ischemia. Digital angiographic methods thus far provide data regarding coronary blood flow only, whereas other factors such as left ventricular hypertrophy and collateral blood flow may influence ischemic consequences of coronary lesions. Nonetheless, any method that accurately measures coronary reactive hyperemia would be extremely useful given the inherent limitations of coronary angiography. Finally, the indicator dilution type of analysis applied here requires subselective cannulation so that the entire bolus of contrast travels down the vessel examined. Thus, if applied in human beings, this technique would require modification of standard catheterization methods.

The results of this study have significant implications for the clinical evaluation of patients with coronary artery disease. The data from this investigation document that the appearance and disappearance of radiographic contrast in digital angiograms can be quantitated and used to estimate relative volumetric coronary artery blood flow. Although additional development will be required to apply these techniques in the clinical arena, the data from the present study have
established that computer analysis of digital subtraction angiograms contains the requisite information to assess the physiologic significance of coronary stenoses.

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References
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