Digital angiographic measurement of radiographic contrast material kinetics for estimation of myocardial perfusion

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ABSTRACT We studied the use of digital angiography for the quantification of regional myocardial perfusion in the dog using selective left coronary arterial injection of radiographic contrast material as a flow dilution indicator. We developed algorithms for generating time-intensity curves from regions of interest over the proximal coronary artery and the myocardium and for densitometric error correction by subtraction of the intensity curve over a small lead blocker before logarithmic transformation. The resultant myocardial time-density curves were analyzed for time from injection to peak concentration (TPC) and for exponential washout rate (k). A linear correlation was found between absolute coronary arterial blood flow and both k (slope = 0.13, r = .85) and 1/TPC (slope = 0.18, r = .85). Reproducibility of TPC and k for repeated studies was 11% and 16%. Induced hyperemia significantly improved the sensitivity to stenosis by increasing the average difference in TPC and k between regions served by normal and stenotic coronary arteries to 65% and 80%, respectively. By combining selective coronary arterial injection with the left lateral x-ray projection it was possible to avoid most overlap of regional perfusion beds in the dog. This study suggests that contrast dilution measurements made during digital coronary angiography provide a means for assessing the hemodynamic significance of stenoses and the efficacy of therapeutic interventions.

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ALTHOUGH selective coronary angiography is the standard by which we both detect coronary artery stenoses and evaluate their severity, only part of the information available in the image formed on the input phosphor of the image intensifier tube is presently used. The image also contains information about the distribution of coronary blood flow, although by the time the physician views the image, the information is so marginally perceptible that it has no practical value. Digital coronary angiography allows the opacification of the myocardium to be enhanced and quantified by videodensitometry. The purpose of this research was to determine whether digital angiography could be used to measure absolute myocardial perfusion with radiographic contrast material as a flow tracer.

Successful development of this technique would be significant for several reasons. First, by measuring the perfusion to the myocardium, the hemodynamic significance of visualized coronary artery stenoses could be assessed. Second, it would provide an image of the regional distribution of myocardial perfusion. Third, this technique could provide on-line perfusion measurements during the performance of therapeutic interventions such as percutaneous transluminal coronary angioplasty.

Materials and Methods

Animal preparation. Ten mongrel dogs weighing 25 to 35 kg were premedicated with morphine (1 mg/kg im) and anesthetized with sodium pentobarbital (35 mg/kg iv). Supplemental sodium pentobarbital was administered as needed to maintain a state of light anesthesia. Respiration was maintained with a Harvard respirator. Heparin (10,000 IU) was given intravenously before instrumentation followed by 5000 IU every 4 hr. A No. 8F straight catheter was placed in the aortic root for arterial pressure monitoring. A No. 7F modified Judkins catheter was advanced to the left main coronary artery for contrast injection. After thoracotomy, the left circumflex coronary artery was dissected, and a calibrated 2.0 or 2.5 mm external flow probe (Micron Instruments) was placed around the artery. A snare
occluder was positioned immediately distal to the flow probe to permit reduction of coronary arterial flow. The electrocardio-
gram, arterial pressure, and electromagnetic flow were moni-
tored continuously with an Electronics for Medicine physiolog-
ic recorder. Calibration of the electromagnetic flowmeter was
performed with both blood and contrast material. To allow
application of our correction algorithm for densitometric error
calculated by radiation scatter and veiling glare, a 0.5 × 0.5 cm ×
1.0 mm thick lead blocker was placed between the x-ray source
and the heart, on the surface of the dog’s chest, so that its image
fell at the center of the left ventricular silhouette. This blocker
was left in place throughout the entire study.

**Imaging procedure.** Fluoroscopic imaging was performed
with animals in the left lateral projection at fixed x-ray tube
potential and current, typically 75 kV and 5 to 15 mA, by means
of a modified portable C-arm fluoroscopic system with a 0.6
mm focal spot rotating anode x-ray tube (OEC-Varian). The imaging
chain consisted of a 25 cm image intensifier (Varian Associates)
equipped with a low noise 1 inch diode gun lead oxide
vidicon television camera (Sierra Scientific/Ampex). The gamma of the lead oxide vidicon was measured to be 0.98,
using a calibrated iris with apertures ranging from f/1.4 to f/16
in half-stop steps. The intensity of the light source was adjusted
so that a peak video level of 750 mV was obtained at f/1.4,
Corresponding to the maximum digital level of 255. Overall
response of the digital x-ray imaging system, excluding the video
recorder, was measured by a series of 3 cm diameter vials
containing projected iodine concentrations from 0 to 100
mg/cm2 in 20 mg/cm2 increments, corresponding to the range
obtained for the myocardium in our canine studies. Measure-
ments were made through a 20 cm thick water phantom to
simulate tissue x-ray filtration. Scatter and veiling glare were
minimized by narrowly collimating the x-ray beam to a 1 × 1
cm cross-section at the image intensifier input. Projected iodine
concentration was calculated from the digitized video images as
the change in the logarithm of the video intensity as the iodine
was added. Measured vs true iodine concentration was highly
linear (r > .995), indicating that beam hardening was insignifi-
cant within the range of concentrations studied (0 to 100
mg/cm2). The response of the system under broadbeam condi-
tions was measured both with water phantoms ranging from 17
to 22 cm and with an anthropomorphic chest phantom (Human-
oid Systems). The uncorrected broadbeam iodine response was
highly linear. Correction for scatter and veiling glare by
subtraction of the level behind an adjacent 0.5 × 0.5 cm × 1.0
mm thick lead blocker before logarithmic subtraction restored the
response to within 5% of the narrow beam results (unpublished
results).

The geometrical magnification was approximately 1.2 because
of the use of a 7.5 cm air gap for scatter reduction (no antiscatter
grid was used). Further optical magnification resulted in a field
of view of about 15 cm diameter at the level of the heart. A 4 ml
bolus of undiluted sodium meglumine diatrizoate (Squibb &
Sons, Inc., Princeton, NJ; Renografin-76, 370 mg/ml iodine)
was hand injected rapidly into the left main coronary artery.
This injection technique produced reproducible boluses with
full width at half maximum of 1.7 ± 0.6 sec as measured by
videodensitometry (described below). No attempt was made to
time the beginning of injection with respect to the cardiac cycle.
The catheter was withdrawn from the coronary ostium immedi-
ately after each injection.

Images were recorded at 30 frames/sec on ½ inch videotape
(Beta/Sony) with linear fixed-gain amplification. The record/
playback response of the recorder was checked by recording a
computer-generated digital test pattern consisting of 15 equally
spaced steps from black to white. The tape was replayed, time-
base corrected, and redigitized. Linear regression of the redigi-
tized step levels vs the original test pattern confirmed the lineari-
y of the analog recorder response (r > .999). The electrocardiogram (ECG) was recorded on one of the audio
channels of the videotape with an FM modulator. Recording
was started 5 sec before the injection to establish the baseline
video intensity and continued for 25 sec after the injection to
allow the washout of contrast from the myocardium. Before
the injection, the dog was hyperventilated for 30 sec by increasing
the rate of the Harvard pump (to 20 strokes/min) to inhibit the
respiratory drive. The respirator was then turned off in end-
expiration for the duration of the imaging to prevent motion
artifact. In four dogs this procedure was inadequate to control
respiratory motion, and perfusion images with stable baseline
intensity could not be obtained. Analysis was carried out on
the remaining six dogs (mean weight 31.0 kg). Four minutes after
the control injection, coronary flow was altered either by pro-
gressive snare occlusion to reduce flow or by an intravenous
infusion of 7 to 10 g/kg/min dipyridamole to increase it. A 4 min
minimum interval was maintained between injections for coro-
nary blood flow to return to normal after the hyperemic response
to the injection of contrast material.

**Acquisition of region-of-interest time-intensity curves.** To
analyze each injection, images were digitized from video tape in
time real time (30 frames/sec) to 512 × 512 × 8 bit resolution with a
Gould/DeAnza IPS500 digital image processor via a video time
base corrector (Harris Video Systems, Inc., Model 516). The tape was first played to digitize a still image at a time after
injection at which both the coronary arteries and the opacified
myocardium were visualized (figure 1). From this image a light
pen was used to select up to eight 10 × 10 pixel (approximately
3 × 3 mm) regions of interest over the myocardial areas to be
analyzed. In this study a single region of interest was chosen
over the myocardium served by the left circumflex artery. Care

![FIGURE 1. Digital angiogram illustrating the experimental configuration. Contrast material was injected into the left main coronary artery. The electromagnetic flowmeter probe (EMQ) was placed around the left circumflex coronary artery (LCX), and the snare occluder (not visualized) was placed just distal to the probe. The lateral projection was used to minimize overlap of the LCX and left anterior descending perfusion beds. A 10 × 10 pixel region of interest (ROI) was placed over the myocardium served by the LCX. Scatter and veiling glare (SVG) was determined by measuring the intensity over a lead blocker placed adjacent to the myocardial region of interest.](https://circ.ahajournals.org/content/cir/71/2/687/F1.large.jpg)
was taken to avoid placing this myocardial region of interest over prominent coronary arteries. In addition to the myocardial region of interest, one region was placed over the coronary artery just distal the catheter tip to define the time of injection and record the shape of the injection bolus, and another was placed over the lead blocker to record the intensity caused by scatter and veiling glare. When the tape was played the second time, the image intensities of the pixels within each region of interest were linearly digitized then sent to the system’s host computer (DEC LSI 11/23), where the average intensity of the 100 pixels with each region of interest was calculated and stored on the fly on digital disk. The time required for data transfer and calculation of the region of interest averages limited the sampling rate to every third video frame (10 Hz).

**Analysis of curves.** The data were then processed to produce plots of projected iodine concentration vs time. Figure 2, A, shows typical time-intensity curves after injection of a 4 ml bolus of Renografin-76 into the left main coronary artery. The curves represent the video image intensity over the lead blocker, the catheter tip, and the posterior wall of the myocardium. Correlation for radiation scatter and image intensifier veiling glare (SVG) was made by linearly subtracting the lead blocker intensity, which consists entirely of the SVG contribution, from the intensity of the myocardial region of interest. Since the contrast injection itself alters the magnitude of scatter and veiling glare, this subtraction was performed for each individual point of the curve, as illustrated in figure 2, B. The “projected iodine concentration” curve in figure 2, C, which represents the mass of iodine per unit image area, was calculated from the change in the logarithm of the SVG-corrected intensity curve relative to the preinjection value.

Several features of the corrected concentration curves were considered in the design of the analysis algorithm. Since there is cyclic variation in myocardial projected concentration within the stationary region of interest due to cardiac motion, time domain filtration was performed by a uniformly weighted moving average over 2 heart beats, as shown in figure 2, D. This removed rapid cyclic variations but preserved the low-frequency information involved in determination of time to peak and washout rate. Some of our time-concentration curves displayed a secondary maximum 5 to 10 sec after peak opacification, coincident with the arrival of contrast in overlying pulmonary vessels. Therefore we designed the algorithm to analyze only the arrival and initial washout portions of the curve. A simple monoeponential model was adopted for analysis of washout. The washout decay constant was determined by linear least-squares fitting of the logarithm of the washout portion of the curve. To eliminate data corrupted by baseline shift and by inclusion of coronary arteries within region of interest, a curve was analyzed only if it satisfied a set of three criteria: (1) the postinjection concentration had to remain above the preinjection baseline, (2) the curve had to exhibit a single smooth peak, and (3) the correlation coefficient of the fit had to be greater than r = .995.

Regional myocardial perfusion was calculated from the washout decay constant k using the Kety formula, \[ F/V = k, \] where F/V is the flow per unit contrast material distribution volume.

A second index of myocardial perfusion was derived from the arrival portion of the time-concentration curve. The time to peak concentration (TPC) was defined as the time from injection, measured at the catheter tip region of interest, to the peak in the myocardial curve. Taking TPC to be a first approximation of the mean transit time, average myocardial perfusion was calculated as F/V = 1 / TPC, where F is the flow in the coronary artery at the injection point and V is the contrast distribution volume of all regions with mean transit times less than or equal to TPC. 2, 3

We plotted washout rate and 1/TPC vs electromagnetic flow to determine the sensitivity of the method to changes in flow. Linear regression was used to obtain the slope, which under the

**FIGURE 2.** Processing steps used to obtain accurate time-concentration curves. A, Raw data over myocardium (region of interest, ROI) and lead blocker (scatter and veiling glare, SVG). B, Subtraction of SVG (note change of scale). C, Logarithmic subtraction of data from preinjection intensity. D, Moving average (two cardiac cycles) applied to each point in panel C to filter high-frequency intensity variations.
assumptions of the model should equal the inverse of the volume of distribution of contrast material passing through the flowmeter.

### Results

Of the 66 intracoronary injections made in six dogs, 44 (67%) of the time-concentration curves over the myocardium met the criteria for analysis. The yield of useful curves by dog and by flow category are given in table 1. The two causes of failure were respiration-induced baseline variations that occurred even with the Harvard pump turned off, and low myocardial iodine contrast.

Figure 3, A, illustrates the typical qualitative temporal relationship between the coronary blood flow and the myocardial time-concentration curve after an intracoronary injection of radiographic contrast material in the resting state. No reduction of blood flow was noted upon insertion of the catheter before contrast injection.
There was a transient reduction in coronary flow of $36 \pm 16\%$ approximately 3 sec after injection. Although the response of the electromagnetic flowmeter to flow of contrast material was previously measured during calibration to be approximately 10% lower than to flow of blood, this effect was insufficient to account for the observed postinjection flow reduction. Immediately thereafter the blood flow increased rapidly, peaking at 200% of the resting flow rate at 10 sec. Below the flow tracing is shown the simultaneous recording of myocardial video contrast intensity. Videodensity reached a peak at approximately 2 sec after injection, roughly corresponding with the minimum rate of flow. The concentration then fell rapidly, reaching half maximum at about 5 sec after injection. Figure 3, B, shows simultaneous electromagnetic flowmeter and videodensity curves during dipyridamole-induced hyperemia in a critically stenosed coronary artery. There was less postinjection flow reduction compared with the control, and practically no contrast hyperemia. The average coronary blood flow during the first washout half-time was nearly identical for the two studies, but the measured washout rate was 19% lower with the critical stenosis.

Figure 4 shows the reproducibility results for serial repeat injections in individual dogs. Heart rate, blood pressure, and coronary artery blood flow were allowed to return to preinjection values between injections. The root mean square deviation of the washout rate data (left panel) from the line of identity is 16%. The right panel shows 1/TPC, which had a variability of 11%.

Figure 5 shows the relationship between preinjection coronary artery blood flow and the two derived time-concentration variables: washout rate and 1/TPC.

The range of coronary flow was from 20 to 150 ml/min. There was a positive linear correlation between flow and both time-density variables ($r = .85$). The slopes of the curves were similar, giving average calculated theoretical contrast distribution volumes of 7.7 ml based on washout rate and 5.6 ml based on time to peak. Both regression lines had a positive y intercept.

Figures 6 and 7 show the mean values of k and 1/TPC vs flow for studies performed at rest and during dipyridamole-induced hyperemia. The data are further divided into a normal coronary artery group and a group with critical or greater coronary stenoses, i.e., the stenoses produced at least some reduction in resting flow. At rest, neither k nor 1/TPC for the critical stenosis group differed significantly from the normal group. During infusion of dipyridamole, however, k was 80% and 1/TPC was 65% greater ($p < .01$) in the normal group compared with the stenosis group. The mean effective distribution volumes (EMQ/k or EMQ*TPC) were higher for the group with normal coronary arteries during infusion of dipyridamole (5.6 ml, 3.9 ml) compared with the groups with stenosis at rest and with stenosis during infusion of dipyridamole (3.75 ml, 2.6 ml).

**Discussion**

Our study demonstrates that there is a linear correlation between derived absolute regional perfusion and coronary artery blood flow supplying the region over a wide range of flow, suggesting that radiographic contrast material is an acceptable tracer for regional myocardial perfusion. Our study is distinct from videodensitometric measurements of flow in blood vessels,
since those methods rely on accurate measurement of coronary dimensions and orientations to derive arterial flow whereas our method measures regional perfusion (flow/volume) from the rate of arrival and/or disappearance of myocardial contrast.

Smith et al.7 published mask subtraction images of the coronary microcirculatory blush and suggested that these images might contain information related to myocardial perfusion, but they did not pursue this prospect, citing the problems of making absolute density measurements from a two-dimensional projection of the myocardium. Projection images actually present two distinct problems. The first is that the thickness of the contrast material distribution is unknown, so it is impossible to determine the absolute concentration (mg/cc) of contrast in the myocardium. This is not a limitation in our technique, however, since only relative concentration measurement is required to determine the time-to-peak and washout rate of contrast within a region of interest, from which the average absolute perfusion within the myocardial volume corresponding to the region of interest can be calculated.

The second problem related to projection imaging is that perfusion is unlikely to be homogeneous throughout the myocardial volume corresponding to even small regions of interest, since each region of interest represents a two-dimensional projection through the myocardium. Overlap of volumes with differing rates of perfusion is a real limitation that this technique shares with planar thallium and xenon nuclear scintigraphy. One important consequential limitation is the inability to measure the endocardial/epicardial flow ratio directly. Thus the measurements presented in this article represent transmyocardial average perfusion.

Another consequential limitation is that it is not possible to determine regional perfusion reliably if there is overlap of normal and ischemic circulatory beds. We found that choosing the lateral projection produced circumflex territory regions of interest that were free from overlap with the left anterior descending perfusion territory, the left ventricle, and the right atrium. In clinical application it is probable that most of the overlap between simultaneously opacified major circulatory beds can be eliminated by selective injection of contrast and appropriate choice of projection. There would remain the problem of overlap of regions of differing perfusions with a single circulatory bed produced by distal lesions, reducing the sensitivity of the method for detection of small regions of ischemia. For proximal coronary artery stenoses, however, the results of our study suggest that digital perfusion angiography should be a useful technique for measuring the hemodynamic effect of stenoses on the regional myo-

FIGURE 5. Perfusion indexes vs coronary artery blood flow measured by electromagnetic flowmeter for 31 studies in six dogs. Flow was varied from 0.2 to 2.4 ml/sec by snare oculder and dipyridamole. Washout rate (upper curve) varied from approximately 0.1 to 0.4/sec, while the inverse of time-to-peak concentration (lower curve) varied from 0.2 to 0.6/sec. The differences in slope and correlation coefficient between the two indexes were not significant. The inverse of the slopes, which represents the average model-derived contrast material distribution volume, had an average value of 6.9 ml.

FIGURE 6. Washout rate data grouped according to presence or absence of a critical stenosis with and without dipyridamole.
cardiac perfusion rate. Increased sensitivity to smaller regions of ischemia might be obtained with multiple projections as is the practice in thallium scintigraphy.

The approach taken in this work is similar to an algorithm described by Vogel et al.4 for determining relative regional blood flow. In their method, an image in each of six consecutive cardiac cycles after intracoronary injection are digitized from cine film by retrospective electrocardiographic gating, or more recently by ECG-gated direct digital acquisition.9 These investigators found good correlation (r = .92) between relative regional blood flow and mean contrast density divided by mean appearance time. Reproducibility was 13%. Unlike Vogel et al., we have investigated the measurement of absolute, rather than relative, regional perfusion. Although measurement of absolute regional perfusion requires corrections to obtain linear densitometry, it allows a direct calculation of contrast distribution volume and regional flow per unit volume for validation of the physiologic assumptions underlying contrast transit flow measurements. We used 10/sec sampling of videodensity under continuous fluoroscopic examination as opposed to ECG-gated exposures. This more rapid sampling followed by time-domain filtration to eliminate cardiac motion provides improved temporal resolution of the time-density curve over the myocardium and particularly at the injection site, making it possible to apply either threshold (e.g., time-to-half-max), maximum first derivative, or time-to-peak criteria to obtain transit times.

This procedure may obviate power injection because the injection time is precisely determined directly from the images.

Since we acquired data in 10 × 10 pixel regions of interest, x-ray quantum fluctuation for the region of interest average was a factor of 10 less than the single-pixel quantum noise, so adequate statistics could be obtained at fluoroscopic exposures of only 1 to 5 μR/image. The 30 frame/sec fluoroscopic data could have been retrospectively gated with the ECG recorded on the audio channel of the videotape. The method of data collection and analysis we chose, however, was to acquire data from a region of interest every 0.1 sec throughout the cardiac cycle. Although it was a technical limitation that prevented us from sampling at 30 frames/sec, this would not have significantly improved the quality of the data, since 10 frames/sec provided adequate quantum statistics and temporal resolution. In clinical practice a factor of three dose reduction would be possible without loss of information by pulsing the x-ray beam at the actual data sampling rate rather than discarding data as we did in this study.

Because of the motion of the heart, the region of myocardium sampled by the region of interest in each image changes throughout the cardiac cycle. Subsequent time domain averaging of these samples over two complete cardiac cycles is equivalent to blurring the region of interest. The size of the blurred effective region of interest is determined by the extent of the motion of the heart under the region of interest throughout this averaging time. Since we were interested in investigating myocardial perfusion within regions served by the major coronary arteries, we believed that enlargement and blurring of the region of interest was desirable to reduce the effect of heterogeneity of washout rate due to small arteries that unavoidably fell within the region of interest no matter how small. In most cases it was possible to select a position for the region of interest that confined the blurred region of interest to within the myocardial borders and avoided any overlap with major coronary arteries.

One disadvantage of the fluoroscopic technique we used was that it does not permit accurate visualization of percent stenosis for correlation with myocardial perfusion. However, the degree of stenosis can be inferred from its relationship to coronary artery blood flow as established by Gould et al.10

The most important source of densitometric error in our system was scatter and veiling glare. For scatter conditions typical in these studies, neglect of SVG correction will result in errors as large as 25% in wash-
out rate. Thus it is important to subtract the bias caused by SVG from the image before performing logarithmic transformation of the data. The most direct method for measuring SVG in the image is to block the primary x-ray beam so that only the SVG component remains, which is the method used in this study. Although SVG is not spatially uniform, we have found that by moving the lead blocker to different locations, SVG varies slowly enough over the cardiac silhouette that only a small error is introduced if the myocardial region of interest is placed adjacent to the lead blocker as shown in figure 1. Use of the lead blocker technique reduces the densitometric error in washout rate to about 5%, which is less than half the overall variability found in these studies. This residual 5% error is mainly due to nonlinearity caused by x-ray beam hardening. Beam hardening error was relatively insignificant in this study because the maximum iodine projected concentrations encountered over the myocardium were only about 100 mg/cm², compared with concentrations two to four times as great over major coronary arteries and up to 10 times as great during direct injection left ventriculography. Thus we chose to select an x-ray technique to maximize iodine contrast (75 kVp) rather than to minimize beam hardening (high kVp, high filtration). Time-to-peak is unaffected by densitometric errors.

There are substantial differences between most other flow tracers and the radiographic contrast agent we used that make it a less-than-ideal indicator. Sodium meglumine diatrizoate causes both coronary artery flow rate and the volume within the myocardial circulation to increase significantly after injection. Although it does not enter normal erythrocytes or muscle cells and remains intravascular in normal brain, it is neither freely diffusible as is xenon nor strictly intravascular as is indocyanine green. In myocardium it eventually diffuses into an extravascular space with a volume of distribution nearly twice the intravascular volume. Our estimate of the left circumflex distribution volume for Renografin-76 was 7.7 ml based on the washout rate and 5.6 ml based on time-to-peak, assuming a single well-mixed intravascular compartment. By means of published ventricle-to-body weight ratios and the mean fractional left circumflex perfusion territory-to-heart weight ratio, the estimated mean perfusion territory for our six dogs was 64 g. Our calculated contrast material distribution volumes, therefore, represent 12 ml/100 g (washout) and 9.0 ml/100 (time-to-peak) of the perfused myocardium, in good agreement with published morphometric and radiolabeled tracer studies of normal canine myocardial capillary and whole blood volume (in the range 4.5 to 9.69 ml/100 g). The fact that the contrast dilution volumes are higher than the estimated blood volumes may reflect a real increase in intracapillary volume at hyperemic flows caused by dipyridamole-induced vasodilation. This effect would decrease both TPC and k for the hyperemic flows, reducing the slope of the regression line and producing a positive zero-flow intercept, as observed in our data. If significant extravascular diffusion of contrast material had occurred during this first-pass study, the opposite effect (i.e., relative depression of perfusion index at low flows with less effect at high flows) should have been observed. We conclude that the contrast material remains essentially intravascular during the first pass and that the “mixing chamber” in our model corresponds to the intravascular volume. Thus we are measuring the perfusion (flow per volume) of regional myocardial capillary lumina rather than true perfusion of myocardial cells, which requires an indicator that freely diffuses myocardial tissue.

Although videodensitometric indexes changed in a directly appropriate manner in individual dogs, there was only a modest overall correlation between washout rate and flow (r = .85) and TPC and flow (r = .85). In addition to variability of distribution volume at rest, we identified three other potential sources of variability: low-frequency motion artifact related to respiration, variation of hand injection rate and point in the cardiac cycle, and the effect of contrast-induced changes in blood flow and distribution volume. The arbitrary selection criteria we applied eliminated the most severe cases of motion artifact. Although no attempt was made to inject at a specific phase of the cardiac cycle, this was probably not critical for washout rate, since the injection time was longer than an entire cardiac cycle, but may have introduced a variability in TPC of up to half the cardiac period (average = 0.2 sec). The contribution of contrast-induced hyperemia to variability can be evaluated qualitatively by comparing the correlation of coronary flow to time-to-peak, which is insensitive to contrast hyperemia, and to the washout data, which might be more sensitive. The linear correlation coefficients were the same for both k and 1/TPC (r = .85), suggesting no major influence. The effect of the contrast material on flow and volume could have been reduced by use of a nonionic contrast material for this study, although these materials do not entirely eliminate contrast hyperemia. We saw no evidence of catheter-induced changes in coronary flow. The transient 36% reduction in flow immediately after injection was probably
caused by the high viscosity of undiluted contrast material.

Since the data show significant overlap of both washout rate and TPC between regions receiving normal resting flow, e.g. 50 ml/min, and ischemic regions served by arteries with half this flow, these indexes measured at rest have little sensitivity to detect even quite severe coronary artery stenoses. Using direct electromagnetic flowmeter measurements, Gould et al.\textsuperscript{10} found little change in resting flow with increasing coronary artery stenosis up to 85% diameter narrowing. Coronary artery blood flow varies more sensitivity and over a much wider range with changes in coronary artery stenosis, however, when the autoregulating capacity of the coronary circulation is saturated.\textsuperscript{23} Thus the overlap between washout rates for normal and stenotic arteries should be reduced during hyperemic stimuli such as exercise or pharmacologic coronary vasodilation. In addition, measurement of washout during stable maximal hyperemia, e.g., by dipyridamole, should minimize the transient flow variation associated with injection of contrast medium. In our study, videodensity variables in the presence of critical stenosis did not change significantly during dipyridamole-induced hyperemia. These data are consistent with the measurements of Vogel et al.,\textsuperscript{4} who used double injection of contrast material in humans, in which the ratio of myocardial contrast appearance times for the first vs the second injection (during contrast hyperemia) was 1.01 \pm 0.12 for patients with greater than 70% coronary stenosis and 1.82 \pm 0.33 for those with normal coronary arteries.

On the basis of these animal laboratory data, we believe that the major practical problem that may affect human cardiac application is the error caused by respiration. Although respiratory motion is a serious problem in all clinical digital cardiac angiographic studies, in myocardial perfusion washout analysis the changes in video intensity caused by respiration are particularly problematic because they can be larger than those caused by the contrast material. As in other applications of digital subtraction angiography, this method will require careful breath holding by the patient.

Angiographic assessment of myocardial perfusion would be simpler to perform than xenon-133 washout or thallium-201 studies because these techniques (1) require that a gamma camera be available at cardiac catheterization, (2) require an extra injection and associated imaging procedure over and above the conventional coronary angiogram, (3) require special care to achieve precise correspondence between regions-of-interest nuclear scan and the angiographically defined coronary anatomy, and (4) add a substantial cost for the indicator. In addition, xenon requires a means for venting the radioactive isotope exhaled by the patient. Therefore if digital myocardial perfusion angiography is able to provide an index of regional blood flow before and after interventions or stress, it would be practical as a routine clinical tool.

**Conclusions.** Digital analysis of density in planar x-ray images of contrast material in the myocardium after intracoronary injection produces reproducible time-concentration curves. Both time-to-peak and washout rate correlate reasonably well with coronary flow over a 300% range from rest to dipyridamole-induced hyperemia. Induced hyperemia significantly improves the ability to distinguish between myocardium distal to normal and stenosed vessels, allowing detection of coronary stenoses that do not cause reduced perfusion at rest. Despite a number of theoretical and practical limitations, digital coronary angiography may provide a convenient means for assessing the rate and distribution of myocardial perfusion through coronary stenoses and coronary artery bypass grafts, and after interventions such as percutaneous transluminal coronary angioplasty.

**References**


Erratum
In a recent “Perspective” by Dr. Alberto Malliani (Circulation 73: 201, 1986), a line of type was inadvertently omitted. The last paragraph beginning in the left-hand column on page 203 should have read: “According to this hypothesis, when the activation of the cardiac sympathetic afferent fibers is widely and homogeneously distributed, as in the case of intracoronary injections of bradykinin or, more currently, during a marked increase in arterial pressure,13 central inhibitory modulations16 will prevent the onset of pain. Conversely, recent thoracic surgery, by inducing a localized somatic afferent barrage, could decisively contribute, through mechanisms of convergence at spinal level, to genesis of the peculiar algogenic code.”
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