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EXPERIMENTAL STUDIES

# Assessment of Myocardial Perfusion by Videodensitometry in the Canine Model

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**Assessment of the functional severity of coronary stenoses has become increasingly important as the intrinsic limitations of coronary angiography have been documented. Videodensitometric coronary flow reserve has been proposed as a means to assess the physiologic significance of a coronary stenosis in humans. This study compared videodensitometric assessment of coronary flow with microsphere quantitation in the closed chest canine model.**

**In five dogs, flow rates were assessed at baseline, after vasodilation with adenosine, after vasoconstriction with vasopressin and during rapid cardiac pacing. The videodensitometric peak density, time to one-half peak density and washout time (time from peak to one-half peak density) were compared at each flow state with flow assessed by microsphere injection. Reproducibility of videodensitometric measurements from two different coronary injections during the same flow state was best with peak density ($r = 0.94$).**

**Videodensitometric flow ratios (flow state under study to flow at rest) using peak density demonstrated a fair correlation with flow ratios by microsphere ($r = 0.81$). There was poor correlation between flow ratios when time to one-half peak or washout time was used.**

**Videodensitometric flow measurements used in vivo to assess a wide range of drug-induced coronary flows may not accurately reflect coronary flow measured by microsphere.**

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Assessment of the severity of coronary artery stenoses by selective coronary angiography is essential in evaluating the need for interventions such as coronary artery bypass grafting and percutaneous transluminal coronary angioplasty (1). The presence and severity of a coronary artery stenosis have been assessed at the time of angiography by visual estimation of the minimal diameter of the coronary artery in the area of stenosis and comparison with an adjacent, presumably normal, vessel diameter. Although this method is the one most frequently used to evaluate patients with coronary disease, it has intrinsic limitations, mainly because it is based on anatomic criteria that may not reflect the physiologic significance of a specific coronary stenosis. In addition, there is significant interobserver variability in visual readings (2) and poor correlation between angiographic estimation of stenosis and pathologic data (3) and direct Doppler echocardiographic measurements of coronary flow (4). Finally, only the lumen of the coronary artery is visualized, so that the amount of narrowing of a diffusely diseased vessel of small caliber can be underestimated.

In the experimental laboratory, coronary flow reserve has been shown to be an accurate, reproducible measurement of the physiologic significance of a given coronary stenosis (5). By measuring coronary blood flow at rest and flow during maximal dilation, one can obtain a ratio that progressively decreases as the degree of coronary obstruction increases, because of a reduction in the reserve flow. This concept of coronary flow reserve has been used intraoperatively by application of a Doppler probe directly on epicardial arteries to measure flow before and after coronary occlusion (4). This technique has documented the discrepancy between the anatomic criteria and the physiologic significance of a coronary stenosis.

In the clinical setting, assessment of coronary flow is more difficult. Recently, a videodensitometric method assessing the spatial and temporal distribution of contrast medium through the myocardial arteriolar and venous phases was proposed (6,7) as a means to measure the hyperemic response to contrast medium or pacing. This technique has

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potential for widespread clinical application, because it can be performed during routine coronary angiography (8). However, few studies (9–11) have specifically evaluated the accuracy of videodensitometric changes in quantitating coronary blood flow. Accordingly, the present study was undertaken to compare videodensitometric information obtained at different coronary flow rates with microsphere quantitation of flow in the dog.

## Methods

**Instrumentation.** Five mongrel dogs of both sexes, weighing 15 to 30 kg, were anesthetized with a combination of fentanyl and droperidol (Innovar Vet) given intramuscularly (0.25 ml/kg) and then were ventilated with a nitrous oxide and oxygen mixture (65:35). This anesthetic combination resulted in bradycardia, which allowed continuous pacing throughout the experiment. One catheter was inserted through the internal jugular vein and was placed by a transseptal approach into the left atrium for radioactive microsphere injection. Another catheter was placed into the abdominal aorta through a femoral arteriotomy for arterial pressure measurements and collection of four microsphere reference samples. The pacing catheter was introduced into the internal jugular vein and inserted into the coronary sinus for continuous pacing throughout the procedure. A specifically designed coronary guide catheter was inserted into the left internal carotid artery and was advanced to engage the left main coronary artery. A 1 mm catheter was advanced to allow selective drug infusions into the left anterior descending coronary artery. Aortic pressure, left ventricular pressure, left atrial pressure and heart rate were recorded simultaneously.

**Experimental protocol.** Coronary injections consisted of 6 ml of full strength sodium meglumine diatrizoate (Renografin-76) into the guide catheter placed in the ostium of the left main coronary artery. Contrast medium was introduced by a power injector to produce a constant pressure during the injection. The injection was timed to begin on the R wave of the QRS complex. The ventilator was stopped at full lung inflation before and during the injection to prevent respiratory motion of the heart. A 30° left anterior oblique view was used to image all selective coronary injections. Video imaging was performed for 10 seconds before, during and for 30 seconds after the coronary injection of contrast medium. The video imaging was done with a General Electric catheterization laboratory X-ray unit with a 9 inch (22.9 cm) image intensifier and a Videocon camera. The X-ray settings were at 90 kV and not more than 5 mA during the video imaging. The electronics for the video system were modified to widen the video amplifier bandwidth from 2 to 3 MHz; all circuits were directly coupled to prevent black-level biasing of the picture. The image data were stored on 1 inch (2.54 cm) videotape by an Ampex VPR-2 recorder.

*Coronary injections were performed at four different coronary flow states (Table 1).* Ten minutes was allowed between each coronary flow state for equilibration of flows: A) The rest state consisted of pacing at 80 beats/min. B) For vasodilation, adenosine (1 mg/min) was infused selectively into the left anterior descending coronary artery through the 1 mm catheter during pacing at 80 beats/min. C) For vasoconstriction, vasopressin (0.4 units/min) was infused selectively into the left anterior descending coronary artery during pacing at 80 beats/min. D) Pacing was performed at 160 beats/min. Two intracoronary injections of contrast medium were made at each flow state, 5 minutes apart, to determine the variability of the videodensitometric measurements. Adenosine and vasopressin interventions were varied randomly. The heart was actively paced throughout the entire experiment.

**Microsphere quantitation of coronary flow.** At each of the four flow states, 1.5 million radioactive microspheres, 15 $\mu$m in diameter, were injected into the left atrium. To minimize the effect of contrast medium on coronary flow, the microspheres were injected from 7 to 10 minutes after the last contrast injection. Flow calibration was performed by withdrawal of a reference flow sample from the abdominal aorta at a rate of 7.6 ml/min. A different microsphere label (cobalt-57, tin-113, scandium-46 and strontium-85) was used at each of the four flow states. The sequence of isotope labels was varied in each experiment. After all measurements were obtained, an alpha-zurine blue dye was injected into the left anterior descending coronary artery through

**Table 1.** Coronary Flow States

| |
|---|
| A. Rest: pacing at 80 beats/min |
| 1. Videodensitometric flow × 2* |
| 2. Microsphere injection, cobalt-57 |
| 3. Equilibration for 10 minutes |
| B. Hyperemia: selective infusion of adenosine; pacing at 80 beats/min |
| 1. Videodensitometric flow × 2* |
| 2. Microsphere injection, tin-113 |
| 3. Equilibration for 10 minutes |
| C. Vasoconstriction: selective infusion of vasopressin; pacing at 80 beats/min |
| 1. Videodensitometric flow × 2* |
| 2. Microsphere injection, scandium-46 |
| 3. Equilibration for 10 minutes |
| D. Tachycardia: pacing at 160 beats/min |
| 1. Videodensitometric flow × 2* |
| 2. Microsphere injection, strontium-85 |
| 3. Equilibration for 10 minutes |

*At each flow state, two videodensitometric flow measurements were performed 5 minutes apart.

the subselective catheter to outline the area perfused by the left anterior descending coronary artery. The dog was then killed by injection of 10% potassium chloride, and the heart was fixed in formalin.

*Tissue counts for the four isotope labels* were obtained by segmentation of the formalin-fixed heart into 1.0 to 1.5 g sections according to a predetermined protocol (12). Isotope counts of each segment and segment weight were recorded. Isotope counts in the blue-stained tissue segments were used to represent flow in the left anterior descending coronary artery.

**Image processing.** The video images obtained during selective coronary angiography were transferred from the 1 inch videotape to a digital radiographic computer (General Electric DF.3000). Each digitized image consisted of a 512 × 512 × 8 bit matrix. The frame in which contrast medium first appeared in the coronary artery was identified visually. Ten consecutive frames before the injection of contrast medium were averaged and used as a mask. Sixteen consecutive end-diastolic images beginning at the onset of the contrast injection were identified. Mask-mode subtraction of the end-diastolic frames was then performed using a preinjection mask.

**Image analysis.** A region of interest (20 × 20 pixels) was placed in an area of "myocardial blush" supplied by the left anterior descending coronary artery; care was taken not to place it over visible epicardial arteries. This same region of interest was used for the different flow measurements of each dog. A pixel density was determined as the intensity of each pixel from 256 possible gray scale levels. This measurement was relative and not absolute, varying from animal to animal. The average pixel density within each region of interest was then determined for each of the end-diastolic images. A plot of the pixel density against time was made for each injection of contrast material at the four different flow states.

For each injection, there was an initial rise in pixel intensity over time (Fig. 1). A subsequent rapid decrease in pixel intensity was followed by a slower rate of decrease. The point at which the slow washout kinetics began was identified visually. A gamma variate fit was then used, beginning at the onset of the contrast material injection and continuing to the point at which the slow washout kinetics began.

*Values determined from the curve of the gamma variate fit were:* 1) peak density, 2) time to one-half peak density, and 3) time from peak density to one-half peak density (washout). A mean transit time could not be reliably determined from the data because the slow kinetics of the washout phase frequently could not be separated out.

**Statistical analysis.** A least squares linear regression was used to compare all three videodensitometric values with microsphere flows as flow ratios (coronary flow during intervention divided by rest coronary flow). The variability of the technique was determined from a least squares fit comparing the videodensitometric measurements from the two coronary injections during the same coronary flow state.

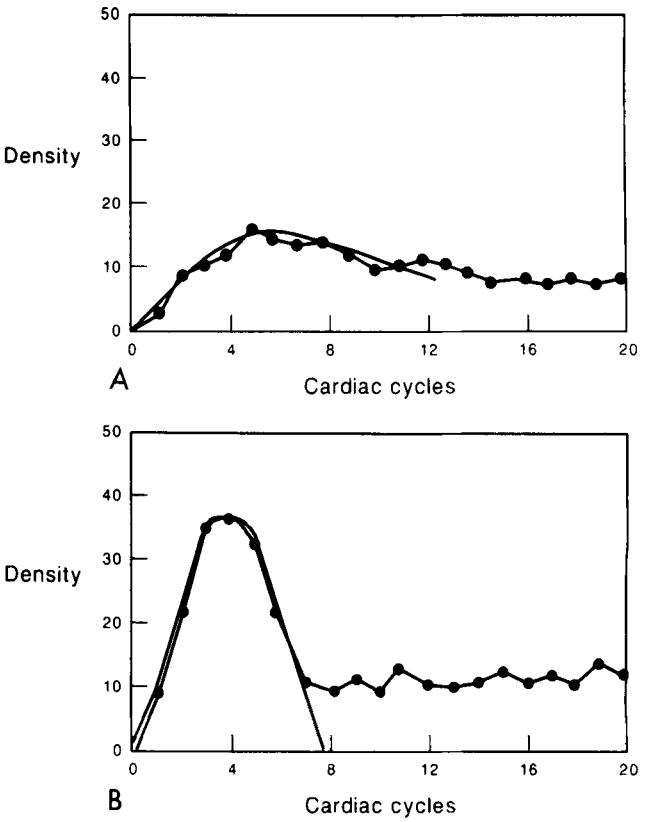



**Figure 1.** Pixel density of contrast medium in region of interest plotted against time for each injection of medium. **Solid lines** indicate gamma variant fit, which was used from onset of contrast medium injection to point at which slow washout kinetics began. **A,** Rest state. **B,** After adenosine infusion.

## Results

**Absolute measurements.** The results of the three videodensitometric measurements (peak density, time to one-half peak density and washout time) and the absolute flow by microsphere in the five dogs are shown in Table 2. Values for pacing were not obtained in Dog 1 because of the onset of ventricular fibrillation. In Dog 4, the left atrial catheter fell back into the right atrium during the experiment, so that there were no microsphere determinations during the adenosine infusion or pacing at 160 beats/min. The mean flow at rest by microsphere was 0.83 ml/min per g (range 0.43 to 1.12). In the four dogs in which microsphere flows were measured during adenosine infusion, the flow increased to a mean of 2.9 ml/min per g (range 1.5 to 4.2). After vasopressin infusion, the flow returned toward rest values, with a mean of 0.92 ml/min per g (range 0.37 to 1.71).

With rapid pacing, the flow increased in two of the three dogs in which it was measured by microsphere.

*The values obtained at each experimental condition using peak density correlated best with the measured flows.* The use of time to one-half maximum (washout time) did not correlate with changes in microsphere flow measurements. In part, this lack of correlation was the result of problems in determining these measurements. It was difficult to accurately determine the time from peak density to one-half peak density at the lower flows because of the appearance of the slow kinetic compartment (Fig. 1).

**Flow ratios.** The flow ratios from the videodensitometric measurements were compared with the flow ratios by microsphere at each flow state. There was fair correlation utilizing the peak density (r = 0.81) (Fig. 2). However, this positive correlation was because of the three points at the upper end of the spectrum (flow ratio utilizing maximal vasodilation with adenosine). There was no correlation when these points were excluded. The correlation between flow ratios with the time to half of peak density was less (r = −0.52) (Fig. 3). There was no correlation between flow ratios when the washout time calculated from videodensitometric measurements was examined. Unlike results in previous work (6), the correlation between flow ratios of videodensitometric and microsphere measurements did not improve when the ratio of peak density divided by time to half of peak density was used.

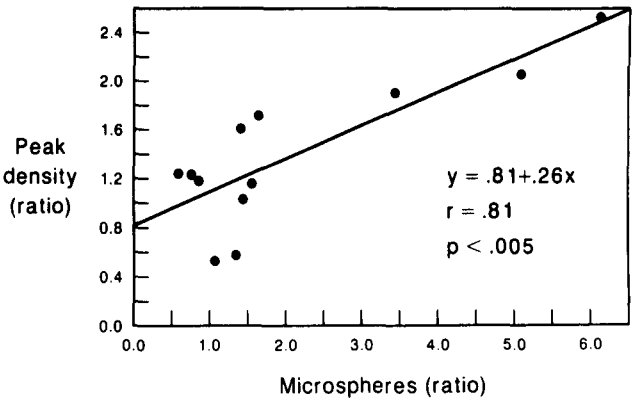



**Figure 2.** Ratio of peak densities plotted against ratio of microsphere flow. The ratios are derived from flow measurement during the interventional state divided by flow measurement at rest. SEE = 0.35.

**Variability of the technique.** The videodensitometric measurements from two coronary injections during the same flow states were determined. The best reproducibility was

**Table 2.** Microsphere Flow and Videodensitometric Measurements in Five Dogs

| | Microsphere Flow (ml/min per g) | Peak Density (units) | Time to One-half Peak Density (cycles) | Washout (cycles) |
|---|---|---|---|---|
| Dog 1 | | | | |
| R | 0.69 | 15.2 | 1.9 | 3.3 |
| A | 4.20 | 37.4 | 1.7 | 2.5 |
| V | 0.97 | 15.3 | 2.7 | 4.1 |
| P | — | — | — | — |
| Dog 2 | | | | |
| R | 1.12 | 15.3 | 3.2 | 7.0 |
| A | 3.82 | 28.4 | 0.9 | 4.8 |
| V | 1.71 | 17.2 | 3.0 | 7.0 |
| P | 0.86 | 18.5 | 2.7 | 8.0 |
| Dog 3 | | | | |
| R | 0.95 | 20.3 | 1.7 | 7.2 |
| A | 1.53 | 34.3 | 1.3 | 4.4 |
| V | 0.97 | 10.4 | 3.5 | 5.4 |
| P | 1.24 | 11.4 | 2.1 | 6.5 |
| Dog 4 | | | | |
| R | 1.00 | 10.9 | 1.8 | 5.8 |
| A | — | 32.0 | 0.7 | 3.8 |
| V | 0.59 | 13.1 | 2.0 | 7.5 |
| P | — | 24.7 | 1.3 | 5.2 |
| Dog 5 | | | | |
| R | 0.43 | 10.7 | 1.9 | 6.3 |
| A | 2.16 | 21.3 | 0.3 | 5.2 |
| V | 0.37 | 12.4 | 3.0 | 6.0 |
| P | 0.59 | 17.0 | 1.0 | 4.5 |

A = adenosine (1 mg/min); P = pacing (160 beats/min); R = rest; V = vasopressin (0.4 units/min); Washout = time from peak density to time of one-half peak density.

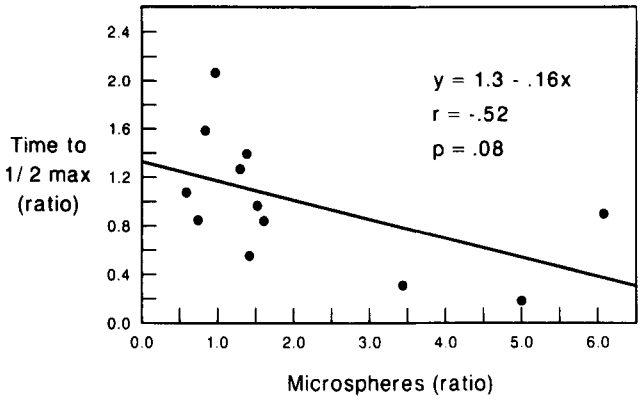



**Figure 3.** Ratio of time to one-half maximal (max) peak density obtained by videodensitometry plotted against ratio of microsphere flow. The ratios are derived from flow measurement during the interventional state divided by flow measurement at rest.

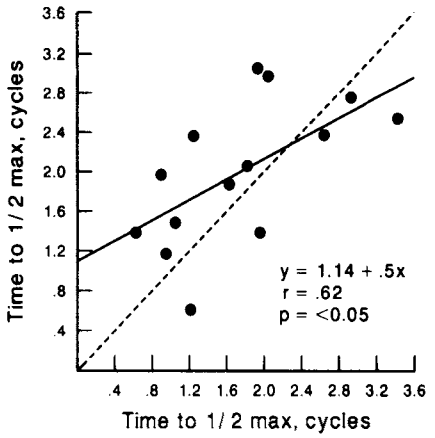



**Figure 5.** Correlation between time to one-half maximal peak density derived from two injections of contrast material performed during the same flow state. **Dashed line** is the line of identity.

with the peak density (Fig. 4). There was poor correlation between the two measurements with both the time to half of peak density (Fig. 5) and the washout time (Fig. 6). When these measurements (time to half of peak density and washout time) were used to compare the first injection at each flow level with the second injection, there was no consistent difference.

## Discussion

**Previous videodensitometric studies.** Initial work with videodensitometry to evaluate coronary blood flow was performed by measurement of mean transit time of dye down an epicardial artery (13–15). This method, which required direct measurement of coronary artery diameter, had inherent error. In addition, only the proximal, straight or nonbranching portions of an artery could be analyzed. Movement of the heart throughout the cardiac cycle necessitated a large sample window, which in itself decreased the sensitivity of the measurement.

Smith et al. (14) demonstrated a spatial dispersion of contrast medium into the microcirculation as a "myocardial blush." With the advent of the newer digital computer applications, it is now possible to obtain time-density measurements of this "myocardial blush" from routine coronary angiography. Vogel et al. (6) and Bates et al. (7), applying this technique to patients, demonstrated improved flow reserve after coronary artery bypass grafting and after coronary angioplasty in patients with coronary artery disease. Correlation of the actual videodensitometric measurements with other techniques of measuring coronary flow has been limited to use of direct electromagnetic flowmeter measurements in an open chest canine model (9–11). Our study is the first that compares the currently used videodensitometric techniques with a method of measuring coronary flow (that is, microspheres) in a closed chest model.

**Figure 4.** Correlation of peak densities obtained with two injections of contrast medium during the same flow state. **Dashed line** is the line of identity.

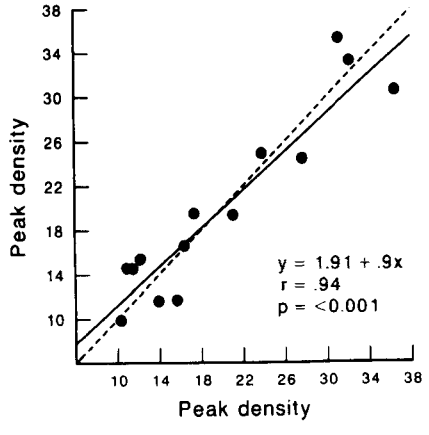
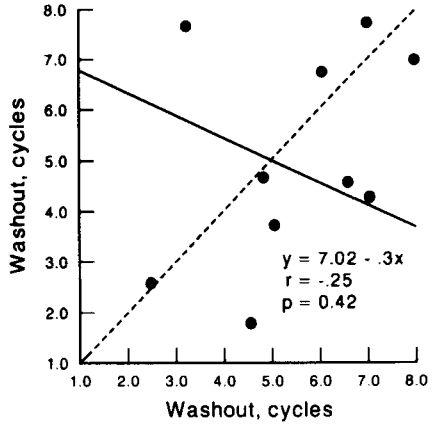



**Figure 6.** Correlation of washout (time from peak density to time of one-half peak density) derived from two injections of contrast medium during the same flow state. **Dashed line** is the line of identity.



**Method of analysis for videodensitometry.** The optimal method for analyzing the data obtained from videodensitometry remains to be determined. After a bolus injection, the descending limb of the concentration curve is thought to be represented by a monoexponential function (16). Application of this function is believed to represent the rate of washout, which should be proportional to coronary blood flow. However, analysis of the downslope of the curve of the "myocardial blush" was difficult, because a slow kinetic compartment could not be accurately separated from the faster downslope. In addition, it has been shown (17) that the rate of washout may well be due to viscosity effects of the contrast medium itself.

*Color encoding of the mean transit time* of each pixel of the entire video image has been used to allow a visual interpretation of the microcirculation of the entire myocardium in a two-dimensional picture (7–9). Although color encoding has been shown to predict the degree of stenosis (18), the analysis is purely subjective. The average mean transit time of all pixel densities within a "blush" supplied by a single epicardial artery has been used in initial work as a means of analyzing videodensitometric information (6). This technique is from the initial work of Meier and Zierler (19), who used mean transit time for measurement of blood flow from indicator-dilution methods. This analysis later included the radiographic density within the region of interest, because it was thought that the regional vascular volume is represented by the peak density and will change during drug hyperemia. In our study, a mean transit time could not be determined, because the slow kinetics of the washout phase of the descending limb of the curve could not be separated out; therefore, time to one-half peak density was used. Our measurements of time to half-peak demonstrated a low sensitivity for detection of changes in blood flow. The variability in measurement of the time to half peak density during the same blood flow states was high.

*Analysis of peak density alone appeared to give the most reproducible measurements.* It has been shown that a given concentration of sodium meglumine diatrizoate is directly proportional to the videodensity obtained (20) and that the linearity remains over different depths and concentrations of contrast material (21). Thus, the peak density of a region of interest should reflect the peak amount of contrast medium entering the myocardium. The absolute value of peak density from a given study cannot be used to calculate absolute blood flow because of multiple factors in the Lambert-Beer law that affect absorption of radiation, but flow ratios determined at two different flow states using the same imaging standards should be feasible. However, there was only fair correlation in this study when flow ratios obtained from peak density measurements were compared with flow ratios measured by microspheres.

**Theoretical problems.** Many theoretical problems remain in the use of videodensitometry to examine the coronary flow patterns from coronary angiography in normal persons and patients. The problem of overlap is foremost, because a three-dimensional spatial extent of perfusion is displayed on a two-dimensional image. This problem may be partially overcome when flow ratios are used instead of absolute flows. Second, the contrast material used is not inert and not an ideal indicator. Capillary solubility, uptake by myocardial cells, extravasation into the extracellular space and the effect of the high viscosity and osmotic pressure of the dye itself on the small vessels all influence videodensitometric measurements of perfusion. Third, recirculation of dye through the coronary sinus into the right-sided cardiac chambers poses a problem with this technique.

*All videodensitometric techniques using selective coronary angiography have the inherent problem* that intracoronary injection of contrast material changes coronary blood flow. Therefore, the actual coronary flow measured during the video imaging is not going to be that of the rest state before injection of contrast material. The microsphere injections in our study were performed at a time when effects of contrast material on coronary flow would be minimal in order to determine the usefulness of the technique in evaluating a specific flow state in a clinical setting.

**Conclusion.** Although videodensitometric measurements can document changes throughout a wide range of drug-induced coronary flows, it is not known whether the technique is sensitive enough to differentiate flow ratios with varying degrees of stenosis. This less than optimal correlation between videodensitometric analysis of the "myocardial blush" and other methods of measuring coronary flow was also demonstrated by Nissen et al. (11). Further work will need to be performed before the technique can be applied to evaluate the effect of a stenosis or an intervention on coronary physiology in humans.

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