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Myocardial Contrast Echocardiography for the Assessment of Coronary Blood Flow Reserve: Validation in Humans

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Objectives. **The aim of this study was to validate the use of myocardial contrast echocardiography to determine coronary blood flow reserve in humans.**

Background. **Although myocardial contrast echocardiography has been used to accurately quantify coronary flow reserve in animals, validation for its use in humans to measure flow reserve is lacking.**

Methods. **We analyzed the time-intensity curve from the anteroseptal region of the left ventricular short axis produced after a left main coronary artery injection of sonicated albumin before and after intracoronary administration of papaverine in 16 patients without angiographically significant coronary artery disease. The ratio of half-time of video intensity disappearance from peak intensity, variable of curve width, area under the time-intensity curve and corrected peak contrast intensity after papaverine compared with baseline were correlated with coronary flow reserve measured simultaneously with an intracoronary Doppler probe in the left anterior descending coronary artery.**

Results. **There was a strong inverse correlation with half-time of contrast washout and coronary flow reserve ($r = -0.76$, $p = 0.0007$) and a strong positive correlation between the variable of curve width (which is inversely proportional to curve width) and coronary flow reserve ($r = 0.71$, $p = 0.002$). There was a weak but significant inverse correlation between area under the time-intensity curve and coronary flow reserve ($r = -0.54$, $p = 0.03$) but no correlation between corrected peak contrast intensity and coronary flow reserve ($r = -0.36$, $p =$ NS). Despite the strong correlation for the ratios for half-time of contrast washout and variable of curve width and actual coronary flow reserve measured with intracoronary Doppler probe, the transit time ratios consistently underestimated coronary flow reserve.**

Conclusions. **Myocardial contrast echocardiography performed with left main coronary artery injections of sonicated albumin can be utilized to measure coronary flow reserve in humans. Transit time variable ratios (half-time of contrast washout and variable of curve width) derived from the time-intensity curve correlate most strongly with coronary flow reserve.**

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The measurement of absolute coronary flow reserve during diagnostic cardiac catheterization determines whether a coronary vessel is functionally diseased irrespective of the presence or absence of a significant anatomic stenosis (1–3). Measurement of coronary flow reserve in humans has been performed with intracoronary Doppler catheters (1,2), coronary sinus thermodilution (3), digital angiographic techniques (4) and myocardial contrast echocardiography (5,6). However, myocardial contrast echocardiography has not been validated as a method of quantitating flow reserve in humans as it has in animals. The aim of this study was to validate the use of myocardial contrast echocardiography by analyzing time–video intensity curves for the assessment of coronary blood flow reserve in humans. Because intracoronary Doppler study is an accepted method of assessing coronary flow reserve in humans, ratios of specific variables of the time-intensity curve after intracoronary administration of papaverine compared with baseline values were correlated with this value.

Methods

Nineteen patients (17 men and 2 women) with essentially normal epicardial coronary arteries at the time of diagnostic cardiac catheterization were chosen for the study. All patients were in stable condition after orthotopic heart transplantation. Their mean age was 42 ± 5 years. The study was approved by the Committee on the Conduct of Human Research at Virginia Commonwealth University and the Research Committee of the McGuire Veterans Affairs Medical Center.

At the completion of the diagnostic cardiac catheterization, 10,000 U of intravenous heparin was given and an 8F guiding catheter was inserted under fluoroscopic guidance

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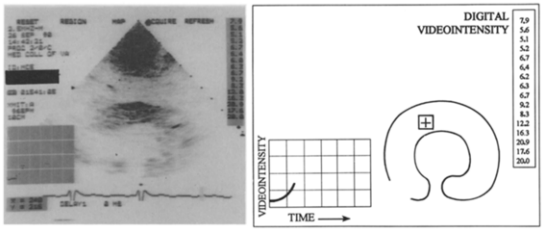


Figure 1. Example of the on-line acquisition of a time-intensity curve after a left main coronary artery injection of sonicated albumin. The 21 × 21-square pixel region of interest (represented as a cross hair) is placed in the myocardial distribution of the left anterior descending coronary artery. Digitized video intensity is recorded at the right of the screen and plotted as a function of time at the lower left of the screen.

into the left main coronary artery. A 0.014-in. (0.036 cm) guide wire was then advanced under fluoroscopy into the distal left anterior descending artery, and a 3.5F Millar Instruments Doppler catheter (DC-101) was advanced over the wire into a straight nonbranching segment of the artery. A mean and phasic Doppler velocity recording was obtained that was stable and unaffected by patient respiration. Doppler signals were displayed together with intracoronary pressure and electrocardiographic (ECG) signals on a strip chart recording at 25-mm/s paper speed at baseline and after injection of papaverine, 12 mg, into the left main coronary artery. With this technique coronary flow reserve was calculated as the ratio between the peak mean velocity after papaverine administration and baseline velocity.

Preparation of sonicated albumin. Five percent human albumin was obtained from the blood bank. Eight-milliliter aliquots of albumin were placed in a 10-ml syringe (Becton Dickinson), and a commercially available sonicating system (Heat Systems Ultrasonics, model W-375) was used to create microbubbles, as described elsewhere (7). Briefly, with the sonicating horn initially placed just below the surface of the albumin, continuous sonication at 20,000 Hz and a power output of 210 W proceeded for approximately 40 s. The solution was then immediately stored in a sterile container and used within 24 h. Representative samples of sonicated albumin obtained with this technique were analyzed with a Lab-Tec 100 Laser Particle Analyzer (Lasentec East). Microbubble mean size was 6 to 8 μm and 75% to 80% of the microbubbles were <8 μm.

Myocardial contrast echocardiography. Two-dimensional echocardiograms were obtained with the patient quietly breathing in the supine position. Parasternal short-axis views were obtained at the midpapillary muscle level. The compression control was set to linear mode of operation, and time gain compensation was constant over the region of interest. These settings have been shown by Zwehl et al. (8) to create a linear relation between returning radiofrequency signal and measured video intensity. On-line mean video intensity in a 21 × 21-square pixel region of interest positioned in the anteroseptal distribution of the left ventricular short-axis image was determined with software designed in conjunction with the Hewlett-Packard Company and the Hewlett-Packard Sonos 1000 phased array imaging system. The region of interest was repositioned slightly during the acquisition of the curve in all patients because of the small changes in myocardial position due to cardiac translation. This region of interest usually was 21 × 21 square pixels and was chosen from several other pixel sizes (11 × 11, 31 × 31 or 41 × 41) because it consistently stayed within the epicardial and endocardial borders during acquisition of the time-intensity curve (Fig. 1). However, an editing function, available after acquisition of the curve, allowed removal of points that were obtained from outside the region of interest. This editing function was used in only two patients. In each case it was used to correct an error in baseline video intensity and affected the transit time variables by <4%. The curves were otherwise generated on line in real time at baseline flow, with a 1- to 3-ml bolus injection of sonicated human albumin into the left main coronary artery given over a constant interval of 6 s. The constant time interval of 6 s was chosen in an attempt to decrease shear stress on the microbubbles. Different initial bolus volumes were injected to generate for each patient a time-intensity curve that had an optimal signal to noise ratio visually but did not create attenuation of signals over the region of interest. Once the optimal volume of sonicated albumin was determined, this dose was kept constant for the injections performed at baseline and after administration of papaverine. Therefore, injection speed was constant for each patient. The injection of microbubbles after intracoronary papaverine administration was given when intracoronary Doppler velocity had just reached a maximum.

Time-intensity curve analysis. Kaul et al. (9) found that in individual dogs a measure of curve width defined as alpha correlated strongly with changes in coronary blood flow. This variable can be determined from a gamma variate function by using a nonlinear least-squares curve fit to the time-intensity curve. Because others (10,11) have utilized corrected peak contrast video intensity, half-time of contrast washout from peak video intensity and area under the time video intensity curve to determine changes in coronary blood flow, these variables, in addition to curve width, were determined on line to characterize the time-intensity curves. Figure 1 illustrates an example of the time-intensity curve

being generated from the left anterior descending artery perfusion bed after a bolus injection of sonicated albumin into the left main coronary artery. All variables were obtained at baseline and at peak hyperemia induced by intracoronary papaverine. The ratio of the variable obtained at peak velocity to the same variable at baseline flow was then correlated with coronary flow reserve obtained with intracoronary Doppler study.

Statistical analysis. Comparisons of velocity ratios before and after papaverine administration using an intracoronary Doppler probe (coronary flow reserve) were compared with the previously mentioned variables of the time-intensity curve ratios obtained with linear regression. A Pearson correlation coefficient was calculated for each comparison. Coronary flow reserve using an intracoronary Doppler probe was calculated by an independent investigator without knowledge of the ratios derived from each variable of the time-intensity curve. In eight patients time-intensity curves were generated after two separate intracoronary papaverine injections to determine the reproducibility of flow reserve measurements by myocardial contrast echocardiography. An intraclass correlation coefficient (12) was used to assess the reproducibility of this method in determining coronary flow reserve.

Results

A total of 19 stable heart transplant patients were studied. In two patients the intracoronary Doppler peak velocity was low with an inadequate signal to noise ratio and variable baseline, and therefore the flow ratios obtained with papaverine could not be used. A third patient had video intensity attenuation across the myocardium at all possible injection volumes, and time-intensity curves could not be evaluated. In the remaining 16 patients, time-intensity curves obtained before and after papaverine injection were suitable for analysis. In general, patients who had coronary flow reserves exceeding 2.0 by intracoronary Doppler study had decreases in the area under the curve and decreases in transit time variables (decreased half-time and increased variable of curve width) after papaverine injection. Figure 2 is an example of time-intensity curves obtained before and after papaverine from a patient with a coronary flow reserve of 3.5 by Doppler study.

Hemodynamic and ECG changes. No clinical symptoms were reported by the patients during the sonicated albumin or papaverine injections. One patient had transient inverted T waves after the sonicated albumin injection. After intracoronary papaverine, transient inversion of the T wave was seen in six patients. One patient had approximately 1-mm ST segment elevation, and another had ST segment depression compared with baseline. Both of these changes resolved within 2 min of the papaverine injection. Mean intracoronary pressure was unchanged after sonicated albumin injections (106 ± 9 mm Hg before vs. 107 ± 9 mm Hg after injection). Mean intracoronary pressure fell slightly but significantly at peak Doppler flow after papaverine injection (107 ± 11 mm Hg vs. 98 ± 11 mm Hg, $p < 0.05$).

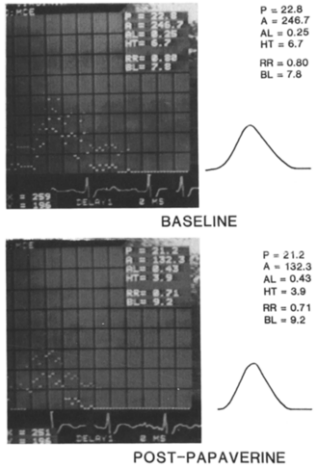


Figure 2. Example of a time-intensity curve at baseline and after papaverine (POST-PAPAVERINE) in a patient with a simultaneous coronary flow reserve of 3.5 determined by intracoronary Doppler probe. After papaverine the half-time (HT) is decreased, the curve width is decreased (corresponding to a higher value for the variable of curve width, AL), the area under the curve(A) is less and corrected peak contrast intensity (P) is unchanged. BL = baseline video intensity; RR = mean RR interval(s) during acquisition of the curve.

Time-intensity curve variables and coronary flow reserve. Table 1 lists the time-intensity curve variables measured before and after intracoronary papaverine injection, the ratios before and after papaverine injection and actual coronary flow reserves measured by intracoronary Doppler probe for each of the 16 patients in the study. Mean coronary flow reserve estimated with intracoronary Doppler probe in the 17 patients was 2.4 ± 0.6 (range 1.1 to 3.7). The mean value for flow reserve using the variable of curve width alpha was 1.3 ± 0.3 (range 0.8 to 1.9). The range for the ratio of half-time of video intensity washout was 0.51 to 1.17. All seven patients who had a coronary flow reserve ≥2.5 had a half-time ratio <0.80, and all but one of these had a curve width (alpha) ratio >1.4.

Area under the curve ratios (area obtained after papaverine injection divided by area at baseline flow rates) ranged from 0.25 to 1.06 and were <0.85 for any patient who had a Doppler-derived coronary flow reserve >2.0. However, three patients with a coronary flow reserve <2.5 also had an

Table 1. Variables of the Time-Intensity Curves After Left Main Coronary Artery Injections of Sonicated Albumin Before and After Papaverine Injection and Coronary Flow Reserve Determined by Intracoronary Doppler Probe

	Alpha			Area			HT			CPCI			
Pt No.	1	2	Ratio	1	2	Ratio	1	2	Ratio	1	2	Ratio	CFR
1	0.16	0.24	1.5	508	293	0.58	10.8	6.9	0.64	29.0	26.1	0.9	3.7
2	0.24	0.24	1.0	413	423	1.02	7.0	6.9	0.99	36.2	38.0	1.0	2.0
3	0.21	0.20	1.0	149	158	1.06	8.0	8.4	1.05	11.5	11.9	1.0	1.9
4	0.29	0.39	1.3	94	41	0.44	5.8	4.4	0.76	9.9	5.8	0.6	2.2
5	0.29	0.42	1.4	59	53	0.90	5.8	4.0	0.69	6.4	8.2	1.3	2.0
6	0.26	0.30	1.2	194	162	0.84	6.4	5.7	0.89	18.7	17.6	0.9	2.3
7	0.18	0.35	1.9	258	49	0.19	9.3	4.7	0.51	17.8	6.3	0.4	3.1
8	0.35	0.31	0.9	156	131	0.84	4.7	5.5	1.17	16.8	17.6	1.0	1.1
9	0.34	0.45	1.3	42	26	0.62	5.1	3.7	0.73	5.3	4.3	0.8	2.3
10	0.38	0.48	1.3	57	36	0.63	4.4	3.5	0.80	8.0	6.4	0.8	1.9
11	0.31	0.52	1.7	42	23	0.55	5.4	3.5	0.65	4.9	4.5	0.9	2.8
12	0.20	0.26	1.3	154	111	0.72	8.5	6.7	0.79	11.1	10.3	0.9	2.7
13	0.22	0.41	1.9	128	51	0.40	7.5	4.1	0.55	10.6	7.7	0.7	2.5
14	0.28	0.48	1.7	236	108	0.46	6.0	3.6	0.60	24.0	18.3	0.8	3.6
15	0.32	0.40	1.3	64	16	0.25	5.3	4.2	0.79	7.5	2.3	0.3	2.5
16	0.33	0.43	1.3	171	103	0.60	5.0	4.0	0.80	21.0	16.4	0.8	1.9
Mean	0.27	0.37	1.4	170.3	111.5	0.63	6.6	5.0	0.77	14.9	12.6	0.8	2.4
SD	0.06	0.10	0.3	128.3	106.4	0.25	1.8	1.5	0.18	8.8	9.1	0.2	0.7

Alpha = variable of curve width in s (−1); Area = area under the time-intensity curve; CFR = coronary flow reserve; CPCI = corrected peak contrast intensity; HT = half-time of contrast washout; Pt = patient; 1 = measurement at baseline flow; 2 = measurement at peak hyperemia after intracoronary administration of papaverine.

area ratio <0.85. The ratio of corrected peak contrast intensity after papaverine compared with baseline ranged from 0.3 to 3.2.

Figure 3 demonstrates the correlation between the ratios of half-time of contrast washout after papaverine injection compared with baseline flow and coronary flow reserve obtained with intracoronary Doppler study. There was a strong correlation between the half-time ratio and coronary flow reserve, with a correlation coefficient of −0.76 ($p = 0.0007$; $y = -2.8x + 4.6$, SE = 0.5). There was also a significant correlation (Fig. 4) between the ratios of the variable of curve width and coronary flow reserve ($r = 0.71$, $p = 0.002$; $y = 1.6x + 0.2$, SE = 0.5). There was a weak but significant negative correlation between coronary flow reserve by intracoronary Doppler probe and area under the time-intensity curve ($r = -0.54$, $p = 0.03$; $y = -1.4x + 3.3$,

Figure 3. Correlation between the ratio of half-time of contrast washout after papaverine administration compared with baseline (HT2/HT1) and coronary flow reserve obtained with intracoronary Doppler flow probe.

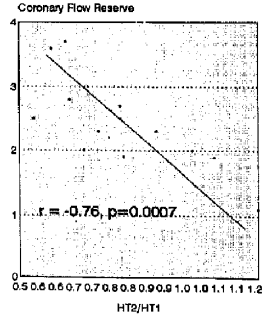
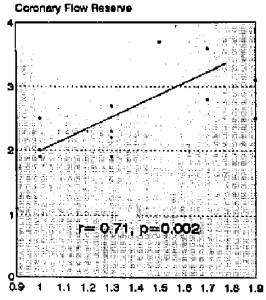


Figure 4. Correlation between the ratio of the variable of curve width after papaverine administration compared with baseline (Alpha2/Alpha1) and coronary flow reserve obtained with intracoronary Doppler flow probe.



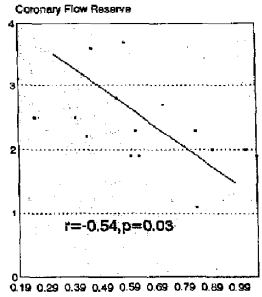


Figure 5. Correlation between the ratio of area under the time-intensity curve after papaverine administration compared with baseline (Area2/Area1) and coronary flow reserve obtained with intracoronary Doppler flow probe.

SE = 0.6) (Fig. 5). Finally, there was no significant correlation between the ratios of corrected peak contrast intensity after papaverine administration compared with baseline and intracoronary Doppler flow ratios ($r = -0.36$, p = NS).

Reproducibility of myocardial contrast echocardiography. In eight patients more than one intracoronary papaverine injection was performed to determine the reproducibility of this technique in measuring coronary flow reserve. With use of the half-time of contrast washout, repeat measurements of coronary flow reserve resulted in a good intraclass correlation coefficient (9) ($r = 0.72$). The reproducibility of the variable of curve width ratio was fair ($r = 0.57$).

Discussion

In this study we injected a small microbubble preparation (sonicated albumin) into the left main coronary artery of patients without epicardial coronary artery disease and measured myocardial video intensity versus time in the left anterior descending myocardial distribution before and after intracoronary papaverine injection. We found a good correlation between Doppler-derived coronary flow reserve and transit time variables (half-time of video intensity decay and variable of curve width). Because the index of curve width used in this study is inversely related to curve width, we found a strong positive correlation between this transit time variable and Doppler-derived coronary flow reserve. The reason for the findings observed can be explained by the site of injection of the microbubbles, the physical properties of the intravascular ultrasound tracer used and the absence of unbalanced coronary artery disease in the study patients.

Site of injection of microbubbles. Because we injected the same quantity of sonicated albumin at the same speed into the left main coronary artery before and after papaverine injection for each patient, the time-intensity curves we obtained from the myocardium were mainly influenced by two factors: changes in left main coronary blood flow (width of the input function) and changes in myocardial blood flow in the left anterior descending artery distribution. After intracoronary papaverine injection, there was an increase in left main coronary blood flow. Although this affected the concentration of microbubbles entering each branch, we assumed that the ratio of microbubbles that entered the left anterior descending distribution compared with the left circumflex bed did not change (because both vessels were angiographically normal), and therefore the ratio of transit time variables after papaverine injection compared with baseline accurately reflected coronary blood flow reserve. Decreases in half-time of video intensity washout after intracoronary papaverine (11) or intravenous dipyridamole (6) in angiographically normal coronary arteries after left main coronary artery injections of ultrasound contrast medium have been observed by others. Kaul et al. (9), using the same variable of curve width used in this study, found that this transit time variable accurately detected changes over a wide range of coronary blood flows.

Despite the strong correlation between the ratio of transit time variables and coronary flow reserve obtained with left main coronary artery injection of microbubbles, there was a consistent underestimation of the flow ratios with the transit time variables. This discrepancy can be explained by the changes in myocardial blood volume that occur with papaverine (13). Transit time variables are inversely proportional to flow changes but directly related to volume changes. Because intracoronary papaverine increases myocardial blood volume, it will increase the width of the time-intensity curve and delay video-intensity washout (14). Therefore, any time-intensity curve variable used to measure flow will be affected by volume changes regardless of the site of injection of the microbubbles. Other possible explanations for the underestimation of flow ratios by transit time variables could be related to the on-line methods used in this study. Because relatively few points described the rise and fall of the video-intensity curve, the curve fit used to describe the contrast appearance and disappearance may be inaccurate. However, this error could lead to overestimations of flow as well. Because the transit time variables consistently underestimated flow, inadequate curve fit is less likely to account for the findings we observed.

Ultrasonic contrast agent. The ultrasonic contrast agent used in this study has been shown to behave as a true intravascular tracer and follow indicator-dilution principles (15). This is why area under the time-intensity curve decreased after intracoronary papaverine injection. However, ultrasonic contrast microbubbles used by others are larger and may behave instead as partial deposit tracers. Because these agents would be trapped in the coronary circulation, increases in flow and volume to a region of myocardium would result in increased deposition and greater video

intensity. Rovai et al. (16) found that the area under the curve increased in angiographically normal coronary arteries after intravenous dipyridamole injection when they injected intracoronary sonicated iopamidol (mean microbubble size = 12 ± 4 μm). However, when they iniected a preparation with smaller microbubbles into an in vitro flow system, they found that the area under the time-intensity curve decreased with increased flow rates. Because sonicated albumin does not become trapped in the coronary circulation and acts as a red blood cell tracer (15,17), increased flow will result in more rapid transit of microbubbles through the region and a decrease in area under the curve. In contrast, agents with larger microbubble sizes, such as heat-sonicated meglumine diatrizoate (Renografin) (5 to 12 μm), sonicated iopamidol and hydrogen peroxide mixed with blood (10 to 100 μm) (18) will be trapped in the coronary circulation. Therefore, increases in intracoronary flow and volume that occur with papaverine will result in increased amounts of these microbubbles in the myocardium and an increased area under the time-intensity curve.

The type of ultrasonic contrast agent used also plays an important role in determining the correlation between peak contrast intensity and coronary flow. Cheirif et al. (19) used intracoronary sonicated meglumine to demonstrate that increases in peak contrast intensity after intracoronary papaverine administration were seen in patients without angiographically significant coronary artery disease. Similarly, Ten Cate et al. (20) demonstrated with intracoronary sonicated iopamidol that an increase in peak contrast intensity occurred in angiographically normal vessels after papaverine. In contrast, our study did not show a correlation between peak contrast intensity and intracoronary Doppler velocity changes after papaverine. As stated previously, our different findings in humans can be explained by the differences in microbubble size and concentration used in our study. The larger microbubbles used by others are trapped in the coronary circulation, and video intensity would in this case be related to the amount of microbubbles deposited in the region of interest. Sonicated albumin has smaller microbubbles but also differs from other ultrasonic contrast agents in that it has a higher concentration of microbubbles. This higher concentration may paradoxically decrease video intensity (21). Therefore, if intracoronary papaverine resulted in increased peak concentrations of sonicated albumin in the region of interest, they may not have been accurately quantified by video intensity.

Presence or absence of coronary artery disease. The results of this study apply to patients who have no significant epicardial stenoses or have, as in the heart transplant patients in this study, balanced coronary artery disease. The distribution of microbubbles after papaverine administration will be altered when a critical stenosis exists in either the left anterior descending or left circumflex coronary artery. In this setting, intracoronary papaverine would theoretically result in a different ratio, as well as a different concentration of microbubbles entering the two different arteries and their respective perfusion beds. When such a model is created in an animal preparation, a left main coronary artery injection of microbubbles after intracoronary papaverine results in a decreased area under the time-intensity curve in the underperfused bed because of a decreased ratio of microbubbles delivered to this region compared with that during the injection at rest (10). In this setting, transit time variables have also not accurately quantified changes in coronary blood flow. However, Cheirif et al. (22) have demonstrated that area under the curve can be used to describe relative flow changes in the presence of unbalanced (one vessel with a critical stenosis) coronary artery disease if injections of ultrasonic contrast agents are given into the aortic root (22). Because increases in left main coronary artery flow in this model should also be accompanied by increases in microbubble concentration, relative flow changes were accompanied by alterations in the area under the time-intensity curve that directly correlated with flow determined by radiolabeled microspheres. Conversely, with left main coronary artery injections of microbubbles, Kaul et al. (9) have shown that only the ratio of area under the time-intensity curve between the underperfused and normal myocardium can detect relative changes in flow after papaverine administration.

Limitations of the study. This study demonstrates that an on-line method of measuring video intensity and instantaneous analysis of the curve can be applied in the cardiac catheterization laboratory to determine coronary flow reserve. However, the ultrasound system design requires further development. Cardiac translation and rotation prohibit maintenance of the cross hair in the same region of myocardium. Jayaweera et al. (23) have developed a cross-correlation method that allows frame by frame alignment of the region of interest as long as the degree of translation is minimal. Furthermore, multiple regions cannot be analyzed with one injection. Because this may be necessary for determining relative coronary flow reserve in the setting of unbalanced coronary artery disease (10), digital storage of the image with subsequent time-intensity curve analysis of two different myocardial perfusion beds will be necessary.

The patients chosen for this study should not be considered a normal study group because they were heart transplant recipients and thus may have had significant transplant arteriopathy not detected by angiography. They may also have had decreased coronary flow reserve as a result of increased left ventricular mass (24). However, other factors related to transplantation, such as denervation, increased rest heart rate and abnormal coronary endothelial function, do not affect the measurement of coronary flow reserve (24,25). Although our study group should not be considered normal, it was ideal for assessing the ability of contrast echocardiography to determine normal and abnormal coronary flow reserve because the patients exhibited a wide range of flow reserve (1.1 to 3.7).

It is evident that the intracoronary Doppler probe also has limitations in determining coronary flow reserve. Epicardial

vessel size is increased slightly with intracoronary papaverine injection (26), and these geometric changes are not measured with intracoronary Doppler study alone. The use of this technique also requires a guiding catheter positioned in the left main ostium, which may obstruct hyperemic blood flow.

Finally, changes in intramyocardial blood volume with papaverine injection have a variable effect on curve variables. Certain variables of the time-intensity curve, such as area under the curve, have been shown by others (27) to correlate more strongly with changes in myocardial blood volume than with flow. Because we want to determine coronary flow and not volume changes, variables of the time-intensity curve that are either independent of volume changes (or can be corrected for volume changes) need to be determined.

Conclusions. Myocardial contrast echocardiography performed with left main coronary artery injections of sonicated albumin can potentially be used with an on-line ultrasound system to instantaneously determine coronary flow reserve in humans with angiographically normal coronary arteries. This system should also be applied to assess coronary flow reserve in the setting of unbalanced coronary artery disease in humans and thus provide a quick, safe means of determining functional stenosis severity at the time of diagnostic cardiac catheterization. However, the role of intramyocardial blood volume changes on the flow reserve ratios obtained from the time-intensity curve must be investigated. In addition, further development in the existing on-line video intensity analysis system to include digital storage, as well as computer algorithms to correct for cardiac translation, is needed to enhance the application of this technique in detecting coronary flow reserve in the cardiac catheterization laboratory.

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