Myocardial contrast two-dimensional echocardiography: comparison of contrast disappearance rates in normal and underperfused myocardium

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ABSTRACT A computer algorithm was developed and applied to measure brightness decay rates of myocardial contrast opacification observed with two-dimensional echocardiography (2DE). An agitated mixture of diatrizoate meglumine and saline (Renograin-saline) was injected into the left main coronary artery of 17 closed-chest dogs during the control state as well as after placement of an intracoronary plug to induce 85% stenosis in the left anterior descending coronary artery (LAD) in five dogs. In 12 dogs, injections were also performed distally to complete intracoronary balloon occlusion of the LAD. For each injection, up to 35 electrocardiographic-gated, end-diastolic 2DE frames were digitized into an image-processing computer that determined mean pixel brightness of each of 12 myocardial segments per 2DE short-axis cross-section. Time-activity curves for each segment were generated, and contrast decay half-life (t½) was calculated. Mean t½ for control-state injections was found to be 24.1 ± 7.7 sec, as opposed to 293.8 ± 164.5 sec after complete coronary occlusion (p < .001). In the five dogs in which 85% LAD stenosis was induced, prolongation of contrast t½ from 18.3 ± 8.9 sec during control to 44.3 ± 21.0 sec (p < .001) after plug insertion occurred in myocardial segments subserved by the stenosed vessel. No significant change occurred in segments that were not supplied by the stenosed vessel (21.9 ± 9.1 sec during control vs. 24.9 ± 11.6 after plug insertion into the LAD). A reproducibility study of injection-to-injection t½ in the control state indicated a correlation coefficient of r = .84 and a standard error of the estimate (SEE) equal to 5.86 sec, while interobserver t½ reproducibility was r = .91 and SEE = 5.21 sec. The t½ measurement derived by computer analysis of myocardial contrast 2DE may serve as an index for characterization of regional myocardial blood flow and may be applicable to evaluate interventions that alter perfusion. Circulation 69, No. 2, 418–429, 1984.

ALTHOUGH two-dimensional echocardiography (2DE) has been used increasingly to evaluate global and regional cardiac function,1–5 its potential for study of myocardial perfusion has not become apparent until recently.6–11 Injections of various contrast agents into coronary arteries or the aortic root have been reported to provide more accurate 2DE delineation of underperfused zones induced by experimental coronary occlusion than does wall motion analysis,7 which frequently overestimates the ischemic zone.12–14 So far, attempts to use contrast 2DE to quantify the degree of myocardial perfusion have been unsuccessful, since no correlation could be established between absolute levels of echocardiographic contrast brightness and magnitude of blood flow measured by means of radionuclide microspheres.7

Since the rate of tissue clearance of various diagnostic agents has previously been shown to correlate with regional myocardial blood flow,15–17 we aimed our current study at developing a method that permits determination of rates of change of myocardial opacification after injection of echocardiographic contrast agent. For this purpose, we developed a computer algorithm.
for image analysis and, in a preliminary application of this method, compared the rates of disappearance measured in normal and underperfused myocardium.

Methods

Preparation. We studied 17 closed-chest dogs weighing 28.2 ± 7.4 kg (range 21 to 39) that were premedicated with morphine (1.5 mg/kg im) and anesthetized with sodium pentobarbital (30 mg/kg iv). Ventilation was performed with a Harvard respirator and a cuffed endotracheal tube. A No. 7F catheter, placed into the descending aorta via the right femoral artery, was used for systemic pressure monitoring. A No. 9F angiographic catheter was inserted through the left carotid artery for selective contrast injections into the left main coronary artery; the angiographic catheter was subsequently used for passage of a No. 4F double lumen balloon catheter, which was used for intracoronary balloon occlusion of the left anterior descending coronary artery (LAD).

Myocardial contrast echocardiography. 2DE examinations were performed with a 3 MHz transducer and a 90 degree mechanical sector scanner (ATL Mark III) equipped with a digital clock, which provided continuous and precise time displays on the viewing screen next to the echocardiographic sector. All studies were performed as previously reported, with the dog on its right side and the transducer placed on the right chest wall pointing upward. In this manner, high-quality short-axis cross-sectional views of the left ventricle were obtained at the level of the midpapillary muscle. Gain settings were individually adjusted at the beginning of each study and were not changed throughout its course. Images as well as digital clock readings were recorded on half-inch videotape for subsequent analysis. A 1:1 diatrizoate meglumine–saline mixture was used as the echocardiographic contrast agent. The mixture was agitated as previously described by repeatedly flushing it between 10 ml syringes via a three-way stopcock. Microbubbles produced by this technique have been shown to have diameters ranging from 5 to 32 μm, averaging 16 ± 13 μm (mean ± SD). In no cases were macroscopically visible bubbles used for injection.

Experimental protocol

Control. After preparation of the dog, baseline echocardiograms were recorded. Subsequently, 2 ml of the echocardiographic contrast agent were injected over a period of 1 to 2 sec into the left main coronary artery via the No. 9F angiographic catheter. Simultaneous fluoroscopic verification of the injection site was possible because of the diatrizoate meglumine contained in our mixture. Approximately 1 min before each contrast injection 2DE recordings were begun and continued for 3 to 5 min, while the 2DE transducer was carefully maintained in a stable position. Repeat injections were performed in 10 min intervals, until at least two to three satisfactory recordings of global opacification of the left ventricular short-axis section could be obtained in association with simultaneous radiographic visualization of both LAD and circumflex coronary arteries. Accidental subselective injections into either one of the left coronary artery branches, which occurred occasionally because of the shortness of the left main coronary artery of the dog, were excluded from analysis.

Complete coronary occlusion. In 12 dogs, 15 min after the last control contrast injection, the LAD was occluded below the first septal branch by threading the No. 4F catheter through the larger angiographic catheter and inflating the balloon with 0.5 to 1.0 ml of diatrizoate meglumine. Ten minutes after the coronary occlusion, 1 ml of agitated diatrizoate meglumine–saline mixture was injected over a period of 1 to 2 sec distal to the site of occlusion via the central lumen of the occluding catheter. This resulted in localized myocardial opacification of the underperfused area, which generally corresponded to the left ventricular zone exhibiting wall motion abnormalities. One minute before this contrast injection, 2DE recording was begun and continued for 6 to 8 min.

Coronary stenosis. In five additional closed-chest dogs, contrast injections into the left main coronary artery during the control state were followed by placement of a specially designed plug into the proximal third of the LAD. The 7 mm long plug has the shape of a truncated cone with an outer diameter tapering from 2.5 to 2.25 mm. It contains two passages, one of which serves as an 85% coronary artery stenosis (diameter 0.37 mm). The second passage has a lumen of 1.07 mm and is occupied by a catheter, which is permanently attached to the plug and serves for measurement of intravascular LAD pressure distal to the stenosis.

After 15,000 units of intravenous heparin was administered, the stenotic plug was introduced under fluoroscopic control into the LAD by means of a guidewire and was firmly wedged inside the vessel. The presence of a gradient between aortic pressure and distal LAD pressure was used to corroborate the effectiveness of plug-induced coronary stenosis. These pressures were continuously monitored to observe for possible changes in the transstenotic gradient, which could indicate dislocation of the plug or thrombotic obstruction of the stenotic lumen.

After placement of the plug and stabilization, 2DE and contrast injections into the left main coronary artery were repeated, as described for the control setting. Simultaneous fluoroscopic control was again used to verify that the injection delivered the contrast material to the LAD as well as circumflex branches and to assure plug patency.

Anatomic delineation of the zone subserved by the stenosed artery. After the 2DE recordings were completed, a double-lumen balloon catheter was introduced into the LAD and was advanced until its tip was immediately above the plug. Injection of diatrizoate meglumine through the central lumen of the balloon catheter provided angiographic proof that no coronary branches originated between the balloon and the plug site. The balloon was then inflated to totally occlude the LAD, and 12 to 15 ml of monastral blue dye was injected through a left ventricular catheter. The dog was killed 1 min later by means of intravenous injection of KCl. The heart was promptly excised and cut from apex to base to 1 cm thick transverse slices parallel to the atrioventricular groove. A transparent plastic foil was placed over each slice; epicardial and endocardial outlines were traced, and the extent of dye-dye distribution was carefully marked. The location of the blue dye defect was used to identify the 2DE segments supplied by the stenosed vessel. For this purpose we overlaid the drawing of the midpapillary left ventricular slice over a hard-copy image of the corresponding end-diastolic 2DE cross-section, which had been obtained with a strip chart recorder.

Segments corresponding to the blue dye–free zone (zone subserved by the stenotic vessel) were considered separately from those in the area of dye uptake (zone subserved by normal vessels). Border segments, where the two zones adjoined (two per 2DE cross-section), were not included in the data analysis.

Image analysis. Image analysis was performed with an image processing computer with 128 K 16-bit word main-frame memory and 256 K remote memory. An 80 megabyte disk drive was used for data storage. This computer can differentiate 256 levels of gray and is capable of digitizing video images in real time, at up to 256 × 256 matrix resolution.

For time-activity analysis (figure 1) of a given intracoronary contrast injection, 18 to 35 electrocardiographic– gated, end-diastolic frames of 2DE short-axis images were sequentially digitized into a 64 × 64 pixel matrix window that had been set...
selectively over the left ventricular portion of the echocardiographic image. This technique helped avoid acquisition of data points not relevant to analysis, thus allowing for the region-of-interest to be represented by a maximum number of pixels.

The total observation period generally varied between 60 sec for control studies and 180 sec for occlusion studies; this observation period was selected to cover the visually perceived time span of myocardial opacification. For each end-diastolic frame, a time marker was simultaneously entered, permitting temporal identification of events throughout the course of each study. For this purpose, times were obtained from digital clock readings that had been recorded onto videotape on the same frame as the corresponding 2DE image. The entered information was stored in disk memory for subsequent analysis. After all end-diastolic frames for a particular injection had been entered, they were viewed in closed cine-loop format to check for stability of the short-axis images in relation to each other and to observe the time course of the contrast opacification in condensed format.

For each still frame, the endocardial and epicardial outlines were drawn by an observer using a computer-aided outlining technique. This was done by adjusting a series of 16 points that were elliptically distributed in a graphics overlay in the general areas of endocardium and epicardium. The outlines were then smoothed with a numerical curve-smoothing algorithm (cubic B-spline interpolation). The papillary muscles were excluded from the outlined region. Subsequently, the junction of the anterior papillary muscle with the anterior wall endocardium was identified by the observer as a reference point (figure 2, bottom). After all outlines and reference points were entered, the identified myocardial region in each frame was automatically subdivided into 12 30 degree sectors. A line between the reference point and the center of gravity of the epicardial outline was used for indexing of the subdivision.

Statistical estimates of the mean pixel brightness were then computed for each of the 12 myocardial segments. Segment to segment mean brightness distribution was automatically plotted for each frame and was displayed as a segmental intensity curve above the digitized and subdivided 2DE image (figure 2, top). This procedure was repeated for each of the digitized and outlined frames in the study. Time-activity curves were generated for each individual segment by plotting mean brightness amplitude as the coordinate on the vertical axis and the corresponding time marker on the horizontal axis.

The preinjection baseline intensity was subtracted from all the points in the time-activity curves to compensate for the intrinsic brightness of the echocardiographic image, which is not related to the contrast injection. The descending slope of the time-activity curve was assumed to follow an exponential decay pattern, similar to dye-dilution curves. Thus, a monoexponential function was fitted to the decay slope after the peak with a standard linear least-squares curve fit to the logarithm of the curve points. For this fitted curve, the exponential decay rate (k) was determined by computing the logarithmic slope of the fitted points. The $t_{1/2}$ of the time-activity relationship was then computed according to the formula:

$$t_{1/2} = \ln \frac{2}{k}$$

Values for $t_{1/2}$ obtained before and after coronary occlusion as well as before and after coronary stenosis were compared with Student's t test for paired data.

Reproducibility analysis. To study the reproducibility of $t_{1/2}$ measurements of segmental myocardial contrast between two separate injections in seven dogs in the control state, we compared the results generated from injections into the left main coronary artery performed 10 min apart of each other. Only animals were used in which both the first and second attempt constituted true injections into the left main coronary artery as assessed by simultaneous fluoroscopy.

For study of interobserver reproducibility, two blinded observers performed a complete analysis of the same injection images. The results of the interinjection and interobserver studies were compared segment by segment. Regression analyses were performed and r values, regression equations, and SEE were calculated.
Results

Control state. Injection of the echocardiographic contrast agent into the left main coronary artery during control state resulted in global opacification of left ventricular myocardium in the 2DE short-axis cross-section, with myocardial brightness increasing to a peak and then successively decreasing to the control level. Generally, the return to preinjection brightness levels occurred within 1 min, could be appreciated visually on the 2DE images (figure 3), and was reflected in a corresponding computer-generated time-activity curve (figure 4).

Among a total of 144 myocardial segments studied in the 12 dogs during the first control injection of the echocardiographic contrast agent, 119 (82.6%) derived segmental time-activity curves proved suitable for determination of t½. The remaining 25 segments were excluded a priori from analysis because their time-activity curves were found to be too noisy and the morphologic characteristics of the curve proved too erratic for meaningful and representative exponential curve fitting. The exclusions appeared to be randomly distributed among the segments, ranging from one exclusion for segment 1 (see figure 2 for segment locations) to four exclusions for segment 10. Retrospective visual analysis of the 2DE images from which the excluded curves had been derived revealed the following factors to be most likely responsible for noisy curves: (1) lung interference with 2DE imaging, (2) intermittent dropout artifacts occurring in only some of the frames, and (3) artifacts ascribed to either the video recorder or the videotape. A similar number of exclusions were present in the reproducibility studies with repeat contrast injections.

The segment-to-segment variation of t½ of myocardial contrast decay after control-state injections is illustrated in figure 5. No significant differences were observed between the various segments, although the
t½ in segment 1 appeared to be slightly prolonged when compared with that of the others.

For the first control injection into the left main coronary artery, contrast t½ of the 119 time-intensity curves that could be analyzed measured 23.6 ± 11.1 sec (mean ± SD), ranging from 8.2 to 55.2. When contrast t½ for entire cross-sections in individual dogs were calculated (by averaging all the segments in each section), t½ was 24.1 ± 7.7 sec, ranging from 14.2 to 41.7.

**Coronary occlusion.** Injections distal to the LAD occlusion could be performed in nine of the 12 dogs studied. Two dogs had to be excluded because ventricular fibrillation ensued shortly after coronary occlusion before the planned injection into the ischemic zone could be performed. The third dog was excluded because leakage of the occluding balloon resulted in accidental reperfusion.

The injections performed distal to intracoronary LAD balloon occlusion resulted in a regional myocardial opacification of two to five myocardial segments per dog. Compared with the control injections, disappearance of myocardial contrast was significantly slower after coronary occlusion, with a significant degree of opacification of the 2DE image persisting well beyond 1 min (figure 6). The decay slope of the generated time-activity curves was much shallower when compared with the slope of curves representing the control state (figure 4, B).

Twenty-eight (80%) of the total of 35 time-activity curves derived from acutely ischemic myocardial segments could be analyzed by means of exponential curve fitting. The remaining seven were excluded for reasons similar to those mentioned for the control state. Contrast t½ for injections distal to the LAD occlusion was found to be 259.6 ± 188.1 sec (mean ± SD), ranging from 85.7 to 789, compared with 21.8 ± 12.1 sec (range 8.8 to 44.0) for the same segments before occlusion. When contrast t½ for entire ischemic zones in individual dogs were calculated (by averaging the segments comprising each ischemic zone) and compared with the preocclusion values for the same zones, the values were 293.8 ± 164.5 sec for occlusion and 22.3 ± 7.0 sec for the control state (see table 1). Thus, contrast t½ in the ischemic zone was significantly longer (p < .001) than in the control state.

**Coronary stenosis.** Insertion of the stenotic plug into the LAD resulted in a diastolic pressure gradient of 40.8 ± 16.7 mm Hg (mean ± SD) between the aorta and distal LAD, ranging from 23 to 55 mm Hg.

Contrast injections into the left main coronary artery in the presence of 85% LAD stenosis resulted in myocardial opacification of the entire left ventricular cross-section observed by 2DE, followed by a decrease in brightness intensity, which generally appeared to be slowest in the region of the anterior wall.

**Blue dye-free region.** A total of 18 segments were

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**FIGURE 3.** Contrast injection into the left main coronary artery during control state results in global opacification of the myocardial cross-section, followed by brightness decrease to preinjection levels within 60 sec. A, Before injection; B, 3 sec after injection; C, 15 sec after injection; D, 60 sec after injection.
found to lie entirely within this zone, which was presumed to be subserved by the stenosed vessel, ranging from two to four segments per dog. Three of these segments had to be excluded a priori from analysis because of noisy myocardial contrast time-activity curves, which were deemed to be unanalyzable. For the remaining 15 segments, the decay slope of the generated time-activity curves was shallower after stenotic plug insertion than it was during the control state (figure 7). Echocardiographic contrast t½ for injections performed in the presence of a LAD stenotic plug measured 44.3 ± 21.0 sec (mean ± SD), ranging from 20 to 84 sec, compared with 18.3 ± 8.9 sec (range, 7 to 54) for the same segments during control state (figure 8). The ratio between stenosis t½ and control t½ for a given segment was 3.0 ± 2.5, ranging from 1.6 to 10.8. Thus, in segments subserved by a stenosed coronary artery, contrast t½ was significantly longer (p < .001) than during control state.

Region of blue-dye uptake (segments not subserved by the stenosed artery). Thirty-two segments were found to lie entirely within the zone of blue-dye uptake, and time-activity curves were analyzable in 26 of them. The t½ in presence of the stenotic plug measured 24.9 ± 11.6 sec (range 12 to 55), as compared with 21.9 ± 9.1 sec (range 9 to 41) during the control state (figure 8). Thus, in segments that were not subserved by the stenosed artery, there was no significant difference in
FIGURE 5. Segment-to-segment variation of myocardial contrast decay half-lives ($t_{1/2}$) is shown, representing the 119 curves found suitable for analysis after the first injection into the left main coronary artery (mean ± SD). No significant differences between the various segments were noted, although the decay time appeared slightly longer in segment 1.

t_{1/2} (sec)

SEGMENT NUMBER

$\frac{t}{2}$ ($p = .16$) between control state and after plug insertion.

Reproducibility. The results of the reproducibility studies of segmental contrast $t_{1/2}$ for seven dogs in the control state are outlined in figure 9. Correlation coefficients were .84 for interinjection reproducibility and .91 for interobserver reproducibility, with respective SEE equal to 5.86 and 5.21 sec. Similar results were obtained when all the segments for each particular dog were analyzed separately or when the same segment locations for all the dogs were evaluated.

Discussion

Myocardial contrast 2DE. Injections of various contrast agents into coronary arteries or the aortic root have recently been shown to result in 2DE opacification of left ventricular myocardium with intact vascular supply, thus reliably delineating areas rendered

FIGURE 6. Contrast injection distal to intracoronary balloon occlusion of the LAD results in regional myocardial opacification (8 to 11 o'clock). Contrast disappearance is significantly slower than during control state, with myocardial opacification persisting for several minutes. A, Before injection; B, 3 sec after injection; C, 15 sec after injection; D, 60 sec after injection.
ischemic by occlusion of a coronary artery.\textsuperscript{7-9} Attempts to characterize myocardial perfusion beyond mapping of its general distribution have so far been unsuccessful. Videodensitometric measurements of the degree of brightness of echocardiographic contrast, as measured with a light meter off the video screen, failed to correlate with the absolute level of myocardial blood flow determined by the radioactive microsphere technique.\textsuperscript{7} On the other hand, the physiologic rate of myocardial disappearance of various agents, such as Xe-non,\textsuperscript{16,17} has been shown to be proportional to the degree of regional perfusion and can be used for measurements in an experimental and clinical setting. As attempted in a preliminary study,\textsuperscript{21} we applied this "washout" principle and developed a computer algorithm to analyze the time course of myocardial contrast intensities.\textsuperscript{22} Our study suggests the feasibility of such a computerized myocardial contrast 2DE method; in a preliminary investigation, significant differences were seen in the rates of postinjection brightness decay among myocardium in the control state, after induction of coronary artery stenosis, and after complete coronary occlusion. Correlation of these decay rates with more subtle differences in the degree of blood flow remains to be proven through validation against established measurements of myocardial perfusion.
The \( t^{1/2} \) measurements performed with our method exhibit a fair degree of reproducibility between two separate observers analyzing the same set of myocardial contrast echocardiographic images. Reasons for the slightly lesser degree of correlation between repeat injections in the same animal are not entirely clear. They could at least in part represent differences in injection force or in the degree of agitation performed to prepare the contrast agent.

In addition, variations in myocardial blood flow may have occurred, since the repeat injections were performed more than 10 min apart to avoid effects of hyperemia induced by diatrizoate meglumine. No systematic information is as yet available about postinjection alterations in myocardial blood flow caused directly by agents containing microbubbles. With the advent of newer well-standardized contrast agents containing smaller and more homogeneous bubbles and with more standardized injection techniques, a higher degree of injection reproducibility might be expected.

Myocardial echocardiographic contrast agents. A variety of contrast agents have been used in attempts to develop a 2DE method for study of myocardial perfusion. These include commercially manufactured encapsulated microbubbles, carbon dioxide, hydrogen peroxide, and the agitated diatrizoate meglumine-saline mixture used in this study. The latter has the advantage of "radiopacity," "easy availability," relatively low cost, and ease of handling. Unlike other agents, both components of this mixture are known to be safe for intracoronary injections. Nevertheless, in view of deliberate generation of microbubbles, the safety of this echocardiographic contrast agent remains to be proven. A preliminary experimental study in our laboratory showed only transient minor hemodynamic and electrocardiographic changes, all of which reverted to baseline within 1 min after intracoronary injection of contrast agent, but extensive safety studies will have to be performed before application in humans can be considered.

Microscopic examination of the contrast agent used in this study has shown it contains microbubbles averaging 16 µm, ranging from 5 to 32. When a drop of the agent was covered by a thin glass cover slide, 50% of the bubbles continued to persist after 5 min of observation. In this setting, no significant evidence of bubble breakup or confluence was seen. Examination of this echocardiographic contrast agent in a tube flow system in vitro revealed a significantly higher degree of ultrasonic reflectance compared with that of a series of other agents studied. When flow in this system was interrupted to study the "intrinsic decay rate" of the agent in vitro, its echocardiographic brightness persisted much longer (11.5 ± 2.8 sec) than with hydrogen peroxide or carbon dioxide (both <1 sec). The relevance of these observations in relation to conditions in vivo is currently only partially understood.

Transit of contrast agent through myocardial vasculature. The \( t^{1/2} \) of the 2DE contrast opacification observed by us in normal physiologic states was significantly longer than myocardial transit times previously measured with hydrogen electrodes and fluorescently labeled erythrocytes, or that observed with digital angiography. This finding suggests that the microbubbles, which we presume are responsible for ultrasonic contrast effect, are not simply passing through the myocardial vasculature, but are perhaps temporarily entrapped in the microcirculation. Such temporary entrapment has already been documented by Kort and Kronzon, who performed light microscopic examinations in vivo of capillaries in mesentery of the rat. Temporary obstruction (lasting up to 200 sec) of individual capillaries by large microbubbles was observed and is corroborated by our laboratory. The hypothesis of temporary microvascular obstruction also receives some support by the data obtained in vitro that indicate that the microbubbles in our agent measured 16 ± 13 µm, thus being significantly larger than the diameter of myocardial capillaries. Thus, the rate of ultrasonic contrast decay probably reflects the rate of washout by coronary blood flow as well as the rate at which microbubbles dissolve in blood. Further extensive studies are needed to determine bubble size in vivo and to elucidate the process of bubble transport and persistence within the myocardial vasculature.

Limitations of methods. Before the myocardial contrast 2DE technique can be used for quantitative measurements of blood flow, a number of possible limita-
tions have to be overcome and several questions have to be answered. As already indicated, it is necessary to learn more about the biological fate and potential toxicity of microbubbles in echocardiographic contrast agents. It may be assumed that smaller bubbles will have a lesser tendency to obstruct the microvascular bed and would therefore be less toxic; the smaller bubbles would also opacify the myocardium for a shorter period of time than the agent used in the present study. Greater homogeneity of bubble sizes could be expected to result in more standardized and reproducible time decay measurements. The effects of different carrier agents as a further variable and the properties of newer encapsulated microbubbles also deserve close scrutiny.

Variations in the force and velocity of injection and in the degree of contrast agitation may also affect t½ measurements and need to be investigated.

An additional potentially important limitation is posed by the currently available echocardiographic equipment, which is primarily designed to deliver optically pleasing images and to enhance delineation of blood-to-structure interface, rather than to provide quantitative analysis of echocardiographic brightness. Different quantities of ultrasonic energies reflected by the examined tissues are generally not displayed as linearly related signals, but rather in terms of complex logarithmic scales of amplification. Adjustments of gain, time-gain compensation, as well as signal before and after processing have a major impact on differences in brightness display. Artifacts, such as blooming, attenuation, and reverberation phenomena, could conceivably also alter such measurements. Further signal degradation may occur during recording and playback from videotape. The above factors may at least in part explain why attempts to correlate absolute brightness levels with degree of blood flow measured with radioactive microspheres have so far remained unsuccessful. On the other hand, the measurements of decay rates described in this study may be affected to a lesser degree, as they determine relative changes over the course of time rather than absolute levels of brightness.

Limitations in our current computer method include the use and selection of end-diastolic frames, which could eventually be overcome with real-time image acquisition, although the currently available computer memory limits this approach in studies requiring long periods of analysis. Manual drawing introduces a potential operator-induced variable that may be overcome in the future with advances in automatic edge-detection algorithms. The role of segment size and pixel number representing a given image deserve further evaluation. Finally, our assumption of monoeponential decay may need to be scrutinized more closely, although it seems to be supported by our current experience. Our intracoronary plug model may be limited by the difficulty to accurately predict effects of a given coronary stenosis on regional myocardial perfusion. Nevertheless, previous work suggests that an 85% reduction in coronary artery diameter generally results in significant decrease in resting coronary blood flow; severe blunting of the hyperemic response induced by radiographic contrast agents has been shown to occur with even lesser degrees of stenosis.

FIGURE 8. Changes in segmental t½ after 85% LAD stenosis in five dogs. A. In segments subserved by the stenosed artery (blue dye-free zone), significant prolongation in t½ occurred after insertion of the stenotic plug. B. No such change occurred in segments supplied by other vessels (zone of blue-dye uptake).

FIGURE 9. Segmental interinjection and interobserver reproducibility studies for control state.
tical problems, such as leakage around the intracoronary plug as well as partial or complete thrombotic occlusion of its lumen, may also have to be considered. To overcome some of these potential problems we continuously monitored the transstenotic gradient and also verified all diatrizoate meglumine–saline contrast injections by simultaneous fluoroscopy. We applied myocardial blue-dye staining for anatomic identification of the zone subserved by the stenosed vessel. This method may not allow for precise segment-by-segment correlation of the stained myocardial slice with the 2DE short-axis cross-section. To minimize such inaccuracy, we used all available internal landmarks to correlate between the 2DE and the postmortem study and excluded all segments containing the junction between the stained and blue dye–free zones.

Contrast injections distal to the intracoronary occlusion may represent a physiologically unsound situation, since they could conceivably cause regional flow alterations and are, furthermore, not likely to be used clinically. Contrast application into ischemic myocardial zones may nevertheless eventually have some relevance, since we were able to reliably achieve it by means of retrograde coronary venous injections. In the current study, injections distal to the coronary occlusion helped establish extremes of the spectrum between the control state and a low-flow situation. Furthermore, we could show that the “intrinsic decay rate” of the contrast agent in vivo is significantly longer than the one observed in a tube setup in vitro.

Significance and future potential of myocardial contrast 2DE. The importance of obtaining information in vivo about myocardial blood flow is attested to by the widespread use of myocardial imaging with thallium and the interest in newer techniques, such as digital angiographic perfusion studies. Myocardial contrast 2DE may constitute an alternative method, and our preliminary investigations point to the potential of using the echocardiographic opacification decay rate as an index of perfusion. Future developments may permit further application of this method for study of alterations of blood flow. Study of differential perfusion of discrete epicardial to endocardial layers in a given myocardial segment and development of combined computer algorithms, permitting simultaneous evaluation of myocardial perfusion and function, constitute realistic possibilities. Such detailed measurements may enhance our understanding of interventions such as thrombolysis and percutaneous coronary angioplasty, which attempt reestablishment or significant improvement of tissue perfusion. Development of safe standardized contrast agents, improvement of echocardiographic equipment, and validations against established techniques for measurement of myocardial blood flow may ultimately permit more widespread application of this method as an index of myocardial perfusion in an experimental and clinical setting.

References


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