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EXPERIMENTAL STUDIES

Myocardial Contrast Echocardiography in Acute Myocardial Infarction Using Aortic Root Injections of Microbubbles in Conjunction With Harmonic Imaging: Potential Application in the Cardiac Catheterization Laboratory

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Objectives. **The aim of this study was to evaluate myocardial contrast echocardiography using aortic root injections with harmonic imaging in experimental acute myocardial infarction to determine the potential of this approach in the cardiac catheterization laboratory.**

Background. **It would be desirable to have an adjunctive procedure that could evaluate myocardial perfusion at the time of cardiac catheterization in patients with acute myocardial infarction. A single injection of contrast medium in the aortic root would provide complete information on myocardial perfusion in a cross section of the heart. High quality images would provide on-line assessment of myocardial perfusion without recourse to image processing. These data could be very valuable for determining patient management.**

Methods. **Perfusion defects on myocardial contrast echocardiography were measured during coronary occlusion and reflow, using fundamental and harmonic imaging in both continuous and intermittent modes in nine open chest dogs. These defects were compared with risk area on technetium-99m autoradiography and infarct size on tissue staining.**

Results. **Whereas harmonic imaging increased myocardial video intensity by more than twofold ($p < 0.001$) compared with fundamental imaging after aortic root injection of contrast medium, intermittent imaging was not superior to continuous imaging. The improved signal to noise ratio of harmonic imaging allowed on-line definition of risk area ($r = 0.98$) and infarct size ($r = 0.93$) without recourse to off-line processing. Similar results could be obtained with fundamental imaging only after off-line processing.**

Conclusions. **Aortic root injections of contrast medium coupled with harmonic imaging can be used to provide accurate on-line assessment of risk area and infarct size during acute myocardial infarction. These results have important implications for the catheterization laboratory.**

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In the cardiac catheterization laboratory, direct intracoronary injections of microbubbles have been used to assess myocardial perfusion with contrast echocardiography in patients with acute myocardial infarction (1–6). This approach requires separate engagements of the left main and right coronary arteries, as well as multiple injections of microbubbles, to obtain information on myocardial perfusion in a single echocardiographic cross section. An aortic root injection of microbubbles can provide information on myocardial perfusion in one cross section with a single injection, which may be more expeditious and allow assessment of myocardial perfusion without changing coronary hemodynamic variables (7–11).

Many patients currently undergo primary angioplasty as a means of treating acute myocardial infarction (12). The decision to intervene and the success of the intervention are based primarily on the appearance of the epicardial coronary artery, which does not provide an accurate assessment of the status of myocardial perfusion (13). An adjunctive procedure that could define myocardial perfusion at the same time may provide important information that may help in determining the need for an intervention and evaluate its success (3–6).

The aim of the present experimental study was to evaluate the ability of myocardial contrast echocardiography to accurately assess myocardial perfusion using aortic root injections of microbubbles during acute myocardial infarction. Technical issues relating to the use of harmonic versus fundamental imaging, as well as the value of off-line data analysis, were also

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evaluated. In addition, the safety of a coronary vasodilator during acute myocardial infarction to unmask abnormalities of coronary microvascular reserve after reflow was studied. The overall purpose of the study was to determine whether these approaches have potential application in the cardiac catheterization laboratory during acute myocardial infarction.

Methods

Animal preparation. The protocol conformed to the "Position of the American Heart Association on Research Animal Use" adopted by the Association in November 1984, and was approved by the Animal Research Committee at the University of Virginia. Nine mongrel dogs were used for the study. They were anesthetized with 30 mg/kg body weight of sodium pentobarbital (Abbott Laboratories), intubated and mechanically ventilated using a respirator pump (Harvard Apparatus, model 607). A 7F polyethylene catheter was placed in each femoral artery for duplicate reference sample withdrawal during radiolabeled microsphere injection, and one of these catheters was also used for arterial pressure monitoring. The femoral veins were cannulated with 7F catheters for intravenous infusion of fluids and drugs. Additional anesthesia was administered during the experiment as needed.

A left lateral thoracotomy was performed, and the heart was suspended in a pericardial cradle. A 7F pigtail catheter was inserted in the left carotid artery, and its tip was positioned in the proximal aortic root. It was connected to a power injector (model 3000, Liebel-Flarsheim Co.) for aortic root injection of microbubbles during myocardial contrast echocardiography. A 7F catheter was placed in the left atrium for measurement of pressures as well as for injection of technetium-99m–labeled albumin macroaggregates.

The left jugular vein was cannulated with a thermodilution pulmonary artery floatation catheter (Baxter-Edwards Laboratory), and its tip was advanced to the main pulmonary artery. The proximal port of this catheter was used to measure right atrial pressure. The catheter was attached to a computer (model 9520A, Edwards Laboratory) for measuring cardiac output using the thermodilution technique. The proximal or mid portions of the left anterior descending and left circumflex coronary arteries were dissected free from the surrounding tissue, and a custom-designed screw occluder was placed around one of them. A 2-mm ultrasound time of flight flow probe (series SB, Transonics), was placed on each artery and was connected to a digital flow meter (model T206, Transonics) for continuous monitoring of coronary blood flow.

The arterial, left atrial and pulmonary artery catheters were attached to fluid-filled transducers (Gould Electronics), which in turn were connected to a multichannel physiologic recorder (model ES2000, Gould Electronics). The flow meter was also attached to the physiologic recorder. The recorder was interfaced with a 80386-based personal computer (model 2531, DTK Inc.) by means of an eight-channel analog/digital convertor (DAS-16, Metrabyte Corp.). Mean pressures and coronary blood flow were sampled at 200 Hz using Labtech Notebook (Labtech Technologies Corp.). After the experiment, the data were transferred from Labtech Notebook to RS/1 (Bolt, Beranek, and Newman) for further analysis.

Myocardial contrast echocardiography. Sonicated albumin microbubbles (Albunex, Molecular Biosystems Inc.) were used as the contrast agent (14). It has been shown (14,15) that this product does not significantly alter systemic or coronary hemodynamic variables in the doses used in this study. Although the dose of microbubbles (1 to 5 ml) required for optimal myocardial opacification (defined as the dose that resulted in visually perceptible myocardial opacification without shadowing) varied between dogs, it was held constant in each dog. The microbubbles were power injected into the aortic root over 1.5 s during simultaneously performed echocardiography.

One of the aims of the study was to evaluate the influence of harmonic imaging on our data quality. For this purpose, we used a prototype ultrasound system (Hewlett-Packard Corp.) that has a transducer with the capability to transmit ultrasound at a mean frequency of 2 MHz but receive at both 2-MHz (fundamental) and 4-MHz (harmonic) frequencies. We performed fundamental and harmonic imaging both continuously and intermittently (once every systole) by gating to the ECG (16).

A saline bath served as an acoustic interface between the transducer and the anterior surface of the heart. The transducer was placed within the bath using a clamp attached to the procedure table, allowing imaging of the same short-axis plane at each stage. The maximal dynamic range of 60 dB was used. The system was set at the postprocessing mode where, as defined by the manufacturer, the relation between backscatter and video intensity is most linear (curve A).

Because tissue backscatter is much lower at harmonic compared with fundamental frequencies, and because special filters are used to minimize the amount of returning fundamental frequency displayed in the harmonic images, the receive gain was increased for harmonic imaging to produce baseline images with the same myocardial gray scale as during fundamental imaging. The gains were held constant for each form of imaging (fundamental and harmonic) after their initial optimization. Images were recorded on 1.25-cm videotape using a high fidelity recorder (Panasonic AG-7350, Matsushita Electric).

Our approach to the off-line analysis of contrast images has been previously described (17,18). For fundamental imaging, three precontrast end-diastolic images were averaged, and three similar contrast-enhanced images depicting maximal disparity in the opacification between the left circumflex and left anterior descending coronary artery beds were also averaged. The averaged precontrast and contrast-enhanced frames were aligned, and the precontrast image was then digitally subtracted from the contrast-enhanced image. The signal to noise ratio of the harmonic images was favorable enough to simply align one precontrast image with one contrast-enhanced image before digital subtraction.

The video intensity scale in the subtracted images was expanded to a dynamic range of 128 gray levels, whereby the

pixel with the greatest contrast change was assigned a level of 128, and all others were assigned proportionally lower values. Each pixel with a gray scale value of >10 (values ≤10 were considered to represent noise) was relegated a color based on the degree of contrast enhancement, where shades of red, progressing to hues of orange, yellow and white, represent incremental contrast opacification. Contrast defects were planimetered and expressed as a percent of the left ventricular short-axis slice (9).

Perfusion defect sizes were also measured from the gray-scale contrast-enhanced image without digital processing. The aim of this exercise was to determine whether any form of imaging resulted in data of sufficient quality to allow an accurate on-line assessment of perfusion defects, without having to use sophisticated image processing techniques, which, by the nature of their complexity, require off-line analysis.

Using previously described methods (17,18), time-intensity plots were also generated from images obtained at baseline using the four imaging modalities (continuous and intermittent fundamental, and continuous and intermittent harmonic) to determine the influence of these imaging modalities on myocardial peak video intensity and mean microbubble transit rates. A gamma-variate function ($y = Ate^{-\alpha t}$) was applied to the background-subtracted time-intensity plots, where A is a scaling factor, t is time, and α is proportional to the mean myocardial microbubble transit rate. $A/\alpha e$ represents the peak myocardial video intensity.

Technetium autoradiography. Approximately 30 min before reperfusion, 20 mCi of Tc-99m–labeled albumin macroaggregates were injected into the left atrium (19). After the experiment, the heart slice corresponding to the echocardiographic short-axis image was cut and placed on a clear plastic sheet so that the endocardial and epicardial borders of the slice could be traced. Radiographic images were obtained using a gamma camera (Technicare 420, Ohio Nuclear) with a parallel-hole collimator at a centerline peak of 147 keV and a 20% spectral window. The image was transferred from the computer to X-ray film using a compact video imager (1020, Matrix Instruments). The film was processed with a developer (M35A, Eastman Kodak). A back-illuminated image of the autoradiograph was captured into the off-line computer (Kontron) using a video camera (66 series, Dage-MTI Corp.). The risk area was planimetered and expressed as a percent of the myocardial short-axis slice (20).

Infarct size determination. At the conclusion of the experiment, the heart was excised, and a 1-cm slice corresponding to the echocardiographic imaging plane was immersed in a solution of 1.3% 2.3.5-triphnyltetrazolium chloride (Sigma Corp.) and 0.2 mol/liter Sörensen's buffer in distilled water, pH 7.4, at 37°C for 20 min, followed by fixation in 10% formalin (21). Video images of the basal and apical sides of the stained slice were captured into the off-line computer (Kontron). Infarct size was determined by planimetering the unstained portions of the basal and apical sides of the specimen, taking their average and expressing it as a percentage of the left ventricular short-axis slice (22).

Experimental protocol. After acquiring hemodynamic and echocardiographic data at baseline, either the left circumflex or left anterior descending coronary artery was occluded for 3 to 5 h to cause infarctions of varying sizes. Toward the end of the occlusion period, contrast echocardiography was performed, and Tc-99m–labeled albumin macroaggregates were injected into the left atrium. Fifteen minutes after the release of the occlusion, hemodynamic and echocardiographic measurements were performed before and during hyperemia induced by an intravenous infusion of 0.4 μg/kg per min of WRC-0470 (Discovery Therapeutics Inc.) a novel adenosine-A_{2a} selective agonist (23). At the end of the experiment, the dog was killed.

Statistical methods. Correlations between echocardiographic perfusion defects, risk area and infarct size were made using linear regression analysis. Comparisons between all stages were made using repeated measures analysis of variance, and significant differences between two stages were measured using the Student *t* test with the Bonferroni correction for a two-tailed p value.

Results

Risk area measurement. Figure 1A illustrates a Tc-99m autoradiograph from one of the dogs. Figure 2 shows gray-scale images acquired during continuous and intermittent imaging using fundamental and harmonic modes. For the same dose of microbubbles, harmonic imaging resulted in a greater disparity in gray scale between the hypoperfused and normally perfused myocardium. Consequently, the measurement of risk area using this approach was more accurate than fundamental imaging. Thus, as depicted in Figure 1B, the correlation between risk area on Tc-99m autoradiography and perfusion defects was closer with harmonic than with fundamental imaging, although the difference between the two did not reach statistical significance. The rate of ultrasound transmission (continuously vs. once every cardiac cycle) did not affect these results.

As illustrated in Figure 1C, when image processing and color coding are used, the correlations between risk area measured on Tc-99m autoradiography and myocardial contrast echocardiography are not significantly different between harmonic and fundamental imaging. However, the color-coded images from fundamental imaging (Fig. 3, A and B), required the averaging of three precontrast and three contrast-enhanced images before digital subtraction. In contradistinction, only one precontrast and one contrast-enhanced image were used for digital subtraction when harmonic imaging was used (Fig. 3, C and D). The demarcation between perfused and nonperfused myocardium was clearer on the color-coded images when harmonic versus fundamental imaging was used. The harmonic frequency in our study (4 MHz) was twice that of the fundamental (2 MHz) frequency, allowing not only better signal to noise, but also better spatial resolution.

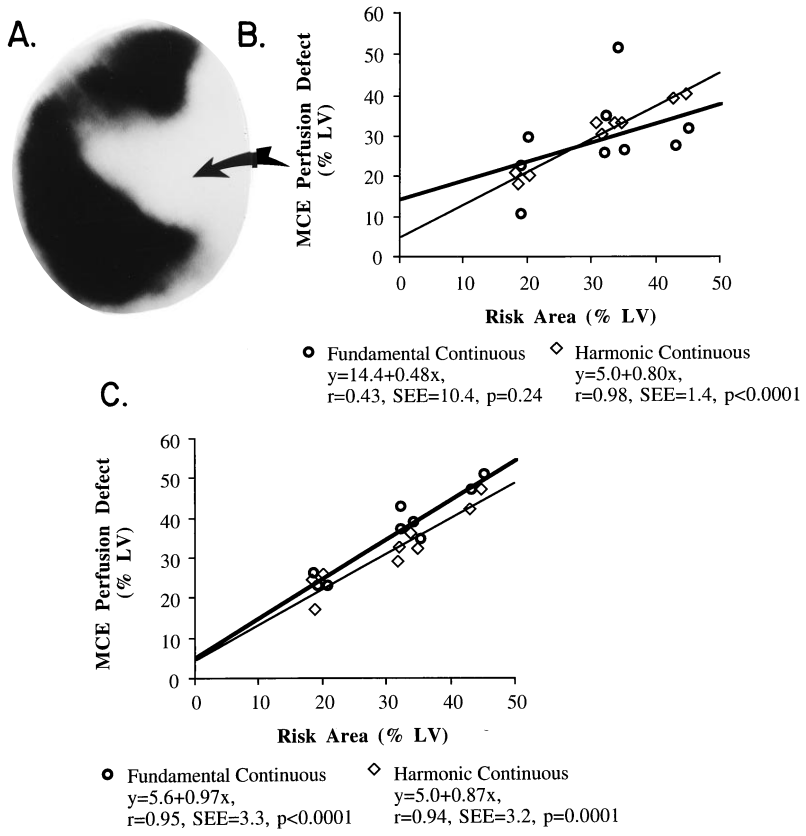

Figure 1. A, Technetium-99m autoradiograph from a dog during coronary occlusion. The relation between risk area defined on autoradiography and defect size on myocardial contrast echocardiography (MCE) using **(B)** gray-scale and **(C)** color-coded images acquired using fundamental (2 MHz) and harmonic (4 MHz) frequencies. %LV = percent of left ventricular short-axis slice.

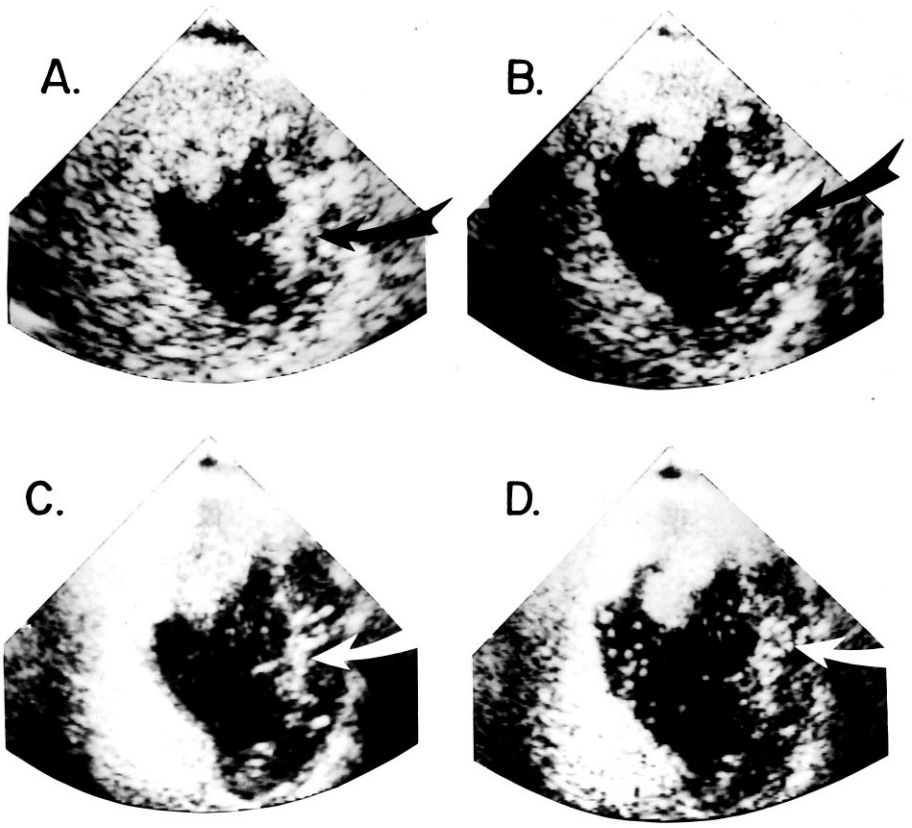

Figure 2. Examples of gray-scale images during coronary occlusion using continuous and intermittent imaging at the fundamental **(A, B)** and harmonic **(C, D)** frequencies.

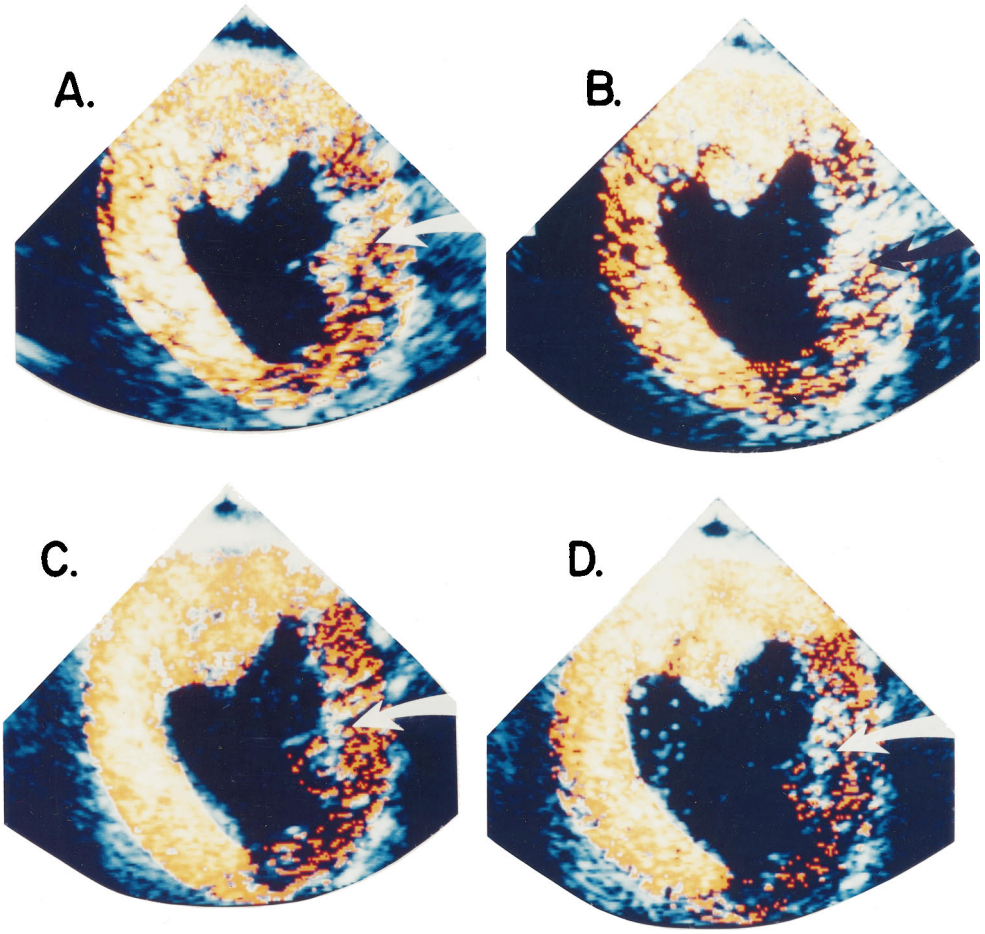

Figure 3. Color-coded images during coronary occlusion using continuous and intermittent imaging at the fundamental **(A, B)** and harmonic **(C, D)** frequencies. These images correspond to the gray-scale images in Figure 2.

Infarct size measurement. We previously showed (7,24) that myocardial contrast echocardiography performed within the first few hours after reflow underestimates infarct size. This phenomenon is due to reactive hyperemia in the infarct bed and is particularly relevant when there is no residual stenosis in the infarct-related artery that can attenuate the hyperemic response. It is for this reason that we used a coronary vasodilator during reflow to create a relative flow deficiency within the infarct zone compared with the normal bed, which has been demonstrated to accurately reflect infarct size (7,22).

Figure 4A illustrates infarction in one of the dogs. Figure 5 shows gray-scale images acquired in the same dog during fundamental and harmonic imaging using both continuous and intermittent imaging. For the same dose of microbubbles, harmonic imaging results in a greater disparity in gray scale between the infarcted and normal myocardium than fundamental imaging. Consequently, the measurement of a perfusion defect using harmonic imaging more accurately reflects infarct size than that using fundamental imaging, although the differences are not statistically significant (Fig. 4B). The rate of ultrasound transmission (continuously vs. once every cardiac cycle) did not influence the results. When image processing and color coding are used, the correlation between infarct and perfusion defect sizes is not significantly different between harmonic and fundamental imaging (Fig. 4C). Despite this finding, the demarcation between infarcted and normal myocardium is clearer on the color-coded images using harmonic than fundamental imaging (Fig. 6).

Effect of harmonic frequency and intermittent imaging on peak myocardial video intensity and mean microbubble transit rate. Table 1 illustrates the effect of harmonic and intermittent imaging on the peak myocardial video intensity. Because we adjusted the receive gain while using harmonic imaging, the background myocardial video intensity was not different between fundamental and harmonic modes. However, the peak video intensity was significantly (more the twofold) higher during harmonic than fundamental imaging and was not influenced by the rate of ultrasound transmission (continuosly at 30 frames/s or intermittently once every cardiac cycle).

Table 1 also illustrates the effect of harmonic and intermittent imaging on the mean microbubble transit rates obtained at baseline. The mean microbubble transit rates tended to be higher during harmonic than fundamental imaging, although this difference did not reach statistical significance. Continuous (30 frames/s) or intermittent (once every cardiac cycle) imaging did not influence the measurement of mean microbubble transit rate at either receive frequency.

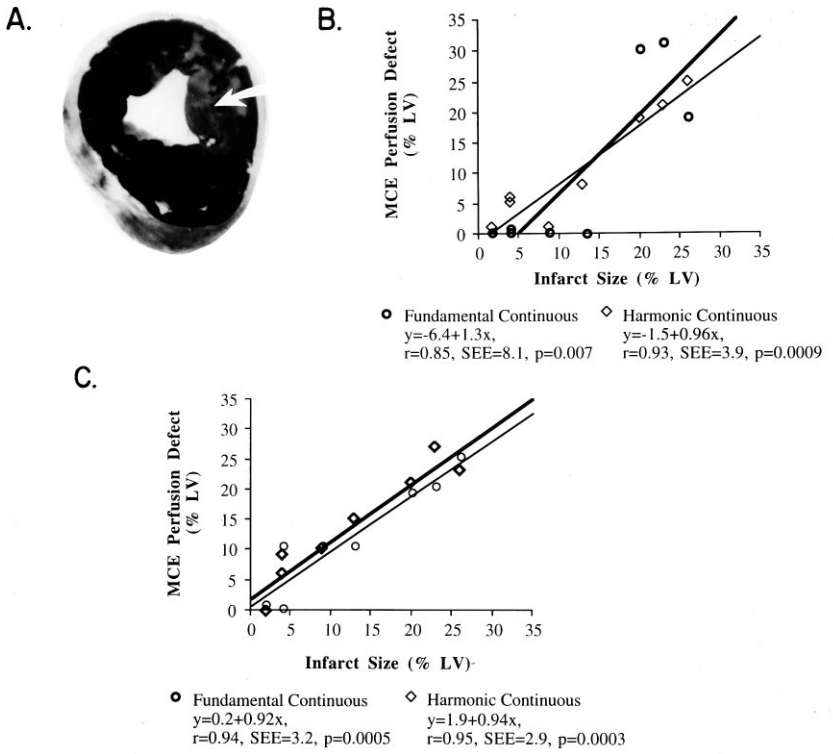

Figure 4. A, Infarct size obtained on triphenyltetrazolium chloride staining of the heart. Relation between infarct size by triphenyltetrazolium chloride and perfusion defect size on myocardial contrast echocardiography (MCE) in the presence of coronary vasodilator using gray-scale images acquired with fundamental (2 MHz) and harmonic (4 MHz) frequencies (**B**). The same comparison, based on color-coded images, is presented in **C.** %LV = percent of left ventricular short-axis slice.

Hemodynamic effects of WRC-0470. Table 2 depicts heart rate; mean aortic, left and right atrial pressures; and cardiac output after reflow before and during maximal vasodilation with WRC-0470. There was no effect of WRC-0470 on heart rate or on left or right atrial pressures. A small decline (mean of 10%) in mean aortic pressure and an increase in cardiac output were noted during the infusion of this drug.

Discussion

The major new finding of this study is that the improved signal to noise ratio of harmonic imaging provides excellent gray-scale images from which accurate assessments of risk area and infarct size can be made on-line. We also found that a novel coronary vasodilator, WRC-0470, which is a selective adenosine-A_{2a} agonist, causes minimal hemodynamic changes in the acute phase of myocardial infarction and successfully unmasks coronary reserve abnormalities within the infarct zone. In so doing, an accurate measurement of infarct size with myocardial contrast echocardiography using aortic root injections of contrast medium can be achieved.

Feasibility of aortic root injections of contrast medium. When myocardial contrast echocardiography was performed in the cardiac catheterization laboratory in patients with acute myocardial infarction, intracoronary injections of microbubbles were used (1–6). For the most part, this route of injection was dictated by the use of sonicated radiographic contrast agents that have a half-life of only a few seconds, barely enough to attempt a rapid intracoronary injection. The safety of these bubbles when injected into the aortic root has also been a concern.

The availability of precision microbubbles with a much longer shelf-life and a good safety profile has now made aortic root injections feasible (7–9). Unlike coronary injections that require separate engagements of the left main and right coronary arteries, as well as multiple injections of microbubbles to assess myocardial perfusion in a single echocardiographic cross section, an aortic root injection can provide information regarding myocardial perfusion in one cross section with a single injection (7–11). Single injections in two or three different cross sections can provide a rapid and comprehensive evaluation of myocardial perfusion of the entire left ventricle without causing any pertubation of coronary hemodynamic variables, which in itself could affect assessment of myocardial perfusion (25,26).

Aortic root injections have previously been used in experimental studies with considerable success in models of infarction and reperfusion (9–11). Although this route has not been used in patients with acute myocardial infarction, it has been utilized in patients with chronic coronary artery disease (7,8). Acheiving myocardial opacification at baseline with this approach has been disappointing (8). After hyperemia is induced, myocardial perfusion is seen in a larger number of patients because more bubbles enter the coronary circulation. However, the success rate of myocardial opacification with conventional imaging, even with hyperemia, is not high enough to allow its routine clinical use.

Compared with aortic root injections, during direct coro-

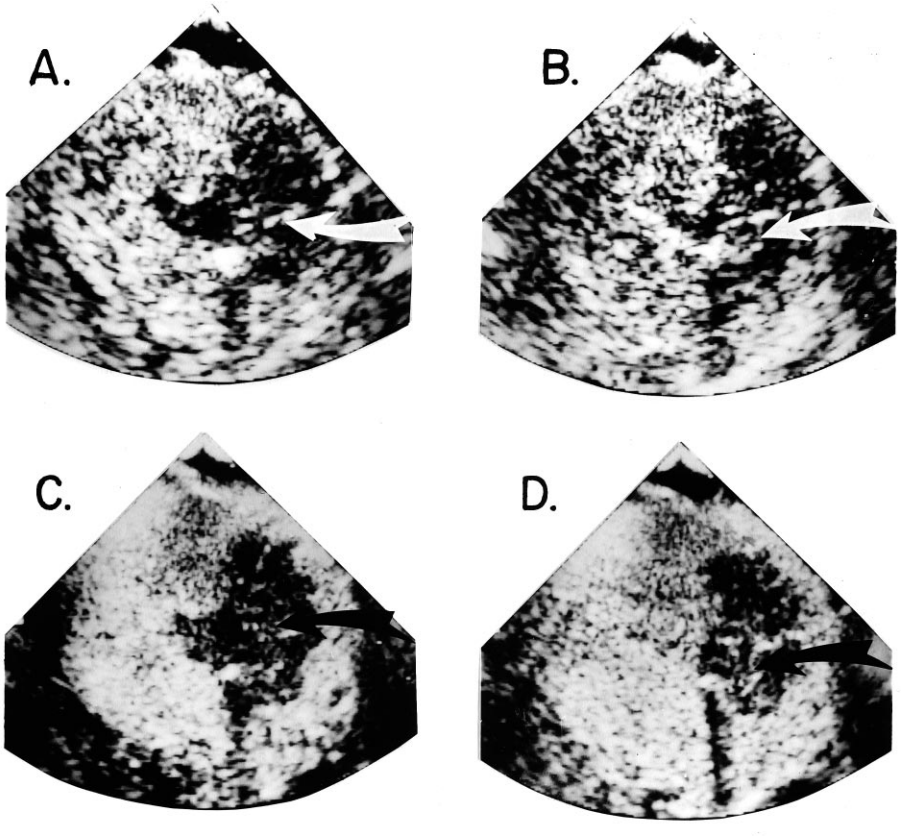

Figure 5. Examples of gray-scale images 15 min after reflow in the presence of a coronary vasodilator. The images were acquired using continuous and intermittent imaging at the fundamental (**A, B**) and harmonic (**C, D**) frequencies.

nary injections, microbubbles are delivered into the myocardial microcirculation in sufficient concentrations to result in images with a high signal to noise ratio, even with conventional imaging. An accurate estimation of both risk area (20,22) and infarct size can therefore be made using this approach (22,24). By comparison, when they are injected into the aortic root, only a small fraction of bubbles enter the coronary microcirculation, resulting in images with a poor signal to noise ratio, which as demonstrated in our study causes an underestimation of both risk area and infarct size. The limitation in image quality can be overcome by image processing techniques that enhance the signal to noise ratio. Although highly effective (9,24), these methods are time-consuming and require off-line analyses, precluding an immediate assessment of myocardial perfusion in the cardiac catheterization laboratory.

Fundamental versus harmonic imaging. Bubbles exposed to their resonant frequency can develop nonlinear oscillations, where their alternate expansion and contraction are unequal. When this phenomenon occurs, the backscatter emitted by the bubble contains harmonics (27,28). Harmonic imaging takes advantage of the ability of bubbles to resonate in the ultrasound field using transducers that can emit one frequency (the fundamental frequency) and receive another frequency (the harmonic frequency). Because microbubbles resonate significantly more than tissue or blood, which comprise the background, the signal to noise ratio is enhanced. When we increased the receive gain during harmonic imaging to bring the baseline myocardial video intensity to the level obtained on fundamental imaging, for the same dose of microbubbles, the background-subtracted myocardial video intensity was more than two-fold higher during harmonic than fundamental imaging.

This increase in signal to noise ratio is enough to provide excellent gray-scale images from which an accurate assessment of risk area and infarct size can be made. More important, this assessment can be performed on-line, with a clear visual assessment of perfusion defects in real time, without being dependent on image processing techniques. For quantitative assessment, an image can be frozen, and perfusion defect size can be planimetered and expressed as a percent of the left ventricular short-axis slice. This approach provides a very practical advantage in the cardiac catheterization laboratory, where decisions often need to be made immediately.

Using intracoronary injections of contrast medium in the cardiac catheterization laboratory, we previously demonstrated (2,3) the importance of defining the spatial distribution of collateral perfusion within the infarct zone. It is possible that this information could also be obtained with an aortic root injection. Although we did not study this issue in our current experiments, others have previously reported (10,11) that collateral perfusion can be assessed using intraaortic injections of bubbles.

Influence of intermittent imaging. It has recently been demonstrated (16,29) that when microbubbles are injected intravenously, intermittent imaging resulted in greater myocardial

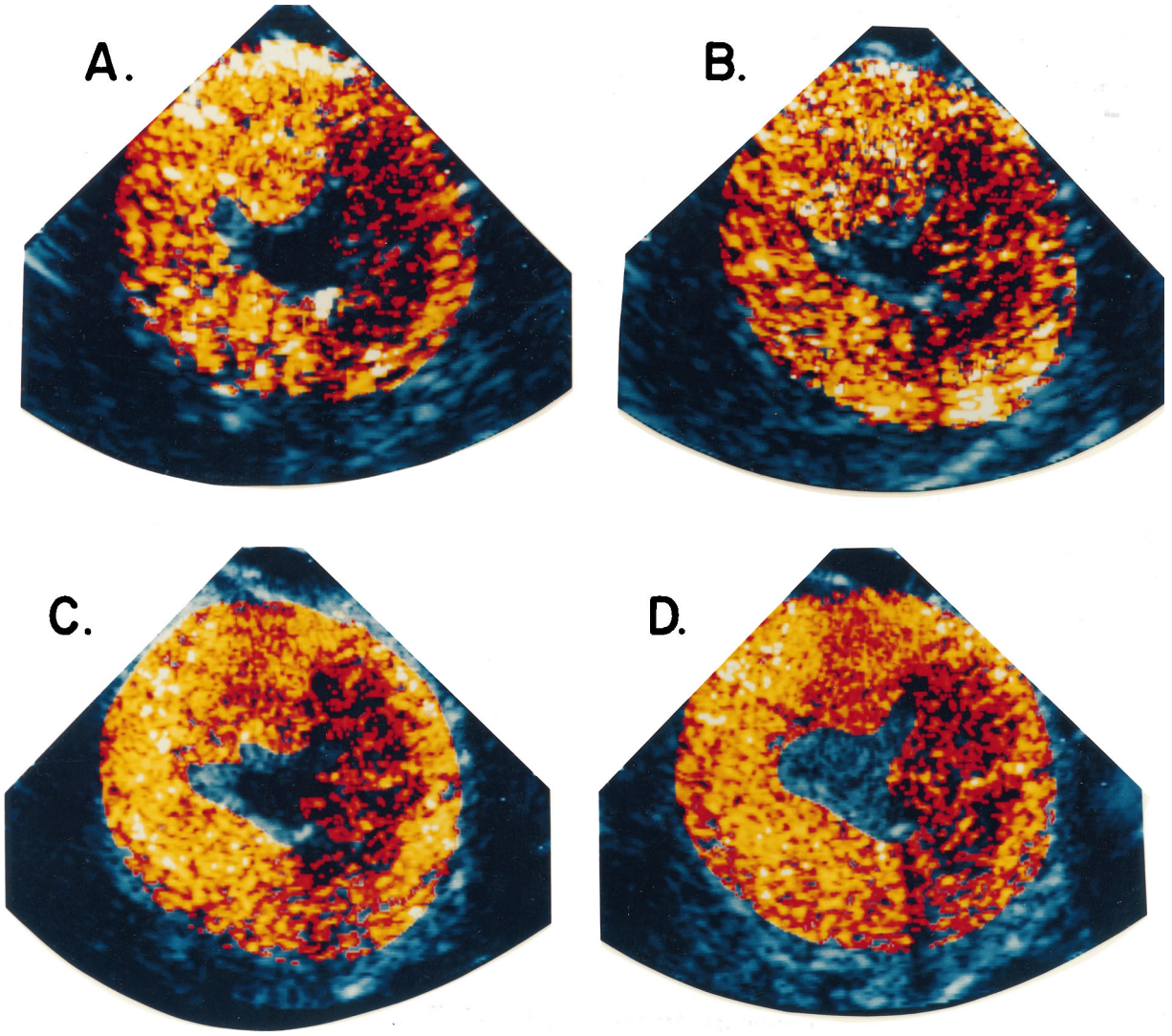

Figure 6. Examples of color-coded images 15 min after reflow in the presence of a coronary vasodilator. The images were acquired using continuous and intermittent imaging at fundamental **(A, B)** and harmonic **(C, D)** frequencies. These images correspond to the gray-scale images in Figure 5.

opacification than continuous imaging. The microbubble destruction caused by ultrasound was minimized by occasional rather than constant ultrasound transmission, resulting in increased myocardial signal. Whether the same effect is seen with aortic root injection of microbubbles is not known. We found that whereas the background-subtracted myocardial peak video intensity was more than twofold higher during harmonic than fundamental imaging (Table 1), there was no difference in the peak video intensities at either receive frequency during intermittent or continuous imaging. Similarly, whereas the measured microbubble transit rates tended to be higher (although not significantly so) during harmonic than fundamental imaging (Table 1), there were no differences in the transit rates during intermittent or continuous imaging.

These results indicate that, unlike the setting of a venous injection (16,29), there is no advantage to using intermittent over continuous imaging during aortic root injection of microbubbles. This finding may be related to the smaller concentration of microbubbles in the myocardium during venous than during

Table 1. Effect of Harmonic and Intermittent Imaging on Baseline Peak Myocardial Video Intensity and Mean Microbubble Rates

	Fundamental Imaging		Harmonic Imaging	
	Cont	Int	Cont	Int
Videointensity				
Background	51 ± 15	52 ± 14	49 ± 16	48 ± 14
Peak	80 ± 17	83 ± 19	123 ± 20*	118 ± 23*
Background subtracted	29 ± 8	31 ± 13	76 ± 20*	73 ± 20*
Microbubble transit rate (s^{-1})†	1.06 ± 0.20	1.11 ± 0.24	1.26 ± 0.25	1.33 ± 0.42

*$p < 0.01$ versus fundamental imaging. †No significant difference between stages in the nine dogs. Data presented are mean value ± SD. Cont = continuous; Int = intermittent.

Table 2. Hemodynamic Effects of WRC-0470 During Reflow

	HR (beats/min)	CO (liters/min)	Mean AoP (mm Hg)	Mean RAP (mm Hg)	Mean LAP (mm Hg)
Before drug	123 ± 21	2.2 ± 1.3	88 ± 12	9 ± 4	14 ± 5
During drug	124 ± 19	3.0 ± 1.5*	75 ± 8*	9 ± 3	14 ± 3

*$p < 0.01$. Data presented are mean value ± SD. AoP = aortic pressure; CO = cardiac output; HR = heart rate; LAP = left atrial pressure; RAP = right atrial pressure.

aortic root injections such that destruction of even a portion of them causes their concentration to fall below the threshold of the echocardiographic system. It is also possible that during venous injections, bubbles are exposed to ultrasound during their transit through the right and left heart, where they may be subjected to destruction or alterations even before they enter the myocardium. Such is usually not the case with aortic root injections because in most views, the aorta is not included in the same cross section as the myocardium. The practical advantage of this finding is that during aortic root injections of contrast medium, harmonic imaging can be performed in real time without loss of any information in the temporal domain.

Use of a coronary vasodilator. The basis for perfusion defects after reflow is the "no-reflow" phenomenon, which is seen in the center of the infarction and is associated with dense cellular necrosis and microvascular damage (30). Areas surrounding this region, but still within the infarct boundary, may have normal to hyperemic flow, especially when there is no significant residual stenosis of the infarct-related artery (31,32). A marker of perfusion may therefore underestimate infarct size. However, despite the presence of hyperemia, microvascular reserve is impaired within the infarct zone (33,34), and measuring regions with abnormal flow reserve can provide an accurate assessment of infarct size after reflow (9,27,35). The results of the present study confirm our previous observations that myocardial contrast echocardiography, when combined with a coronary vasodilator, provides an accurate assessment of infarct size in the first few hours after reflow (7,24,32).

The use of a coronary vasodilator during the acute phases of myocardial infarction raises questions of safety. Hypotension is frequent with nonselective coronary vasodilators, such as dipyridamole (36) and adenosine (37). In a patient with chronic stable angina, the side effects of these drugs are well tolerated (36,37). However, in patients with acute myocardial infarction, the earliest administration of one of these drugs for myocardial perfusion imaging has traditionally been 3 to 4 days after the event (38). To define infarct size in the cardiac catheterization laboratory, it would be necessary to give the vasodilator within minutes after reflow.

One approach would be the direct injection of the vasodilator into the coronary arteries to avoid the systemic side effects of the drug (39). However, intracoronary injections of drugs are tedious to perform, and because of the short half-life of adenosine or papaverine, the drug would have to be infused for each coronary injection of microbubbles. It would also require two femoral punctures—one for the aortic root catheter and another for the coronary infusion catheter. A much simpler approach would be the use of a systemic agent that is safe and has minimal side effects. WRC-0470 is a novel adenosine-A_{2a} agonist, which at the correct dose, causes coronary vasodilation with minimal effects on smooth muscles not present in the coronary arteries (22). Even in our anesthetized dogs, where reflexes are abolished, the decrease in aortic pressure was minimal. In a conscious human, no change in blood pressure or heart rate would be anticipated. It is therefore likely that this or a similar agent could be used safely in the setting of acute myocardial infarction.

Limitations of aortic root injections. Successful myocardial opacification from aortic root injections of microbubbles requires optimal positioning of the catheter in the aortic root. This can be accomplished with fluoroscopy and test injections of microbubbles. Despite optimal positioning, the dose of contrast agent needed for myocardial opacification varied, and no standard dose can be recommended. Different doses have to be tried at baseline, and the best dose is that which achieves mild but perceptible myocardial opacification. More intense opacification invariably results in attenuation, if not at baseline, then surely during hyperemia.

Albunex is pressure sensitive, and care must be taken not to unduly expose it to aortic pressure. To preserve the microbubbles, the stopcock connecting the catheter to tubing containing the contrast agent should be closed until just before injection. Because of the fragility of Albunex, it cannot be injected very rapidly. We injected it over 1.5 s, encompassing the time taken for an entire cardiac cycle. If a rapid (0.3 s) injection can be synchronized to diastole, it would make opacification more reproducible but will require more robust microbubbles. Adequate images may not be available in all patients using transthoracic echocardiography. Intracardiac echocardiography may allow similar, if not better, quality images. Finally, apical views were not obtained in the present study, although they are most useful for assessing the regional distribution of myocardial perfusion in the cardiac catheterization laboratory (3–5).

Conclusions. The results of this study indicate that it is possible to obtain accurate information regarding risk area during coronary occlusion and infarct size after reperfusion by myocardial contrast echocardiography using aortic root injections of contrast medium. Fundamental imaging imprecisely estimates both risk area and infarct size without the use of off-line image analysis, because of suboptimal signal to noise ratio. This limitation is overcome by harmonic imaging, which can provide excellent gray-scale images from which an accurate assessment of risk area and infarct size can be made on-line. Use of a selective

adenosine-A_{2a} agonist, which has minimal hemodynamic effects and successfully unmasks coronary reserve abnormalities within the infarct zone, can provide accurate and safe assessment of infarct size with myocardial contrast echocardiography. These findings can form the basis for the use of aortic root injections of contrast medium in the cardiac catheterization laboratory in patients with acute myocardial infarction.

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