Quantitative Assessment of Myocardial Perfusion During Graded Coronary Artery Stenoses by Intravenous Myocardial Contrast Echocardiography

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OBJECTIVES
The purpose of this study was to examine whether coronary stenoses of variable severity could be quantitatively assessed by analysis of myocardial perfusion as determined by intravenous (IV) myocardial contrast echocardiography.

BACKGROUND
Recently, new contrast agents and imaging technology have been developed that may enable improved assessment of myocardial perfusion by IV contrast injection.

METHODS
Variable obstruction of the left anterior descending (LAD) coronary artery in dogs was produced by a screw occluder. Coronary artery flow was measured with a transit time flowmeter during baseline, pharmacological vasodilation, a non-flow-limiting stenosis at rest in conjunction with vasodilation, a flow-limiting stenosis, and total occlusion. Myocardial contrast echocardiography was performed after IV injection of the contrast agent NC 100100. Time-intensity curves were obtained off-line for the LAD risk area and the adjacent left circumflex (LCx) territory, and peak background-subtracted video intensity was determined. Fluorescent microspheres were injected at each intervention for determination of regional myocardial blood flow.

RESULTS
During non-flow-limiting stenosis, flow limiting stenosis and total occlusion, LAD/LCx ratios of peak myocardial videointensity and blood flow decreased proportionately. Both LAD/LCx ratios of video intensity and blood flow identified the non-flow-limiting and the flow-limiting stenoses as well as total occlusion of the LAD artery. A significant correlation between LAD/LCx video intensity and blood flow ratios was observed (r = 0.83, p < 0.0001).

CONCLUSIONS
The degree of blood flow mismatch between ischemic and normal myocardial regions during graded coronary stenoses can be estimated in the dog by quantitative assessment of myocardial perfusion produced by IV myocardial contrast echocardiography. (J Am Coll Cardiol 2001; 37:624–31) © 2001 by the American College of Cardiology

The ability to evaluate myocardial perfusion by a quick and simple noninvasive method would be of great value in patients with coronary heart disease. Myocardial contrast echocardiography (MCE) is a promising method for the assessment of myocardial perfusion. The injection of contrast produces increased ultrasonic signals that opacify the myocardium if myocardial perfusion is normal. Although the opacification is generally uniform in the setting of normal flow, a number of variables typically result in some heterogeneity of regional intensities. Areas of myocardial ischemia or infarction are usually accompanied by perfusion defects, and contrast echocardiography has been validated for the assessment of risk area during total coronary occlusion with intra-arterial injections of contrast (1,2). Recent development of second-generation contrast agents containing microbubbles that traverse the pulmonary circulation has made it possible to obtain myocardial opacification after intravenous (IV) injection of contrast (3–5), and coronary stenoses have been evaluated by venous injections of other contrast agents (6–9). However, the ability of IV contrast echocardiography to assess myocardial perfusion quantitatively during graded coronary stenoses with and without stress has not been fully determined. The aim of the present study was to assess myocardial perfusion by MCE after IV injection of contrast during graded coronary stenoses and total coronary artery occlusion.

METHODS
Animal preparation. The study was approved by the Animal Research Committee at the University of California–San Diego and conformed to the “Principles of the American Heart Association on Research Animal Use,” (AHA, November 11, 1984). Eight mongrel dogs were anesthetized, intubated and ventilated with a respirator. Arterial blood gases and pH and body temperature were kept within normal limits. The heart was exposed through a left lateral thoracotomy and suspended in a pericardial cradle. Catheters were introduced into the pulmonary artery, left atrium, left ventricle (LV), femoral veins and femoral artery to inject, withdraw, and measure pressures. The proximal portion of the left anterior descending coronary artery...
(LAD) was dissected free from the surrounding tissue and a custom-designed screw occluder and a transit-time flow probe (Transonic series 2RB) connected to a digital flowmeter (model T201, Transonic Systems, Ithaca, New York) were placed snugly around the vessel.

**Experimental protocol.** The experimental protocol is shown in Figure 1. Baseline recordings, MCE and fluorescent microsphere injections were obtained when hemodynamic stability had been achieved approximately 30 min after instrumentation. Thereafter, vasodilation to approximately 300% of the baseline LAD flow was induced by IV infusion of 4 to 8 mg/kg/min WRC-0470 (2-cyclohexylmethylidenehydrazinoadenosine), a novel adenosine A2A receptor agonist (10) (Discovery Therapeutics, cyclohexylmethylidenehydrazinoadenosine), a novel adenosine A2A receptor agonist (10) (Discovery Therapeutics, Richmond, Virginia), and MCE and microsphere injections were repeated. After the vasodilator was discontinued and hemodynamics had stabilized, a stenosis that was not flow limiting at rest was created on the LAD. Vasodilation was again induced, and MCE and microsphere injections were performed. After return to baseline, subsequent MCE and fluorescent microsphere injections were performed during a flow-limiting stenosis at rest obtained by tightening the occluder to approximately 50% of resting LAD blood flow. Each period of flow reduction lasted between 10 and 15 min. The last intervention was a total LAD occlusion that was maintained throughout the rest of the study (approximately 15 min until euthanasia). Hemodynamic variables were monitored continuously and recorded prior to, and 1 and 3 min following injection of the contrast agent, after which fluorescent microspheres were injected to determine regional myocardial blood flow. A minimum of 30 min were allowed between each contrast injection.

**MCE.** The contrast agent used in this study, NC 100100, consists of a proprietary formulation of perfluorocarbon microbubbles in a shell (11), and was provided by Nycomed Imaging (Oslo, Norway). After reconstitution of the powder with sterile water to a homogeneous solution containing 17.5 million microbubbles/ml, 2.5 μl of the suspension of contrast agent per kilogram mixed with 0.5 ml dextrose was manually injected intravenously as a bolus over 3 to 4 s via the short catheter in the femoral vein and flushed with 10 ml saline. The MCE was performed with an ATL HDI 3000 echocardiograph (ATL, Bothell, Washington) equipped with a broadband 4–7-MHz transducer. Harmonic two-dimensional imaging in short axis view at the level of the papillary muscle was performed during triggering on the R-wave of every beat. End-diastolic triggering was chosen because it is less dependent on changes in heart rate, the images are easier to align than those obtained with end-systolic triggering, and coronary flow is maximal in diastole. The energy to the microbubbles was kept constant by employing the same mechanical index (0.4) and focus depth for all animals, which produced fairly homogenous opacification with every heart beat during triggered imaging at baseline. Imaging gain settings were optimized and thereafter kept unchanged. A linear postprocessing curve was used. A latex bag filled with degassed saline functioned as an acoustic interface between the surface of heart and the transducer. The transducer was placed within the bag, affixed to a metal stand clamped to the operating table, and positioned in order to obtain an image of the LAD and adjacent left circumflex coronary artery (LCx) beds. The data were recorded on 1.25-cm SVHS videotape, and recordings were obtained from 30 s prior to, until 4 min after, injection of contrast.

Echocardiographic images were analyzed with an off-line computer system (Tomtec Imaging Systems, Boulder, Colorado). Starting with approximately 15 beats prior to the injection of contrast, 100 consecutive end-diastolic frames were digitized with 640 × 480 pixel resolution on a scale of 256 gray levels and transferred to the memory of the computer. The LAD bed was identified as the region demonstrating a perfusion defect during total occlusion. Transmural regions of interest, including as much of the anterior myocardium as possible, were drawn in the LAD and LCx beds, avoiding the bright endocardial and epicardial borders (Fig. 2, left) and adjusted manually to correct for motion of the heart. The shape and size of the region of interest were constant in all experiments. Background intensity (average video intensity from the 15 beats in the region of interest before injection of contrast) was subtracted from the peak intensity (average of the three highest data points) in the same region after injection of contrast (Fig. 2, right). The variation in the precontrast

**Figure 1.** The outline of the study protocol. MCE = myocardial contrast echocardiography; MBF = myocardial blood flow assessed with fluorescent microspheres; NFLS + Vasodilation = non-flow-limiting stenosis at rest in conjunction with vasodilation.
echocardiographic signal intensity was low, with a coefficient of variation of 6.5% for five repetitive measurements in the same dog and 4.4% variation between dogs. The coefficient of variation between the peak echocardiographic signal intensities measured from three contrast injections in the same animal was on average 7.0%.

**Myocardial blood flow measurements.** Approximately $10^3$ fluorescent microspheres (Molecular Probes, Eugene, Oregon) suspended in saline, 0.02% Tween-20 and 0.02% thimerosal, were injected into the left atrium at each intervention. Reference blood samples were withdrawn from the femoral artery over 60 s with a constant-rate withdrawal pump starting 5 s prior to injection of microspheres. The short-axis slice of the LV corresponding to the echocardiographic image was identified by piercing the heart with spinal needles in the plane of the transducer after the last intervention. At the end of the experiment the dog was sacrificed and the heart excised with the spinal needles in place. Evans blue dye (Sigma Chemical, St. Louis, Missouri) was injected into the coronary ostia while the occlusion of the LAD remained on the vessel. This procedure stained the nonischemic myocardium blue, while the ischemic LAD bed was left unstained. The heart was cut along its short axis into 1-cm-thick slices. The myocardial slice corresponding to the image of the MCE was identified as described above. Three wedge-shaped specimens from the ischemic and three from the nonischemic myocardium were divided into epicardial and endocardial portions. The specimens were weighed and processed for determination of myocardial blood flow by spectrofluorometry according to the standard method described by Glenny et al. (12).

**Statistics.** The data were analyzed with a one-way repeated measurements analysis of variance with a Student Newman-Keuls extension for multiple comparisons. When comparing the means of two different sets of data, an unpaired $t$ test was used. Correlation between LAD/LCx video intensity ratio and regional blood flow ratio was performed with linear regression analysis. A $p$ value of $p < 0.05$ was considered statistically significant. All values are presented as means ± SEM.

**RESULTS**

Technically adequate studies with visible contrast opacification of the myocardium were obtained in all animals. After injection of the contrast agent there was no significant change in the baseline hemodynamic values. Moreover, no significant changes in the hemodynamic values occurred during the experiments (Table 1). Administration of the vasodilator WRC-0470 in the doses used in this study did not have any significant hemodynamic effect on other parameters than myocardial blood flow measured by the flow-meter. These parameters were also unchanged during and after injection of the fluorescent microspheres.

Figure 3 shows short axis end-diastolic video images of the LV at the papillary muscle level from each intervention.

**Table 1.** Hemodynamic Parameters

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<th>Baseline</th>
<th>Vasodilation</th>
<th>NFLS + Vasodilation</th>
<th>FLS</th>
<th>Total Occ</th>
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<tr>
<td>LVSP (mm Hg)</td>
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<td>117 ± 5</td>
<td>110 ± 6</td>
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<tr>
<td>Mean AP (mm Hg)</td>
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<td>106 ± 7</td>
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<tr>
<td>Mean PAP (mm Hg)</td>
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<td>17 ± 1</td>
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<td>19 ± 2</td>
<td>19 ± 2</td>
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<tr>
<td>HR (beats/min)</td>
<td>139 ± 5</td>
<td>135 ± 7</td>
<td>138 ± 6</td>
<td>138 ± 6</td>
<td>138 ± 5</td>
</tr>
<tr>
<td>Flow LAD (ml/min)</td>
<td>19 ± 2</td>
<td>55 ± 6*</td>
<td>30 ± 5†</td>
<td>10 ± 1†</td>
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*p < 0.05 vs. baseline; †p < 0.05 vs. vasodilation. Values are means ± SEM.

AP = arterial pressure; FLS = flow-limiting stenosis; HR = heart rate; LAD = left anterior descending coronary artery; LVSP = left ventricular systolic pressure; NFLS + Vasodilation = non-flow-limiting stenosis at rest in conjunction with vasodilation; PAP = pulmonary artery pressure; Total Occ = total occlusion.
in one representative dog. The transducer was positioned on the anterior LV wall to record both LAD and LCx regions at the top of the image and to minimize attenuation from the right ventricular cavity. Before contrast injection the homogenous LV cavity appears black and the myocardium exhibits minimal reflections apart from the epicardial and endocardial borders (Fig. 3, upper left). After contrast injection there was an apparent homogenous opacification of the entire anterior wall including LAD and LCx regions (Fig. 3, upper right). During pharmacological vasodilation a further increase in the intensity of myocardial opacification was apparent (Fig. 3, middle left). During the non-flow-limiting stenosis, pharmacological vasodilation caused the LCx region to appear brighter than the LAD region (Fig. 3, middle right); brightness in the LCx region was similar to the brightness in the previous picture. During the flow-limiting stenoses (Fig. 3, lower left) there is fairly good opacification of the LCx region, but only weak, speckled opacification of the LAD region. During the total LAD occlusion a perfusion defect is clearly shown in the LAD region, whereas the LCx region shows normal opacification (Fig. 3, lower right).

Changes in blood flow in the LAD observed during the various interventions applied are depicted in Figure 4. LAD blood flow at baseline measured $19 \pm 2$ ml/min, and it nearly tripled with vasodilation to $55 \pm 6$ ml/min. In the setting of a non-flow-limiting stenosis, pharmacological vasodilation, LAD flow was $30 \pm 5$ ml/min, while the flow-limiting stenosis reduced LAD blood flow to $10 \pm 1$ ml (both $p < 0.05$). Total occlusion resulted in an absence of measurable LAD blood flow by the transit time method.

The changes in the ratios of LAD/LCx regional myocardial blood flow and background-subtracted video intensity, which accompanied the alterations in LAD blood flow, are shown in Figure 5. At baseline, the LAD/LCx regional blood flow ratio measured by microspheres was $1.07 \pm 0.07$, a value similar to the video intensity ratio of $0.98 \pm 0.10$. Vasodilation produced relatively little change in LAD/LCx ratio in either value; regional blood flow ratio was $1.07 \pm 0.11$ and the video intensity ratio was $0.9 \pm 0.1$ (difference between ratios = NS). The combination of non-flow-

![Figure 3. Echocardiograms during specific interventions in a representative experiment. End-diastolic echocardiographic images of the anterior half of the left ventricle in short-axis are shown. Upper left: Precontrast, prior to contrast injection; upper right: Baseline, after contrast injection; middle left: Vasodilation, during pharmacological vasodilation; Middle right: NFLS + Vasodilation, a non-flow-limiting LAD stenosis at rest in conjunction with pharmacological vasodilation; lower left: FLS, a flow limiting stenosis that reduces coronary blood flow by 50% at rest; lower right: Total Occ; total occlusion of the LAD. Arrows depict the border between the LAD and LCx region. LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery.

![Figure 4. Graph showing left anterior descending coronary artery (LAD) flow measured by transit-time flowmeter during the various interventions. NFLS + Vasodilation = non-flow-limiting stenosis at rest in conjunction with vasodilation; FLS = flow-limiting stenosis; Total Occ = total occlusion. *p < 0.05 vs. baseline; †p < 0.05 vs. vasodilation.]
limiting stenosis and pharmacological vasodilation reduced the ratio of LAD/LCx values both in terms of blood flow (0.81 ± 0.1, p < 0.05) and video intensity (0.68 ± 0.08, p < 0.05), which were further reduced by a flow-limiting stenosis to 0.63 ± 0.07 and 0.59 ± 0.08, respectively. The lowest LAD/LCx ratio values were observed in the presence of total occlusion, where a visually apparent contrast defect was observed in all animals, and measured 0.14 ± 0.05 for both flow and video intensity (both p < 0.05 vs. baseline).

The results of linear regression analysis between background-subtracted video intensity and blood flow ratios derived from a total of 40 flow states are shown in Figure 6, left panel (y = 0.96x + 0.11). There is a good correlation between the two variables (r = 0.83, p < 0.0001, SEE = 0.24). Figure 6 (right panel) shows the results normalized to the baseline values for each dog (y = 0.97x + 0.01). The correlation coefficient observed for normalized data was 0.93 (p < 0.001, SEE = 0.15).

During baseline, the precontrast video intensity in the LAD region of 60 ± 4 gray levels was similar to the 57 ± 2 gray levels in the LCx region (difference: NS). There was no significant difference between the precontrast video intensities in the LAD and LCx region at any of the interventions. Furthermore, the video intensities prior to injection of contrast remained constant throughout the experiment.

**DISCUSSION**

Despite limitations of spatial definition and variables capable of influencing contrast-intensity measurements, the present study demonstrates that MCE provides a reliable method for assessing myocardial perfusion after IV injection of contrast in dogs. Our data establish that the myocardial video intensity ratio between ischemic and normal myocardial regions is altered in the presence of coronary stenoses. We demonstrate that the degree of reduction in video intensity ratio differs for variable grades of coronary obstruction, and it correlates significantly with the degree of blood flow mismatch. Moreover, our data show that reduced perfusion with non-flow-limiting stenoses at rest can be reliably assessed by IV MCE in conjunction with pharmacological vasodilation, and that reduced perfusion with stenoses that are flow limiting at rest or total coronary artery occlusion can be evaluated without pharmacological vasodilation.

**Assessment of myocardial perfusion during non-flow-limiting stenosis.** Data regarding the quantitative assessment of relative myocardial perfusion during non-flow-limiting coronary stenoses are few, even with echocardiography obtained by intracardiac injection of contrast (13–15). However, a few studies of graded coronary stenoses have demonstrated good correlation between the ratios derived from normal and ischemic myocardium for video intensity and regional myocardial blood flow after both intra-aortic (13) and left or right atrial injection of contrast (11). After complex analysis with magnification of video intensity...
measurements from ischemic and normal myocardium, Firschke et al. (8) were able to demonstrate perfusion mismatch during pharmacological vasodilation after venous injection of FS-069. Wei et al. (16) used another contrast agent (AFO150) to study stenoses that produced pressure gradients of variable severity. They examined only stenoses that were non-flow-limiting at rest, and only during hyperemia, and they showed a correlation between the ratio of peak video intensity and myocardial blood flow in the stenosed to normal beds. Our findings confirm these results with non-flow-limiting stenoses at rest using another contrast agent, diastolic gating, and standard quantitative methods.

**Assessment of myocardial perfusion during flow-limiting stenosis.** In the present study we found that stenoses that were flow limiting at rest significantly reduced the ischemic-to-normal myocardial contrast-intensity ratio. This demonstrates for the first time that IV MCE can detect a decreased intensity produced by severe stenoses without the need for pharmacological vasodilation. Previously, flow-limiting stenoses have required pharmacological hyperemia to quantify myocardial blood flow with contrast echocardiography, even after injection of contrast into the aortic root (14,16).

Coronary vasodilators have well-known potential side effects, including hypotension and chest pain, and patients with severe lesions may be more vulnerable to such side effects. Hence, the assessment of coronary stenoses without pharmacological vasodilation would be advantageous in the clinical setting.

**Assessment of myocardial perfusion during total coronary occlusion.** During total occlusion of the LAD we observed a visible perfusion defect in all dogs, and we found that the ratio between ischemic and normal myocardial regions was similar for both blood flow and video intensity. Perfusion defects after IV injection of contrast have previously been demonstrated to correlate with area at risk or infarct size expressed as the magnitude of wall-motion abnormalities or by means of tissue staining (3,4,7). In addition, the location and reversibility of perfusion abnormalities detected by IV MCE have been found to be similar to that depicted by sestamibi single-photon emission computed tomography (9). Because of lateral dropout of the echocardiographic image in our study, which was most likely related to anisotropy of fiber orientation (17), the posterior borders of the LAD and LCx beds could not be defined. Thus, the absolute size of the perfusion defect was not measured.

In a carefully performed study using somewhat different methodology, Meza et al. (6) found that peak contrast intensity during coronary occlusion showed a modest but significant correlation to blood flow measured by radiolabeled microspheres, after normalization of the ultrasound peak intensity values to baseline. In our study, however, normalization of the intensity values to baseline was not necessary to obtain a significant correlation to regional blood flow. The importance of this becomes evident in the clinical setting of coronary occlusions where a normal baseline contrast echocardiogram is rarely available for evaluation of patients with coronary heart disease.

**Factors affecting video intensity during contrast echocardiography.** The precise mechanism for the changes in video intensity remains unresolved. However, as described below, several alternatives are possible. The video intensity is related to the number of microbubbles within the ultrasound beam (18), which depends on blood volume and microbubble transit rate through the imaging field. Furthermore, video intensity measurements are affected by ultrasound power (18,19), which can lead to destruction of microbubbles and to a decrease in microbubble size. In our study, microbubbles were probably destroyed by ultrasound, even though a mid-range ultrasound power and triggered imaging were used. Based on a maximal transit velocity in myocardial capillary arterioles and vessels, the 4 to 5 mm thickness of the ultrasound beam, and the heart rate of 135, the interval between each heart beat would be too short for complete replenishment of new bubbles, and the video intensity would be influenced by destruction of microbubbles during the previous exposure.

An alternative mechanism for the change in video intensity involves the fact that blood volume and transit rate increase during vasodilation (20). In the presence of a non-flow-limiting stenosis at rest combined with hyperemia, it has been shown that the vasodilator-induced increase in both flow and blood volume is less in the myocardium distal to a stenosis than in the normal bed (21–23). Hence, video intensity in the ischemic region would be reduced compared to the normal region and thus the video intensity ratio would be decreased similarly to the myocardial blood flow ratio.

It has now been shown that the time-course of replenishment of microbubbles into the imaging field following bubble destruction is a function of flow velocity and cross-sectional microvascular volume (24). These determinants are expressed as the rate of intensity increase and the peak plateau intensity, respectively. Thereby, the replenishment of contrast intensity can be fit by the exponential function $Y = A(1 - e^{tb})$, where $b$ represents the rate of increase and $A$ represents peak intensity. The fact that $A$ decreases following vasodilation in the presence of stenosis is evidence of reduced microcirculatory blood volume and supports the concept that capillary closure or derecruitment to maintain perfusion pressure is the mechanism for reduced contrast intensity in the bed of stenotic vessels.

**Methodological considerations.** Although reproducibility of peak contrast intensities between animals is limited, our study revealed a low variation when assessments of peak signal intensities were determined by repetitive injections of contrast in the same animal. Hence, we compared video intensity ratios to blood flow ratios in an ischemic and normal myocardial region in the same animal. In the presence of generalized disease of all three coronary vessels, equivalent reductions in flow might mask hypoperfusion.
However, assessing relative changes in myocardial perfusion by comparing ratios between ischemic and normal myocardial regions is a widely used method for evaluation of coronary stenoses.

Measuring Doppler velocity reserve in individual coronary arteries may obviate this problem in the future (25). In our study, the peak value derived from the time-intensity curve was used to assess changes in myocardial blood flow with MCE. Because the relation between video intensity and myocardial blood flow is linear only at low concentrations of microbubbles (26), we used a low dose of the contrast agent. This dose produced homogenous myocardial opacification during baseline conditions. To compare differences in video intensity during various interventions, it is imperative that the baseline does not change during the experiment (23). No significant changes occurred in the baseline values before the various contrast injections in the LAD or the LCx region during our experiments. Although there was a trend toward a reduction in myocardial backscatter during the flow-limiting stenosis and total occlusion, this did not reach statistical significance in our study. This might be related to the fact that echocardiographic images were obtained shortly after coronary occlusion before the development of histopathological changes in the myocardial tissue.

In the previous studies cited, the pharmacological hyperemia necessary to identify ischemia was produced by vasodilators, such as dipryridamole, dobutamine, or adenosine (7). In the current protocol, vasodilation was produced by infusion of WRC-0470, a novel adenosine A2A receptor agonist-producing coronary vasodilator without the hypertensive effect of traditional vasodilators (10). In our study, no significant hemodynamic effects were observed with WRC-0470 infusion, other than the increase in coronary blood flow. Because changes in aortic pressure and heart rate would affect myocardial perfusion, the avoidance of significant alterations in these parameters is important for evaluating myocardial perfusion.

Clinical implications. Our study establishes the ability to assess graded coronary stenoses from MCE in open-chest dogs with high-quality echocardiographic images.Thoracic imaging in humans may be compromised by attenuation from the chest wall and lung, as well as by artifacts and a lesser signal-to-noise ratio. Shadowing at peak contrast intensity can be reduced by imaging from apical views.

Because the methods used in this study relate to a ratio between contrast intensity between ischemic and normal myocardial regions, it is reasonable to expect similar results for lower doses of contrast or measurements at a later time after the injection of contrast.

To compare myocardial regions with different blood flow values in our experiments, adjacent myocardial regions from the anterior aspect of the left ventricle were evaluated. Whether the results of our study will be reproduced with ischemia in other areas remains the subject of further investigation. However, our data indicate that IV MCE may prove suitable both for the detection of myocardium at risk of ischemia during pharmacological stress and for the detection of manifest stenoses and coronary occlusions, even in the absence of pharmacological intervention. Finally, these data establish the potential of myocardial perfusion by IV MCE to be a valuable diagnostic tool in the assessment of patients with coronary heart disease.

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