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Stress Testing

Real-Time Assessment of Myocardial Perfusion and Wall Motion During Bicycle and Treadmill Exercise Echocardiography: Comparison With Single Photon Emission Computed Tomography

Sarah Shimoni, MD,* William A. Zoghbi, MD, FACC,* Feng Xie, MD,† David Kricsfeld, BS,† Sherif Iskander, MD,* Lisa Gobar, MD,‡ Issam A. Mikati, MD,* John Abukhalil, RT,* Mario S. Verani, MD, FACC,* Edward L. O'Leary, MD, FACC,† Thomas R. Porter, MD, FACC†

Houston, Texas and Omaha, Nebraska

OBJECTIVES We sought to determine the feasibility and accuracy of real-time imaging of myocardial contrast echocardiography (MCE) in detecting myocardial perfusion defects during exercise echocardiography compared with radionuclide tomography.

BACKGROUND Ultrasound imaging at a low mechanical index and frame rate (10 to 20 Hz) after intravenous injections of perfluorocarbon containing microbubbles has the potential to evaluate myocardial perfusion and wall motion (WM) simultaneously and in real time.

METHODS One hundred consecutive patients with intermediate-to-high probability of coronary artery disease underwent treadmill (n = 50) or supine bicycle (n = 50) exercise echocardiography. Segmental perfusion with MCE and WM were assessed in real time before and at peak exercise using low mechanical index (0.3) and frame rates of 10 to 20 Hz after 0.3 ml bolus injections of intravenous Optison (Mallinckrodt Inc., San Diego, California). All patients had a dual isotope (rest thallium-201, stress sestamibi) study performed during the same exercise session, and 44 patients had subsequent quantitative coronary angiography.

RESULTS In the 100 patients, agreement between MCE and single photon emission computed tomography (SPECT) was 76%, while it was 88% between MCE and WM assessment. Compared with quantitative angiography, sensitivity of MCE, SPECT and WM was comparable (75%), with a specificity ranging from 81% to 100%. The combination of MCE and WM had the best balance between sensitivity and specificity (86% and 88%, respectively) with the highest accuracy (86%).

CONCLUSIONS The real-time assessment of myocardial perfusion during exercise stress echocardiography can be achieved with imaging at low mechanical index and frame rates. The combination of WM and MCE correlates well with SPECT and is a promising important addition to conventional stress echocardiography. (J Am Coll Cardiol 2001;37:741–7) © 2001 by the American College of Cardiology

Assessing myocardial perfusion and wall motion (WM) during exercise stress is important for the diagnosis and risk stratification of patients with coronary artery disease (CAD) (1). Recent developments in contrast echocardiography have resulted in the opacification of left-sided cardiac structures with intravenous administration of contrast. However, conventional continuous imaging destroys too many microbubbles to allow myocardial contrast enhancement. Intermittent imaging reduces microbubble destruction and, hence, produces consistent myocardial opacification (2–4). Although intermittent harmonic imaging clearly improves the detection of CAD during vasodilator stress (3,4), technical considerations limit its feasibility during exercise. Accelerated intermittent imaging (AII) is a recently introduced method that uses low mechanical index and frame rates that reduce microbubble destruction while still permitting simultaneous imaging of myocardial contrast and WM in real time (5,6). This study was designed to evaluate first the feasibility of evaluating perfusion and WM in real time with AII during supine bicycle and post-treadmill exercise echocardiography and, second, to assess the agreement between perfusion with AII, WM and simultaneous radionuclide single-photon emission computed tomography (SPECT) in detecting CAD.

METHODS

Patient population. Patients with an intermediate-to-high probability of CAD based on clinical criteria (7) who were referred for exercise testing or were already scheduled for coronary angiography were approached for enrollment. The study was performed in two centers: The University of Nebraska Medical Center and Baylor College of Medicine. Patients were excluded if they were hemodynamically un-

From the *Section of Cardiology, Baylor College of Medicine, Houston, Texas; the †Department of Internal Medicine, Section of Cardiology; and the ‡Department of Radiology, University of Nebraska Medical Center, Omaha, Nebraska.Supported by an investigator-initiated grant from Molecular Biosystems Inc. and Mallinckrodt Inc.
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Abbreviations and Acronyms

AII	= accelerated intermittent imaging
CAD	= coronary artery disease
CX	= circumflex
LAD	= left anterior descending
MCE	= myocardial contrast echocardiography
RCA	= right coronary artery
SPECT	= single photon emission computed tomography
WM	= wall motion

stable, had known left main CAD, severe valvular disease or significant ventricular dysfunction (ejection fraction <40%). The institutional review boards of both institutions approved the study protocol, and all patients provided informed consent.

Study design. All patients had myocardial contrast echocardiography (MCE) and SPECT performed during the same exercise test. A resting thallium-201 SPECT study was followed by resting echocardiography with intravenous injection of contrast (Optison). The patients then underwent an exercise test, either treadmill or supine bicycle. Contrast was injected at peak exercise, and images were acquired at peak exercise during supine bicycle or immediately after treadmill exercise. Tc-99 sestamibi was administered intravenously 1 min before the completion of exercise and SPECT images obtained 30 to 60 min later.

Stress testing. Patients enrolled at the University of Nebraska Medical Center underwent treadmill stress while patients at Baylor College of Medicine underwent bicycle exercise. For the treadmill, the standard Bruce protocol was used; for the bicycle, a variable load supine bicycle ergometer was used (8) with standard electrocardiographic and blood pressure monitoring.

Myocardial contrast echocardiography (MCE). Images were obtained using an HDI 3000 ultrasound harmonic scanner (1.7/3.4 MHz; Advanced Technology Laboratories, Bothell, Washington). The mechanical index was lowered to 0.3 to 0.4. The dynamic range was 60 dB; the gain was adjusted at the beginning of the rest study and held constant thereafter. The frame rates were adjusted with a Macintosh computer (5,6) in relation to heart rate as follows: 10 Hz for heart rates 50 to 70 beats/min, 12 Hz for 70 to 90 beats/min, 14 Hz for 90 to 100 beats/min, 18 Hz for 100 to 120 beats/min and 20 Hz for >120 beats/min.

Optison was injected as a bolus (0.3 to 0.6 mL) during rest and peak stress. For the treadmill protocol, contrast was injected 10 s before termination of exercise, and imaging was started with the apical windows. Images from the apical four-, two- and three-chamber views were acquired using AII and standard frame rates (>30 Hz). Both frame rates were digitized in full disclosure mode (Eastman Kodak, Allendale, New Jersey) and displayed on a quad screen. The parasternal long- and short-axis images were obtained using standard frame rates and were also digitized for WM analysis.

Echocardiographic analysis. A 17-segment model of the left ventricle was used for the analysis of MCE, WM and SPECT (9). An independent observer in each center, blinded to all clinical data, analyzed all studies (quad screens, videotapes). Segments were assigned a coronary artery territory as previously described (8).

MCE analysis. Segmental myocardial contrast was graded as: 1= normal bright opacification and 2 = reduced contrast enhancement relative to other regions. An inducible defect was one that was evident only during exercise, while a fixed defect was evident at rest and during stress. If a contrast defect was limited to one basal segment of a coronary territory, the territory was still considered normal and the defect attributed to attenuation. Territorial defects were considered present if they involved the midsegments or distal segments of that territory in addition to the basal segment. Fifty of the studies were read by another observer to assess interobserver variability, while twenty were read again by the same observer to assess intraobserver variability.

WM analysis. Wall motion was interpreted according to established criteria (8). A normal response was defined as a normal or hyperdynamic function during exercise, and ischemia was defined as the development of new WM abnormalities or worsening of resting hypokinesia. A fixed abnormality was defined as a WM abnormality at rest without developing ischemia.

SPECT. All patients underwent dual isotope, myocardial perfusion SPECT. Thallium-201 (3 to 4 mCi) was injected at rest and SPECT imaging initiated 10 min later. Tc-99 sestamibi (20 to 30 mCi) was injected during peak exercise and imaging initiated 30 to 60 min later. Acquisitions were performed using a two-detector (ADAC, Milpitas, California) or three-detector (Picker, Cleveland, Ohio) camera to get 32 projections over 180° (ADAC) or 40 projections over 120° (Picker) for 40 or 25 s. Rest and stress images were reconstructed by back projection using a low pass ramp filter and reoriented in three orthogonal planes using standard techniques. Radioisotope uptake was graded by an independent observer in each center without knowledge of other data. A percent uptake <70% of the highest region was considered abnormal. A normal response was defined as normal uptake (>70%) at rest and stress; ischemia was defined as normal uptake at rest and reduced (<70%) during stress, and fixed defect was defined as reduced uptake at rest without worsening during stress.

Quantitative coronary angiography. Coronary angiography was performed in multiple projections using the standard Judkins technique within two weeks of enrollment. An independent experienced observer quantitated the angiograms (CAAS System, Pie Medical Instruments, Maastricht, the Netherlands). Coronary artery stenosis was defined as >50% narrowing of the reference lumen diameter.

Statistical analysis. Data are presented as mean ± standard deviation. Categorical variables were compared using the chi-square test. Analysis of variance was used to compare hemodynamics of patients undergoing the two modes

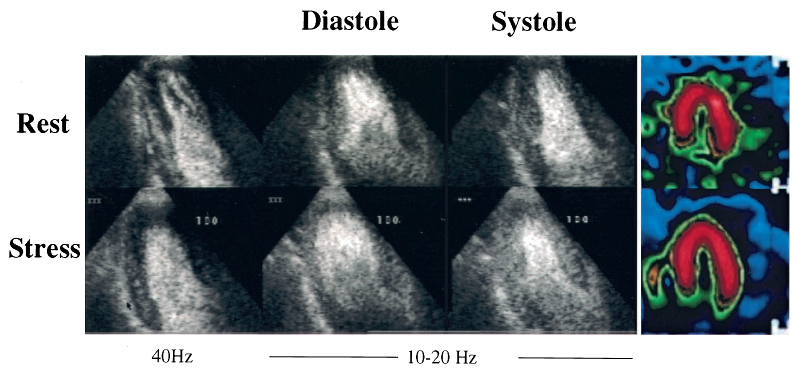

Figure 1. An example of normal myocardial contrast enhancement and the corresponding single photon emission computed tomography during bicycle exercise. At low mechanical index and frame rate, uniform contrast enhancement is seen at rest and is more prominent during exercise. Less contrast is seen when imaging at high frame rate (systolic frame shown), because of more bubble destruction.

of exercise. If the F value was significant, a Student-Newman-Keuls test was performed. Agreement among MCE, WM and radionuclide uptake was assessed using kappa statistics. Analysis was performed by segments, coronary territories and by patients. To evaluate whether myocardial regions subtended by the respective coronary arteries responded in a statistically independent manner compared with adjacent regions, types of response from rest to exercise with AII, SPECT and WM were correlated between regions using Pearson Product Moment Correlation. Sensitivity and specificity of the different techniques for CAD were assessed. The combination of MCE and WM was also compared to coronary angiography, with an abnormal study defined as an abnormality by either modality or a normal study as normal by both modalities.

RESULTS

A total of 101 consecutive patients were enrolled. One hundred patients underwent exercise (50 supine bicycle, 50 treadmill). One patient was excluded because of a very poor echocardiographic windows at baseline. There were 67 men and 33 women with a median age of 57 (36 to 84) years. Thirty patients had diabetes, 51 hypertension, 65 hyperlipidemia, and 28 had a history of smoking. Angina was present in 51 patients, prior revascularization in 26, prior infarction in 17; all patients had an ejection fraction >40%. Patients undergoing bicycle stress had similar characteristics as those undergoing treadmill, with the exception of a higher incidence of men (80% vs. 54%) and prior revascularization (36% vs. 16%), both $p < 0.05$. Twenty-one patients were given nitrates, 40 patients received beta-adrenergic blocking agents and 21 patients received calcium channel blocking agents. Beta-adrenergic blockers were discontinued on the day of the test in 75%. Patients undergoing bicycle and treadmill exercise had similar baseline hemodynamics. The treadmill group, however, achieved a higher maximal heart rate (157 $\pm$ 19 vs. 124 $\pm$ 17 beats/min), percent maximal age-predicted heart rate (96 $\pm$ 9 vs. 76 $\pm$ 14%) and a higher double product (28,812 $\pm$ 6,926 vs. 22,489 $\pm$ 4,594 mm Hg $\times$ beats/min, all $p < 0.05$).

Feasibility of perfusion and WM assessment. Myocardial contrast could be visualized and evaluated in 100 patients. In one patient, the circumflex (CX) artery territory could not be analyzed because of shadowing of the lateral wall and in another the inferior wall was not well seen. Both patients had perfusion abnormalities in other regions that could be assessed. Analysis of perfusion was, therefore, feasible in 100 left anterior descending (LAD) regions, 99 CX and 99 right coronary artery (RCA) territories.

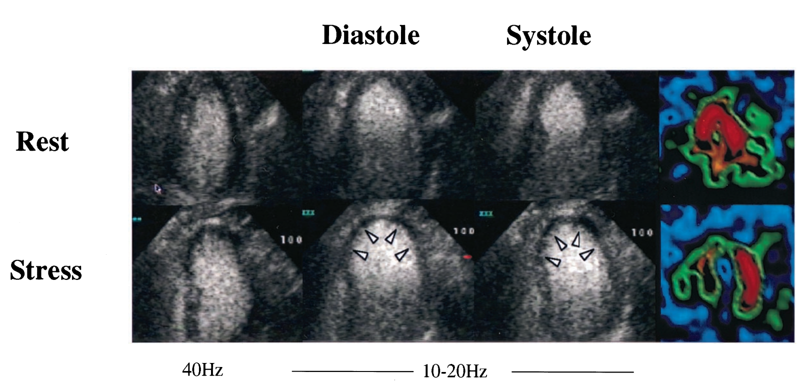

Figure 2. An example of an inducible anteroseptal and apical wall motion abnormality and contrast defect **(arrows)** with accelerated intermittent imaging during supine bicycle stress. The corresponding SPECT defect, which extends into the midseptum, is shown. Display is similar to Figure 1. SPECT = single photon emission computed tomography.

Table 1. Agreement Between MCE, SPECT and Wall Motion Abnormalities: Analysis by Patients

		SPECT		Wall Motion	
		Normal	Abnormal	Normal	Abnormal
MCE	Normal	48	14	55	7
	Abnormal	10	28	5	33
	Kappa	0.50		0.75	
	Agreement	76%		88%	

MCE = myocardial contrast echocardiography; SPECT = single photon emission computed tomography.

Of the 3,400 segments, interpretation of MCE was feasible in 97%; 87 segments (2.6%) were not seen because of attenuation by contrast, and three were not visualized due to technical reasons. In 213 additional segments (6%), a lesser degree of attenuation was noticed. In these segments the readers could still assess contrast enhancement. Attenuation was primarily in basal segments and seen more often during stress imaging (62% of all the segments with attenuation). Wall motion was evaluated in all the patients, but ten segments (0.5%) could not be seen.

Comparison of MCE with SPECT and WM. ANALYSIS BY PATIENTS. In the 100 patients, MCE was normal in 62 and abnormal in 38. Figures 1 and 2 show illustrative examples. Of the 38 abnormal studies, 29 had reversible contrast defects, and nine had fixed defects. In comparison, SPECT was normal in 58 patients and abnormal in 42 (33 inducible and nine fixed defects) while WM was normal in 60 patients and abnormal in 40 (30 inducible, 10 fixed). Agreement among modalities is shown in Table 1. Figure 3 shows differentiation of basal lateral attenuation from a true contrast defect.

Analysis by coronary territory. The exercise responses in WM, perfusion by MCE and SPECT in the various coronary territories were independent of each other and correlated poorly among each other (MCE: r range 0.06 to 0.4, p = 0.2 to 0.58; WM: r = 0.02 to 0.40, p = 0.1 to 0.86; SPECT: r = −0.11 to 0.15, p = 0.15 to 0.9). Table 2 compares the agreement among modalities in the 298 territories that could be analyzed. The agreements between MCE and SPECT in the LAD, CX and RCA territories were 89%, 86% and 76%, respectively. The concordance in the LAD region was significantly higher (p = 0.02) than the concordance in the RCA region. The agreement between MCE and WM was 94%, 87% and 89% for LAD, CX and RCA territories, respectively. Results were similar if the analysis was performed separately for treadmill or bicycle exercise (p range 0.2 to 0.8).

Segment by segment analysis. Three thousand three hundred five segments were analyzed. There was 92% concordance (kappa = 0.39) when MCE and SPECT were compared. Myocardial contrast echocardiography and WM had a 94% concordance (kappa = 0.6). In the resting study, segmental agreement between MCE and SPECT was 96% and 95% between MCE and WM. The concordance for segments during exercise was 88% (kappa = 0.4) between MCE and SPECT and 93% (kappa = 0.67) between MCE and WM. After combining baseline and peak exercise, MCE, SPECT and WM identified 1,438, 1,453 and 1,423 segments, respectively, as normal; 156, 150 and 156, respec-

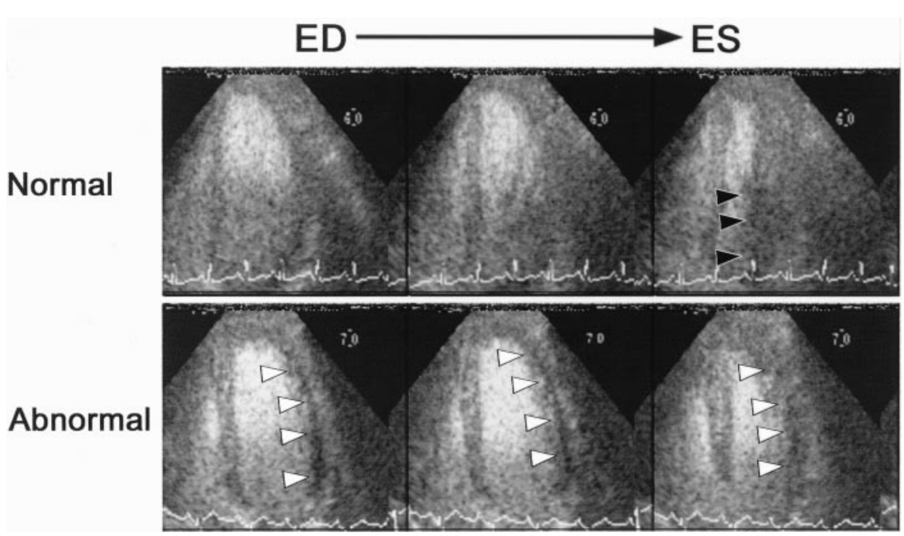

Figure 3. Lateral wall myocardial contrast enhancement using accelerated intermittent imaging during treadmill exercise stress in two different patients. The **top panels** show normal basal lateral segment attenuation, while the **bottom panels** show the dynamic images in a patient with a lateral wall contrast defect. Note that the perfusion defect in the patient with a true defect **(bottom panels)** extended out to the distal segment of the lateral wall, which would be uncharacteristic of attenuation. ED = end-diastole; ES = end-systole.

Table 2. Agreement between MCE, SPECT and Wall Motion Abnormalities: Analysis by Coronary Territory

		LAD				CX				RCA				CX/RCA			
		SPECT		Wall Motion		SPECT		Wall Motion		SPECT		Wall Motion		SPECT		Wall Motion	
		Nor	Abn	Nor	Abn	Nor	Abn	Nor	Abn	Nor	Abn	Nor	Abn	Nor	Abn	Nor	Abn
MCE	Nor	76	4	76	4	79	8	81	6	67	14	73	8	57	16	66	7
	Abn	7	13	2	18	6	6	7	5	10	8	3	15	10	15	6	19
Kappa		0.63		0.82		0.4		0.38		0.27		0.66		0.35		0.7	
agreement		89%		94%		86%		87%		76%		89%		74%		87%	

Abn = abnormal; Cx = circumflex; LAD = left anterior descending; MCE = myocardial contrast echocardiography; Nor = normal; RCA = right coronary artery; SPECT = single photon emission computed tomography; WM = wall motion.

tively, as having inducible ischemia and 36, 27 and 51 segments, respectively, with fixed abnormalities.

Comparison of MCE, WM and SPECT in detecting angiographically significant CAD. Forty-four patients underwent coronary angiography. The overall sensitivity of MCE, WM and SPECT were all 75%; specificity ranged between 81% and 100% (Table 3). When using either a contrast defect or a WM abnormality as a positive test, the sensitivity was 86% with a specificity of 88%. Analysis limited to patients without previous infarction or revascularization (n = 36) yielded similar results. Myocardial contrast echocardiography identified three patients with CAD who were not detected by WM or SPECT; two of them had one-vessel disease and one had two-vessel disease. Wall motion identified three patients with CAD who were not seen by MCE. Overall, the increase in sensitivity observed with the combination of MCE with WM compared with individual MCE and WM results did not reach statistical significance.

The concordance between MCE and quantitative angiography in the LAD (75%) and CX (68%) territories was similar to other modalities and angiography (LAD: 75% for SPECT, 73% for WM; CX: 64% for SPECT, 66% for WM) but appeared lower for RCA disease (MCE 73% vs. 82% for SPECT and WM; p = NS). When the CX and RCA territories were combined, the agreement of MCE with angiography (75%) was comparable to SPECT (73%) and WM (75%) analysis.

Interobserver and intraobserver variability. The interobserver agreement for MCE images on the basis of segmental analysis and whether the segment was read normal or abnormal was 93% (kappa = 0.64). The intraobserver agreement was 91% (kappa = 0.69).

DISCUSSION

This study demonstrates the feasibility of assessing myocardial perfusion with AII in real time during supine bicycle and post-treadmill exercise echocardiography. A good agreement was observed between MCE and both SPECT and WM. In the subset of patients undergoing angiography, the best accuracy was observed with the combination of MCE and WM information during exercise.

Relation between perfusion by MCE and SPECT. There are only a few studies comparing MCE with intravenous contrast and radionuclide imaging. The first multicenter trial on MCE showed that, under resting conditions, MCE had a poor correlation with SPECT (10). Good correlations, however, were observed when pharmacologic vasodilator stress was used with intermittent imaging (3,4). This study is the first to use AII during exercise in a large nonselect population, comparing results of MCE to SPECT, WM and angiography. The comparative results to SPECT are similar to investigations using intermittent imaging and vasodilator stress and better than those observed in the study of Marwick et al. (10). The difference

Table 3. Comparison of MCE, SPECT, Wall Motion and the Combination of MCE and Wall Motion With Results of Coronary Angiography: Analysis by Patients (n = 44)

	MCE	SPECT	WM	MCE + WM
Sensitivity				
Overall (n = 28)	75%	75%	75%	86%
One vessel (n = 10)	60%	50%	50%	70%
≥Two vessels (n = 18)	83%	89%	89%	94%
Specificity (n = 16)	100%	81%	88%	88%
Accuracy (n = 44)	84%	77%	80%	86%
Kappa	0.67	0.53	0.60	0.71

Abbreviations as in Table 2.

with the latter is most likely due to the setting in which the data were acquired (rest only vs. rest and stress) and the imaging technique. It is in the setting of hyperemia that correlation between contrast intensity and myocardial blood flow is closest (11).

A lower prevalence of defects by MCE and lower agreement with SPECT in the CX and RCA distribution were observed. The reason for these is most likely multifactorial. First, the relatively high degree of background gray scale in the inferior wall may prevent the visual detection of contrast defects. Secondly, because RCA and CX stenoses subtend basal and midsegments, defects in this distribution are usually smaller and difficult to distinguish from attenuation. Thirdly, it is possible that AII still causes some destruction of microbubbles, especially in the near field. If this were a necessary component to visualize contrast defects with AII, then defects in the basal regions, where attenuation would reduce microbubble destruction, would be detected with a lesser frequency. Finally, soft tissue attenuation may have led to a higher incidence of false defects with SPECT in these territories, which was borne out somewhat in the comparison with an independent standard, angiography.

The improved specificity of MCE compared with previous studies has at least two potential explanations. First, lung and rib artifacts that may appear as contrast defects with intermittent imaging can be more easily recognized with real-time imaging and avoided by rapidly repositioning patients or transducer. Secondly, the reviewers had a better understanding of ultrasound attenuation, the basis for the contrast interpretation scheme.

Detection of coronary stenosis using both MCE and WM. This investigation is the first to compare the accuracy of MCE, SPECT and WM to quantitative coronary angiography. Overall, the sensitivity of MCE was comparable to SPECT and WM, with a high specificity. The addition of MCE to WM resulted in a good balance of sensitivity and specificity. Although the enhanced accuracy of detecting CAD with the combination of MCE and WM did not reach statistical significance, this trend is reminiscent of previous observations regarding simultaneous assessment of WM by echocardiography and perfusion with radionuclide imaging (12), further corroborating the present observations where perfusion and WM were obtained with echocardiography alone.

Study limitations. The number of patients who underwent coronary angiography is relatively small. However, concordance with SPECT imaging was similar to the larger cohort of patients. Patients with large infarctions were excluded because the main aim of the study was to assess the ability of AII to detect ischemia. The evaluation of myocardial contrast enhancement was qualitative. Although quantitative analysis during continuous contrast infusion may better determine the severity of coronary stenoses (13), this would be extremely tedious during exercise and would require greater amounts of contrast and additional time to quantify MCE. This was not possible in our study but may be feasible with newer destruction-replenishment techniques that can be performed in real time (14).

The assessment of MCE and WM was performed on the same image, which may cause bias in the interpretation of both modalities. Because MCE interpretation is a relatively new concept, its interpretation may have been influenced by what the independent reviewer thought of WM. However, concordance between MCE and WM was not perfect, and each modality contributed few cases that were missed by the other. Furthermore, it would be inappropriate to examine perfusion with MCE using still frames only, because the purpose of the study was to determine whether contrast enhancement could be determined in real time during exercise stress.

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Reprint requests and correspondence: Dr. William A. Zoghbi, Echocardiography Research, Baylor College of Medicine, 6550 Fannin, SM-677, Houston, Texas 77030. E-mail: wzoghbi@bcm.tmc.edu.

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