A Randomized Cross-Over Study for Evaluation of the Effect of Image Optimization With Contrast on the Diagnostic Accuracy of Dobutamine Echocardiography in Coronary Artery Disease

The OPTIMIZE Trial

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OBJECTIVES The purpose of this study was to evaluate whether the addition of a contrast agent to dobutamine stress echocardiography (DSE) improves its diagnostic accuracy for coronary artery disease (CAD) and to determine the effect of image quality on the diagnostic impact of contrast agent use in this setting.

BACKGROUND Contrast agents can improve endocardial border definition. To date, however, there are no randomized trials that have evaluated the impact of contrast agent use on the accuracy of DSE.

METHODS Patients referred for stress testing with dobutamine echocardiography underwent 2 DSE studies: 1 with and 1 without a contrast agent, at least 4 h apart in a randomized order and within a 24-h period.

RESULTS A total of 101 patients underwent both DSE studies. Similar hemodynamics were achieved during the 2 stress testing sessions. The use of a contrast agent improved the percentage of segments adequately visualized at baseline (from 72 ± 24% to 95 ± 8%) and more so at peak stress (67 ± 28% to 96 ± 7%); both p < 0.001. Interpretation of wall motion with high confidence also increased with contrast agent use from 36% to 74% (p < 0.001). Segment visualization with the use of a contrast agent improved in all views, but was more pronounced in the apical views. In unenhanced DSE, 36% of studies were normal, 51% had ischemia, and 8% were uninterpretable—all of which became interpretable with the use of a contrast agent. When compared with angiography (n = 92; 55 patients with CAD), accurate detection of ischemia was higher with contrast-enhanced studies versus nonenhanced studies (p = 0.02). As endocardial visualization and confidence of interpretation decreased in unenhanced studies, a greater impact of the use of a contrast agent on DSE accuracy was observed (p < 0.01).

CONCLUSIONS During dobutamine stress echocardiography, contrast agent administration improves endocardial visualization at rest and more so during stress, leading to a higher confidence of interpretation and greater accuracy in evaluating CAD. The lesser the endocardial border visualization, the higher the impact of contrast echocardiography on accuracy. (J Am Coll Cardiol Img 2008;1:145–52) © 2008 by the American College of Cardiology Foundation

From the Methodist DeBakey Heart Center, Department of Cardiology and Baylor College of Medicine, Houston, Texas. This study was presented in part at the 55th Annual Scientific Sessions of the American College of Cardiology, March 11–14, 2006, Atlanta, Georgia. This research was sponsored by an investigator-initiated grant from Bristol-Myers Squibb Medical Imaging. Roberto Lang, MD, served as Guest Editor for this paper.

Manuscript received August 28, 2007; revised manuscript received October 2, 2007, accepted October 4, 2007.
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harmacologic stress testing is a versatile method for identifying patients with coronary artery disease (CAD) and determining prognosis (1–6). Although harmonic imaging has improved image quality, interpretation of stress echocardiograms may still be limited in patients with poor acoustic windows (7). With the advent of intravenous contrast agents, further improvement in image quality and endocardial border definition is now possible, which can enhance interpretation of regional and global function (8,9). There is a paucity of data regarding the use of contrast agents in stress echocardiography. Previous investigations have demonstrated that contrast agents improved visualization of dobutamine stress echocardiography (DSE) images and confidence of interpretation (10–13) and resulted in less use of radionuclide testing (14). To date, however, there are no trials that have shown an increased accuracy of contrast-enhanced DSE in the detection of CAD in the same patients. Furthermore, there are currently no data regarding the threshold of when to use contrast agents in this setting, resulting in the wide variability of contrast agent use in stress echocardiography laboratories. Accordingly, the present study was designed to evaluate the impact of an intravenous contrast agent on the diagnostic accuracy of DSE in comparison with the angiographic standard in an unselected population with regard to image quality. The effect of contrast agent enhancement on endocardial visualization, confidence of interpretation, and on the accuracy of DSE in relation to image quality was assessed.

**METHODS**

**Patient population.** Patients with intermediate to high probability of CAD based on clinical parameters and risk factors, referred to the participating echocardiography laboratories for DSE, were evaluated for enrollment into the study (15). The involved sites were those of the Methodist DeBakey Heart Center, the Ben Taub General Hospital, the Veterans Affairs Medical Center, and the Baylor Heart Clinic in Houston, Texas. By design, patients underwent 2 DSE studies, 1 with and 1 without a contrast agent. Patients were not screened for image quality to allow evaluation of the impact of the use of a contrast agent on accuracy in the whole spectrum of image quality. Patients were excluded if they had history of a recent myocardial infarction (within 1 week), left ventricular (LV) systolic dysfunction (ejection fraction <40%), severe valvular regurgitation or stenosis, unstable angina, heart failure (New York Heart Association functional class III or IV), ventricular tachycardia, systolic blood pressure <90 or >180 mm Hg, or if they elected not to participate. The protocol was approved by the Institutional Review Board of Baylor College of Medicine and the affiliated hospitals. Informed written consent was obtained from all patients.

**DSE tests.** The study was a prospective randomized cross-over trial. The patients underwent 2 DSE studies: 1 with and 1 without a contrast agent. The order of the 2 tests was randomized, and they were performed at least 4 h apart within a period of 24 h. Cardiovascular medications were not withheld before the tests, as is routinely accepted. The ultrasound systems used for acquisition of images were a Hewlett Packard Sonos 5500 (Andover, Massachusetts), an Acuson Sequoia (Mountain View, California) or an Advanced Technology Laboratories (Bothel, Washington) system. To control for sonographer variability in image acquisition, the same sonographer performed both noncontrast and contrast agent DSE studies for a particular subject. Harmonic imaging was used for both studies.

**NONCONTRAST DSE.** Baseline images were obtained in the standard parasternal and apical views. An infusion of dobutamine was started at 5 μg/kg/min and increased every 3 min to 10, 20, 30, and 40 μg/kg/min until the target heart rate was achieved. Atropine in 0.25-mg doses up to a total dose of 1 mg was given if the heart rate reached was <85% of the age-predicted maximal heart rate. The dobutamine infusion was stopped if the target heart rate was achieved or for other routine safety measures. Images at baseline, 5 and 10 μg/kg/min, and maximal dobutamine infusion from the parasternal and apical views were digitized online and stored.

**CONTRAST AGENT DSE.** The stress protocol described above for the noncontrast DSE was also followed for the contrast-enhanced DSE. B-mode harmonic imaging along with a mechanical index between 0.3 and 0.5 for best LV opacification with a contrast agent and endocardial border definition was used. The contrast agent (Definity, Bristol-Myers Squibb Medical Imaging, North Billerica,
Massachusetts) was reconstituted with normal saline to form a total volume of 10-ml solution. Boluses of 0.5 to 1 ml of the diluted contrast agent were given at each stage when images were to be digitized (rest, 5 and 10 \( \mu \text{g/kg/min} \), and peak dose), so that all images to be interpreted were enhanced with the contrast agent.

**Echocardiographic analysis. DSE INTERPRETATION.**

The echocardiographic images were interpreted by a single experienced observer (W.A.Z.), blinded to all data, in a random order over a 2-month period. Regional LV wall motion was scored at baseline, low dose, and maximum dose in a 17-segment model (16). A segment was defined as *normal* if it had normal function at rest and improved function during stress, as *ischemic* if the segment developed a new wall motion abnormality or worsening of resting hypokinesia, and as *scar* if there was a wall motion abnormality at rest without development of ischemia. The interpretation scheme of normal, ischemia, and scar was given for the study as a whole, as well as for each of the individual coronary artery territories of the left anterior descending artery (LAD), circumflex artery (CX), and right coronary artery (RCA), and for non-LAD territory (RCA and CX), as overlap in these territories frequently occurs (16). The interpretation was based on the integration of all of the available views for the individual territories.

**VISUALIZATION OF ENDOCARDIUM.**

Visualization of the endocardium was scored for each segment: 1 = adequate or excellent endocardium, 2 = incomplete endocardial border, 3 = epicardial border only, 4 = not visible (correct view, but not seen), 5 = not obtained (out of plane or foreshortened), and 6 = contrast attenuation (in contrast agent studies).

If a segment was visualized from more than 1 view, the best visualization score was used. Any endocardial visualization was the combination of scores 1 and 2; segments with a score >2 were considered nonvisualized.

**CONFIDENCE OF INTERPRETATION.**

Confidence of interpretation of regional wall motion was scored for each segment: 1 = high, 2 = medium, and 3 = low. An overall confidence of interpretation for coronary territories and for global interpretation was also scored (1 = high, 2 = medium, and 3 = low).

**Quantitative coronary angiography.**

Coronary angiography was performed using the Judkins technique within 30 days of study enrollment. Subjects with myocardial infarction or revascularization be-
tween tests were excluded. Quantitative angiography was performed by an independent observer using the CASS (Cardiovascular Angiographic Analysis System) system (PIE Medical Instruments, Maastricht, the Netherlands). Significant coronary artery stenosis was defined as ≥ 70% narrowing of the reference lumen diameter.

Statistical analysis. Continuous variables are expressed as mean ± SD. The adequacy of visualization of myocardial segments is expressed as a percentage of total segments. The percentage of segments visualized in contrast-enhanced studies was compared to noncontrast studies using paired t test. Sensitivity, specificity, and diagnostic accuracy were determined in interpretable studies using standard definitions for patients (any disease present) and by individual respective coronary territory. Concordance of agreement with angiography (accuracy) between contrast-enhanced and unenhanced DSE studies was calculated using the McNemar test. A general estimating equation (GEE) repeated measures analysis was performed to check for order effects of the test (contrast-agent first group and contrast-agent second group). Statistical significance was set at a p value < 0.05.

RESULTS

Patient population. One hundred eight patients were recruited (Table 1); 91 had a history of chest pain. The baseline ejection fraction was 56.2 ± 6.8%. A total of 101 patients completed the 2 DSE studies, and 92 had a cardiac catheterization, 74% of which were performed after the echo studies: 18 patients (19%) had 1-vessel, 22 (24%) had 2-vessel, and 12 (13%) had 3-vessel, or left main, disease. A total of 87 patients completed all the studies.

Hemodynamics during DSE. Hemodynamics were comparable between the 2 tests (Table 2). Stress-induced ischemia on the electrocardiogram was similar in both DSE studies (23% in each). Adverse events were reported in 10% of either group, the majority of which were chest pain (6% in the contrast-agent group and 4% in the noncontrast group). There were no serious adverse events.

Visualization of endocardium and confidence of interpretation. The contrast agent increased endocardial visualization at rest and particularly during maximal stress. All contrast-enhanced studies were interpretable, whereas 8 (8%) of unenhanced studies were uninterpretable. The percentage of segments with excellent or adequate visualization (score 1) increased with the use of a contrast agent at rest and more so at maximal stress (Fig. 1). The percentage of segments with any endocardial visualization (score 1 or 2) also increased with the use of a contrast agent at rest from 92 ± 11% to 98 ± 4% and at maximal stress from 89 ± 16% to 99 ± 4%.

The GEE repeated measures analysis did not reveal any effect of the order of the test on the results observed. Figure 2 summarizes the impact of contrast agent use on endocardial visualization (score 1) at peak stress from the different views. Whereas the impact was observed in all views, it was more pronounced in the apical views. Similar observations were noted for any endocardial visualization (score 1 or 2): the percentage of segments increased...
from a range of 85% to 91% without a contrast agent, to 96% to 100% with a contrast agent. Contrast agent administration improved the overall confidence of interpretation of the studies (Fig. 1, right panel). The change in confidence of interpretation was better with the use of a contrast agent in 53% of patients, the same in 40%, and worse in 7% of patients, the latter mostly because of attenuation. Examples of the effect of the use of a contrast agent on segment visualization and study interpretation are shown in Figures 3 and 4.

Detection of CAD in enhanced and nonenhanced DSE studies in the total population. In the unenhanced studies, the overall distribution of results was normal in 36%, ischemia in 50%, scar in 6%, and uninterpretable in 8%. This distribution was different in contrast-enhanced studies: normal in 40%, ischemia in 55%, and scar in 5% (p = 0.01). The

![Figure 3. Example of the Effect of Contrast Agent Use on DSE in a Patient With Suboptimal Endocardial Visualization](image)

Quad-screens of end-systolic frames from the 4-chamber view of noncontrast dobutamine stress echocardiographic images (left) (Online Video 1) and contrast-enhanced images (right) (Online Video 2) are shown. Noncontrast images had significant endocardial dropout and identified an apical fixed wall motion abnormality. Contrast agent enhancement clearly delineated the endocardial segments and allowed the identification of ischemia in the lateral wall and apex (arrows) as well as dilation of the ventricle at end-systole at maximal stress. DSE = dobutamine stress echocardiography.

![Figure 4. Example of the Effect of Contrast Agent Use on DSE in a Patient With Excellent Endocardial Visualization](image)

Quad-screens of end-systolic frames of noncontrast (Online Video 3) and contrast-enhanced (Online Video 4) dobutamine stress echocardiographic (DSE) images from the short axis. Noncontrast images are of excellent quality. Contrast agent administration decreased the image quality and endocardial border definition in certain regions. Still, ischemia was observed in the inferoposterior wall (arrows) in both DSE studies.

![Figure 5. Impact of Contrast Agent Use on Accuracy of DSE in Relation to Confidence of Interpretation in Unenhanced DSE Studies](image)

There was no impact of contrast agent use on the agreement of dobutamine stress echocardiography (DSE) with angiography (accuracy) if the confidence of interpretation was high in unenhanced studies. However, a significant impact was seen when the confidence of interpretation was low, with an intermediate effect in studies with medium confidence.
overall concordance of agreement on the presence or absence of CAD with coronary angiography was 57% for unenhanced studies and increased to 68% with contrast enhancement ($p = 0.06$). The sensitivity and specificity for CAD in unenhanced DSE studies that could be interpreted were 75% and 51%, respectively. With the use of a contrast agent, sensitivity and specificity increased to 80% and 55%, respectively, but did not reach statistical significance. Accurate detection of ischemia versus no ischemia was higher with the use of a contrast agent (66% vs. 53%) ($p = 0.02$). Agreement for detection of ischemia versus no ischemia was similar for LAD distribution between unenhanced and enhanced DSE (57% vs. 53%, respectively; $p = 0.3$) but was significantly higher for CX (62% vs. 49%; $p = 0.0009$), RCA (63% vs. 54%; $p = 0.088$), and CX or RCA territories (64% vs. 52%; $p = 0.016$).

Relation of segment visualization and confidence of interpretation to impact of contrast agent enhancement on DSE accuracy. The agreement of detection of CAD with angiography was compared depending on confidence of interpretation in unenhanced studies (Fig. 5). In studies interpreted with high confidence, there was no impact attributable to contrast agent use. A significant impact of contrast agent use was seen in studies with low confidence (68% vs. 36%; $p = 0.01$), with a similar trend starting in the medium confidence group. In the high confidence group, sensitivity and specificity for detection of CAD were similar in contrast-enhanced versus nonenhanced studies. In low and medium confidence interpretation, there was a trend for improvement in both sensitivity and specificity (Fig. 6).

Lower confidence of interpretation in unenhanced studies was associated with a lower number of visualized segments. The number of segments with any endocardial visualization (score 1 and 2) was 16.8 ± 1.0, 16.0 ± 1.2, and 11.8 ± 2.9 segments in the groups with high, medium, and low confidence of interpretation, respectively. The effect of worsening extent of nonvisualized segments on accuracy of interpretation and the impact of the use of a contrast agent in this setting were evaluated (Fig. 7). There was no impact of contrast agent use if all 17 segments were visualized ($p = 0.36$). On the other hand, a significant impact of contrast agent enhancement was seen in patients with >2 nonvisualized segments (59% vs. 28%; $p = 0.005$), with a similar trend in the intermediate group.

**Discussion**

The present study demonstrates the impact of contrast agent enhancement on the accuracy of stress echocardiography in the diagnosis of CAD and in the same population. The worse the extent of endocardial visualization—and hence confidence of interpretation—the higher the impact of contrast agent use on the accuracy of DSE.

**Impact of contrast enhancement in stress echocardiography.** Although overall good sensitivity and specificity are reported for DSE in detecting CAD (1), multiple factors may produce suboptimal image quality that can result in nondiagnostic studies in up to 33% of patients (14,17). In the present study, the
administration of a contrast agent during DSE improved endocardial border definition at rest and during stress. This was observed in all tomographic views, particularly from the apex, and led to an improvement in the confidence of interpretation. In this regard, the current results are consistent with previous data using a different contrast agent (12,13). However, to our knowledge, the present study is the first to show, in the same patients undergoing DSE with and without the use of a contrast agent, that the improvement in image quality and confidence of interpretation leads to an improvement in the diagnostic accuracy of DSE as compared to coronary angiography.

The impact of contrast agent use was related to the extent of segment visualization and confidence of interpretation of unenhanced studies. As visibility and confidence of interpretation decreased, a greater impact of contrast agent use on improving accuracy was observed. In studies with high confidence and where all segments were visualized at rest, there was no impact of contrast agent use as expected, with a possibility of degradation of image quality. The impact of contrast agent use was highest in studies with poor visualization, interpreted with low confidence, and intermediate in the moderate confidence group. The enhancement in overall accuracy was a combination of improvement in both sensitivity and specificity of detecting wall motion abnormalities. Interestingly, the impact was more significant in both the CX and RCA territories compared with the LAD territory. This may be due to the extensiveness of the LAD territory in general; consequently, any wall motion abnormality translates into detection of disease and is easier because the total or partial LAD territory can be assessed from all views. Another possible explanation is the lesser definition and greater heterogeneity of wall motion in the cardiac base, crucial for detection of non-LAD disease (18). No significant side effects were attributed to the use of a contrast agent, similar to previous investigations of safety of contrast agent use during stress (19).

In the present study, we evaluated 2 parameters of the technical quality of DSE: a confidence score—a subjective assessment of the ability of the reader to render an interpretation—and the number of segments visualized—a more objective, semi-quantitative parameter. In patients where all segments were visualized, there was no impact of contrast agent use on accuracy. However, with worsening endocardial visualization, an increasing impact of contrast agent use was seen. In patients with more than 2 nonvisualized segments or low confidence of interpretation, the impact was very significant: the rate of agreement with angiography improved with either definition by 31% and 32%, respectively. This group constituted 25% to 28% of the patient population, which was not selected based on image quality. In the intermediate visualization group (1 to 2 nonvisualized segments or medium confidence, constituting another 21% to 31% of the population), accuracy improved less significantly by 5% to 8%. A threshold of 2 or more nonvisualized segments is recommended for the use of a contrast agent in the evaluation of regional and global ventricular function by the American Society of Echocardiography based on results from rest studies (20). The present investigation extends these observations to stress echocardiography and demonstrates the importance of the use of a contrast agent for optimal DSE accuracy depending on image quality at rest.

Study limitations. Patients with severe ventricular dysfunction were excluded because the diagnosis of CAD is not an issue, whereas residual viability is. The specificity of DSE for CAD is overall lower than earlier published studies. Post-referral verification bias, when coronary angiography is used as the standard, may have contributed to this observation (21). Furthermore, microvascular disease may be present in some cases of ischemia with nonsignificant epicardial CAD because a large number of patients were diabetic. Anti-ischemic medications before DSE were not withdrawn as is usually performed in most laboratories and could have affected adversely the sensitivity of DSE. The above considerations, however, do not invalidate the comparative effect of contrast agent use on accuracy of DSE.

The contrast agent was used at rest and during every stage of stress for uniformity of image quality and ease of interpretation. The contrast agent may be used to salvage later stages of stress only. Although feasible, the decision may be rushed and the interpreter is left to evaluate a mixture of contrast and noncontrast images. A strategy of decision at the beginning of the study, in our experience, is more prudent, still leaving the option of use of a contrast agent in the later stages of stress in a minority of cases.

The contrast agent was not used for myocardial perfusion. Although integration of wall motion and perfusion can be performed when the mechanical index is lowered below levels used in the present study, we wanted to address the question of wall
motion detection, optimize enhancement of endocardial border definition, and not sacrifice frame rate during DSE.

CONCLUSIONS

During dobutamine stress echocardiography, the contrast agent enhances endocardial border definition at rest and more so during stress, leading to a higher confidence of interpretation and accuracy in evaluating CAD. The lesser the endocardial border definition, the higher the impact of contrast agent use on accuracy.

Acknowledgment

The authors acknowledge the additional input of George DeMuth, President, Stat-Tech Services, in the statistical analysis of the data.

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