Incremental Benefit of Myocardial Contrast to Combined Dipyridamole-Exercise Stress Echocardiography for the Assessment of Coronary Artery Disease

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Background—Although assessment of myocardial perfusion by myocardial contrast echocardiography (MCE) is feasible, its incremental benefit to stress echocardiography is not well defined. We examined whether the addition of MCE to combined dipyridamole-exercise echocardiography (DExE) provides incremental benefit for evaluation of coronary artery disease (CAD).

Methods and Results—MCE was combined with DExE in 85 patients, 70 of whom were undergoing quantitative coronary angiography and 15 patients with a low probability of CAD. MCE was acquired by low-mechanical-index imaging in 3 apical views after acquisition of standard resting and poststress images. Wall motion, left ventricular opacification, and MCE components of the study were interpreted sequentially, blinded to other data. Significant (>50%) stenoses were present in 43 patients and involved 69 coronary territories. The addition of qualitative MCE improved sensitivity for the detection of CAD (91% versus 74%, \( P = 0.02 \)) and accurate recognition of disease extent (87% versus 65% of territories, \( P = 0.003 \)), with a nonsignificant reduction in specificity.

Conclusions—The addition of low-mechanical-index MCE to standard imaging during DExE improves detection of CAD and enables a more accurate determination of disease extent. (Circulation. 2004;110:1108-1113.)

Key Words: myocardium • echocardiography • exercise • contrast media • coronary disease

Exercise echocardiography (ExE) is an established clinical tool with a high sensitivity and specificity for the diagnosis of coronary artery disease (CAD). Nevertheless, ExE has a number of limitations, including its dependence on the provocation of wall-motion abnormalities (WMAs) for the diagnosis of ischemia, reliance on qualitative wall-motion scoring, and underestimation of the extent of CAD. Radionuclide perfusion imaging appears to be more accurate for determining the extent of CAD, probably because hypoperfusion occurs before WMAs are evident in the ischemic cascade.

Myocardial contrast echocardiography (MCE) enables assessment of myocardial perfusion by ultrasound. Vasodilator stress MCE, by high-mechanical-index (MI) imaging, has shown good concordance with radionuclide perfusion for assessment of CAD. Low-MI imaging is less technically demanding than triggered imaging and enables simultaneous assessment of myocardial perfusion and wall motion in real time. For both high- and low-MI MCE imaging, vasodilators are the most feasible stressors, but these agents do not reliably provoke inducible WMAs. Conversely, exercise is the preferred stress in active patients but has proven technically challenging for MCE because of immediate postexercise hyperventilation, cardiac translational motion, and the relatively short duration of hyperemia. We therefore sought whether combined dipyridamole (to induce prolonged hyperemia) and exercise stress (to induce ischemia) would facilitate the combination of real-time MCE with ExE. The present study examined the feasibility of this approach and the incremental benefit of MCE for the diagnosis and evaluation of the extent of CAD, as defined by quantitative coronary angiography.

Methods

Patient Population

We prospectively studied 85 unselected patients in 2 groups: 70 with suspected CAD who were undergoing diagnostic coronary angiography and 15 with a low probability for CAD by clinical criteria. We excluded patients with acute coronary syndromes, previous surgical or percutaneous revascularization, and significant valvular regurgitation; those taking oral dipyridamole; and those with a contraindication to intravenous dipyridamole or the contrast agent. All other eligible patients were studied, irrespective of age, sex, body weight, or quality of baseline images; recruitment of patients was based only on the availability of the investigator and the echocardiography machine. Patients gave informed consent for the study, which was approved by the Ethics Committee of the Princess Alexandra Hospital.

Clinical Evaluation

All patients were assessed clinically, including evaluation of cardiac risk factor profile, medication usage, height, and weight.
Exercise-Dipyridamole Stress

Patients were instructed to avoid methylxanthine derivatives for the day before the study. An intravenous line was secured. All patients underwent infusion of dipyridamole (0.56 mg/kg over 4 minutes), followed immediately by symptom-limited treadmill exercise with a standard Bruce protocol and usual end points. Exercise capacity, symptom status, and ECG changes with stress were noted in all patients and were used to calculate the Duke treadmill score, as previously described. Patients with scores above +5 and below −10 were considered as being at low and high risk, respectively.

Imaging Protocol

Standard, resting, grayscale harmonic images were taken in the parasternal long- and short-axis views and the apical 4-, 2-, and 3-chamber views with a commercially available system with a broadband (S3) transducer (Sonos 7500, Philips Ultrasound). Perfluorinated microbubbles with a lipid shell (Definity, Bristol Meyers Squibb Imaging) were prepared in the usual fashion and administered by a slow, continuous, intravenous injection to maintain adequate myocardial perfusion with attenuation at the mitral valve level. Low-power (MI 0.1 to 0.2), real-time images were acquired in the 3 apical views by power modulation imaging on the same equipment. After a high-MI destruction pulse sequence (MI 1.2), images were acquired at 20 frames per second for 10 seconds and stored on a magneto-optical disk. Immediately after completion of exercise, standard, harmonic, grayscale images were acquired rapidly (usually within 60 seconds) in the same 5 views as at rest. Contrast material was then administered in the same fashion, and stress contrast images were obtained again in the 3 apical views (Figure 1).

Qualitative Analysis

All studies were reviewed by 2 observers blinded to clinical, ECG, and angiographic data. Studies were graded as technically challenging if the endocardial border was not visualized in ≥2 segments in the apical 4- or 2-chamber view. To assess the incremental benefit of contrast imaging, each patient’s studies were reviewed sequentially, with the results for standard (noncontrast) imaging, LV opacification (LVO), and myocardial perfusion being recorded independently and proceeding to the next step. Wall motion was assessed qualitatively by standard interpretive criteria. Segments were ascribed to coronary territories as previously described (Figure 2). A diagnosis of the presence or absence of CAD, inducible ischemia, and the involved coronary territory were recorded from the standard grayscale images (standard). This assessment was repeated with the LVO images at rest and stress, and a record was made of additional resting or stress-induced abnormalities that were not apparent on grayscale images (standard+LVO).

Myocardial perfusion was then assessed by comparing rest and poststress apical images by using the rate of microbubble replenishment principle. Resting perfusion was assessed for 5 or 6 cycles after completion of the flash. On poststress images, defects (including subendocardial defects) present at 2 to 3 end-systolic frames after flash (Figure 3) that were not present at rest were considered significant. Segments were identified as uninterpretable in the presence of rib shadowing, attenuation artifact, or insufficient myocardial contrast in any segment; the presence of the same pattern on the resting images was used to minimize the chance of under-scoring a true perfusion defect. For the overall assessment, patients (standard+LVO+MCE) were judged to have CAD if there were demonstrable resting or inducible WMAs evident on the grayscale or LVO images or when inducible perfusion abnormalities were noted. These overall results were compared with those from the pure grayscale assessment.

Coronary Angiography

Selective coronary angiography was performed in a standard fashion. Quantitative coronary angiography (Philips Medical Systems) was performed by an examiner blinded to all other data. Significant CAD was defined as stenoses ≥50% and minimal luminal diameters (MLDs) <1.1 mm.

Statistical Analysis

Data are presented as mean±SD. Categorical variables were compared by the χ² test for unpaired data and by McNemar’s test for paired data. Continuous variables were compared with Student’s t test. Receiver-operating-characteristic curves were generated to examine the relation between false-negative and false-positive rates for predicting significant angiographic stenoses at various thresholds. All analyses were performed with standard software (SPSS version 10, SPSS, Inc).

Results

Clinical, Exercise, and Angiographic Characteristics

The clinical characteristics and exercise performance of the study groups are summarized in Table 1. Risk factors for CAD were highly prevalent in the patients undergoing angiography. None of the patients developed complications with the combined dipyridamole-exercise stress or with the use of intravenous contrast material.

In the 70 patients who underwent coronary angiography, a stenosis severity ≥50% diameter of at least 1 major vessel was present in 43 patients and involved 69 coronary territories. Multivessel CAD was documented in 19 patients. There were 27 patients without obstructive CAD at angiography and 15 low risk (normal) patients. With an MLD of <1.1 mm used to define CAD, there were 37 patients with CAD that involved 60 territories and 33 patients with no CAD.

Results of Standard ExE

The results of standard-imaging wall-motion analysis, LVO, and real-time MCE are compared with the percent stenosis.

Figure 1. Sequence of imaging, contrast, and stress, with anticipated duration of hyperemia.

Figure 2. Cardiac segmentation and coronary territory. LAD indicates left anterior descending coronary artery; LCx, left circumflex artery; and RCA, right coronary artery.
Feasibility and Accuracy of Contrast Stress Echocardiography Assessment

Interpretation of LVO images was feasible in all patients. Technical difficulties precluded perfusion assessment in 3 patients; thus, it was feasible in 82 patients (96%). In these patients, attenuation or artifact precluded assessment of ≥2 segments within a coronary territory in 17 territories, 8 in the territory of the right coronary artery and 9 in that of the left circumflex artery; the left anterior descending coronary artery territory could be assessed in all patients. Thus, interpretation of myocardial perfusion was feasible in 229 of 246 coronary territories (93%).

Of the 14 patients with resting WMAs, 11 had resting perfusion defects. The remaining patients with perfusion defects within a coronary territory and normal wall motion were considered to have an artifact at rest in that territory. Eleven patients with CAD on angiography had a WMA at rest; 9 of these patients had resting perfusion defects in the corresponding territory. Three patients with no significant CAD had a WMA at rest, and 2 of these had resting perfusion defects in the corresponding territory.

The use of contrast echocardiography provided significant incremental benefit to standard ExE, increasing the sensitivity for diagnosis of CAD, as defined by >50% stenosis, to 91% (P=0.02, Table 2). Of the 11 false-negative studies by standard ExE, 5 were identified as abnormal by LVO and an additional 2, by perfusion analysis. This benefit was evident both in patients who achieved a target heart rate (91% sensitive for CAD) and in those who achieved <85% of the maximum predicted heart rate (91% sensitive). When technically challenging studies were excluded, the sensitivity was still 90% (P=0.04).

These results occurred at the expense of a nonsignificant reduction in specificity for CAD to 70% (P=0.25). When basal inferior perfusion defects in patients with technically difficult resting studies and apparently normal wall motion were ignored, then specificity improved to 78% (P=1.0) without losing the increment in overall test sensitivity or recognition of disease extent (see next paragraph). In the low-probability group, a similar nonsignificant reduction in normalcy was observed (66%, P=0.13). Avoidance of identifying inferior defects (as mentioned earlier) would increase this to 73%. When an MLD <1.1 mm was used to define CAD, the results of MCE were similar, with a sensitivity of 97% (P=0.04) and nonsignificantly reduced specificity of 64% (P=0.13, Table 3).

Assessment of Extent of CAD

Of the 69 territories subtended by a >50% stenosis, 45 (65%) were identified by 2D imaging alone. The use of MCE for LVO significantly improved the detection to 53 territories (77%, P=0.01), whereas additional use of MCE correctly
identified 60 territories (87%, P = 0.003). In the 55 territories subtended by significant stenosis but with no resting WMA, the ability to identify ischemia was also significantly increased by MCE (82% versus 60%, P = 0.002).

In the 19 patients (45 territories) with multivessel disease, the use of MCE led to a nonsignificant increment in sensitivity (95% versus 84%, P = 0.47). However, the use of MCE permitted the recognition of more patients as having multivessel disease (79% versus 58%, P = 0.09), and accurate recognition of the extent of disease was significantly improved, with 40 segments subtended by a stenosed vessel accurately recognized with MCE, compared with 30 identified by 2D imaging alone (88% versus 66%, P = 0.01). Addition of MCE also enabled the diagnosis of CAD in more patients with single-vessel disease, although this improvement was not statistically significant (88% versus 67%, P = 0.09).

When an MLD < 1.1 mm was used to define an abnormal territory, MCE led to a similar improvement in the recognition of CAD extent. Of the 60 territories subtended by an artery with an MLD < 1.1 mm, 52 (87%) were recognized after contrast echo, compared with 40 (65%) by standard imaging (P = 0.002).

**Discussion**

The findings of this study are that combined dipyridamole-exercise stress is feasible for combining MCE with ExE, that LVO enhances the sensitivity of ExE with only a minor additional increment from MCE, and that qualitative MCE adds incremental benefit to the assessment of the extent of CAD.

**Dipyridamole-Exercise Stress**

Despite the favorable results of vasodilator stress MCE, several considerations have limited the attractiveness of this approach as a standard clinical technique. First, identification of stress-induced WMAs is a well-accepted and specific marker of ischemia, and vasodilators appear to be less sensitive than dobutamine or exercise stress for inducing WMAs during stress echocardiography. This difference is likely related to the dependence of WMAs on increased myocardial oxygen demand rather than “coronary steal” or reduced aortic pressure. Second, the selection of vasodilator stress echocardiography in patients who would otherwise be able to exercise necessarily relinquishes valuable information relating to exercise capacity, correlation of symptoms with exercise, and ST-segment changes. However, there is a paucity of data regarding the combination of MCE with exercise stress. Although qualitative assessment of perfusion and wall motion from low-MI images immediately after exercise has been shown to have a good correlation with single photon emission CT perfusion defects, the combination of MCE with ExE is technically challenging because of

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**TABLE 2. Evaluation of Standard ExE, With LVO in Combination With MCE**

<table>
<thead>
<tr>
<th>Patients Positive for CAD by</th>
<th>CAD (Sensitivity)</th>
<th>CAD Extent</th>
<th>No CAD (Specificity)</th>
<th>Normalcy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stenosis ≥50% to define CAD, No. of territories</td>
<td>43</td>
<td>69</td>
<td>27</td>
<td>15</td>
</tr>
<tr>
<td>Standard ExE</td>
<td>32 (74)</td>
<td>45</td>
<td>5 (81)</td>
<td>1</td>
</tr>
<tr>
<td>Standard ExE + LVO</td>
<td>37 (86)</td>
<td>53</td>
<td>5 (81)</td>
<td>1</td>
</tr>
<tr>
<td>P (ExE + LVO vs standard ExE)</td>
<td>0.07</td>
<td>0.01</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Standard ExE + LVO + MCE</td>
<td>39 (91)</td>
<td>60</td>
<td>8 (70)</td>
<td>5</td>
</tr>
<tr>
<td>P (ExE + LVO + MCE vs standard ExE)</td>
<td>0.02</td>
<td>0.003</td>
<td>0.25</td>
<td>0.13</td>
</tr>
<tr>
<td>MLD &lt; 1.1 mm to define CAD, No. of territories</td>
<td>37</td>
<td>60</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td>Standard ExE</td>
<td>30 (81)</td>
<td>40</td>
<td>8 (76)</td>
<td>1</td>
</tr>
<tr>
<td>Standard ExE + LVO</td>
<td>35 (95)</td>
<td>45</td>
<td>8 (76)</td>
<td>1</td>
</tr>
<tr>
<td>P (ExE + LVO vs standard ExE)</td>
<td>0.07</td>
<td>0.07</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Standard ExE + LVO + MCE</td>
<td>36 (97)</td>
<td>52</td>
<td>12 (64)</td>
<td>5</td>
</tr>
<tr>
<td>P (ExE + LVO + MCE vs standard ExE)</td>
<td>0.04</td>
<td>0.002</td>
<td>0.13</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Values are n (%) unless otherwise noted. Abbreviations are as defined in text.

**TABLE 3. MCE Studies With Patients Undergoing Coronary Angiography**

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. of Patients</th>
<th>Angiography, n (%)</th>
<th>CAD, n</th>
<th>No CAD, n</th>
<th>Sensitivity of MCE, %</th>
<th>Specificity of MCE, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cwajg et al 23</td>
<td>45</td>
<td>45 (100)</td>
<td>32</td>
<td>13</td>
<td>87</td>
<td>...</td>
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<tr>
<td>Shimoni et al 20</td>
<td>101</td>
<td>44 (44)</td>
<td>28</td>
<td>16</td>
<td>75</td>
<td>100</td>
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<tr>
<td>Heinle et al 6</td>
<td>123</td>
<td>15 (12)</td>
<td>12</td>
<td>3</td>
<td>75</td>
<td>67</td>
</tr>
<tr>
<td>Wei et al 12</td>
<td>54</td>
<td>15 (28)</td>
<td>15</td>
<td>...</td>
<td>100</td>
<td>...</td>
</tr>
<tr>
<td>Rocchi et al 24</td>
<td>25</td>
<td>12 (48)</td>
<td>12</td>
<td>...</td>
<td>89</td>
<td>...</td>
</tr>
<tr>
<td>Olszowska et al 25</td>
<td>44</td>
<td>44 (100)</td>
<td>44</td>
<td>...</td>
<td>97</td>
<td>...</td>
</tr>
</tbody>
</table>

Abbreviations are as defined in text.
Immediate postexercise hyperventilation, cardiac translational motion, and the relatively short duration of hyperemia.

The use of a combined dipyridamole-exercise protocol in this study was designed to enable MCE to be combined more feasibly with ExE. This combination has been used for nuclear perfusion imaging but has not been reported for contrast echocardiography. The underlying rationale was to use exercise to induce WMAs, ST-segment changes, and exercise capacity while dipyridamole was used to induce maximal hyperemia (even in individuals undergoing submaximal stress). Dipyridamole is well suited to this protocol because it induces prolonged hyperemia, with peak hyperemia demonstrated as long as 12 minutes after commencing administration. This permitted MCE acquisition after conclusion of the poststress images, with optimization of image quality after resolution of hyperventilation. The protocol thus enabled postexercise wall-motion assessment to be obtained with standard harmonic grayscale images, thus avoiding the lower frame rate of real-time power modulation images, which may compromise wall-motion assessment. Subsequent real-time LVO images were then considered additive to the diagnosis of ischemia and CAD. The only circumstance under which hyperemia could not be expected to extend beyond standard imaging time would be in patients exercising for >10 to 12 minutes, in which circumstance the likelihood of significant coronary disease or submaximal heart rate would be quite low.

### Incremental Benefit for Diagnosis of CAD

Most validation studies of MCE have compared perfusion analysis with radionuclide perfusion imaging, and good concordance has been demonstrated. However, the presence and extent of CAD at coronary angiography have traditionally been used as the reference standard for the assessment of CAD. Limited comparative data have been obtained between MCE and angiography (Table 3). In 45 patients undergoing mainly dobutamine stress echocardiography, Cwaig et al showed a greater sensitivity for real-time, contrast-enhanced than for standard stress echocardiography (87% versus 56%) and a better recognition of disease extent by MCE (85% versus 39%). These results were surprisingly unfavorable for standard imaging, perhaps reflecting the limitations of lower-frame-rate, real-time imaging. Moreover, no specificity data were available from that study. Shimoni et al performed real-time MCE during ExE in 100 patients; in 44 who proceeded to angiography, the sensitivity and specificity of wall-motion analysis and MCE were not significantly different.

In our study, the largest involving quantitative coronary angiography, addition of contrast to standard ExE significantly enhanced the sensitivity of the test for detection of CAD. Our study differs from previous work in 3 important respects. First, angiography was performed prospectively, irrespective of the results of the stress echocardiogram, thereby reducing concerns about posttest referral bias, which may occur when angiography is contingent on the results of the stress echocardiogram. Moreover, to further examine the bias of studying patients undergoing angiography, we studied a normal group of 15 patients at low clinical risk for CAD who were shown to have similar MCE findings. Second, we sought a more typical diagnostic population by excluding patients with previous revascularization and including only 8% of patients with ECG Q waves. Third, we sought to rigorously examine the incremental benefit by separate analysis of the LVO and MCE components of the study. Some of this increment in sensitivity derived from improvement by LVO. Nonetheless, an important contribution of MCE was the detection of perfusion abnormalities in patients having normal wall motion at submaximal heart rate. This limitation of standard ExE reflects the large number of patients who failed to achieve an 85% maximum predicted heart rate (71% of those studied were on β-blocker therapy); however, this is not an unusual clinical finding, particularly in elderly patients.

The use of MCE in combination with ExE is associated with a small reduction in specificity. Interestingly, the false-positive rate in the normal group was analogous to those with normal coronary arteries, implying a problem with image interpretation rather than unidentified pathophysiology, such as small-vessel disease. Indeed, most of the false-positive results were derived from basal segments in the posterior circulation, and systematic avoidance of identifying defects in the absence of a WMA in these sites would reduce false-positives without reducing the incremental benefit of MCE. Surprisingly, exclusion of patients with technically challenging baseline studies did not significantly alter the overall sensitivity or specificity of the test.

### Incremental Benefit for Assessing the Extent of CAD

The main incremental information supplied by MCE pertains to improving the accurate identification of the extent of CAD. Overall, 65% of territories subtended by a significant stenosis were accurately identified by standard ExE, a figure consistent with previous stress echocardiography studies and known limitations of the technique. This value was significantly increased to 87% by the use of MCE and reflects abnormal perfusion preceeding abnormal function in the ischemic cascade. The clinical significance of this finding relates to the association of perfusion defect extent with mortality; more accurate knowledge of disease extent may facilitate risk stratification after ExE.

### Limitations

The combination of contrast imaging with ExE is widely but not universally practiced. Reasons for failing to adopt contrast for LVO include the requirement to insert intravenous access and the additional cost of the contrast agent. Although the combination of MCE with ExE also carries the potential cost of physician time for additional interpretation, these negative features are balanced by the fact that 33% of patients with CAD derived benefit from the addition of contrast to their study. In half of these patients, the diagnosis of CAD was made only by the addition of contrast material, and in the remainder, use of MCE enabled the accurate recognition of more extensive CAD.

The limitations of angiographic comparisons in relation to the discrepancy between stenosis severity and functional
significance and referral issues are pertinent to this study. Use of angiographic data alone ignores the previous occurrence of coronary events in patients without significant stenoses. Resting WMAs or perfusion defects in these patients are classified as false-positives.

Conclusions
The combination of exercise and dipyridamole stress increases the feasibility of combining ExE with MCE. The use of MCE provides incremental information to ExE alone, with regard to both the diagnosis and evaluation of CAD.

Acknowledgments
This study was supported in part by a grant-in-aid from the Princess Alexandra Hospital Foundation, Brisbane, Australia.

References
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Circulation. 2004;110:1108-1113; originally published online August 23, 2004; doi: 10.1161/01.CIR.0000139905.47128.9F
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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