Myocardial Contrast Echocardiography for the Detection of Coronary Artery Stenosis

A Prospective Multicenter Study in Comparison With Single-Photon Emission Computed Tomography

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The assessment of coronary artery disease (CAD) by single-photon emission computed tomography (SPECT) is well established (1). Myocardial contrast echocardiography (MCE) is a new technique that allows assessment of myocardial perfusion with the use of intravenous contrast agents at the bedside, in real-time, with rapid acquisition of images (2,3). We hypothesized that the efficacy of myocardial perfusion with MCE is comparable to SPECT when investigating patients with known or suspected CAD.

METHODS

Patient selection. A prospective, multicenter study investigating patients scheduled for coronary arteriography for known or suspected CAD was undertaken. Written informed consent was obtained from all patients. The study had received approval from local ethics and radiation protection committees.

Study design. Rest and vasodilator stress SPECT were performed on separate days. Myocardial contrast echocardiography studies were performed concurrently with stress SPECT. Dipyridamole was infused at 0.56 mg/kg for four min and, if tolerated, a further 0.28 mg/kg was infused for two min. After two min, radiotracer injection was followed by contrast administration, after which, stress MCE images were obtained. Patients underwent coronary arteriography within four weeks of noninvasive imaging. All images were analyzed by observers independently of clinical or other imaging data.

Contrast administration. The contrast agent, Sonazoid (Amersham Health, Amersham, United Kingdom), is a lipid-stabilized suspension of perfluorobutane microbubbles with a median diameter of 2.4 to 3.5 μm and was administered intravenously as a continuous infusion. Patients randomly received an infusion of Sonazoid at one of four infusion rates: 0.003, 0.010, 0.015, or 0.030 μl MB/kg of body weight/min.

Imaging protocols. Myocardial contrast echocardiography was performed in the apical four-, three-, and two-chamber views with pulse inversion (HDI 5000, Philips, Eindhoven, the Netherlands) technique. Images were acquired with a mechanical index (MI) of 0.5, preceded by high-intensity pulses (MI 1.0) synchronized to end-systole to facilitate...
myocardial bubble destruction followed by acquisition of 15 end-systolic frames. Single-photon emission computed tomo- 
graphy was performed 60 to 90 min after tracer injection 
of 600 MBq of 99mTc-sestamibi (Bristol Myers-Squibb, 
New York, New York) with the standard technique.

**Coronary angiography.** Selective coronary angiography was 
performed with the Judkins approach. Coronary artery disease 
was defined as a ≥50% luminal diameter narrowing of one 
or more major epicardial arteries or their major branches. The 
presence of CAD was determined in the left anterior descending 
(anterior) circulation and the right coronary artery (RCA) 
and/or left circumflex (LCx) (posterior) circulation. Multives-
sel disease (MVD) was determined to be present when both 
anterior and posterior circulations had a 50% or greater luminal 
diameter stenosis.

**Image assessment.** A 16-segment left ventricular model was 
used together with a three-point semi-quantitative scale for 
both MCE and SPECT. Any myocardial segment with 
normal contrast replenishment at rest that did not fill in 
one to two seconds after dipyridamole was considered to 
demonstrate a reversible MCE perfusion defect (4). On 
SPECT, if the degree of tracer uptake was reduced at stress 
compared with that seen at rest, a reversible defect was 
diagnosed. A perfusion defect at rest that remained un-
changed at stress was considered to be a fixed defect. When 
artifacts were seen in ≥1 myocardial segment(s) in a 
vascular territory where the remaining segments were con-
sidered normal, the region was considered normal. The 
presence of a defect in ≥1 myocardial segment(s) was taken 
to indicate the presence of CAD. Myocardial contrast 
echocardiography was analyzed blinded to the wall thick-
ening data.

**Statistical analysis.** Continuous and categorical variables are 
expressed as mean values (± SD) and as proportions (%), 
respectively. Categorical variables were compared with chi-
square analysis. Continuous variables were compared using 
the Student t test. McNemar’s test was used to compare sensitivity 
and specificity between MCE and SPECT. Comparisons of 
myocardial segments between MCE and SPECT were made 
using the kappa statistic. All analyses were performed with 
standard software (Analyse-It, Leeds, United Kingdom).

**RESULTS**

The population has intermediate-to-high pre-test probability 
of CAD (Table 1). Thirty-one patients each underwent MCE 
in each of the three lower doses and 30 patients received the 
highest dose. There were no significant differences in the 
patient characteristics and coronary arteriographic data be-
tween these four groups. Nearly all, 115 (93%), patients 
received low-dose dipyridamole only, owing to development of 
intolerable symptoms at this dose. No serious adverse events 
were seen in our population.

**Comparison with coronary angiography.** In total, 96 of 
123 (78%) patients had evidence of CAD (stenosis of 
≥50%), of which, almost 90% demonstrated ≥70% stenosis 
(mean diameter stenosis ± SD: 87 ± 15%). The sensitivity 
of MCE for the detection of CAD was comparable to that 
of SPECT, with no difference in specificity, and both 
demonstrated improved sensitivity with increasing degree of 
coronary stenosis (Fig. 1). Furthermore, sensitivity measures 
increased with the severity of stenosis, with no significant 
difference between the two modalities both in the anterior 
and in the posterior circulation (Figs. 2 and 3). In the 
posterior circulation, sensitivity of MCE and SPECT for 

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**Table 1.** Study Population Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Age (yrs) ± SD</th>
<th>Men (%)</th>
<th>Hypertension (%)</th>
<th>Diabetes mellitus (%)</th>
<th>Hyperlipidemia (%)</th>
<th>Smoking history (%)</th>
<th>Previous acute myocardial infarction (%)</th>
<th>Previous percutaneous intervention (%)</th>
<th>Coronary artery disease (%)</th>
<th>Multivessel disease (%)</th>
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<tr>
<td></td>
<td>123</td>
<td>62 ± 12</td>
<td>87 (71%)</td>
<td>73 (59%)</td>
<td>33 (27%)</td>
<td>83 (67%)</td>
<td>65 (53%)</td>
<td>41 (33%)</td>
<td>16 (14%)</td>
<td>96 (78%)</td>
<td>56 (46%)</td>
</tr>
</tbody>
</table>
the detection of RCA disease were 52% and 60% (p = NS), respectively, and for LCx, 58% and 40% (p = NS), respectively. Of the 123 patients, 56 (46%) had evidence of MVD; MCE demonstrated the presence of CAD in 91% of cases compared with 88% by SPECT (p = NS). Figure 4 is an example of a patient with MVD demonstrating reversible perfusion defects in the mid-septum, apex, and posterior wall. Table 2 summarizes the diagnostic accuracy of MCE and SPECT for the detection of CAD in patients without resting perfusion defects. When patients with previous acute myocardial infarction (AMI) and resting perfusion defects were excluded, the respective sensitivity of MCE and SPECT were 75% and 67% with specificity of 62% and 65%, respectively. Both the sensitivity and specificity of MCE to detect the presence of CAD and localization of CAD did not vary significantly with different concentrations of the contrast infused. Figure 5 summarizes the agreement between MCE and SPECT for the presence or absence of CAD. At the subject level, of the 17 patients in whom SPECT excluded CAD but MCE predicted CAD, 12 (71%) demonstrated ≥50% coronary stenosis.

**DISCUSSION**

This is the first large, prospective multicenter study demonstrating that the accuracy of MCE is comparable to that of SPECT, both at patient and vascular territory levels for the detection of significant CAD. The population studied was a representative group, scheduled to undergo coronary arteriography for investigation of chest pain in patients with known or suspected CAD. These patients are usually referred for a stress imaging modality for demonstration of myocardial ischemia before undergoing coronary arteriography.

**Mechanisms for the detection of ischemia.** During vasodilator stress, in presence of a flow-limiting stenosis, there is derecruitment of capillaries leading to an overall reduction in capillary blood volume in this area and, hence, a reduction in relative MCE signal intensity and radionuclide tracer uptake in contrast to the myocardium subtended by non–flow-limiting artery (5–7). Furthermore, there is a four- to five-fold increase in myocardial blood velocity in the normal myocardium compared with slower velocity in the regions subtended by flow-limiting stenosis, which can be detected by MCE but not by SPECT (5).

**Comparisons with other studies.** Heinle et al. (8) and Wei et al. (9) assessed a similar population for CAD and found good agreement between the two techniques in the detection of normal versus abnormal perfusion with vasodilator stress similar to the present study, although coronary angiography data in both those studies were sparse. The present study also compares very well with a previous study comparing MCE and SPECT with coronary angiography, where the sensitivity of MCE was similar despite a lower-risk group with milder coronary stenosis (mean diameter stenosis 65%). Single-photon emission computed tomography showed significantly lower sensitivity in the previous study.
study, however, because unlike MCE, the spatial resolution of SPECT is not optimal to detect perfusion defects confined to the subendocardium, which frequently occurs with milder stenosis. Furthermore, unlike MCE, SPECT cannot detect changes in filling rate, which might be the only abnormality in mild stenosis (5). In the present study, no differences in sensitivity were found between MCE and SPECT, because almost 90% of patients had moderate-to-severe (>70%) coronary stenosis with a mean diameter stenosis of 87% and almost one-third of the patient population had a previous AMI. In the present study, however, when patients with AMI and resting perfusion defects were excluded, the sensitivity of SPECT fell to 67% compared with 75% with MCE. In another recent study, also in a high-risk group but without resting wall motion abnormality, the sensitivity of MCE for the detection of CAD was higher (85%) compared with SPECT (74%) (10). The results of recent studies contrast sharply with an early multicenter study by Marwick et al. (11), where MCE compared poorly with SPECT. The principal reasons for such a result were suboptimal imaging technology (e.g., high-power harmonic imaging without tissue subtraction) and the fact that the investigators at that time were at an early phase of the learning curve in both performing and interpreting MCE.

**Study limitations.** Quantitative SPECT and MCE would have provided objective measures of perfusion for both of these modalities; however, the present study was aimed at comparing the two techniques as used in daily clinical practice, and quantification is not performed routinely. The reasons for the apparent higher sensitivity of both MCE and SPECT for the detection of CAD in the posterior circulation compared with anterior circulation are two-fold: 1) higher prevalence of lesion in posterior (n = 82) versus anterior (n = 70) circulation; and 2) posterior circulation disease included either RCA or LCx disease. Thus, when individual territories were considered, the sensitivities were similar. The specificity of both MCE and SPECT might have improved if wall thickening data on echocardiography was used and gated SPECT was performed. Finally, the concentration of microbubble infused in each patient was not the same, although we found no difference in the accuracy of detection of CAD and localization of CAD between the four concentrations used.

**Conclusions.** Myocardial contrast echocardiography is safe and comparable to SPECT in the detection of CAD not only on a patient basis but in localization of disease by vascular territory.

**REFERENCES**


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**Table 2.** Detection of Coronary Artery Disease in Patients Without Resting Perfusion Defects

<table>
<thead>
<tr>
<th>Overall</th>
<th>Anterior Circulation</th>
<th>Posterior Circulation</th>
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<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>MCE (n = 99)</td>
<td>80%</td>
<td>63%</td>
</tr>
<tr>
<td>SPECT (n = 80)</td>
<td>75%</td>
<td>62%</td>
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**MCE = myocardial contrast echocardiography; SPECT = single-photon emission computed tomography.**

**Figure 5.** Agreement between SPECT and MCE in the detection of coronary artery disease (CAD). Abbreviations as in Figure 1.


