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Comparison of Sulfur Hexafluoride Microbubble (SonoVue)-Enhanced Myocardial Contrast Echocardiography With Gated Single-Photon Emission Computed Tomography for Detection of Significant Coronary Artery Disease

A Large European Multicenter Study

Roxy Senior, MD,* Antonella Moreo, MD,† Nicola Gaibazzi, MD,‡ Luciano Agati, MD,§ Klaus Tiemann, MD,|| Bharati Shivalkar, MD,¶ Stephan von Bardeleben, MD,# Leonarda Galiuto, MD,** Hervé Lardoux, MD,†† Giuseppe Trocino, MD,‡‡ Ignasi Carrió, MD,§§ Dominique Le Guludec, MD,|||| Gianmario Sambuceti, MD,¶¶ Harald Becher, MD,## Paolo Colonna, MD,*** Folkert ten Cate, MD,††† Ezio Bramucci, MD,‡‡‡ Ariel Cohen, MD, PHD,§§§ Gianpaolo Bezante, MD,|||||| Costantina Aggeli, MD,¶¶¶ Jaroslaw D. Kasprzak, MD###

London, Harrow, United Kingdom; Milan, Parma, Rome, Monza, Genoa, Bari, and Pavia, Italy; Münster and Mainz, Germany; Edegem, Belgium; Corbeil-Essonnes and Paris, France; Barcelona, Spain; Edmonton, Alberta, Canada; Rotterdam, the Netherlands; Athens, Greece; and Łódź, Poland

Objectives The purpose of this study was to compare sulfur hexafluoride microbubble (SonoVue)-enhanced myocardial contrast echocardiography (MCE) with single-photon emission computed tomography (SPECT) relative to coronary angiography (CA) for assessment of coronary artery disease (CAD).

Background Small-scale studies have shown that myocardial perfusion assessed by SonoVue-enhanced MCE is a viable alternative to SPECT for CAD assessment. However, large multicenter studies are lacking.

Methods Patients referred for myocardial ischemia testing at 34 centers underwent rest/vasodilator SonoVue-enhanced flash-replenishment MCE, standard ^{99m}Tc-labeled electrocardiography-gated SPECT, and quantitative CA within 1 month. Myocardial ischemia assessments by 3 independent, blinded readers for MCE and 3 readers for SPECT were collapsed into 1 diagnosis per patient per technique and were compared to CA (reference standard) read by 1 independent blinded reader.

Results Of 628 enrolled patients who received SonoVue (71% males; mean age: 64 years; >1 cardiovascular [CV] risk factor in 99% of patients) 516 patients underwent all 3 examinations, of whom 161 (31.2%) had ≥70% stenosis (131 had single-vessel disease [SVD]; 30 had multivessel disease), and 310 (60.1%) had ≥50% stenosis. Higher sensitivity was obtained with MCE than with SPECT (75.2% vs. 49.1%, respectively; $p < 0.0001$), although specificity was lower (52.4% vs. 80.6%, respectively; $p < 0.0001$) for ≥70% stenosis. Similar findings were obtained for patients with ≥50% stenosis. Sensitivity levels for detection of SVD and proximal disease for ≥70% stenosis were higher for MCE (72.5% vs. 42.7%, respectively; $p < 0.0001$; 80% vs. 58%, respectively; $p = 0.005$, respectively).

Conclusions SonoVue-enhanced MCE demonstrated superior sensitivity but lower specificity for detection of CAD compared to SPECT in a population with a high incidence of CV risk factors and intermediate-high prevalence of CAD. (A phase III study to compare SonoVue® enhanced myocardial echocardiography [MCE] to single photon emission computerized tomography [ECG-GATED SPECT], at rest and at peak of low-dose Dipyridamole stress test, in the assessment of significant coronary artery disease [CAD] in patients with suspect or known CAD using Coronary Angiography as Gold Standard–SonoVue MCE vs SPECT; EUCTR2007-003492-39-GR) (J Am Coll Cardiol 2013;62:1353–61) © 2013 by the American College of Cardiology Foundation

Abbreviations and Acronyms

AUC = area under receiver-operating characteristic curve
CA = coronary angiography
CMR = cardiovascular resonance imaging
LAD = left anterior descending artery
LCx = left circumflex artery
MCE = myocardial contrast echocardiography
MI = mechanical index
MVD = multivessel disease
SE = stress echocardiography
SPECT = single-photon emission computed tomography
SVD = single vessel disease

Patients presenting with chest pain and who are suspected of having or known to have coronary artery disease (CAD) require accurate evidence of myocardial ischemia for appropriate therapy and improved prognosis. Both stress echocardiography (SE) and single-photon emission computed tomography (SPECT) are established and widely used techniques for this purpose. However, because SPECT evaluates myocardial perfusion, which becomes abnormal earlier than wall motion during stress, SPECT tends to be more sensitive than SE for detection of CAD, especially in patients with milder CAD and single-vessel disease (SVD) (1). Unfortunately, unlike SE, SPECT cannot be performed at the bedside, is relatively time consuming, and exposes patients to ionizing radiation. Myocardial contrast echocardiography (MCE) on the other hand is a rapid, radiation-free bedside technique that provides simultaneous assessment of perfusion and function in real time (2). MCE, which uses microbubbles that mimic the rheological behavior of red blood cells, has superior spatial and temporal resolution compared to SPECT and is considered more sensitive for the detection of CAD (2–4).

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SonoVue (Bracco Imaging SpA, Milan, Italy) is a microbubble-based ultrasonography contrast agent which contains sulfur hexafluoride gas surrounded by a lipid shell. It is approved in Europe and elsewhere for improved assessment of left ventricular function and structure (2). However, large multicenter trials aimed at comparing SonoVue-enhanced MCE and gated SPECT for CAD detection are lacking. Thus, this large European multicenter trial was performed in patients suspected of having or known to have CAD to compare SonoVue-enhanced MCE with gated SPECT for determination of myocardial ischemia, using quantitative coronary angiography (CA) as the reference standard.

Methods

Patients. Adult patients (≥18 years of age) suspected of having or known to have CAD and who were referred for testing for myocardial ischemia were assessed in a Phase III, open-label, nonrandomized, multicenter study conducted at 34 European centers. Institutional review board and regulatory approval were granted, and all patients provided written informed consent. Patients were enrolled between May 2008 and December 2009.

Patients were ineligible if they had any clinically unstable cardiac condition prior to SonoVue administration; if they had any contraindications to dipyridamole or aminophylline; any known allergy to 1 or more ingredients of SonoVue; had previously undergone coronary artery bypass graft or any revascularization procedure or change of clinical status that might have warranted a change in their CAD status during the clinical testing under evaluation; or if they ingested methylxanthine-containing food or phosphodiesterase inhibitor drugs within 24 h prior to MCE or SPECT. Patients were also excluded if the left ventricle was not visualized at basal echocardiography or if they were pregnant or lactating.

Image acquisition. MYOCARDIAL CONTRAST ECHOCARDIOGRAPHY. MCE was performed in the apical 4-, 2-, and 3-chamber views at rest and during pharmacological stress, 2 min after intravenous administration of 0.56 mg/kg dipyridamole over 4 min. SonoVue was infused initially at a rate of 1 ml/min using a dedicated Vueject pump (Bracco Imaging SpA, Milan, Italy); thereafter, the rate was reduced or increased to obtain the best possible image quality. Images were obtained 1 min after infusion.

A flash-replenishment protocol was used whereby microbubbles were cleared from the myocardium after achieving a steady state of infusion with a mechanical index (MI) of 0.9. Replenishment was assessed using lower power (MI: 0.1) imaging in real time and during end-systole-triggered beats for 8 cardiac cycles. Images were acquired using model IE33 equipment (Philips, Eindhoven, Best, the

From the *Department of Cardiology, Royal Brompton Hospital and Northwick Park Hospital, London, Harrow, United Kingdom; †Cardiology Department, Ospedale Niguarda, Milan, Italy; ‡Cardiology Department, Parma University Hospital, Parma, Italy; §Department of Cardiology, Sapienza University of Rome, Rome, Italy; ‖Department of Cardiology, University of Münster, Münster, Germany; ¶Department of Cardiology, University Hospital Antwerp, Edegem, Belgium; #Medical Clinic II (Cardiology), Johannes Gutenberg University Hospital, Mainz, Germany; **Department of Cardiovascular Sciences, Catholic University of the Sacred Heart, Rome, Italy; ††Service de cardiologie, Centre Hospitalier Sud Francilien, Corbeil-Essonnes, France; ‡‡Department of Cardiology, St. Gerardo Hospital, Monza, Italy; §§Department of Nuclear Medicine, Autonomous University of Barcelona, Barcelona, Spain; ‖‖Nuclear Medicine Department, Bichat Hospital, Paris, France; ¶¶Nuclear Medicine Unit, Azienda Ospedaliera University San Martino di Genova, Genoa, Italy; ##Abacus Mazankowski Alberta Heart Institute, Edmonton, Alberta, Canada; ***Division of Cardiology, Hospital Policlinico of Bari, Bari, Italy; †††Department of Cardiology, Thoraxcenter, Erasmus Medical Centre, Rotterdam, the Netherlands; ‡‡‡Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; §§§Service de Cardiologie, Saint-Antoine Hospital, Paris, France; ‖‖‖Department of Internal Medicine, Cardiology Unit, Azienda Ospedaliera San Martino, Genoa, Italy; ¶¶¶First Cardiology Department, Hippokrateion Hospital of Athens, Athens, Greece; and the ###Department of Cardiology, Biegański Hospital, Medical University of Łódź, Łódź, Poland. This study was supported by Bracco Imaging SpA, Milan, Italy. Dr. Senior has received an investigator's fee, a speaker's fee, and an honorarium from Bracco. Dr. Brecher is a consultant for Bracco. Dr. Colonna has received research funding for the trial in the present study. Dr. Kasprzak has received investigator fees for trials sponsored by Bracco. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Netherlands) in 30 centers and Sequoia 512 equipment (Siemens Medical Systems, Berlin, Germany) in 4 centers.

SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY. A technetium (^{99m}Tc)-labeled radiopharmaceutical agent (either ^{99m}Tc-sestamibi [Cardiolite; Lantheus Medical Imaging; Billerica, Massachusetts] or ^{99m}Tc-tetrofosmin [Myoview GE Healthcare; Arlington Heights, Illinois], according to the practice of the clinical site) was administered for the stress electrocardiography (ECG)-gated SPECT acquisition 1 min after the end of the dipyridamole infusion, performed either for the stress SonoVue-enhanced MCE examination or, if this were not possible for logistical reasons, within 24 h of the MCE examination. SPECT at rest could be avoided if the initial stress SPECT investigation was deemed negative. If considered necessary, an identical ECG-gated SPECT acquisition was performed at rest within 24 h of the stress ECG-gated SPECT acquisition, following a second ^{99m}Tc-labeled radiopharmaceutical administration. In both cases, SPECT was performed at 20 to 60 min after ^{99m}Tc-labeled radiopharmaceutical injection.

CORONARY ANGIOGRAPHY. Coronary angiography (CA) was performed according to the standard technique in all patients within 30 days (before or after) of the MCE examination. In all cases, right anterior oblique and left anterior oblique projections were acquired with both cranial and caudal angulations to provide at least 2 orthogonal views of each coronary artery.

Image evaluation. Images were evaluated by independent experienced cardiologists (3 for MCE, 3 for SPECT, 1 for CA) who were unaffiliated with the investigational sites and blinded to patient identity, clinical profile, and to the results of other readers and other examinations. Myocardial perfusion by both techniques was assessed segmentally (17-segment left ventricle [LV] model).

MYOCARDIAL CONTRAST ECHOCARDIOGRAPHY. Qualitative evaluation of images was performed using both real-time and end-systole-triggered digital clips. Myocardial perfusion was considered normal at rest or stress if the myocardium replenished within 5 cardiac cycles at rest or within 2 cardiac cycles at stress following the flash. Resting perfusion abnormality was considered possible if there was a delay of >5 cardiac cycles or if there was patchy or no filling at rest. Myocardial ischemia was diagnosed if, during stress, there was a delay of ≥3 cardiac cycles or if there was newly visible patchy or subendocardial defect or absent contrast. Any deterioration of wall motion was also considered ischemic.

SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY. SPECT studies were reconstructed into standard views. Short-axis slices were quantified using software for myocardial perfusion (QPS) defect or contraction. The slices were displayed in a standard format for visual and quantitative interpretation and to determine the presence and severity of myocardial perfusion and functional defects. Segmental tracer was assessed in rest and stress images separately, using a semiquantitative scale in which 0 = normal uptake, 1 = mildly reduced uptake, 2 = moderately reduced uptake, 3 = severely reduced uptake, and 4 = absent uptake. A normal segment was defined as a segment with score 0 or 1 at both rest and stress; myocardial ischemia was defined as a change to ≥2 at stress from 0/1 at rest or to ≥3 at stress from 2/3 at rest. Wall motion data during gated SPECT were also used to arrive at the diagnosis.

CORONARY ANGIOGRAPHY. A visual assessment of images was performed to determine: 1) right coronary artery (RCA) dominance; and 2) the presence/absence of coronary stenosis of the LM, left anterior descending artery (LAD), left circumflex artery (LCx), and RCA and their major branches and, if present, the degree of diameter stenosis, that is: ≤20%, >20% but <100%, 100% (occlusion). If stenosis of >20% was detected in any of these vessels, quantitative analysis was performed using dedicated QAngioXA version 7.1 software (Medical Imaging Systems).

Significant CAD was diagnosed if a stenosis of ≥70% was detected in 1 or more of these vessels. Significant CAD was classified as 1-, 2-, or 3-vessel disease. Patients with stenosis of ≥50% were also assessed.

EFFICACY ASSESSMENTS. Segments were assigned to each of the 3 major coronary artery territories (5). The presence of significant ischemia at MCE or SPECT was defined when: 1) at least 2 contiguous segments; or 2) 1 segment contiguous to at least 2 fixed segments demonstrated ischemia.

SAFETY EVALUATIONS. Physical examination was performed within 24 h prior to SonoVue administration. Monitoring for clinical adverse events (AEs) took place from the time of signed informed consent until 24 h after SonoVue administration. Events were classified using standard criteria. All decisions regarding AE severity and a possible relationship to the study agent were made by the investigator at each center.

Measurement of vital signs (blood pressure, heart rate) and recording of electrocardiograms (ECGs) were performed within 24 h and 10 min prior to dose administration, at the beginning and end of SonoVue infusion, at the beginning and end of dipyridamole infusion, and at regular time points up to 2 h after SonoVue administration.

STATISTICAL ANALYSIS. The primary aim was to demonstrate noninferiority (−5% of difference) for MCE relative to SPECT in terms of sensitivity and specificity for the detection of ≥70% coronary artery stenosis. Assuming a power of 80%, a 1-sided significance level (alpha) of 2.5%, expected sensitivity and specificity values for SPECT of 71%, an expected maximum proportion of discordant pairs of 20%, and an expected prevalence of positive and negative patients of 70% (patients with at least 1 stenosis of ≥70%) and 30%, respectively, sample sizes of 230 for sensitivity and 537 for specificity were calculated. Taking the higher number and assuming a maximum patient dropout rate of 10%, a minimum enrollment of 597 patients was considered necessary. As

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coronary artery stenosis of ≥50% is also clinically important, determinations for this cutoff were also performed.

The findings from the 3 independent readers were collapsed into 1 record per patient for both MCE and SPECT, using a majority rule, that is, the result was positive or negative if the diagnosis was positive or negative for at least 2 readers, respectively. Technically inadequate or nonevaluable coronary artery territories were considered false negative if a stenosis of ≥70% was detected at CA or as false positive if no stenosis or a stenosis of <70% was detected at CA. The test of noninferiority (−5% of difference) for MCE relative to SPECT was performed by using the score method proposed by Nam (6) for noninferiority testing based on the difference of paired proportions. The McNemar test was used to assess the significance of differences between MCE and SPECT in terms of sensitivity, specificity, and accuracy for detection of CAD. Inter-reader agreement was determined using generalized weighted kappa (κ) statistics.

All statistical analyses and data processing were performed using SAS software (release 9.2, library V9, SAS Institute, Cary, North Carolina) on a Windows XP (Microsoft Corp., Redmond, Washington) service pack 3 Pro operating system (Microsoft Inc., Seattle, Washington). A p value of <0.05 was considered significant.

Results

A total of 628 of 630 enrolled patients received SonoVue and comprised the safety population. Of these 628 patients, 80 did not undergo CA. Another 6 patients had inadequate CA images. Of the 542 patients with adequate CA, 22 and 4 patients did not undergo SPECT and stress MCE, respectively. Thus, a total of 516 patients underwent all 3 procedures and fulfilled the prospectively defined efficacy population (Table 1). Of these 516 patients, 422 (81.7%) underwent MCE using the Philips system and 94 (18.2%) using the Siemens system.

Coronary angiography. At CA, 161 (31.2%) patients had ≥70% stenosis. These 161 patients included 131 (81%) with SVD and 30 (19%) with multivessel disease (MVD) (26 with 2-vessel; 4 with 3-vessel disease). CAD with ≥50% stenosis was present in 310 (60.1%) patients.

Diagnostic performance of MCE and SPECT. Sensitivity for the detection of ≥70% stenosis across 3 blinded readers ranged from 67.1% to 75.2% for MCE and from 31.1% to 70.8% for SPECT. Conversely, the specificity of MCE was lower than that of SPECT with values across 3 blinded readers ranging from 47.6% to 53.5% for MCE and from 59.2% to 85.4% for SPECT. Based on the 3 readers' collapsed data (Fig. 1) the sensitivity for CAD detection was significantly higher for MCE than for SPECT (75.2% [95% confidence interval {CI}: 68.5 to 81.8%] vs. 49.1% [95% CI: 41.3 to 56.8%]; p < 0.0001) with no differences between vendors (76%, Philips vs. 74%, Siemens). Conversely, the specificity of MCE was lower than that of SPECT (52.4% [95% CI: 46.2 to 58.6%] vs. 80.6% [95% CI: 77.4 to 83%]; p < 0.0001) again with no differences between vendors (53% vs. 50%; Philips vs. Siemens, respectively). The data supported the noninferiority of MCE to SPECT in terms of sensitivity (p < 0.0001) but did not support the noninferiority of MCE for specificity (p = 1.000). Similar results were obtained in patients with ≥50% CAD (Fig. 2); the sensitivity of MCE was again significantly (p < 0.0001) superior to that of SPECT, while specificity was inferior. Notably, both MCE and SPECT showed improved sensitivity with increasing grades of stenosis (Fig. 2A), while specificity decreased with increasing grades of stenosis (Fig. 2B).

Table 1 Patient Characteristics of the Study Population

Age (yrs)	63 ± 10
Men	381 (74)
Chest pain	343 (67)
Chest pain on exertion	265 (51)
Hypertension	388 (75)
Diabetes mellitus	149 (29)
Hyperlipidemia	372 (72)
Smoking history	294 (57)
Previous AMI	136 (26)
Previous PCI	198 (38)
BMI (kg/m^2)	27 ± 4
No. of patients with ≥1 CV risk factor	511 (99)
Prevalence of ≥70% CAD	161 (31)
Single-vessel disease	131 (81)
Multivessel disease	30 (19)
Proximal disease	50 (31)
Location of ≥70% CAD	
LAD	54 (34)
LCx	61 (38)
RCA	80 (50)
Prevalence of ≥50% CAD	310 (60)
Prevalence of ≥20% CAD	385 (75)

Values are mean ± SD or n (%).
AMI = acute myocardial infarction; CAD = coronary artery disease; CV = cadiovascular; LAD = left anterior descending artery; LCx = left circumflex artery; PCI = percutaneous coronary intervention; RCA = right coronary artery.

In terms of accuracy, MCE was less accurate than SPECT for the detection of ≥70% stenosis (59.5% vs. 70.7%, p < 0.0001) but was significantly more accurate for the detection of ≥50% stenosis (62.8% vs. 52.9%, p < 0.0001). Given that the prevalence of disease was 60% in the population with ≥50% stenosis compared with only 30% in the population with ≥70% stenosis, the accuracy measurements should be considered more relevant for the former group.

Among 380 patients with no history of acute myocardial infarction (AMI), the sensitivity of MCE compared with SPECT for the detection of ≥70% stenosis was 66.0% versus 44.3%, respectively
(p < 0.0001), while the specificity was 57.3% versus 83.2%, respectively (p < 0.0001).

The sensitivity of MCE was superior to that of SPECT, independently of the extent of disease (Fig. 3). However, MCE superiority was most marked among the 131 patients

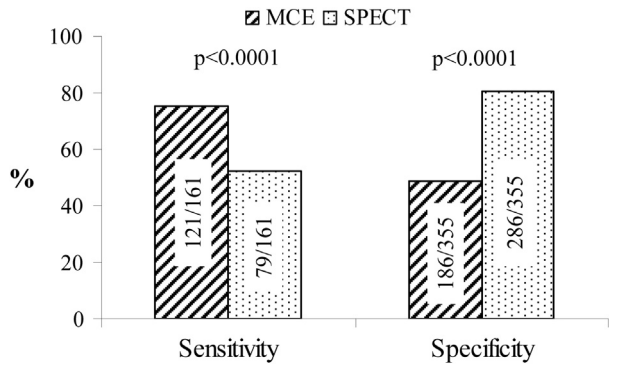

Figure 1 **MCE Versus SPECT for Detection of Significant (≥70% Stenosis) CAD**

The sensitivity of myocardial contrast echocardiography (MCE) was significantly superior to that of single-photon emission computed tomography (SPECT) for coronary artery disease (CAD) detection, although specificity was lower.

with SVD (72.5% vs. 42.7%, respectively; $p < 0.0001$). Although MCE also was superior to SPECT among the 30 patients with MVD (86.7% vs. 76.7%, respectively), significance was not demonstrated because of the small number of patients with MVD. Significantly superior sensitivity of MCE compared to SPECT was also demonstrated in patients with proximal CAD (80% vs. 58%, respectively; $p = 0.005$) (Fig. 3).

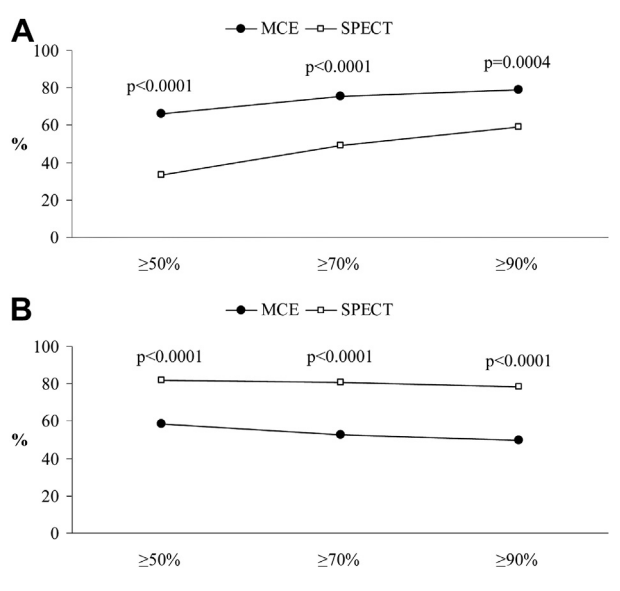

Figure 2 **MCE Versus SPECT for Detection of ≥50%, ≥70%, and ≥90% Stenoses**

The sensitivity **(A)** of MCE for CAD detection was significantly superior to that of SPECT for all grades of stenosis, although specificity **(B)** was lower. Note that the sensitivity of both techniques increased with increasing grade of stenosis, while the specificity of both techniques decreased. Abbreviations as in Figure 1.

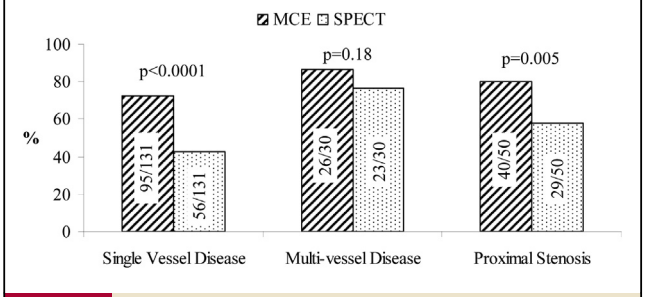

Figure 3 **Sensitivity for CAD (≥70% Stenosis) Detection by Disease Extent**

MCE was significantly superior to SPECT in patients with single-vessel and proximal disease. Superiority in patients with multivessel disease was not significant because of low patient numbers. Abbreviations as in Figure 1.

The sensitivity of MCE was likewise significantly superior to that of SPECT, independently of the location of disease (in 45 of 54 patients [83.3%] vs. 28 of 54 patients [51.9%] patients, respectively, with LAD disease [$p = 0.0007$]; in 48 of 61 [78.7%] vs. 36 of 61 patients [59%], respectively, with LCx disease [$p = 0.0027$]; and in 58 of 80 patients (72.5%) vs. 42 of 80 patients [52.5%], respectively, with RCA disease [$p = 0.0011$]) (Fig. 4).

Concerning CAD localization at the patient level, the sensitivity of MCE versus that of SPECT was 65% versus 41% ($p = 0.005$), respectively, in the LAD territory and 53% versus 43% ($p = 0.0641$), respectively, in the RCA/LCx territory. Corresponding specificities were 71% versus 91% ($p < 0.0001$) and 67% versus 88% ($p < 0.0001$), respectively.

An example of a patient with significant reversible defect of the inferior wall on MCE corresponding to an 80% stenosis of the RCA on quantitative CA and in which SPECT revealed no abnormalities is shown in Figure 5.

Interobserver agreement (κ value) for the detection of ≥70% CAD at the patient level was $\kappa = 0.37$ for the 3 MCE readers and $\kappa = 0.34$ for the 3 SPECT readers. The percentage agreement for any 2 readers ranged from 60% to 84% for MCE and from 65% to 87% for SPECT.

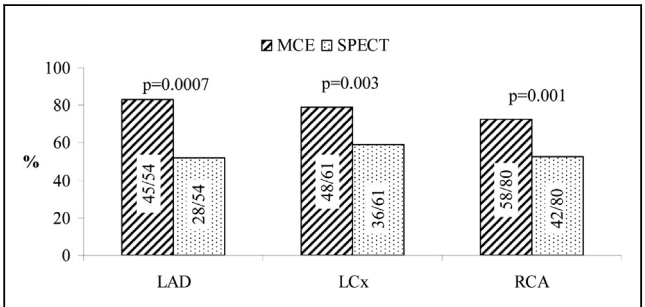

Figure 4 **Sensitivity for CAD (≥70% Stenosis) Detection by Vascular Territory**

MCE was significantly superior to SPECT for detection of significant CAD regardless of disease location. Abbreviations as in Figure 1.

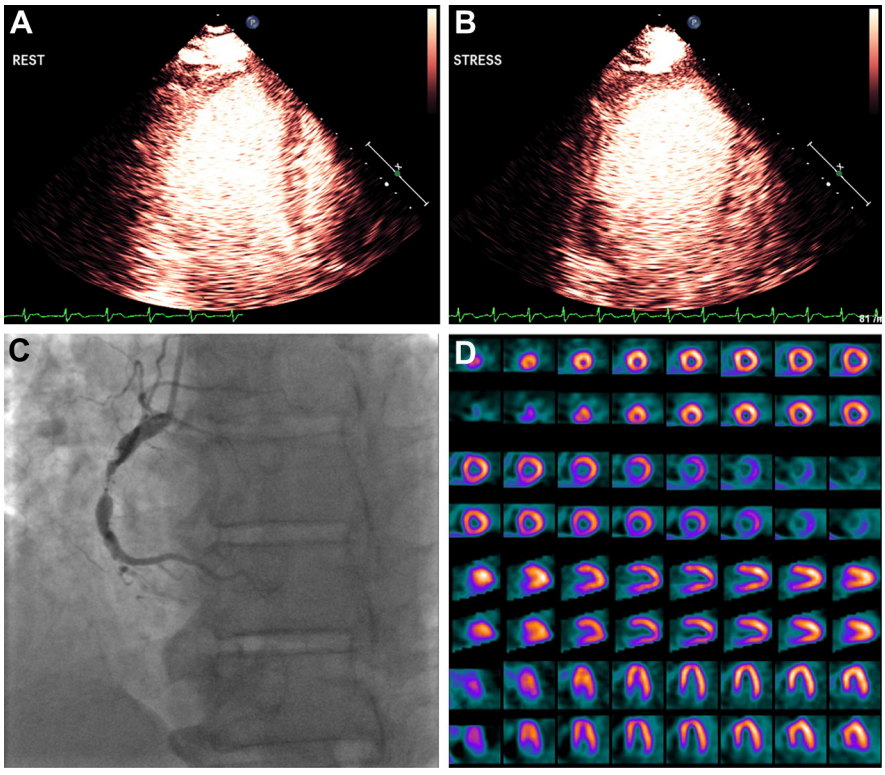

Figure 5 MCE Versus SPECT for Detection of Significant CAD

A 52-year-old man with significant reversible defect of the inferior wall shown by MCE at rest **(A)** and under stress **(B)**, corresponding to an 80% stenosis of the right coronary artery (RCA) on quantitative coronary angiography (CA) **(C)**. SPECT **(D)** revealed no abnormalities. Abbreviations as in Figure 1.

Safety. Nonserious AEs considered related to SonoVue administration were noted in 16 (2.5%) patients. AEs were considered mild in 11 (1.8%) patients. The most frequent nonserious AEs were nausea and headache, which were reported by 4 (0.6%) and 3 (0.5%) patients, respectively. A solitary serious event considered possibly related to SonoVue administration was reported in a 69-year-old female patient with systolic hypertension and suspected myocarditis. After successfully undergoing rest and stress echocardiography, the patient developed hypersensitivity-like symptoms and asystole for 30 s. All symptoms were successfully treated. The duration of the event from the first symptom (pale, sweating) to complete, symptom-free recovery was 57 min. Changes in vital sign and ECG parameters were infrequent and small.

Discussion

This large multicenter prospective trial revealed superior sensitivity but lower specificity for SonoVue-enhanced MCE compared to gated SPECT for the detection of CAD in a population with predominant symptoms of chest pain, a high incidence of CV risk factors, and an intermediate-high prevalence of CAD. The greater sensitivity of MCE compared to that of SPECT was independent of the severity of CAD and increased significantly with higher grades of stenosis. Notably, the superior sensitivity of MCE over SPECT was particularly marked in patients with SVD, which was highly prevalent in our population with CAD. The superior sensitivity of MCE was also notable in patients with proximal disease and was independent of arterial location; significantly greater sensitivity was apparent not only in patients with disease of the LAD but also in patients with disease of the inferoposterior circulation.

Conversely, the specificity of MCE was lower than that of SPECT. In part this may be due to the sensitivity of MCE, which was higher than that of SPECT, for the detection of microvascular abnormalities. Notably, 51% of patients in our population complained of chest pain on exertion, and almost all had at least one cardiovascular risk factor. Given that approximately 75% of our population demonstrated some degree of CAD (≥20% diameter stenosis in a major vessel), underlying microvascular disease in most patients should be considered highly likely (7).

Comparative mechanism of MCE versus SPECT for detection of CAD. MCE utilizes microbubbles which rheologically mimic red blood cells and remain entirely intravascular. During steady state when contrast agent is infused continuously, the signal intensity from the myocardium depicts capillary blood volume (8). Flash imaging,

which results in a transient increase in acoustic power, clears the microbubbles from the myocardium. When this is followed by low power imaging, microbubbles can be seen replenishing the myocardium with minimal destruction. Capillary blood velocity at rest is 1 mm/s (9). Because the imaging sector produced by the echocardiographic transducer has an elevation of 5 mm, a capillary length of 5 mm is imaged. Thus, at rest, it requires 5 s for the capillaries to replenish after clearance during transient high-power imaging. During hyperemia (during dipyridamole infusion), capillary blood velocity increases by 4 to 5 times compared to that at rest in the absence of a flow-limiting stenosis. Thus, myocardium in the absence of flow limitation replenishes in 1 s. In myocardium subtended by flow-limiting stenosis, this process takes >1 s (9). Furthermore, in myocardium subtended by flow-limiting stenosis, derecruitment of capillaries occurs and is depicted by reduced signal intensity on MCE (10). Thus, the hallmark of flow-limiting CAD during MCE is a reduction of signal intensity with slow replenishment. The reduction in signal intensity is very marked in the subendocardium with slow filling progressing from epicardium to endocardium (11). Because MCE has excellent spatial and temporal resolution, this phenomenon can be detected easily.

On the other hand, SPECT detects ischemia based on differential tracer uptake compared with regions of normal uptake. Because of attenuation and Compton scatter, error in the measurement of counts in closed chest patients is approximately 30%. Therefore, a perfusion defect must be of at least this magnitude to be detected by SPECT. Thus, in patients with mild stenosis, differential tracer uptake may not be discernible. Furthermore, uptake of the ^{99m}Tc agents MIBI and tetrofosmin reach plateaus, even if the myocardial blood flow increases several times over that of rest flow (12,13). Hence, if stenosis is mild, the plateau effect of tracer uptake will not produce detectable differences in tracer uptake. Finally, the significantly lower spatial resolution of SPECT precludes adequate appreciation of subendocardial defects which are more common in patients with mild stenosis. Unlike MCE, SPECT has no temporal resolution. Therefore, it is not possible to detect phenomena dependent on myocardial blood velocity. In patients with mild-to-moderate stenosis, the capillary blood volume changes are relatively small compared to changes in myocardial blood velocity (9). This is true also in patients with microvascular disease (14). These drawbacks of SPECT are likely reasons for the lower sensitivity of this technique compared with MCE, particularly in a CAD population with a high prevalence of SVD and likely high prevalence of microvascular disease. Our findings confirm findings of recent single and multicenter studies that have also demonstrated superior sensitivity of MCE for the detection of CAD (2–4).

The sensitivity of SPECT in this study was comparable to values obtained in similarly conducted large multicenter studies (4,15). In a recent multicenter study that compared cardiac magnetic resonance (CMR) imaging with SPECT, the sensitivity of SPECT was 59% (15). In another multicenter trial, the sensitivity of SPECT was 61% (4). In both of those studies, the prevalence of MVD (40%) was roughly twice that in our study. This partly explains the slightly lower sensitivity of SPECT (49%) in our study. Furthermore, in our study, only reversible defects were considered for the diagnosis of significant CAD; in the aforementioned trials, both rest and reversible defects formed the basis of an abnormal SPECT scan. This may also explain the slightly better sensitivity of SPECT in those previous trials. On the other hand, another large single-center study that compared CMR and SPECT for the detection of significant CAD (>70% diameter stenosis) determined a sensitivity of 50% and a specificity of 80% for SPECT on the ROC curve which is similar to the values obtained in our study in a similar patient cohort (16). In all these studies low sensitivity of SPECT can also be attributed to the use of vasodilator only rather than the more widely clinically used combination of vasodilator and low-level exercise.

Better sensitivity and specificity values for both MCE and SPECT have been obtained in single-center studies than in this and other multicenter studies. This can be attributed to the fact that images in large multicenter studies are analyzed in blinded fashion, with readers completely unaware of patient characteristics. This is in contrast to the routine situation in a clinical environment in which patient data and the results of other imaging studies are readily available resulting in better performance for both techniques.

Safety of SonoVue. The safety profile of SonoVue in this study was excellent. Adverse events considered possibly related to SonoVue occurred in just 2.5% of patients. Most events were minor with the most frequent being nausea and headache. This safety profile should be considered excellent for an ultrasound contrast agent that is widely used clinically to improve assessment of cardiac structure and function, particularly in conjunction with stress echocardiography.

Study strengths and limitations. The strengths of our study were its large patient cohort (largest MCE study to date), multicenter design, and use of echocardiographs from 2 vendors (no differences were apparent in terms of MCE diagnostic performance). Furthermore, the protocol used for MCE image acquisition and analysis was that recommended for clinical use by the European Association of Echocardiography (2). Reproducibility among the MCE readers was similar to that among the readers for SPECT, a technique which is already very mature and widely used. These results are similar to those obtained in a previous multicenter trial (4).

There are a few limitations. The standard of reference for this study was quantitative CA. Although measurement of the fractional flow reserve (FFR) is considered superior to lumen measurement for determination of coronary stenoses (17), FFR was not yet in routine use when this study began. On the other hand, dissociation between FFR and myocardial ischemia assessed by SE or nuclear imaging has also been noted (18). Another limitation of our study is that MCE evaluation did not differentiate between perfusion and

wall motion assessment. Thus, the influence of wall motion alone on the diagnostic accuracy of MCE was not determined. A reversible abnormality was the criterion for detection of CAD. It is very unlikely that a reversible wall motion abnormality could have influenced the result because the low dose of dipyridamole used in this trial, which is optimal for vasodilatory response and hence for perfusion assessment, induces only infrequent wall motion abnormalities, particularly in patients with mild disease which was the dominant disease condition in the study (19–21). While baseline wall motion abnormality could have influenced the readers to err on the side of abnormality, excluding patients with previous AMI did not significantly alter the overall result. Despite a much lower prevalence of significant CAD than expected, differences in sensitivity and specificity between MCE and SPECT were relatively large. Notably, although similar findings for sensitivity and specificity to those obtained in patients with ≥70% stenosis were obtained in patients with ≥50% stenosis, the overall accuracy was significantly superior for MCE compared to SPECT. This can be considered a reflection of the greater prevalence of disease (60%) among patients with ≥50% stenosis. Finally, only 3% of SPECT studies were considered nonevaluable compared with 0% of MCE studies. Excluding nonevaluable patients would therefore have little impact on the overall findings of the study.

Clinical implications. SPECT and SE are widely used for the assessment of myocardial ischemia. However, SPECT, unlike SE, requires ionizing radiation, is not a bedside procedure, and is relatively more costly and time consuming. On the other hand, SE has lower sensitivity than SPECT, particularly in patients with SVD (1). This study showed that perfusion assessed by MCE had a superior sensitivity compared to SPECT for the detection of CAD. Thus, MCE is likely to enhance sensitivity when used in conjunction with SE. The specificity of MCE may also improve particularly if used during dobutamine SE as mildly abnormal perfusion in the presence of normal wall motion may not be indicative of significant CAD. Furthermore, prognosis is better in such patients than in patients with additional wall motion abnormality, as this combination reflects significant CAD (22). Nevertheless, it has been shown that patients with a reversible perfusion defect alone have a worse outcome than patients with normal wall motion and perfusion (21). This is possibly because such patients may not have flow-limiting CAD but rather a microcirculation abnormality as the cause of chest pain. Such patients have been shown to have a worse outcome than those with no evidence of ischemia (23). Antianginal therapy may be appropriately instituted in such patients with chest pain and ischemia but non-flow-limiting CAD.

Conclusions

In this multicenter study in a broad, unselected population of patients with predominant symptoms of chest pain, a high incidence of CV risk factors and an intermediate-high prevalence of CAD, SonoVue-enhanced MCE was safe and significantly more sensitive than gated SPECT for the detection of CAD.

Reprint requests and correspondence: Prof. Roxy Senior, Department of Cardiology, Royal Brompton Hospital, London, Cardiovascular Biomedical Research Unit, NHLI, Imperial College, Sydney Street, London SW36NP, United Kingdom. E-mail: roxysenior@cardiac-research.org.

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Key Words: contrast echocardiography ■ ischemia ■ SonoVue.

APPENDIX

For a list of investigators enrolling patients in the study, please see the online version of this article.