Real-time dobutamine stress myocardial perfusion echocardiography predicts outcome in the elderly

Jeane M. Tsutsui1, Feng Xie1, David Cloutier2, Saul Kalvaitis1, Abdou Elhendy3, and Thomas R. Porter1*

1Section of Cardiology, Department of Internal Medicine, University of Nebraska Medical Center, 982265 Nebraska Medical Center, Omaha, NE 68198-2265, USA; 2Creighton University Medical Center, Omaha, Nebraska, USA; 3Department of Cardiology, Marshfield Clinic, Marshfield, WI, USA

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Aims
Although there is an increasing number of studies showing the value of perfusion imaging with real-time contrast echocardiography (RTCE) for detecting coronary artery disease (CAD), no data exist regarding the value of this technique for detecting CAD and predicting outcome in the elderly.

Methods and results
We examined the outcome of 399 patients ≥70 years old who underwent dobutamine stress RTCE for known or suspected CAD. Myocardial perfusion imaging (MPI) was performed using low mechanical index pulse sequence schemes following intravenous small bolus injections of ultrasound contrast. Quantitative coronary angiography (QCA) was performed within 1 month of the stress test in 60 patients. Events were defined as cardiac death or non-fatal myocardial infarction (MI). Sensitivity of MPI for detecting CAD by QCA was 94% [confidence interval (CI) 91–99], specificity was 67% (CI 36–74), and accuracy was 90% (CI 82–95). During a median follow-up of 21 months, 46 events occurred (31 cardiac deaths, 15 non-fatal MI). Univariate predictors of outcome were diuretic use (P = 0.03), abnormal stress wall motion (P < 0.0001), and abnormal stress MPI (P < 0.0001). Abnormal stress MPI, however, was the most significant predictor of outcome (χ² 7.5; P = 0.006).

Conclusion
Myocardial perfusion analysis during dobutamine stress RTCE provides incremental predictive value in determining the outcome of elderly patients being evaluated for the presence of CAD.

Keywords
Myocardial contrast echocardiography • Prognosis • Coronary artery disease • Elderly

Introduction
Coronary artery disease (CAD) is the leading cause of cardiac morbidity and mortality in the elderly.1–4 An age of ≥70 years has been identified as a significant independent predictor of adverse cardiovascular outcomes.5–7 Because of increased life expectancy and improvements in currently available therapeutic modalities, non-invasive tests to detect CAD in this patient population have become increasingly important.8 Exercise stress testing is the most widely used non-invasive test to assess CAD. However, the ability to perform exercise testing is often impaired in elderly patients owing to the high prevalence of joint disease, chronic obstructive airway disease, and other co-morbidities. Dobutamine stress echocardiography (DSE) has been reported as a safe alternative to exercise in elderly patients.9–11

Recently, myocardial contrast echocardiography has been used for myocardial perfusion imaging (MPI) following intravenous injections of ultrasound contrast agents.12–14 Real-time contrast echocardiography (RTCE) using low mechanical index pulse sequence schemes enhances the detection of microbubbles and reduces microbubble destruction, permitting the identification of perfusion abnormalities in real time. RTCE has increased the sensitivity of dobutamine stress for detecting CAD at earlier stages of the infusion and improved the ability of the test to predict cardiac events in a general population.15 This added value of RTCE may be especially useful in elderly patients, where disease prevalence is
high, and intolerance to higher doses of dobutamine may be increased. The aim of this study was to determine the accuracy and prognostic value of dobutamine–atropine stress RTCE for the detection of CAD in ≥70-year-old patients.

Methods

Patients

From March 2000 to August 2004, a total of 470 patients >70 years of age consented to undergo dobutamine stress echocardiography. All patients signed informed consent to undergo dobutamine stress echocardiography with RTCE and were followed up. Out of these, a total of 399 patients did not have exclusion criteria and could be reached at designated follow-up intervals. All studies were performed for the evaluation of known or suspected CAD. All patients signed informed consent to undergo periodic follow-up and were entered into the RTCE Dobutamine Stress Database that has been utilized to examine clinical outcomes of both general patient populations and specific patient subsets. The exclusion criteria were haemodynamic instability, unstable angina, recent myocardial infarction (MI) within the previous 6 months, and severe valvular disease. Diabetes mellitus was defined as a fasting glucose level of 140 mg/dL (7.8 mmol/L) or higher for insulin or oral hypoglycaemic agents. Hypercholesterolaemia was defined as a total cholesterol level >200 mg/dL or treatment with lipid-lowering medications. Hypertension was defined as a systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or treatment with anti-hypertensive medications. The study was approved by the Institutional Review Board of the University of Nebraska Medical Center.

Dobutamine stress real-time contrast echocardiography

RTCE was performed using the commercially available ultrasound scanners HDI 5000 (Philips Medical Systems, Bothell, WA, USA), SONOS 5500 (Philips Medical Systems, Andover, MA, USA), and Sequoia (Siemens Acuson, Mountain View, CA, USA). All equipment had real-time pulse sequence schemes. Mechanical indexes were set to ≤0.3, and frame rates to ≥22 Hz. Time gain compensation and twodimensional gain were adjusted to suppress signals from the myocardium prior to contrast injection. After optimization of system settings, a calibration dose of contrast agents was given followed by setting corrections to optimize gain and minimize any non-linear signals from tissue. Equipment settings were then kept unchanged throughout the study. Although imaging was at frame rates of ≥22 Hz, the assessment of myocardial perfusion was primarily done by examining end-systolic and early-diastolic frames within the cardiac cycle. The contrast agents used were the commercially available albumin-encapsulated microbubble Optison (GE-Amersham, Princeton, NJ, USA) in bolus doses of 0.2–0.3 mL or lipid-encapsulated microbubble Definity (Bristol-Myers Squibb Medical Imaging, Inc., North Billerica, MA, USA) in a bolus of 0.1 mL. Each contrast injection was followed by a 3–5 mL saline flush. A minimum of 15 s of image acquisition was performed following peak myocardial opacification until disappearance of contrast from the myocardium. Analysis of perfusion was based on myocardial contrast appearance during this washout period, as described previously.

Patients were instructed to discontinue beta-blockers at least 24 h prior to the stress test. Dobutamine was infused intravenously at a starting dose of 5 μg/kg/min, followed by increasing doses of 10, 20, 30, 40, up to a maximal dose of 50 μg/kg/min, in 3–5 min stages. Atropine (up to 2.0 mg) was injected in patients without symptoms or signs of myocardial ischaemia to achieve 85% of the age-predicted maximal heart rate (peak stress), calculated as 220 minus age in years. Contrast-enhanced images were obtained in the apical four-, two-, and three-chamber views at baseline, at low doses of dobutamine (5–10 μg/kg/min), if a resting wall motion (WM) abnormality was present, and at peak stress. Endpoints of the stress tests were achievement of the peak stress heart rate, maximal dobutamine/atropine doses, ST-segment elevation of ≥2 mm or higher at an interval of ≥80 ms from the J point in leads without resting Q waves, sustained arrhythmias, severe chest pain, or intolerable adverse effects considered to be due to dobutamine or atropine. Images were recorded on videotape and digitized in continuous loop format for side-by-side analysis. The tests were considered diagnostic if the target heart rate and/or an ischaemic endpoint was achieved. The tests were considered non-diagnostic if the patient failed to achieve the target heart rate without inducible ischaemia.

Echocardiographic analysis

WM and MPI were evaluated during the dobutamine stress RTCE by an experienced observer, blinded to clinical and angiographic data. The left ventricle was divided into 17 segments using the American Heart Association Writing Group guidelines. Studies were interpreted as either normal or abnormal and analysis was performed on a patient and coronary artery territory basis. Patients with normal MPI or WM, both at baseline and at peak stress, were classified as having a normal study. Patients with normal MPI or WM at baseline and a new perfusion defect or WM abnormality with stress were classified as having an inducible perfusion defect or WM abnormality, respectively. Patients with a perfusion defect at baseline without extension observed at peak dobutamine stress were classified as having a fixed perfusion defect, and those with a resting perfusion abnormality who developed a new perfusion defect in other segments were characterized as having fixed plus inducible perfusion defects. Patients with a biphasic response of WM in segments with resting abnormalities were considered to have inducible ischaemia. If a resting WM abnormality was present, peak stress images were compared with resting and low-dose dobutamine images. For the purpose of coronary artery territory analysis, the anterior septum, mid-septum, anterior wall, and adjacent apical segments were assigned to the left anterior descending coronary artery and considered as the anterior circulation. Segments supplied by the left circumflex and right coronary artery were considered as the posterior circulation and included basal and mid-segments of the lateral wall (left circumflex territory) as well as basal and mid-inferior and basal septal (right coronary territory). The apical lateral and posterior segments were considered overlap regions and were assigned to the vascular territory with contiguous abnormalities. Patients were classified according to the extent of abnormality as single-vessel being when the perfusion defect or WM abnormality involved only one coronary artery territory, and multivessel when the perfusion defect or WM abnormality involved more than one coronary artery territory.

Attenuation from contrast or lung interference was defined as present if the endocardial and epicardial borders of a segment could not be visualized, and, thus, were not distinguishable from surrounding tissues. The intraobserver agreement of RTCE in our laboratory for the analysis of myocardial perfusion is 92%, and that for the analysis of WM is 92%. The interobserver agreement for the analysis of myocardial perfusion and WM is 84 and 91%, respectively.

Diagnostic accuracy of real-time contrast echocardiography

The diagnostic accuracy of RTCE for detecting CAD in the elderly was determined in 60 (14%) of the patients who underwent quantitative
coronary angiography (QCA) within 1 month from the stress test at the discretion of the referring physician. Patients were referred to QCA on the basis of the results of the stress echocardiogram or because of chest pain symptoms that were considered diagnostic of CAD. QCA was performed by an experienced interventional cardiologist unaware of the results of RTCE. Any visually evident stenosis was measured using a hand-held electronic caliper (Tesa S.A., Renes, Switzerland) operated with custom-developed PC software. Measurements were expressed as the per cent diameter narrowing using the diameter of the nearest normal-appearing region as the reference. Significant CAD was defined as >50% luminal diameter stenosis in one or more major coronary arteries.

Follow-up

Follow-up was obtained from review of the patient’s hospital chart, electronic records, and telephone interview with the patient. The endpoints of the study were cardiac death and non-fatal MI. Non-fatal MI was defined as a serial increase in cardiac-specific enzymes, with or without new electrocardiographic changes. The cause of death was obtained by the review of patient charts. Cardiac death was defined as death associated with known or suspected MI, life-threatening arrhythmia, or pulmonary edema. Sudden unexpected death occurring without another explanation was included as cardiac death. Follow-up was completed in December 2005.

Statistical analysis

Previous studies in the general population have shown that perfusion imaging with RTCE adds significant predictive value over WM in general, using a sample size of approximately 800 patients. Disease prevalence (and subsequent event rates) is higher in the elderly. Previous studies have suggested a doubling of the disease prevalence rates reduces the sample size required to detect an incremental benefit of a given screening test by 75%. We conservatively chose to reduce the sample size by ~50%.

Continuous variables were expressed as mean and standard deviation and categorical variables as proportions. Two-tailed unpaired and paired Student t-tests were used for inter- and intragroup comparisons, respectively. Percentage of agreement and κ statistics were used to evaluate concordance during dobutamine stress RTCE. The sensitivity, specificity, predictive values, and accuracy of WM and MPI for detecting angiographically significant CAD were calculated according to standard definitions and were presented with their respective 95% confidence intervals (CIs). Fisher’s exact test was used for 2 × 2 contingency tables, and a Wald’s χ² test for n-way contingency tables.

Univariate analysis was performed to evaluate differences in the proportion of cardiac event rates on the basis of any potentially significant or more major coronary arteries. The adjusted prognostic value of any variable used in the univariate analysis. This analysis was performed using logistic regression to determine the predictors of a binary outcome of death or non-fatal MI. The clinical and imaging variables tested in the analyses were those clinically proved to be associated with adverse cardiovascular events and included known cardiovascular risk factors, previous revascularization (CABG or PCI), use of beta blockers, lipid-lowering agents, diuretics, or ACE-inhibitors, as well as resting ejection fraction and WM responses to dobutamine stress.

All analyses were performed with SAS statistical software (SAS Institute Inc., Cary, NC, USA). Kaplan–Meier curves were used to estimate the distribution of time to the endpoint of interest. Three-year event free survival differences were compared between groups. Odds ratios were computed with respective 95% CIs for the combined endpoints of death and non-fatal MI.

Results

The mean age was 78 ± 5 years (range 70–92 years). Clinical characteristics are presented in Table 1. The peak dose of dobutamine was 29 ± 8 μg/kg/min. Atropine was injected in 247 (62%) patients, using a mean cumulative dose of 0.5 ± 0.5 mg. Optison was used in 251 (63%) patients, using a mean cumulative dose of 2.8 ± 0.8 mL. Definity was used in 148 (37%) patients, using a mean cumulative dose of 1.0 ± 0.3 mL. Ninety of the patients (23%) had a history of malignancy and eight had a history of dementia (2%). Some abnormality on the resting EKG (bundle branch block, intraventricular conduction delay, abnormal Q waves) was noted in 12 of the 324 (3.7%) patients.

Table 1

<table>
<thead>
<tr>
<th>Variables</th>
<th>All patients</th>
<th>QCA patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;77 years</td>
<td>204 (51%)</td>
<td>19 (32%)</td>
</tr>
<tr>
<td>Male gender</td>
<td>188 (47%)</td>
<td>29 (48%)</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>88 (22%)</td>
<td>17 (28%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>102 (26%)</td>
<td>20 (33%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>299 (75%)</td>
<td>43 (72%)</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>221 (55%)</td>
<td>38 (63%)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>77 (19%)</td>
<td>16 (27%)</td>
</tr>
<tr>
<td>Previous percutaneous coronary intervention</td>
<td>48 (12%)</td>
<td>15 (25%)</td>
</tr>
<tr>
<td>Previous coronary artery bypass graft surgery</td>
<td>71 (18%)</td>
<td>8 (13%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medications</th>
<th>All patients</th>
<th>QCA patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers</td>
<td>209 (52%)</td>
<td>37 (62%)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>88 (22%)</td>
<td>16 (27%)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>64 (16%)</td>
<td>17 (28%)</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>148 (37%)</td>
<td>32 (53%)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>148 (37%)</td>
<td>24 (40%)</td>
</tr>
<tr>
<td>Abnormal WM</td>
<td>129 (32%)</td>
<td>40 (67%)</td>
</tr>
<tr>
<td>Abnormal myocardial perfusion</td>
<td>183 (46%)</td>
<td>52 (87%)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction &lt; 50%</td>
<td>65 (16%)</td>
<td>9 (15%)</td>
</tr>
</tbody>
</table>

Table 1 Clinical characteristics of all patients in the study and the selected group that went on to coronary angiography (QCA)

Data are number (%) of patients. ACE, angiotensin converter enzyme; QCA, quantitative coronary angiography.
waves, non-specific ST/T wave abnormality, or left ventricular hypertrophy) was present in 147 patients (37%).

Resting left ventricular ejection fraction was abnormal in 65 patients (16%). WM was abnormal at rest in at least one coronary artery territory in 96 patients (24%). Dobutamine stress RTCE resulted in a significant increase in heart rate (from 72 ± 13 to 139 ± 12 b.p.m.; P < 0.001) and decrease in systolic (from 155 ± 25 to 144 ± 32 mmHg; P < 0.001) and diastolic (from 77 ± 12 to 68 ± 15 mmHg; P < 0.001) blood pressures. The predicted maximal heart rate reached at peak stress was 98 ± 9% of predicted for age, and rate-pressure product was 20 284 ± 4934 mmHg/min. The stress test was accomplished without serious complication in any patient. No MI or death during or immediately after dobutamine stress occurred.

**Diagnostic accuracy of dobutamine stress real-time contrast echocardiography**

Among the 60 patients who underwent QCA, significant CAD was detected in 50 (83%) patients. Thirteen patients had single-vessel, 18 had two-vessel, and 19 had three-vessel CAD. Coronary artery stenoses involved the left anterior coronary artery territory in 42, right coronary artery in 35, and the left circumflex in 29 patients. A total of 42 patients had CAD in the posterior circulation (right coronary or left circumflex artery distribution). An abnormal stress test based on WM analysis correctly identified 37 of the 50 patients with CAD. WM was normal in seven patients without CAD, and abnormal in three. On the other hand, an abnormal MPI study correctly identified 48 of the 50 patients with CAD and failed to identify significant disease in two patients (both with single-vessel CAD by quantitative angiography). MPI was normal in six patients without CAD, and abnormal in four. Sensitivity of WM for detecting angiographically significant CAD on a patient basis was 74% (95% CI 62–86), specificity was 70% (95% CI 42–98), and accuracy was 73% (95% CI 62–84). Corresponding values for MPI were 94 (95% CI 91–99), 67 (95% CI 36–74), and 90% (95% CI 82–95), respectively.

![Figure 1](https://academic.oup.com/eurheartj/article-abstract/29/3/377/507540/1)

**Figure 1** Example of dobutamine stress myocardial contrast echocardiography images from the apical two-chamber view in a 74-year-old man who had hypercholesterolaemia and history of cigarette smoking. The patient had normal wall motion and homogenous myocardial contrast enhancement at rest (left panel). At peak stress, patient developed hypokinesis and an inducible perfusion defect in the mid and apical segments of inferior wall (black arrows, mid panel). Subsequent coronary angiography revealed significant lesions in the right coronary artery as indicated by the white arrows (right panel).

![Figure 2](https://academic.oup.com/eurheartj/article-abstract/29/3/377/507540/2)

**Figure 2** An example (at end-systole) of an inducible septal and apical perfusion defect in the apical four-chamber view during dobutamine stress with real-time contrast echocardiography in an elderly patient where wall motion responses were normal.
normal WM responses. The sensitivity of MPI for detecting CAD in the anterior circulation was 86% (95% CI 78–92), and specificity was 67% (95% CI 49–80), whereas the sensitivity in the posterior circulation was 69% (95% CI 61–74) and specificity was 78% (95% CI 59–90). The diagnostic accuracy of MPI was similar in both circulations (Figure 3).

**Prognostic value of dobutamine stress real-time contrast echocardiography**

Follow-up data were available in all patients, and a total of 46 (11.5%) events occurred (31 cardiac deaths, 15 non-fatal MIs). The median follow-up time for patients who did not experience an event was 21 months. Events occurred at a median of 15 months after the dobutamine stress test. The event rate was 4.2% (7/216) in patients with normal MPI, 19.0% (8/42) in patients with a fixed perfusion defect, 18.8% (19/101) in patients with inducible perfusion defect, and 25.0% (10/40) in patients with both fixed plus inducible perfusion defects. The event rates in patients with multivessel and single-vessel patterns of perfusion defects (28.9 and 14.0%, respectively) were significantly different (P = 0.04), and both were significantly higher than patients with normal MPI (P = 0.009 for normal MPI vs. single-vessel perfusion defects and P = 0.0001 for normal MPI vs. multivessel perfusion defects). Figure 4 demonstrates the Kaplan–Meier curves for event-free survival on the basis of abnormal vs. normal myocardial perfusion and WM. As can be seen, an abnormal myocardial perfusion response resulted in a significantly worse outcome, irrespective of WM responses. MPI remained a significant independent predictor of events even after excluding patients in the study who had prior MI, revascularization, or ejection fraction < 50% (Wald χ² 15.3, P < 0.0001).

Figures 5 and 6 demonstrate the effect of the extent and reversibility of the perfusion defect on outcome in the elderly. As can be seen in Figure 5, patients with a multivessel pattern of perfusion abnormalities during dobutamine stress had the worst outcome. Interestingly, the fixed defect group without inducible defects had the same prognosis as those with both fixed and inducible myocardial perfusion defects. This finding could be explained by the lower resting ejection fraction in the patients with fixed defects only. The mean ejection fraction in the patients with fixed only defects and those with fixed and inducible defects was
of outcome in the univariate analysis, MPI was the most significant predictor of adverse events ($\chi^2 7.5$; 95% CI 0.071–0.647; $P = 0.006$), whereas WM was not an independent predictor of events. The other significant predictors of events in the multivariable analysis were age ($\chi^2 3.95$; 95% CI 0.93–1.00; $P = 0.047$) and diuretic use at the time of the stress echo ($\chi^2 5.78$; 95% CI 0.21–0.85; $P = 0.01$). Of the 23 events that occurred in patients on diuretics, seven were on this drug for hypertension and 10 for a history of heart failure. In six patients, no definite indication for diuretic use at the time of the stress echo could be found.

**Discussion**

Elderly patients compose a significant percentage of patients in cardiology practices today and would be expected to have a higher prevalence of CAD as well as other diseases which may affect outcome. Vital statistics data have shown a shift in disease burden towards the older segments of the population. Cardiovascular disease remains the leading cause of death in the elderly, and the costs of both the medical and surgical treatments for CAD are increasing. Therefore, non-invasive tests designed to detect CAD in this age group must be reliable and cost-effective in identifying which patients are at greatest need for these treatments and interventions. In this setting, we found that MPI with RTCE was the most significant predictor of cardiovascular outcome when compared with all other imaging, clinical, and medication variables which may affect outcome.

The dobutamine stress echocardiogram has been reported as a safe and feasible pharmacological method for the evaluation of elderly patients with suspected CAD. However, when compared with myocardial perfusion, WM responses to dobutamine may underestimate the severity of CAD that exists, or fail to detect
CAD if a critical level of demand stress is not achieved.\textsuperscript{12–14,24–26} In this regard, RTCE has been demonstrated to improve the sensitivity and accuracy of DSE by simultaneously assessing myocardial perfusion along with WM. The mechanism for the higher sensitivity of MPI over WM appears to be related to the cascade of pathophysiological events during demand ischaemia, in which myocardial perfusion defects precede WM abnormalities during incremental dobutamine infusion.\textsuperscript{24} As the target heart rate during DSE is defined by patient age, test endpoints in older patients are generally reached at lower heart rates. In this study, the mean heart rate achieved was 138 b.p.m., which was lower than peak heart rates achieved in younger patient populations, examining patient outcome.\textsuperscript{15} At this lower heart rate, MPI may have been abnormal while WM still normal, resulting in both the higher sensitivity and diagnostic accuracy of MPI over WM analysis for detecting CAD.

**Prognostic value of stress tests in elderly patients**

Despite widespread availability of non-invasive tests such as treadmill exercise and pharmacological stress, the prognostic value of these tests has not been fully characterized in patients >70 years. The prognostic role of exercise imaging with echocardiography has been shown to add to other clinical and workload variables.\textsuperscript{27} However, patients >70 years frequently have exercise intolerance due to co-morbidities such as peripheral vascular disease, degenerative joint disease in the lower extremity, or problems with balance on a treadmill. Because of this, it is essential to identify what pharmacological stress imaging variables will provide data that can supplement clinical data in predicting cardiovascular outcome in the elderly. Poldermans et al.\textsuperscript{10} evaluated WM responses in 166 patients ≥70 years of age who underwent dobutamine–atropine stress echocardiography and were followed for a mean of 16 months. The authors demonstrated that the presence of new WM abnormalities was an independent predictor of events including cardiac death, MI, and unstable angina pectoris (odds ratio 5.2; 95% CI 2.0–14.0). However, the sample size was small, and there was still nearly a 7% event rate during this short follow-up period in patients with negative WM responses. In the present study, it was found that WM responses were a univariate predictor of outcome, but not an independent predictor of events when myocardial perfusion responses were also considered. This improvement in the predictive value of MPI over WM can be explained in part by the better accuracy of MPI in detecting both the presence and extent of CAD.\textsuperscript{12–14} Similar to previous studies evaluating perfusion imaging during stress,\textsuperscript{15,28} the extent of the perfusion defect (single-vessel vs. a multivessel pattern) was important in predicting outcome (Figure 5).

We also observed that patients with only a fixed perfusion defect had a significantly worse outcome, equivalent to those with both fixed and inducible defects. These findings are supported by Shaw et al.,\textsuperscript{29} who demonstrated that any defect observed with thallium-201 perfusion (fixed or inducible) was a significant predictor of cardiac death and non-fatal MI in 348 ≥70-year-old patients. These investigators, however, utilized dipyridamole stress and did not examine the incremental value of MPI over other imaging variables (e.g. dobutamine WM responses; resting ejection fraction) which may also have an impact on event-free survival in this setting.

In all age patients referred for dobutamine stress myocardial perfusion studies, 3-year event-free survival was 95% in patients with normal myocardial perfusion responses.\textsuperscript{15} In the elderly patient population in this study with a normal MPI response, 3-year event-free survival was slightly worse at 89%. However, event-free survival was also worse when compared with all age

**Table 2 Predictors of non-fatal myocardial infarction or cardiac death by univariable and multivariable analyses**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate $P$-value</th>
<th>Multivariable $P$-value</th>
<th>Wald $\chi^2$</th>
<th>Multivariable odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>0.060</td>
<td>0.333</td>
<td>0.939</td>
<td>0.764 (0.311–1.876)</td>
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<tr>
<td>Age</td>
<td>0.022</td>
<td>0.047</td>
<td>3.964</td>
<td>0.965 (0.932–0.999)</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>0.079</td>
<td>0.709</td>
<td>0.002</td>
<td>1.666 (0.675–4.113)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.150</td>
<td>0.736</td>
<td>0.114</td>
<td>0.586 (0.242–1.418)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.000</td>
<td>0.557</td>
<td>0.345</td>
<td>0.876 (0.405–0.895)</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>0.529</td>
<td>0.236</td>
<td>1.401</td>
<td>0.983 (0.442–2.187)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>0.691</td>
<td>0.268</td>
<td>1.225</td>
<td>1.135 (0.410–3.140)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>0.232</td>
<td>0.807</td>
<td>0.059</td>
<td>1.978 (0.399–2.400)</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>0.304</td>
<td>0.962</td>
<td>0.002</td>
<td>1.344 (0.649–2.783)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>1.000</td>
<td>0.426</td>
<td>0.6339</td>
<td>1.094 (0.470–0.546)</td>
</tr>
<tr>
<td>Lipid-lowering agents</td>
<td>0.876</td>
<td>0.087</td>
<td>2.937</td>
<td>0.483 (0.175–1.331)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>0.285</td>
<td>0.913</td>
<td>0.012</td>
<td>1.023 (0.479–2.181)</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>0.256</td>
<td>0.954</td>
<td>0.003</td>
<td>0.418 (0.207–0.845)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>0.034</td>
<td>0.015</td>
<td>5.899</td>
<td>0.99 (0.478–2.05)</td>
</tr>
<tr>
<td>Ejection fraction &lt; 50%</td>
<td>0.031</td>
<td>0.740</td>
<td>0.110</td>
<td>1.448 (0.685–3.059)</td>
</tr>
<tr>
<td>Abnormal WM</td>
<td>&lt;0.0001</td>
<td>0.159</td>
<td>1.98</td>
<td>0.215 (0.072–0.648)</td>
</tr>
<tr>
<td>Abnormal MPI</td>
<td>&lt;0.0001</td>
<td>0.006</td>
<td>7.469</td>
<td>0.867 (0.372–2.018)</td>
</tr>
</tbody>
</table>

ACE, angiotensin converter enzyme; CABG, coronary artery bypass graft; CI, confidence interval.

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patients) for patients with abnormal myocardial perfusion (79% for those with abnormal myocardial perfusion compared with 84% in all age groups). Elderly patients with fixed perfusion defects had 60% event-free survival, compared with 79% survival in the general population. These findings indicate the importance of associated co-morbidities in the elderly in affecting outcome.

The assessment of perfusion imaging with RTCE has distinct advantages over perfusion scintigraphy. One such advantage is the significantly higher resolution (>10 mm radionuclide imaging vs. <2 mm for contrast echo). Thus, RTCE can detect subendocardial perfusion defects that would otherwise go undetected by scintigraphy. Other distinct advantages of MPI with RTCE include no ionizing irradiation, immediate availability of results, lower costs, and the ability to perform and interpret stress and rest images in the same setting.

Study limitations
The indication for coronary angiography was performed at the discretion of the referring physician, and not because of study protocol. Since the results of the DSE were made available to the referring physician, it is likely that only patients with positive studies had angiograms within 1 month of the DSE. This will impact our test sensitivity results to a greater degree, since we cannot truly ascertain how many false-negative studies occurred.

It is possible that WM abnormalities induced by dobutamine could have been missed when using the slower frame rates (25–30 Hz) utilized with real-time perfusion imaging. However, the increased ability to visualize the endocardial border with ultrasound contrast may have aided in the detection of dobutamine-induced hypokinesis. Small trials comparing these lower frame rates utilized with RTCE and more conventional frame rates have shown no difference in the ability to identify significant CAD.

This study was performed at one site, with several years of experience in performing RTCE. Multicentre trials will be required to determine the true ability of this technique to detect CAD and predict outcome when compared with conventional WM analysis during dobutamine stress.

Conclusions
Dobutamine stress RTCE provides independent information for predicting cardiac events in the elderly. The assessment of myocardial perfusion responses may be more important than clinical variables or traditional imaging variables (ejection fraction, WM responses) in identifying unstable elderly patients at higher risk for cardiac death or non-fatal MI.

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References
13. Elhendy A, O’Leary EL, Xie F, McGrain AC, Anderson JR, Porter TR. Comparative accuracy of real-time myocardial contrast perfusion imaging and wall motion analysis during dobutamine...