Long-term prognostic value of dipyridamole stress myocardial contrast echocardiography

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Received 1 April 2011; accepted after revision 13 July 2011; online publish-ahead-of-print 10 August 2011

Aims
The aim of this prospective study was to determine long-term prognostic value of myocardial contrast echocardiography (MCE) combined with high-dose dipyridamole stress echocardiography (DSE) in patients undergoing diagnostic work-up for stable coronary artery disease (CAD).

Methods
A total of 202 consecutive patients (67% males, age 57 ± 8 years) with suspected or known stable CAD scheduled for coronary angiography underwent high-dose dipyridamole/atropine stress echocardiography (dipyridamole 0.84 mg/kg, iv; atropine up to 1 mg, iv) with MCE at baseline and peak stress. In 102 patients MCE was performed using electrocardiographic-triggered end-systolic harmonic imaging and in 100 patients using real-time MCE. Contrast enhancement was obtained by repeated iv boluses of contrast and was visually scored in 18 segments by consensus of 2 experienced observers. All patients completed prospective follow-up regarding major adverse cardiovascular events (cardiac mortality, revascularization, infarction and unstable angina) for a mean period of 32 ± 11 months (range: 1–89 months). The prognostic value of inducible wall motion abnormalities (WMA) and perfusion defects (PD) was then analysed.

Results
CAD defined as ≥70% stenosis was found in 152 patients (75%). During follow-up major adverse cardiovascular events (MACE) occurred in 109 (54%) patients (10 deaths, 16 infarctions, 83 revascularizations). The presence of inducible WMA in DSE was associated with high risk of MACE [hazard ratio (HR): 5.4; 95% CI: 3.64–8.05, \( P, 0.0001 \)]. Cardiovascular complications were best predicted by the presence of any inducible abnormality—PD or WMA (HR: 6.1; 95% CI: 4.1–9.1, \( P, 0.0001 \)).

Conclusion
Stress MCE is highly predictive of cardiovascular events in patients with suspected or known CAD in long-term follow-up.

Keywords
Coronary artery disease • Myocardial contrast echocardiography • Dipyridamole stress echocardiography • Prognosis

Introduction
Detection of reversible ischaemia and assessment of the physiological significance of coronary lesions are the most important applications of stress echocardiography (SE). Its important advantage is the possibility to perform the test in patients who cannot undergo standard electrocardiographic (ECG) exercise stress testing or whose ECG test result is equivocal. Several studies documented the prognostic importance of SE results with the possibility to identify patients with low risk of coronary events.1,2 Myocardial perfusion abnormalities occurring during stress, which also have both diagnostic and prognostic significance, are traditionally demonstrated with radionuclide imaging. The development of ultrasound contrast agents expanded the possibilities of echocardiographic diagnosis of myocardial ischaemia.3,4 Intravenous injection of ultrasound contrast agents is currently used to obtain left ventricular cavity opacification,5 but myocardial perfusion imaging remains a promising target. The aim of our prospective study was to assess the prognostic value of the dipyridamole-atropine stress echocardiography (DSE) with assessment of myocardial perfusion using intravenous injections of contrast agent in unselected group of patients undergoing diagnostic work-up for exertional chest pain.

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doi:10.1093/ejechocard/jer133
Methods

Patient population and protocol

The study group comprised 202 consecutive subjects (67% males), with suspected or known coronary artery disease (CAD) scheduled for coronary angiography in our institution. Exclusion criteria were related to DSE protocol and included bronchial asthma, atrioventricular block grade II and III, unstable angina, symptomatic arterial hypotension. Study population characteristics are shown in Table 1. Within 30 days preceding coronary angiography all patients underwent DSE in conjunction with myocardial contrast echocardiography (MCE). The results of SE did not influence the initial qualification for coronary angiography. The study protocol was approved by the Ethics Committee of our institution and written consent was obtained from all participants.

Stress echocardiography

SE was performed using high-dose dipyridamole protocol. Patients were instructed to avoid methylxanthine derivatives for 24 h before this procedure. All other medications were continued as prescribed.

One hundred and two patients underwent standard dipyridamole protocol (two stages within 10 min—0.56 mg/kg over 4 min, followed by 4 min pause and additional 0.28 mg/kg over further 2 min). The remaining 100 patients underwent accelerated dipyridamole protocol (total dose of 0.84 mg/kg given over 4 min). If myocardial ischaemia was absent and the heart rate did not achieve 85% of age-predicted maximal heart rate (220; age), atropine was administered (up to 1 mg, iv dose). After each test 250 mg aminophyllin was administered intravenously regardless of the presence of ischaemia. The study was performed under continuous monitoring of ECG, blood pressure, and the heart rate.

Echocardiographic images were acquired at baseline, peak stress, and during recovery in three standard apical views using grayscale harmonic imaging (Acuson Sequoia C236, Siemens Medical Solutions USA, Inc., Malvern, PA, USA). Regional systolic function analysis was performed using 16-segment left-ventricular model and a 4-point scale for visual assessment of contractility (1 = normal, 2 = hypokinesis, 3 = akinesis, 4 = dyskinesis). Echocardiographic images were interpreted by consensus of two experienced observers and both wall motion and thickening were considered for analysis. Inducible ischaemia was defined as worsening of contractility during stress in two or more adjacent segments, which were initially normokinetic or hypokinetic.

Myocardial contrast echocardiography

After recording standard, grey-scale echo images, MCE was performed using commercially available perfluorocarbon-containing, albumin-encapsulated microbubble Optison (GE-Amersham, Princeton, NJ, USA) at rest and peak stress. It was injected slowly in bolus doses of 0.2–0.5 mL (mean 2.4 mL ± 0.6)—the doses were determined individually at the lowest level ensuring myocardial opacification of basal, middle, and apical segments of the left ventricle.

In the group of 102 patients MCE was performed using a high mechanical index, ECG triggered (end-systolic frames) harmonic imaging sampled with a frequency 1/4 heart cycles. In the remaining 100 patients undergoing accelerated dipyridamole protocol, MCE images were acquired using contrast pulse sequencing (CPS) technology. CPS is a low mechanical index (0.17–0.25), non-linear imaging technique for real-time contrast studies.

MCE was visually scored by consensus of two experienced investigators using a 3-point scale: 0—no contrast enhancement, 1—reduced (incomplete or patchy, non-homogenous or delayed) enhancement, 2—complete enhancement. Grades 0 and 1 were considered abnormal. An inducible perfusion defect was defined as a reduction in myocardial opacification in two or more adjacent segments.

Coronary angiography

Selective coronary angiography was performed using the Judkins or Sones technique. The angiograms were analysed quantitatively (Centricity AI 1000 GE/Met GE QCA 2.0, Camtronic Medical Systems Inc., Hartland, WI, USA) by a single investigator blinded to all other data.

Clinical follow-up

Patients were prospectively followed up for a mean period of 32 ± 11 months (range 1–89 months) by scheduled visits. If necessary, data were obtained by reviewing patients’ records from the outpatient clinic visits and hospitalizations.

Major adverse cardiovascular events (MACE) were defined as: cardiac death, acute coronary syndromes (ACS; myocardial infarction or unstable angina) or revascularization—coronary artery-bypass grafting (CABG), or percutaneous coronary intervention (PCI).

Statistical analysis

Continuous and categorical variables are expressed as mean ± SD and as percentages (%), respectively. For the analysis of event-free survival,

Table 1  Study population characteristics and coronary angiography results (n = 202).

<table>
<thead>
<tr>
<th>Demographic data</th>
<th></th>
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</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>57 ± 8</td>
<td></td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>135/67</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>27 ± 4</td>
<td></td>
</tr>
<tr>
<td>Clinical data (%)</td>
<td>2.2 ± 0.6</td>
<td></td>
</tr>
<tr>
<td>CCS class</td>
<td>83 (41)</td>
<td></td>
</tr>
<tr>
<td>History of Q-wave myocardial infarction (%)</td>
<td>36 (18)</td>
<td></td>
</tr>
<tr>
<td>History of non-Q wave myocardial infarction</td>
<td>44 (22)</td>
<td></td>
</tr>
<tr>
<td>Previous PCI (including primary PCI)</td>
<td>6 (3)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>152 (75)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>30 (15)</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>126 (62)</td>
<td></td>
</tr>
<tr>
<td>Current smokers</td>
<td>29 (14)</td>
<td></td>
</tr>
<tr>
<td>Current anti-ischaemic pharmacological treatment (%)</td>
<td>176 (87)</td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>22 (11)</td>
<td></td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>186 (92)</td>
<td></td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>85 (42)</td>
<td></td>
</tr>
<tr>
<td>Long-acting nitrates</td>
<td>152 (77)</td>
<td></td>
</tr>
<tr>
<td>Coronary angiography results (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>69 (34)</td>
<td></td>
</tr>
<tr>
<td>Single-vessel</td>
<td>65 (32)</td>
<td></td>
</tr>
<tr>
<td>Three-vessel</td>
<td>18 (9)</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as the mean value ± SD or number (% of patients). CCS, Canadian Cardiovascular Society; ECG, electrocardiographic; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.
patients were divided into subgroups according to the presence of wall motion abnormalities (WMA) and perfusion defects. Kaplan–Meier curves of event-free survival were generated and hazard ratios (HR) were calculated. Effect of covariates on outcome was determined using the Cox proportional hazard regression in a stepwise manner. Clinically relevant variables with a P-value < 0.1 on univariate analysis were included in the multivariate model. P-value of less than 0.05 was considered to indicate statistical significance. Positive and negative prognostic values for individual tests were evaluated using standard definitions. Statistical analysis was performed using MedCalc software, version 9.6.4.0 (Belgium).

Results

Stress echocardiography and angiography results

The DSE protocols and the contrast administration were well tolerated by patients and no significant adverse events were observed during the test and in recovery phase. The result of DSE assessed on the basis of WMA was positive for ischaemia in 91 (45%) of patients, whereas the result of stress MCE was positive for ischaemia in 123 (61%) of patients. Normal MCE results were observed in 54 (27%) patients, whereas 25 (12%) patients had resting perfusion abnormalities.

Coronary angiography revealed significant coronary artery stenosis (defined as ≥70% diameter stenosis or ≥50% left main coronary artery diameter stenosis) in 152 (75%) patients (Table 1).

Clinical follow-up

During the follow-up period (mean 32 ± 11 months; range: 1–89 months) MACE occurred in 109 patients (54%): 10 patients (5%) died, 16 patients (8%) had ACS and 83 patients (41%) underwent coronary revascularization (including 58 PCIs and 25 CABGs). The decisions to revascularize were not influenced by MCE results.

The number of stenotic arteries was a significant prognostic factor for MACE (P = 0.0008). However, within the group of patients with confirmed coronary artery disease there was no significant relationship between the MACE rate and the number of diseased coronary arteries (P = 0.26).

The presence of inducible WMA in DSE was associated with high risk of MACE (HR:5.4; 95% CI: 3.64–8.05, P < 0.0001). Figure 1 presents event-free survival curves in patients with and without inducible WMA during DSE. However, cardiovascular complications were best predicted by the presence of any inducible abnormality—perfusion defect or WMA (HR: 6.1; 95% CI: 4.1–9.1, P < 0.0001) as presented on Figure 2. The criterion of any inducible abnormality had high negative and positive predictive value for the occurrence of MACE—73 and 91%, respectively. Similar results were obtained after excluding from analysis 29 patients who underwent early revascularization (within 1 month of MCE)—the presence of inducible WMA in DSE was still associated with high risk of MACE (HR: 4.85; 95% CI: 3.1354–7.5134, P < 0.0001), but the prognostic value of the criterion of any inducible abnormality—perfusion defect or WMA was higher (HR: 5.155; 95% CI: 3.3161–8.0145, P < 0.0001).

Moreover, in our study group in the multivariate model the only independent risk factor of MACE was the presence of any inducible abnormality (WMA or perfusion defect) on DSE (HR: 3.20; 95% CI: 1.61–6.36; P = 0.0009). The prognostic value of inducible WMA did not reach statistical significance (HR: 1.96; 95% CI: 0.99–3.89; P = 0.0548).

The choice of MCE imaging technique (triggered vs. real-time) and stress protocol (standard vs. accelerated) did not influence the predictive value of test.

Discussion

Our study demonstrated that enriching standard DSE procedure with semiquantitative myocardial perfusion assessment enhances prognostic value of the test regarding the occurrence of combined clinical cardiovascular endpoint in long-term follow-up.
**Myocardial contrast echocardiography for perfusion assessment in stable coronary artery disease**

The standard modality used for the assessment of myocardial perfusion is radionuclide imaging, with proven high negative prognostic value for cardiac complications. Wei et al. have shown that intravenous MCE with a continuous infusion of microbubbles and assessment of reflow kinetics is a potential way of assessing myocardial perfusion. This was reinforced by other studies demonstrating the potential of the method for absolute quantification of coronary flow using MCE. Echocardiographic contrast agents applied during SE allow the differentiation of the well-perfused regions from hypoperfused regions of myocardium. Inducible perfusion defects precede the development of WMA thus increasing the sensitivity of SE and well correlates with radionuclide detection of ischaemia. It should also be emphasized that the spatial resolution of echocardiography is superior to that provided in radionuclide methods. However, the clinical application of contrast agents to detect stress-induced myocardial perfusion abnormalities remains an area of intense clinical investigation, especially with regard to prognostic value of the test.

**Myocardial contrast echocardiography for prognosis assessment in stable coronary artery disease**

Our paper is one of the first in the literature reporting the long-term prognostic significance of echocardiographic stress test in which myocardial perfusion was assessed parallel to contractile function. Similar results have been shown by Tsutsui et al. in a retrospective analysis 788 patients undergoing real-time contrast echocardiography during dobutamine SE. During a median follow-up of 20 months, 75 events (9.6%) occurred (58 deaths, 17 non-fatal myocardial infarctions). Abnormal myocardial perfusion had significant incremental value over clinical factors, resting ejection fraction, and wall motion responses in predicting fusion had significant incremental value over clinical factors, 17 non-fatal myocardial infarctions). Abnormal myocardial perfusion was the only significant independent risk factor of MACE during 32-month follow-up. In the multivariate model, the presence of any inducible abnormality (WMA or perfusion defect) on DSE was the only significant independent risk factor of MACE (HR: 3.20; P < 0.001). By multivariate analysis, abnormal myocardial perfusion was an independent predictor of death and non-fatal events (HR: 5.2; P < 0.0009), whereas the prognostic value of inducible WMA did not reach statistical significance (HR: 1.96; P = 0.0548).

**Limitations**

The patient population is relatively small and reflects the practice of a tertiary cardiology centre with underrepresentation of low-risk patients. High rate of coronary angioplasty might be related to low mortality rate, precluding the survival analysis at a given sample size.

We used only the visual method of evaluation of wall motion and perfusion abnormalities which carries the risk of subjectivity. Unlike quantitative techniques, visual assessment does not require time-consuming off-line analysis. Therefore, it can be more easily incorporated into clinical practice. Moreover, qualitative analysis of MCE has been shown to be highly reproducible—the intra- and interobserver concordances reported by Peltier et al. were 93% (κ = 0.84) and 92% (κ = 0.81), respectively. In our study, in order to minimize the subjectivity of analysis, the perfusion assessment was performed by consensus of two investigators.

Presently, the use of 17-segment model of the left ventricle is recommended. In this study, we used the 18-segment model, which is less widespread, but had also been used by some investigators.

To reflect everyday clinical practice, the study protocol was based on dipyridamole-atropine stress test performed in patients on standard anti-ischaemic treatment. Therefore, application of study results in population of untreated patients should be very cautious.

**Conclusion**

Stress-induced myocardial perfusion abnormalities assessed visually during a standard DSE carry additional long-term prognostic value in a group of patients undergoing diagnostic work-up regarding aetiology of exertional chest pain.

**Conflict of interest:** none declared.

**Funding**

This study was financially supported by budgetary measures for science.

**References**

Compression of the right atrium can be caused by many different aetiologies. Right atrial compression due to neoplasias is very rare. Malign or benign masses may compress the right atrium and the differential diagnosis is very important because of the prognostic difference between two groups. Although rare, right atrial compression might be due to the neighbouring neoplasm, such as mediastinal or lung tumours. Pericardial fatty tissue may be seen as a mass near the right atrium. Aortic, coronary artery and saphenous vein graft aneurysms and tortuous aorta may compress the right atrium. Abdominal structures may also compress the right atrium such as cystic lesion of other organs such as the liver and kidney. Diaphragmatic hernia and protruding intra-abdominal organs can cause a similar finding. Diaphragmatic hernia and protruding intra-abdominal organs may compress the right atrium. Abdominal structures may also compress the right atrium such as mediastinal or lung tumours. Pericardial fatty tissue may be seen as a mass near the right atrium. Aortic, coronary artery and saphenous vein graft aneurysms and tortuous aorta may compress the right atrium. Abdominal structures may also compress the right atrium such as cystic lesion of other organs such as the liver and kidney. Diaphragmatic hernia and protruding intra-abdominal organs can cause a similar finding. Diaphragmatic elevation can rarely be seen as a mass compressing the right atrium in transthoracic echocardiography. In our patient, there was neither a neoplasm nor a neighbouring structure compressing the right atrium according to the CT imaging, and the only finding was the right diaphragm elevation. Diaphragm elevation must be remembered as a rare aetiological cause of mass appearance compressing the right atrium.