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Stress echocardiography for the risk stratification of patients following coronary bypass surgery

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Abstract

Objectives: The aim of the study was to assess the prognostic value of stress echocardiography after surgical revascularization.
Methods: We evaluated 500 (100 women) patients who had undergone exercise or pharmacological SE after a median of 69 months after coronary artery by-pass grafting (CABG). Of these, 351 (70%) complained of symptoms suggestive of ischemic origin while 149 (30%) were tested for asymptomatic progression of the disease.
Results: SE was positive for ischemia in 196 (39%) patients. During a median follow-up of 25 months, 61 patients died, 33 had a nonfatal myocardial infarction, and 112 underwent late (>3 months) revascularization. Multivariable Cox' regression analysis indicated age (HR = 1.04; 95% CI 1.01–1.06; $p < 0.003$), and peak WMSI (HR = 3.07; 95% CI 1.96–4.81; $p = 0.0001$) as independent predictors of hard (total mortality and myocardial infarction) events. SE information provided a significant improvement in predictive power of the statistical model (chi-square increase 34%, $p < 0.0001$ for hard and 91%, $p < 0.0001$ for major events, respectively). Survival analysis showed ischemia at SE to be associated with significantly higher hard and major event rate in both symptomatic and asymptomatic patients.
Discussion: SE represents an effective tool for the risk stratification of patients with previous CABG independently of the presence of symptoms suggestive of ischemic origin.

Keywords: Coronary Artery by-grafting; Coronary artery disease; Stress echocardiography

1. Introduction

The need for stress testing after coronary artery bypass grafting (CABG) is based upon the possible presence of incomplete revascularization, the development of new disease in bypass grafts, and/or the progression of native coronary disease. Present guidelines from the American College of Cardiology/American Heart Association recommend exercise or pharmacologic stress with imaging using nuclear scan or echocardiography [1]. This recommendation is supported by the lower sensitivity of exercise ECG testing alone to identify ischemia and the need to document both site and extent of ischemia after revascularization.

The diagnostic accuracy of stress imaging techniques following CABG has been evaluated in a number of studies demonstrating an almost significant trend toward greater sensitivity of echocardiography compared to radionuclide perfusion scintigraphy [2]. Less attention, however, has gone to the assessment of the prognostic value of stress imaging, in particular with echocardiographic technique. In addition, physical exercise has been the most used stressing modality, even though a substantial proportion of post-CABG patients are unable to achieve adequate levels of exercise. Thus, we sought to evaluate the prognostic value of exercise or

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pharmacologic stress echocardiography (SE) in a consecutive series of patients who had undergone previous CABG.

2. Methods

2.1. Study population

From a prospective data bank including 8940 consecutive subjects with known or suspected coronary artery disease undergoing SE between 1995 and 2006, we selected 500 patients (100 women) according to the following criteria: 1) previous CABG, 2) no acute coronary syndromes occurring after the index CABG, 3) no significant valvular and/or congenital heart disease, 4) no prognostically relevant comorbidities, 5) adequate acoustic window. Patients had undergone SE at a median time of 69±24 months following CABG. Reasons for testing were the presence of symptoms suggestive of ischemic origin in 351 (70%) and screening for asymptomatic progression of the disease in 149 (30%) patients.

Informed consent was obtained from all patients before testing, and the study protocol was approved by the institutional ethical committee. Stress echo data were collected and analysed by stress echocardiographers not involved in patient care.

The stressor used (40 exercise, 349 dipyridamole and 111 dobutamine) was chosen on the basis of specific contraindications, local facilities and physician's preferences. Pharmacological stress echocardiography was used when patients were unable to exercise maximally, or when exercise electrocardiography result was nondiagnostic or inconclusive. Two-hundred forty seven (49%) patients were taking antianginal medical therapy (β-blockers in 121, calcium-antagonists in 113, and nitrates in 153) at the time of testing.

Diabetes [3], hypertension [4], and hypercholesterolemia [5] were defined according to standard criteria. All investigators of contributing centers passed quality control criteria for regional wall motion prior to entering the study as previously described [6].Data are entered in the data bank at the time of testing on the same day of test performance. Follow-up information on outcome is updated by a dedicated team of technicians supervised by physicians not involved in patient care. Physicians responsible for updating the follow-up information were unaware of stress echo and coronary angiography data.

2.2. Stress echocardiography

Exercise stress echo was conducted using a semi-supine bicycle ergometer with 25 W incremental loading every 2 min. Dipyridamole (up to 0.84 mg over 10 min with co-administration of atropine up to 1 mg, or up to 0.84 mg over 6 min) and dobutamine (up to 40 mg/kg/min with co-administration of atropine up to 1 mg) stress echo were performed according to the well-established protocols [7]. Echocardiographic images were semiquantitatively assessed using a 17 segments, 4-point scale model of the left ventricle [8]. A wall motion score index (WMSI) was derived by dividing the sum of individual segment scores by the number of interpretable segments. Stress-induced ischemia was defined as new or worsened wall motion abnormality or biphasic response (i.e. low-dose improvement followed by high-dose deterioration). Necrotic pattern was akinetic or dyskinetic myocardium with no thickening during stress.

2.3. Outcome measures

Outcome was determined from patients' interview at the outpatient clinic, hospital chart reviews and telephone interviews, if necessary. The clinical events recorded during the follow-up were death, myocardial infarction early (<3 months) and late (>3 months) coronary revascularization (surgery or angioplasty). Overall instead of cardiac mortality was considered in order to avoid misclassification of the death cause [9]. Only the first event was taken into account for analysis. Myocardial infarction was defined according to typical symptoms, electrocardiographic, and cardiac enzyme changes. Follow-up data were separately analyzed for the prediction of hard events (death, and myocardial infarction), and major events (death, myocardial infarction, and late revascularization).

2.4. Statistical analysis

Continuous and categorical variables are expressed as mean±SD and percentage, respectively. Differences between groups were compared using Student's t and chi-square test, as appropriate. The association of selected variables with outcome were assessed with the Cox's proportional hazard model using univariate and stepwise multivariate procedures. A significance of 0.05 was required for a variable to be included into the multivariate model, whilst 0.1 was the cut-off value for exclusion. Clinical, resting echo and SE information were sequentially entered into the model. A significant increase in global X2 of the model after the addition of individual variables indicated an incremental predictive value.

Survival rates were estimated with Kaplan–Meier curves and compared by the log-rank test. Statistical significance was set at $p<0.05$. Statistical Package for the Social Sciences (SPSS release 15.0, Chicago, Illinois) was used for analysis.

3. Results

Baseline characteristics of the study population are reported in Table 1.

Of the initial population, 52 patients were revascularized within 3 months from the index test (8 surgery and 44 PCI). Of them 36 (69%) had a positive test for myocardial ischemia.

During a median follow-up of 25 (1st quartile 7, 3rd quartile 49) months, 61 patients died, 33 had a nonfatal myocardial infarction, and 112 were revascularized at >3 months after the

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Table 1
Characteristics of the study population.

Age (years)	67±9
Males	400 (80%)
Prior myocardial infarction	316 (63%)
Left bundle branch block	23 (5%)
Diabetes mellitus	143 (29%)
Arterial hypertension	265 (53%)
Hypercholesterolemia	311 (62%)
Currently smokers	180 (36%)
β-blockers	121 (24%)
Calcium antagonists	113 (23%)
Nitrates	153 (31%)
At least one medication	247 (49%)
Resting wall motion score index	1.40±0.40
Resting wall motion abnormalities	363 (73%)

index SE. Thus, 94 (18%) patients experienced hard and 206 (41%) major events. Among patients with stress-induced ischemia, 48 hard (24%) and 78 (40%) major events were observed.

Univariate and multivariate predictors of hard and major events are reported in Table 2. After adjusting for the most significant covariates, age and peak WMSI were independent predictors of hard events. Same variables were significant predictors of major events. Sequential inclusion of rest and SE information significantly improved the predictive value of the model (Fig. 1).

Survival analysis showed ischemia at SE to be associated with significantly higher hard and major event rate (Fig. 2). Ischemia at SE was similarly associated to higher rate of major events in both symptomatic and asymptomatic patients (Fig. 3).

4. Discussion

The results of the present study demonstrate that rest and SE represent an effective tool for the risk stratification of patients with previous CABG. In particular, the evidence of ischemia at SE adds significant prognostic information to that provided by clinical data and resting echo. This reinforces previous observations with exercise [10], dobutamine [11], and dipyridamole [12] SE. Arruda et al. [10] reported echocardiographically assessed exercise ejection fraction and diabetes mellitus as independent predictors of outcome in 718 patients undergoing CABG 5.7±4.7 years before the index SE. Qualitatively assessed abnormal left ventricular end-systolic volume response to exercise independently predicted the combination of nonfatal myocardial infarction and cardiac death, whilst workload was an independent predictor of cardiac death. Though baseline echocardiographic measurements were not fully detailed. Authors acknowledged that the population studied was at increased risk of cardiac events, as also demonstrated by the inability to achieve maximal levels of exercise in 40% of patients. Noteworthy, rest and peak exercise WMSI but not exercise-induced ischemia were included as covariates in multivariate analysis. Bountioukos et al. [11] reported myocardial ischemia during dobutamine SE to be an independent predictor of the combined endpoint of cardiac death, nonfatal infarction and late revascularization in a mixed group of 293 patients who previously underwent either percutaneous or surgical coronary revascularization. All patients included were unable to perform an exercise test because of different prognostically relevant comorbidities. Therefore, also this study dealt with a population at increased risk of unfavourable outcome. More recently, Rossi et al. [12] investigated the prognostic value of dipyridamole SE in 104 symptom-free patients with recent (<12 months) complete revascularization either by CABG or percutaneous coronary intervention. In this low-risk population, ischemia at SE was a multivariable predictor of the composite endpoint of cardiac death and nonfatal acute coronary syndrome. Differently, our patients were consecutively considered for analysis independently of their risk profile and the stressor used, thus making results more transferable to routine clinical practice.

Table 2
Univariate and multivariate predictors of hard and major events.

	Hard events				Major events			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value HR	(95% CI)	*p* value
Age (years)	1.04 (1.01–1.06)	0.003	1.04 (1.02–1.07)	0.002	1.02 (1.00–1.04)	0.05	1.03 (1.00–1.04)	0.02
Gender (male)	1.69 (0.90–3.17)	0.10			1.63 (0.98–2.71)	0.06		
Symptoms vs no symptom	1.18 (0.75–1.86)	0.47			1.24 (0.85–1.80)	0.26		
Prior infarction	1.18 (0.75–1.85)	0.47			1.00 (0.70–1.42)	1.00		
Diabetes mellitus	1.45 (0.93–2.25)	0.10			1.43 (0.99–2.05)	0.05		
Arterial hypertension	1.28 (0.85–1.93)	0.24			1.10 (0.78–1.54)	0.58		
Hypercholesterolemia	1.06 (0.70–1.61)	0.80			0.95 (0.68–1.33)	0.77		
Smoking habit	1.12 (0.74–1.69)	0.59			1.32 (0.95–1.84)	0.10		
Left bundle branch block	0.92 (0.33–2.55)	0.88			1.06 (0.49–2.31)	0.88		
Resting WMSI	2.20 (1.39–3.46)	0.001			1.81 (1.23–2.65)	0.002		
Therapy at the time of test	0.99 (0.66–1.49)	0.97			0.98 (0.71–1.37)	0.93		
Peak WMSI	3.03 (1.93–4.77)	<0.0001	3.07 (1.96–4.81)	<0.0001	2.39 (1.64–3.48)	<0.0001	2.23 (1.52–3.28)	<0.0001

HR=hazard ratio; CI=confidence interval.

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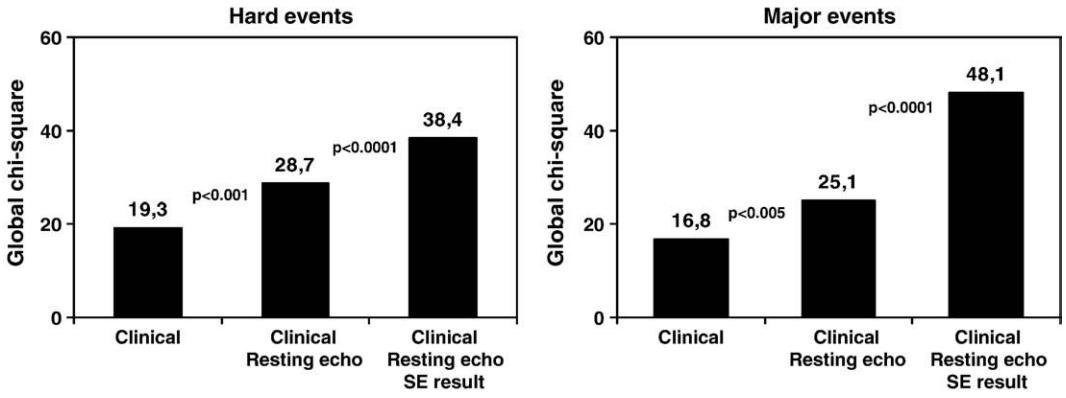

Fig. 1. Incremental value of stress echocardiography (SE) in predicting cardiac hard and major events. The sequential addition of rest and SE to the clinical information significantly increased the global chi-square of the predictive model.

The role of stress imaging for the evaluation of post-CABG patients is generally considered to depend upon the presence or absence of symptoms and the time from the surgical procedure. Although stress testing in patients with chest pain is appropriate, and multiple major society guidelines have argued against routine testing of all asymptomatic patients after CABG [13–15], symptoms are commonly atypical and cannot be considered as reliable determinants of restenosis or graft occlusion. In keeping with previous results with dobutamine SE [11], we found recurrence of chest pain not to be associated with increased risk of subsequent events at follow-up. Moreover, ischemia at SE was equally effective in predicting an increase risk of adverse outcome in symptomatic and asymptomatic patients. On the other hand, significant reversible perfusion defects suggestive of ischemia occur in about one-quarter of patients by one year after CABG; not all of these patients have angina [16,17]. Saphenous vein graft patency begins to decline rapidly after five years, while patency rates for arterial grafts remain high [18,19]. Stress perfusion imaging provided important prognostic information in patients >5 years post-CABG, irrespective of symptoms, and in symptomatic patients who were ≤5 years post-CABG [16,17,20]. So far, data have been more limited on the value of SE. The results of our study confirm that, independently of the stressor used, SE is an effective means of risk stratification at a median time of >5 years in post-CABG patients with or without ischemic symptoms and, therefore, it provides guidance to appropriate management. Likely to those with moderate to severe reversible perfusion defect on stress nuclear perfusion imaging [21], patients with inducible ischemia on SE should be considered for coronary angiography.

4.1. Clinical implications

Recent guidelines on appropriateness criteria for stress echocardiography released by the American College of Cardiology Foundation and the American Society of Echocardiography have identified (score=8, on a scale of 1 to 9) the execution of stress echo as “appropriate” in symptomatic patients after CABG, not in the early post-procedure period. Our results corroborate this indication, since there was a clear added prognostic value of stress echo in symptomatic patients after CABG [22].

The same guidelines consider stress echo “inappropriate” (score=2) in asymptomatic patients less than 5 years after CABG, and of “uncertain” appropriateness in asymptomatic

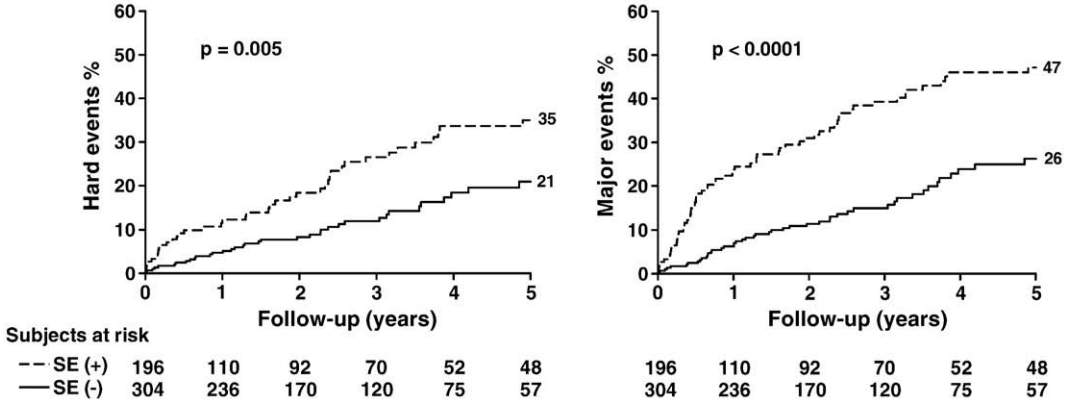

Fig. 2. Hard and major event rate curves according to the presence (+) or absence (−) of ischemia at stress echocardiography (SE).

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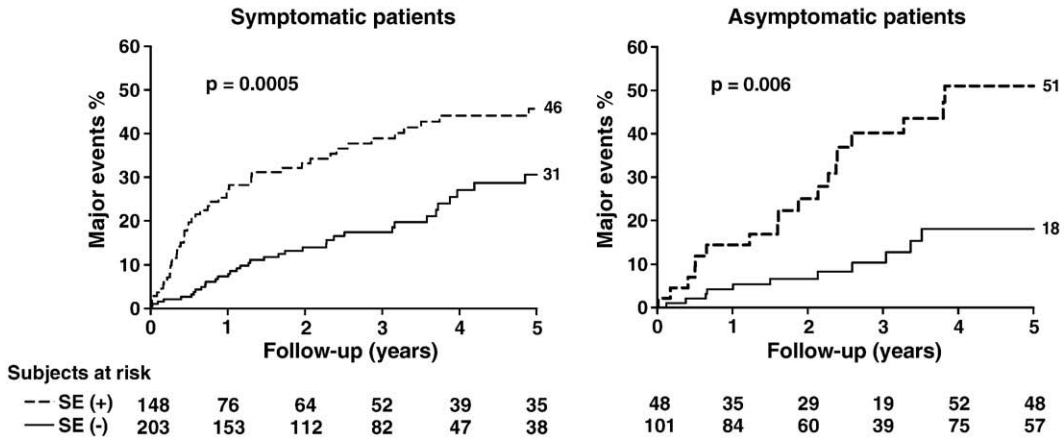

Fig. 3. Major event rate curves in symptomatic and asymptomatic patients according to the presence (+) or absence (−) of ischemia at stress echocardiography (SE).

patients evaluated at greater than or equal than 5 years after CABG. In this latter group, the score is 5 in patients who were asymptomatic (e.g., silent ischemia) prior the previous revascularization and 6 in patients who were symptomatic prior to revascularization. In this diagnostic "gray zone", we certainly need more evidence. The results of the present study document a clear added value of stress echo over clinical and resting echo variables. This extra-value was high in asymptomatic patients, and of the same order of magnitude as in symptomatic patients. Interestingly, these data are consistent with current practice in the real world. In a comment released for Heartwire on appropriateness guidelines, a stress echo practitioner stated that "I also feel strongly that periodic stress testing is helpful in patients who required intervention despite the fact that their course was asymptomatic until their heralding event. I would not feel comfortable waiting five years post-CABG – as it is recommended – in patients who have continued to smoke or who have developed diabetes in the interim, for example" [23]. The data of the present study may help to reconcile the gap between current practice and guidelines recommendations, shifting the evidence in favour of an earlier and more liberal approach to stress imaging, especially considering the relatively low cost and lack of radiation exposure of stress echo, impacting favorably on cost-benefit [24], risk-benefit [25], and patient's acceptance [26], profile when compared to myocardial perfusion imaging or cardio-CT [27].

4.2. Study limitations

Pooled results of exercise, dipyridamole and dobutamine stress echo are presented. Although they can induce ischemia by different mechanisms, their prognostic value [28–32] is comparable when state of the art protocols are used. Due to the long recruitment period, the outcome based on stress test results may have been potentially influenced by evolution of methodology, technology, expertise, advances in medical and interventional treatments. In this study, there was no central reading. Stress echocardiography was interpreted in the peripheral centers and entered directly in the data bank. This system allowed substantial sparing of human and technologic resources but it was also the logical pre-requisite for a large scale study, designed to represent the realistic performance of the test rather than the results of a single lab – or even a single person – working in a highly dedicated echo laboratory. Because the assessment of the echocardiograms was qualitative and subjective, variability in reading the echocardiograms might have modulated the results of individual centers. However, all our readers in individual centers had a long lasting experience in echocardiography, and passed the quality control in stress echo reading as previously described [6]. Incomplete coronary revascularization may have influenced stress test results and on its turn outcome for the present patient population. However, we may assume the number of incomplete revascularizations to be very small, if not negligible.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [33].

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