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Prognostic Value of Pharmacological Stress Echocardiography in Diabetic Patients

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Our study was undertaken to assess the prognostic significance of pharmacological stress echocardiography in 325 diabetic patients. Pharmacological stress echocardiography was performed for diagnosis of coronary artery disease in 128 patients, and for risk stratification in 197 patients. Follow-up was 34 months. Cardiac-related death and non-fatal myocardial infarction were considered hard events. During the follow-up period, there were 38 deaths and 23 acute non-fatal myocardial infarctions. By univariate analysis, a pharmacological stress echocardiography positive response for ischaemia indicated an increased risk of cardiovascular death. However, by multivariate analysis, advanced age and peak ejection fraction <40% were the only independent predictors of cardiac death. The same peak ejection fraction (EF) <40%, rest wall motion score index and previous myocardial infarction were independent predictors of hard events. After dividing the population into two subgroups on the basis of EF at rest, only a peak EF <40% and a pharmacological stress echocardiography positive test were powerful independent predictors of cardiovascular mortality.

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Key Words: stress echocardiography; prognosis; coronary artery disease; diabetes mellitus; ejection fraction.

Introduction

Patients with diabetes mellitus have an increased risk of ischaemic cardiovascular morbidity and mortality[1,2]. Therefore, the non-invasive diagnosis of ischaemic heart disease in these patients is essential for their management and risk stratification[3–9].

Pharmacological stress echocardiography is a widely used tool for both diagnosis of ischaemic heart disease and risk stratification in different clinical situations. Its efficacy has been demonstrated in patients with known or suspected ischaemic heart disease[10–14], after uncomplicated acute myocardial infarction (AMI)[15,16] and before major vascular surgery[17–19]. Pharmacological stress echocardiography for identifying diabetic patients at high risk of cardiac events remains less evaluated. Recent studies have shown an overall good prognostic power of the pharmacological stress echocardiography[4–9], but these studies are not directly comparable because they differ in follow-up duration, definition of cardiac events and analysis of pharmacological stress echocardiography variables. Therefore, this study was undertaken to assess the prognostic significance of pharmacological stress echocardiography to predict late cardiac events in diabetic patients with proven or suspected ischaemic heart disease during a follow-up of 34 months.

Methods

Patients Population

The initial cohort included 350 diabetic patients who underwent pharmacological stress echocardiography

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from July 1996 to December 2000 for chest pain or evaluation of their cardiac risk. Diabetes mellitus was defined by the presence of a fasting blood glucose >140 mg/dl (7.77 mmol/l) on at least two occasions and/or requiring insulin or oral hypoglycaemic agents. Nineteen patients underwent coronary artery revascularization 3 months after the pharmacological stress echocardiography, and six patients were lost to follow-up.

Patient outcome and their clinical status were assessed in 325 patients for a mean period of 33.9 months (range 4–60 months). Pharmacological stress echocardiography was performed for diagnosis of suspected ischaemic heart disease in 128 patients (39.4%), and for risk stratification of known ischaemic heart disease in 197 patients (60.6%). Medical treatment was not discontinued.

Follow-up data were obtained by reviewing patient's hospital records, by periodical follow-up visit in our institution or by interview over phone. In case of death of a patient, data were collected over phone from a household family member.

Pharmacological Stress Echo

Patients unable to exercise underwent pharmacological stress echocardiography. Dobutamine was used in 195 (60%) patients and dipyridamole in 130 (40%) patients, following a standard protocol. The test started with a dose of 5 and 10 μg/kg/min in a 5-min period in patients with resting abnormal wall motion, followed by 10, 20, 30 and 40 μg/kg/min in 3-min stages. The dipyridamole infusion included a low dose of 0.56 mg up to a high dose of 0.84 mg over 10-min. During the tests, 12-lead ECG and blood pressure were continuously monitored. Both protocols included atropine administration if the test was negative at the peak dose or heart rate did not reach 85% of maximal age-predicted heart rate[19]. Criteria for test interruption were: maximal heart rate, new or worsening wall motion abnormalities, severe chest pain, horizontal or down-sloping ST-segment depression ≥2 mm, ST-segment elevation ≥1.5 mm (only in patients without abnormal Q waves in the same ECG leads), systolic blood pressure >220 mmHg, diastolic blood pressure >120 mmHg, reduction in systolic blood pressure ≥30 mmHg and supraventricular or ventricular tachyarrhythmias.

Two-dimensional images were obtained in four standard views (parasternal long-axis, parasternal short-axis, apical four- and two-chamber views), using Acuson 128 XP-10 or Acuson Sequoia ultrasound systems (Mountain View, CA, U.S.A.) at baseline, at each dobutamine and dipyridamole dosage and during recovery. Super-VHS videotape recordings were used for subsequent analysis, and in the last 130 patients, images were also recorded using a quad-screen cine-loop system.

Echocardiographic Analysis

All examinations were reviewed by two independent observers with extensive experience in interpretation of pharmacological stress echocardiography and blinded to the clinical data. For left ventricular wall motion analysis, the standard 16-segment model of the left ventricle of the American Society of Echocardiography was used[20]. Left ventricular wall motion score index was calculated at baseline and at the peak of drug infusion, dividing the sum of individual segments scores by the number of considered segments. Left ventricular ejection fraction (EF) was measured at baseline (bEF) and at peak stress (pEF), using a commercially available software program that applied Simpson's rule on the two-chamber and four-chamber views. Receiver operating characteristic (ROC) curve analysis selected 'a priori' left ventricular EF <40% as optimal cut-off values for prognostically significant left ventricular dysfunction, both at rest and at peak dosage[17,21].

In patients with normal rest wall motion score index, the test was considered positive for myocardial ischaemia in case of development of a transient regional dyssynergy. In case of development of regional dyssynergy limited to a single segment, the test was considered positive only in case of adequate visualization of the same segment in at least two different views. In patients with rest wall motion abnormalities, the development of a new or worsening wall motion abnormality was considered indicative of residual myocardial ischaemia. The ECG was indicative of myocardial ischaemia if a horizontal or down-sloping ST-depression >1 mm, 80 ms after J point, developed with stress.

Follow-up

Cardiac-related death and non-fatal myocardial infarction were considered *hard events*. The definition of *cardiac-related death* required documentation of significant arrhythmias or cardiac arrest, or both, or death attributable to congestive heart failure or myocardial infarction in the absence of any other precipitating factors. *Non-fatal myocardial infarction* was defined as cardiac event requiring admission to the hospital, with development of new ECG changes and increase in cardiac enzyme level.

Statistical Analysis

Descriptive statistics procedure were used to analyze the distribution of each variable. Patients' groups were compared by Student's *t*-test for continuous variables and the χ^2 test for categorical variables. ROC curve analysis was performed to select optimal cut-off values for echocardiographic measurements.

Inter- and intra-observer variabilities for echocardiographic measurements were examined using

Bland–Altman analysis. Ninety-five per cent confidence limits of a single estimate of the measurements were calculated as $2 \times SD/\sqrt{2}$, and reported as a per cent from the mean value. Independent predictors of late cardiac events (death, hard events) were identified through univariate and multivariate Cox proportional-hazard regression models. The 0.05 probability level was adopted to consider the significance of the association between predictive variables and events. The risk associated with a given variable was expressed by a hazard ratio with corresponding 95% confidence intervals. In the multivariate analysis, an automatic backward stepwise procedure was adopted. The cumulative probability of freedom from cardiac events was calculated by Kaplan–Meier life-table analysis and compared between groups by use of the log-rank test.

Results

Study Population

The final study population included 325 patients (198 males and 127 females). Analysis of cardiac risk factors and resting echo characteristics was performed in all patients (Table 1).

Pharmacological Stress Echocardiography Safety and Feasibility

Dipyridamole was infused to a maximal dose of 0.84 mg/kg in 124 of the 130 patients. In six patients, pharmacological stress echocardiography was positive at a low dose. Dobutamine was infused to a mean peak dose of 32 ± 4 μg/kg/min. Thirty-two tests were interrupted because of low-dose ischaemic positivity, and five tests were prematurely stopped because of side effects: non-sustained ventricular tachycardia in three, severe chest pain in absence of a new wall motion abnormality in one and severe hypertension in one. All side effects were reversed by antidote administration. No major complication occurred. Of the 325 tests, the endpoint target rate was not reached in 26 (8%), of which 19 were receiving beta-blockers.

Table 1. Clinical findings in the study population.

Clinical data	*n*	%
Age	59.4±8.6	
Male sex	198	60.9
Family history IHD	87	26.7
Use of insulin	155	47.7
Hypoglycaemic agents	116	35.7
Diet alone	54	16.6
Hypercholesterolaemia	136	41.8
Hypertension	114	35.1
Obesity	29	8.9
Cigarette smoking	163	52.9
Previous angina	97	29.8
Previous AMI	182	56.0
Previous PTCA	26	8.0
Previous CABG	30	9.2
Use of beta-blockers	48	14.7

IHD, ischaemic heart disease; AMI, acute myocardial infarction; PTCA, percutaneous coronary angioplasty; CABG, coronary artery by-pass graft.

Pharmacological Stress Echocardiography Results

In baseline conditions, the mean value of wall motion score index was 1.58 ± 0.46, and the mean EF was 48.6 ± 11.4%. In particular, in 119 patients (36.6%), an impaired left ventricular global systolic function (EF <40%) was detected. Wall motion abnormalities were present in 212 patients (65.3%), despite the evidence of ECG abnormalities only in 114 patients (35.1%). The stress-echo test was positive for ischaemia in 149 patients (45.8%). Conversely, the ECG was suggestive of ischaemia in 97 patients (29.8%). In addition, during the test, only 53 patients (16.3%) experienced angina. At the peak dosage, the mean wall motion score index was 1.68 ± 0.46, and the mean EF was 57.7 ± 11.6%. A multivessel distribution of pharmacological stress echocardiography-induced wall motion abnormalities was detected in 81 patients (24.9%).

Inter-observer variability was ±4.9% for left ventricular pEF, ±6.1% for wall motion score index. Intra-observer variability was similar: ±4.3% for left ventricular pEF, ±5.8% for wall motion score index.

Cardiac Events

During the follow-up period, there were 61 hard events (18.7%), including 38 deaths (11.6%) and 23 acute non-fatal myocardial infarctions (7.1%). The other cardiac events were: angina pectoris in 52 patients (16%), heart failure in 12 (3.6%), percutaneous coronary angioplasty (PTCA) in 26 (8%) and coronary artery by-pass graft (CABG) in 42 (12.9%).

Death

By univariate analysis, the following variables were predictive for cardiac death (in descending order): pEF <40%, age, multivessel distribution of pharmacological stress echocardiography-induced wall motion abnormalities, rest wall motion score index, previous myocardial infarction and positive stress test for ischaemia (Table 2). By multivariate analysis, utilizing an automatic stepwise procedure, the combination of clinical, rest and stress test variables identified peak EF <40% and advanced age as the strongest independent predictors of cardiac death (Table 3). The mean five-year survival time, free of cardiac death, according to pEF was 43.6 months

Table 2. Univariate predictive value of clinical risk factors and pharmacological stress echocardiography results for cardiac events.

	Death			Hard events		
	P value	HR	95% CI	*P* value	HR	95% CI
Clinical data						
Age	<0.001	4.9	3.5–5.8	ns	2.0	1.4–5.2
Family history IHD	ns	1.6	0.7–3.4	<0.01	3.2	2.3–4.0
Previous AMI	<0.01	4.0	3.3–7.0	<0.001	4.7	3.4–5.6
Rest echocardiographic data						
Rest EF <40%	<0.01	3.3	1.1–4.7	<0.01	3.4	1.7–4.9
Rest WMSI	<0.01	3.8	2.3–6.1	<0.001	4.6	3.4–5.8
Stress echocardiographic data						
Positive PSE	<0.01	2.9	1.8–5.3	<0.001	4.0	1.9–5.6
Multivessel PSE wall motion abnormalities	<0.01	3.1	2.6–4.2	ns	2.2	1.3–5.6
Peak EF <40%	<0.0001	5.8	4.2–8.2	<0.00001	6.3	3.8–9.6

PSE, pharmacological stress echocardiography; WMSI, wall motion score index; HR, hazard ratio; see Table 1 for other abbreviations.

if pEF was >40% vs 55.6 months in patients with pEF <40% (Fig. 1).

Hard Cardiac Events (Death—Non Fatal Myocardial Infarction)

In the overall population, by univariate analysis among the different variables, the following resulted significantly predictive for hard events (in descending order): peak EF <40%, rest wall motion score index, previous myocardial infarction, positive stress test for ischaemia and family history for ischaemic heart disease (Table 2). In multivariate analysis, the combination of clinical, rest and stress variables identified peak EF, rest wall motion score index and previous AMI as independent predictors of hard events (Table 3).

Table 3. Multivariate predictive value of clinical risk factors and PSE results for cardiac events.

Variables considered	Model χ^2	*P* value	Variables selected (partial χ^2; *P* value)
Death			
Clinical	26.3	0.01	Age (4.6; <0.01)
Clinical + Rest echocardiography	38.8	0.001	Rest EF <40% (4.9; <0.01)
Clinical + Rest echocardiography + Stress echocardiography	55.6	0.00001	Peak EF <40% (10.8; <0.00001)
Hard events			
Clinical	29.6	0.001	Previous AMI (6.4; <0.01)
Clinical + Rest echocardiography	35.7	0.0001	Rest WMSI (8.6; <0.001)
Clinical + Rest echocardiography + Stress echocardiography	61.6	0.00001	Peak EF <40% (15.2; <0.00001)

See Tables 1 and 2 for abbreviations.

Subgroup Analyses

On the basis of left ventricular EF assessment at rest, we performed separate multivariate analyses between diabetic patients with and without an impaired left ventricular global systolic function (left ventricular bEF <40%). In 206 patients (63.3%) with normal left ventricular EF at rest, a positive pharmacological stress echocardiography response for ischaemia was a powerful independent predictor of cardiac death (χ^2 6.3, $P < 0.001$), together with pEF <40% (χ^2 13.8, $P < 0.00001$). Event rate was lower in patients with normal, as compared with those with abnormal, pharmacological stress echocardiography response for ischaemia (Fig. 2). Conversely, in the subgroup of 119 patients with impaired left ventricular EF at rest, only the assessment of a left ventricular EF at peak of pharmacological stress echocardiography dosage <40% was independently associated with increased risk of cardiac mortality (χ^2 15.4, $P < 0.00001$).

In a further multivariate analysis, we compared the prognostic value of either dobutamine (195 patients) or dipyridamole (130 patients) pharmacological stress echocardiography in the overall population of diabetic patients. Both tests allowed an effective and grossly comparable risk stratification for cardiac events. In particular, left ventricular EF at peak dosage <40% was the strongest independent determinant of cardiac-related mortality in both dobutamine (χ^2 12.4, $P < 0.00001$) and dipyridamole (χ^2 8.3, $P < 0.0001$) group.

Discussion

Main Findings

The present study confirms the usefulness of pharmacological stress echocardiography to assess long-term

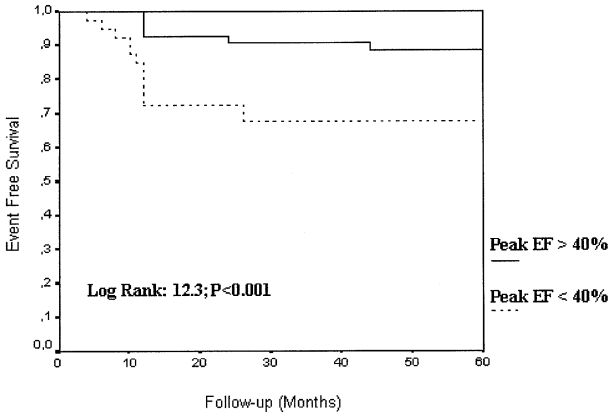

Figure 1. Kaplan–Meier curves for cardiac death during follow-up by results of peak ejection fraction (pEF) in the overall population of diabetic patients. Cumulative survival rate according to the value of pEF. Solid lines: pEF >40%; dashed lines: pEF <40%.

risk of cardiac events in a population of diabetic patients with proven or suspected ischaemic heart disease. An overall good prognostic power of the ischaemic response during pharmacological stress echocardiography in diabetic patients has also been recently outlined by Bates *et al.* and Marwick *et al.*[4,9]. Conversely, Hung *et al.* showed that a shorter dobutamine time had a higher prognostic value in detecting future cardiac events in diabetic patients[5]. On the other hand, Elhendy *et al.* reported that the multivessel distribution of exercise echocardiographic abnormalities was the best predictor of cardiac events[6] in diabetic patients, while in the analysis of Bigi *et al.*, peak wall motion score index was the only independent prognostic indicator of death[7]. Finally, Kamalesh *et al.* also reported a high risk for cardiac events in diabetic patients with negative pharmacological stress echocardiography[8].

In this study, among 325 diabetic patients with known or suspected ischaemic heart disease who underwent pharmacological stress echocardiography, 61 patients (18.7%) experienced hard events at follow-up. Of note, the event rate of our population was higher than the one reported before in diabetic patients[4–9]. This may be the consequence of high prevalence in our study group of documented ischaemic heart disease (60.6%) and impaired left ventricular systolic function at rest (36.6%).

In the overall population of the present study, peak left ventricular EF <40% was the strongest independent predictor of hard endpoints, in accordance with the findings of Coletta et al.[21], who reported an abnormal left ventricular end-diastolic volume response and EF <40% to be independent predictors of unfavourable outcome. Furthermore, rest wall motion score index carried out in the present study was a strong predictive value for hard events, as previously pointed out by other researchers in diabetic patients[7] and in patients with known or suspected ischaemic heart disease[12,15].

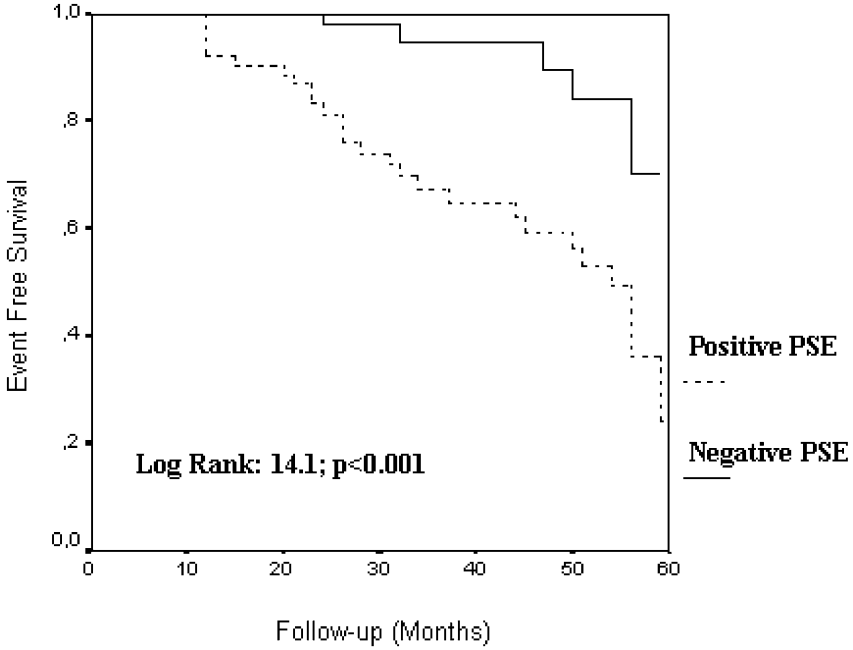

Figure 2. Kaplan–Meier curves for cardiac death during follow-up by results of pharmacological stress echocardiography in the subgroup of diabetic patients with normal left ventricular EF at rest. Cumulative survival rate according to the ischaemic response to pharmacological stress echocardiography. Solid lines: negative pharmacological stress echocardiography; dashed lines: positive pharmacological stress echocardiography.

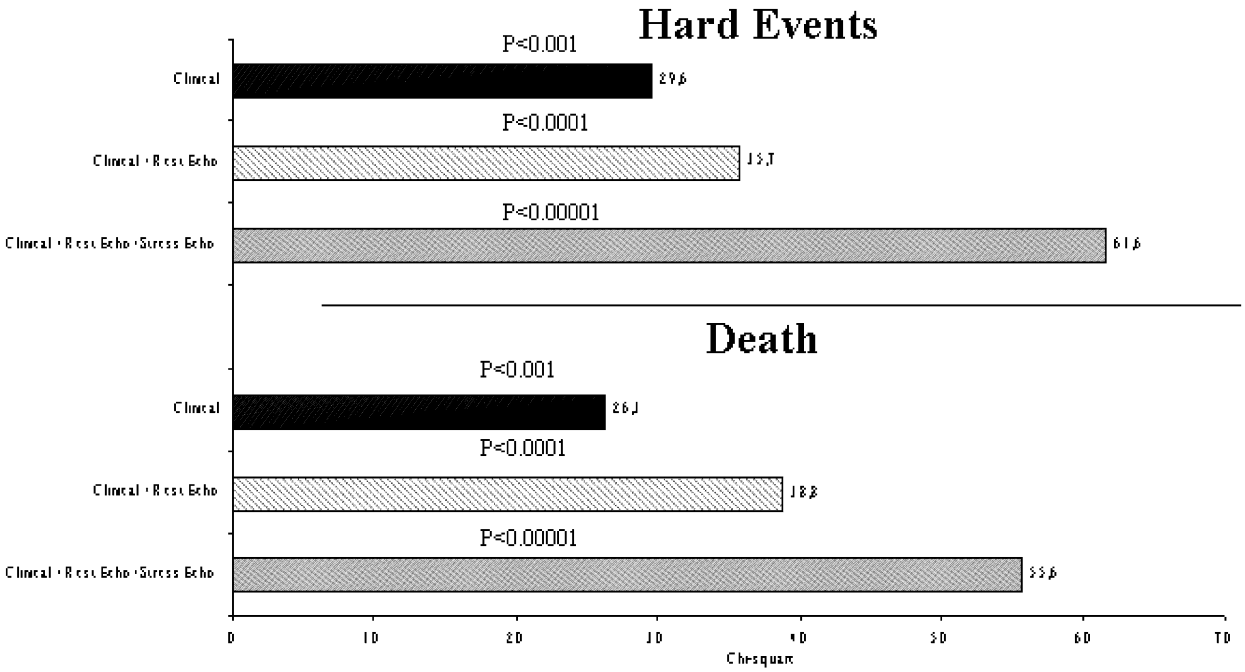

Figure 3. Incremental value of pharmacological stress echocardiography in predicting late cardiac events.

Our results, in keeping with previous studies[10–15], showed that information obtained by pharmacological stress echocardiography resulted in additional data, independent of that provided by clinical and rest echocardiographic data. In fact, the addition of pharmacological stress echocardiography variables increased the global χ^2 values of the multivariate model to 55.6 for death and 61.6 for hard events (Fig. 3).

Of interest, after dividing our population into two subgroups on the basis of left ventricular EF in baseline conditions, absence of stress-induced myocardial ischaemia determined a good prognosis only in diabetic patients with normal global systolic function at rest (>40%). On the other hand, only the evaluation of clinical variables as well as a peak left ventricular EF value <40% selected patients at greatest risk of cardiac death in a better way in diabetic patients with impaired resting left ventricular EF. These findings may be the consequence of the different physiological mechanisms implicated in the determination of cardiac endpoints[22]. In fact, some echocardiographic parameters (i.e. positive pharmacological stress echocardiography for ischaemia) seem related to the degree of single coronary stenoses, and may accurately stratify patients at higher risk even in absence of an impairment of resting left ventricular EF. Conversely, other pharmacological stress echocardiography variables (i.e. peak EF) outline an impaired global left ventricular function secondary to a multivessel coronary artery disease[17,21], which is more related to the risk of cardiac death in case of abnormal response during pharmacological stress echocardiography.

Study Limitations

In our study protocol, we collected data from both dipyridamole and dobutamine stress echo. However, in patients at low-to-moderate risk of cardiac events, pharmacological stress echocardiography with either dobutamine or dipyridamole allowed comparable risk stratification on the basis of the severity and extension of the induced ischaemia[12,16]. In addition, in our population, subgroup analysis confirmed the comparable prognostic value of both kinds of pharmacological stress echocardiography.

An unsatisfactory intra- and inter-observer variability in pharmacological stress echocardiography interpretation has been previously reported[23]. However, in our study all patients were evaluated in a single echo laboratory, and inter- and intra-observer variabilities were examined using Bland–Altman analysis.

In most of the patients, wall motion score index analysis was qualitatively performed with video tape. However, digital acquisition has not been shown to improve pharmacological stress echocardiography diagnostic value[24].

There is a controversy whether PTCA and CABG have to be considered cardiac events, because the decision to undergo these procedures may be subjective. Therefore, we preferred not to include these events among the endpoints of our study.

The duration and the type of diabetes mellitus were not defined in this study.

Clinical Implications

Exercise or pharmacological stress myocardial perfusion imaging has been recommended by the American Heart Association for the prognostic evaluation of ischaemic heart disease in diabetic patients[1,5]. However, pharmacological stress echocardiography has the advantages of wider availability and lower cost, avoids the injection of radioactive material and is useful to analyse global left ventricular systolic function. Our findings confirm the prognostic role of recognized clinical risk factors and pharmacological stress echocardiography variables for cardiac events also in diabetic patients, emphasizing the usefulness of the additional features of a pharmacological stress echocardiography in depicting the cardiac risk profile better than the sole use of the ischaemic response to the stress.

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