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Prognostic role of stress echocardiography in hypertrophic cardiomyopathy: The International Stress Echo Registry

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ABSTRACT

Background: Stress echo (SE) may have a role in the outcome in patients with hypertrophic cardiomyopathy (HCM).
Objectives: The aim was to assess the prognostic value of SE in a retrospective multicenter study in HCM.
Methods: We enrolled 706 HCM patients. The employed stress was exercise (n = 608) and/or vasodilator (n = 146, dipyridamole in 98 and adenosine in 48). We defined SE positivity according to clinical/hemodynamic criteria including: symptoms (all stress modalities), exercise-induced hypotension (failure to increase or fall >20 mm Hg, exercise) and exercise-induced left ventricular outflow tract obstruction (left ventricular outflow tract obstruction >50 mm Hg); and ischemic criteria, such as new wall motion abnormalities (new wall motion abnormality) and/or reduction of coronary flow reserve velocity (CFVR ≤ 2.0) on left anterior descending coronary artery with vasodilator stress assessed in 116 patients. All patients completed the clinical follow-up.
Results: Positive SE showed more frequently CFVR reduction, exercise-induced hypotension, left ventricular outflow tract obstruction, and symptoms (38, 23, 20 and 15% respectively), but new wall motion abnormality only in 6%. During a median follow-up of 49 months 180 events were observed, including 40 deaths. Clinical/hemodynamic criteria did not predict outcome (X_2 0.599, p = 0.598), whereas ischemia-related SE criteria (X_2: 111.120, p < 0.0001) was significantly related to outcome. Similarly, mortality was predicted with SE ischemic-criteria (X_2 16.645, p < 0.0001).
Conclusions: SE has an important prognostic significance in HCM patients, with ischemia-related end-points showing greater predictive accuracy than hemodynamic endpoints. New wall motion abnormalities and impairment of CFVR should be specifically included in SE protocols for HCM.

1. Introduction

Hypertrophic cardiomyopathy (HCM) is a heterogeneous inherited cardiomyopathy with variable phenotypic expression that ranges from asymptomatic status to heart failure to sudden death, which occurs in <1%/year [1–2].

The recent European Society of Cardiology guidelines assign IB class of recommendation to perform exercise SE in symptomatic patients without a resting left ventricular outflow tract obstruction to detect exercise-induced left ventricular outflow tract obstruction and mitral regurgitation [3]. Gradients ≥50 mm Hg, either at rest or after stress, represent the "conventional threshold for surgical or percutaneous intervention if symptoms cannot be controlled with medication" since they can possibly be responsible for symptoms [4–5]. Moreover, stress

Abbreviations: CFVR, coronary flow velocity reserve; HCM, hypertrophic cardiomyopathy; SE, stress echocardiography.

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echocardiography (SE) may be used to enhance other signs potentially related to outcome such as transient regional wall motion abnormalities [6], stress-induced ST segment depression [7], and reduction in coronary flow velocity reserve (CFVR) (in the absence of regional wall motion abnormalities) due to microvascular impairment [8].

SE might give clinicians more information than is currently acknowledged by guidelines, but convincing evidence is missing.

The aim of the study was to retrospectively analyze SE data with different modalities (exercise and vasodilators) to assess the long-term prognostic value of stress-induced left ventricular outflow tract obstruction, wall motion abnormalities and CFVR.

2. Methods

2.1. Patients population

From an International SE data-bank, 772 HCM patients were retrospectively collected from 1984 to 2015. Follow-up data were not available in 40 patients and 26 patients were excluded because of history of coronary artery disease at time of enrolment (n = 13) or during follow-up (n = 13). The remaining 706 HCM patients made the final study sample.

We enrolled 608 HCM patients who underwent exercise SE in 6 centers: Florence, Italy (n = 204); La Coruña, Spain (n = 243); Almada, Portugal (n = 49); Naples, Italy (n = 49); Belgrade, Serbia (n = 48) and Pisa (n = 15). We enrolled, also, 146 HCM patients who had undergone dipyridamole SE in 5 Italian cardiology institutions: Lucca, Mestre, Cesena, Pisa (n = 75) and Parma (n = 23); in 48 patients who underwent treadmill exercise in Belgrade, CFVR was also evaluated with adenosine on the same day.

HCM was defined as a wall thickness ≥15 mm in one or more left ventricular myocardial segments that is not explained solely by loading conditions able to induce the magnitude of left ventricular hypertrophy observed [2–3,9].

All patients were required to have an adequate transthoracic echocardiogram from which resting regional wall function could be assessed (the echocardiogram was considered adequate if >13 of the 16 segments were visualized in at least 1 view). Exclusion criteria were: 1) technically poor acoustic window precluding satisfactory imaging of the left ventricle (for 2D echo); 2) left ventricular ejection fraction <45%; 3) history of coronary artery disease; 4) significant comorbidities reducing life expectancy to <1 year, and 5) missing follow-up data.

2.2. Resting and stress echocardiography

Resting and SE were performed by experienced cardiologists according to standard criteria of execution and interpretation recommended by the American Society of Echocardiography [10] and European Association of Cardiovascular Imaging [9,11]. In particular, we calculated a wall motion score index (each segment scored from 1 = normal to 4 = dyskinetic in a 16-segment model of the left ventricle) both at baseline and at peak stress, and a new wall motion abnormality was defined as an increase of 1 grade in at least 2 adjacent segments at peak stress [11].

During exercise (treadmill or semi-supine bicycle), left ventricular outflow tract obstruction was defined as a gradient ≥50 mm Hg [3–4,12]. During dipyridamole (up to 0.84 mg/kg in 6 or 10 min) [7–8] or adenosine (0.14 mg/kg in 2 min), CFVR [13] sampled by pulsed Doppler on mid-distal left anterior descending artery was defined as the ratio between hyperemic peak and resting peak diastolic coronary flow velocities. A CFVR value ≤2.0 was considered abnormal [8].

Coronary flow parameters were analyzed offline by the use of the built-in calculation package of the ultrasound unit. At each time point (baseline and peak stress), 3 optimal profiles of peak diastolic Doppler flow velocities were measured, and results were averaged. Intra-observer variability and inter-observer variability for measurement of Doppler recordings analysis and assessment were consistently <5% and 10% respectively, as previously reported [8]. All observers of the recruiting centers with CFVR data were trained by the same senior investigator (FR) who granted consistency in data acquisition storage and interpretation also through intensive joint reading sessions [8].

The main reasons for terminating SE were: achievement of diagnostic end-points; causes of test cessation: intolerable symptoms, muscular exhaustion, hypertension (>220/120 mm Hg), symptomatic hypotension (>40 mm Hg) or arrhythmias (supraventricular tachycardia, atrial fibrillation, frequent or complex ventricular ectopy); the patient becoming symptomatic or any hemodynamic or significant electrocardiographic changes (>2.0 mV in these patients, who frequently have resting ST–T segment changes) [14].

We defined as clinical, rest and echocardiographic sudden death risk factors the presence of: familial history of aborted sudden death, history of ventricular tachycardia, left ventricular outflow tract obstruction a rest >30 mm Hg, and maximal wall thickness >30.

2.3. SE positivity criteria

The sample under investigation was separated into 3 groups, according to SE results: negative SE, positive SE for clinical/hemodynamic criteria and SE positive for ischemic criteria. Clinical/hemodynamic criteria were defined as the presence of symptoms (chest pain and/or dyspnea, defined as exertional shortness of breath during exercise); exercise-induced hypotension: [hypotensive blood pressure response was defined as: the failure to increase of systolic blood pressure by >20 mm Hg or fall of systolic blood pressure >20 mm Hg during exercise [15]]; exercise-induced left ventricular outflow tract obstruction (>50 mm Hg at peak exercise stress).

SE ischemic criteria were defined as the presence of new wall motion abnormalities and/or abnormal CFVR.

2.4. Follow-up data

Follow-up data were obtained from at least 1 of the following 4 sources: review of the patient's hospital records, personal communication with the patient's physician and review of the patient's chart, a telephone interview with the patient conducted by trained personnel, a staff physician seeing the patient at regular intervals in the out-patient clinic. By selection, clinical follow-up data were obtained in all patients.

We defined a composite cardiac event including death for all causes, heart transplantations, sustained ventricular tachycardia, acute heart failure and atrial fibrillation. Sudden cardiac death was defined as a sudden and unexpected collapse in patients who previously had relatively uneventful clinical courses. According to the study protocol follow-up information was obtained every six months.

2.5. Statistical analysis

Data are expressed as mean ± standard deviation for continuous variables and as frequency (percent) for categorical variables. We divided the patients into three groups, based on SE results: negative SE, clinical/hemodynamic SE criteria and ischemic SE criteria. The differences between groups were analyzed by one-way analysis of variance (ANOVA) for repeated measures. If any interactions were significant, post hoc comparison was performed using unpaired t-test with Bonferroni correction to detect differences between two groups. The individual effect of variables on event-free survival was evaluated with a Cox regression model. The analysis was performed according to an unmodified, forward-selection, stepwise procedure. In this analysis, variables were entered into the model on the basis of a computed significance probability; accordingly, the variable that seemed to have the most significant relationship with the dependent outcome was selected for inclusion in the model, and a solution to the functional form