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Negative stress echo: Further prognostic stratification with assessment of pressure–volume relation

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Abstract

Background: A maximal negative stress echo identifies a low risk for subsequent hard events subset. However, the potentially prognostically relevant information on global contractile reserve on the left ventricle is missed by standard regional wall motion assessment, and can be obtained by end-systolic pressure–volume relationship (PVR) evaluation.
Aim: To assess the relative prognostic value of PVR in patients with negative stress echo.
Methods: We enrolled 99 consecutive patients (age = 61 ± 14 years; 81 males, LVEF 47 ± 14%, WMSI = 1.42 ± 0.50) with negative exercise stress echo for standard wall motion criteria. To build the PVR, the force was determined at rest and peak stress as the ratio of the systolic pressure/end-systolic volume index. All patients were followed-up on medical therapy.
Results: Median follow-up was 21 months (interquartile range 12–26). Twenty-nine events have been observed: 6 deaths, 10 heart failure related hospitalization and 13 worsening NYHA class of ≥ 1 grade. Using Cox's proportional hazard model the best independent predictor of total events was SP/ESV index change (rest–stress) < 1.5 mm Hg/ml/m^2 as determined by ROC analysis cut-off (RR = 29, p = 0.001, sensitivity = 80%, specificity = 93%). The overall survival and event-free survival was 34% in patients with change (rest–stress) SP/ESV index < 1.5 mm Hg/ml/m^2 and 97% in whose with > 1.5 mm Hg/ml/m^2.
Conclusions: In patients with negative stress echo, a preserved global contractility response can be easily identified through stress-induced variation in SP/ESV index, with powerful further risk stratification.

Keywords: Stress echocardiography; Contractile reserve; Pressure–volume relation; Prognosis

1. Introduction

Patients with negative stress echo are a low risk group, but the hard event-rate in some patients' subset can be as high as 5% per year [1,2]. However, the potentially prognostically relevant information on global contractile reserve on the left ventricle (LV) is missed by standard regional wall motion assessment. Recently, a non-invasive echocardiographic method has been proposed in order to assess the changes in contractility, as mirrored by end-systolic pressure–volume relationship (PVR), during physical exercise [3], external pacing echo in patients with permanent pacemakers [4], or dobutamine stress echo [5]. This novel approach is based upon the proven assumption that positive inotropic interventions are mirrored by smaller end-systolic volumes and higher end-systolic pressures. During exercise and dobutamine stress echo, the assessment of pressure–volume relation (PVR) involves both the force–frequency relationship and the effect of inotropic stimulation. Experimental studies showed that beta-adrenergic receptor stimulation produces an important enhancement of myocardial contractility, which is impaired in heart failure [6]. In failing hearts in which the basal cAMP content of cardiomyocytes is

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decreased because beta-adrenergic receptors are down-regulated, the force–frequency relationship is altered [7,8].

The aim of this study was to assess the prognostic value of PVR in patients with negative stress echo.

2. Methods

2.1. Study patients

We prospectively studied 145 in hospital patients with both suspected or known coronary disease, previous myocardial infarction, previous PTCA or by pass surgery, left ventricular dilation. They have been enrolled in the study starting from January 2003 to February 2005 from the Cardiology Division of S Raffaele Hospital. Milan ($n=66$), Cardioangiology Unit, Federico II University, Naples in cooperation with Clinica Montevergine, Mercogliano ($n=17$) and Pisa, CNR ($n=62$).

2.1.1. Patient selection

All patients were referred to clinically-driven exercise stress echo and met the following inclusion criteria: 1) satisfactory imaging of left ventricle at rest and during stress; 2) negative exercise stress echo by standard wall motion criteria; 3) enrolment in a follow-up program. Exclusion criteria were the following: 1) technically poor acoustic window precluding satisfactory imaging of left ventricular wall motion or calculation of left ventricular volumes; 2) moderate-to-severe valvular disease; 3) incapability or refusal to give written informed consent.

Of the 145 patients initially selected for the study, 5 (3.6%) have been excluded for inadequate wall motion analysis, 17 (12%) for stress echo positivity, 15 (11%) for valvular heart disease and an additional 5 (3.6%) patients were lost at follow-up. One patient underwent heart transplant and 3 the implant of a biventricular pacemaker. Therefore, 99 patients (age $=61\pm14$ years; 81 males) represented the final study group. The study has been approved by the institution review board. All patients have given their written informed consent before entering the study.

The characteristics of the study patients are reported in Table 1. The underlying diagnosis was coronary artery disease in 37, idiopathic dilated cardiomyopathy (with angiographically normal coronary arteries) in 15, hypertension in 30 patients; 17 patients underwent stress for routine screening. Coronary artery disease was defined by the presence of angiographically assessed coronary stenosis (with quantitatively assessed diameter reduction in major coronary vessels) or previous myocardial infarction. Patient's functional classification was based on the NYHA Class.

Table 1
Characteristics of the study patients

Pts	99
Age (years)	61 ± 14
Gender (M/F)	81/18 (82/18%)
LVEF %	47 ± 14
Hypertension	30 (30%)
Previous MI	31 (31%)
PTCA/Bypass (previous)	18 (18%)
CAD	37 (37%)
DCM	15 (15%)
NYHA class (I–IV) I	59 (60%)
II	34 (34%)
III	6 (6%)

2.2. Semi-supine bicycle exercise

Graded bicycle semi-supine exercise echo was performed starting at an initial workload of 25 W lasting for 2 min; thereafter the workload was increased stepwise by 25 W at 2 min interval. A 12-lead electrocardiogram and blood pressure determination were performed at baseline and every minute thereafter. Criteria for interrupting the test were severe chest pain, diagnostic ST segment shift, fatigue, excessive blood pressure rise (systolic blood pressure >240 mm Hg; diastolic blood pressure >120 mm Hg); limiting dyspnoea, or maximal predicted heart rate in the absence of ischemia. The maximum rate pressure product (heart rate × systolic blood pressure) and maximal workload (in minutes), calculated at peak stress, were also evaluated [9].

2.3. Data acquisition

All patients underwent transthoracic echocardiography at baseline and during stress. Left ventricular end-diastolic and end-systolic volumes were measured from apical four- and two-chamber view, by an experienced observer using the biplane Simpson-method [10]. Only representative cycles with optimal endocardial visualization were measured and the average of three measurements was taken. The endocardial border was traced, excluding the papillary muscles. The frame captured at the R wave of the ECG was considered to be the end-diastolic frame, and the frame with the smallest left ventricular cavity the end systolic frame. Images were acquired at baseline and at each increase in heart rate of 10 beats during stress.

2.4. Data analysis

2.4.1. Regional wall motion analysis

The Wall Motion Score Index (WMSI) was calculated in each patient at baseline and peak stress, according to the recommendations of the American Society of Echocardiography from 1 = normal-hyperkinetic to 4 = dyskinetic in a 17 segment model of the left ventricle [11,12]. The WMSI was derived by dividing the sum of the individual visualized segment scores by the number of visualized segments [13]. All studies have been performed by an experienced cardiologist with documented experience in stress echocardiography and who passed the quality-control procedures of stress echocardiography reading according to criteria