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Prognostic value of cardiac power output to left ventricular mass in patients with left ventricular dysfunction and dobutamine stress echo negative by wall motion criteria

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Aims Cardiac power output to left ventricular mass (power/mass) is an index of myocardial efficiency reflecting the rate at which cardiac work is delivered with respect to the potential energy stored in the left ventricular mass. In the present study, we sought to investigate the capability of power/mass assessed at peak of dobutamine stress echocardiography to predict mortality in patients with ischaemic cardiomyopathy and no inducible ischaemia.

Methods and results One-hundred eleven patients (95 males; age 68 ± 10 years) with 35 ± 7% mean left ventricular ejection fraction and a dobutamine stress echocardiography (up to 40 μg/kg/min) negative by wall motion criteria formed the study population. Power/mass at peak stress was obtained as the product of a constant ($K = 2.22 \times 10^{-1}$) with cardiac output and the mean arterial pressure divided by left ventricular mass to convert the units to W/100 g. Patients were followed up for a median of 29 months (inter-quartile range 16–72 months). All-cause mortality was the only accepted clinical end point. Mean peak-stress power/mass was 0.70 ± 0.31 W/100 g. During follow-up, 29 deaths (26%) were registered. With a receiver operating characteristic analysis, a peak-stress power/mass ≤0.50 W/100 g [area under curve 0.72 (95% CI 0.63; 0.80), sensitivity 59%, specificity 80%] was the best value for predicting mortality. Univariate prognostic indicators were age, male sex, peak-stress ejection fraction, peak-stress stroke volume, peak-stress cardiac output, peak-stress cardiac power output ≤1.48 W, and peak-stress power/mass ≤0.50 W/100 g. At multivariate analysis, age (HR 1.08, 95% CI 1.04; 1.14; $P = 0.004$) and peak-stress power/mass ≤0.50 W/100 g (HR 4.05, 95% CI 1.36; 12.00; $P = 0.01$) provided independent prognostic information. Three-year mortality was 14% in patients with peak-stress power/mass >0.50 W/100 g and 47% in those with peak-stress power/mass ≤0.50 W/100 g (log-rank 20.4; $P < 0.0001$).

Conclusion Power/mass assessed at peak of dobutamine stress echocardiography allows effective prognostication in patients with ischaemic cardiomyopathy and test result negative by wall motion criteria. In particular, a peak-stress power/mass ≤50 W/100 g is a strong and multivariable predictor of mortality.

Keywords cardiac power output • dobutamine stress echocardiography • left ventricular dysfunction

Introduction

Cardiac power output, expressed as the product of cardiac output (CO) and the mean arterial blood pressure (BP),[1–3] is an index of left ventricular (LV) function reflecting the rate of energy expenditure by the heart to pump the blood into the systemic circulation. The prognostic importance of impaired cardiac power output assessed during stress echocardiography has been previously

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demonstrated in patients with chronic heart failure.[4] In patients with LV remodelling secondary to coronary artery disease, structural and functional abnormalities include LV systolic dysfunction and hypertrophy of the non-infarcted segments. In these patients, LV remodelling involves both the myocyte and interstitial elements of the myocardium which produces interstitial fibrosis.[5] The assessment of power/mass at peak stress may contribute to better identify patients with maladaptive LV remodelling who are at risk of untoward outcome.[6] In a previous study, power/mass at peak of exercise stress echocardiography was useful to discriminate and risk stratify patients with advanced heart failure adding prognostic power to that of ejection fraction (EF).[7] However, exercise capacity is often impaired in patients with heart failure limiting the feasibility of physical testing, and the use of a pharmacologic stressor may be more convenient accordingly. In spite of this, the prognostic value of power/mass during echocardiographic stress test should be better elucidated. The present study was aimed at investigating the prognostic meaning of power/mass at peak of dobutamine stress echocardiography in patients with LV dysfunction and no inducible ischaemia.

Methods

Patients

The initial population comprised 170 patients (recruited at the Division of Cardiology of Lucca Hospital, Italy from January 2007 to December 2012) with ischaemic cardiomyopathy (LV EF $\leq$ 45%) who underwent dobutamine stress echocardiography for the identification of obstructive epicardial coronary artery disease or detection of viable myocardium. Exclusion criteria were significant aortic valvular disease, congenital heart disease, hypertrophic cardiomyopathy, significant comorbidity reducing life expectancy to $<$1 year, and unsatisfactory imaging of left ventricle at rest or during stress. Of these patients, 59 were excluded because of inducible ischaemia at stress echo ($n = 41$, 24%), limiting side effects requiring premature test interruption ($n = 14$, 8%), or no available follow-up data ($n = 4$, 2%). Thus, the study population refers to 111 patients (95 males; age 68 $\pm$ 10 years) with stress echo negative by wall motion criteria. Informed consent was obtained from all patients (or their guardians) before testing. Stress echo data were collected and analysed by stress echocardiographers not involved in patient care. Stress echocardiography was performed on β-blocker therapy in 19 (17%) patients. Diabetes[8] and hypertension[9] were defined according to standard definitions.

Stress echocardiography

Two-dimensional echocardiography and 12-lead electrocardiographic monitoring were performed in combination with high-dose (up to 40 μg/kg/min) dobutamine. During the procedure, BP and the electrocardiogram were recorded each minute. Non-echocardiographic criteria for ending the test were peak dobutamine dose, achievement 85% of target heart rate (determined according to the equation: predicted target heart rate = 220 − age), and severe chest pain. The test was also stopped in case of intolerable symptoms or limiting side effects, including hypertension (systolic BP $>$ 220 mmHg; diastolic BP $>$ 120 mmHg), hypotension (relative or absolute: $>$30 mmHg decrease in BP), supraventricular arrhythmias (supraventricular tachycardia or atrial fibrillation), ventricular arrhythmias (ventricular tachycardia, frequent, polymorphous premature ventricular beats), and bradyarrhythmias. Echocardiographic images were semi-quantitatively assessed using a 17-segment, 4-point scale model of the left ventricle.[10] A wall motion score index (WMSI) was derived by dividing the sum of individual segment scores by the number of interpretable segments. Ischaemia was defined as stress-induced new and/or worsening of pre-existing wall motion abnormality or biphasic response (i.e. low-dose improvement followed by high-dose deterioration). By selection, all patients had negative stress echo by wall motion criteria. Myocardial viability was any improvement of WMSI between rest and peak of stress. A peak-to-rest WMSI $>$ 0.4 indicated substantial viable myocardium.[8,9]

Power/mass assessment

LV volumes and EF were calculated according to the biplane Simpson's rule.[10] LV mass was determined using the two-dimensional method according to the recommendations of the American Society of Echocardiography.[10] The LV outflow tract (LVOT) anteroposterior diameter was measured in the parasternal long-axis view, and the LVOT area was calculated as πr^2 (square centimetres). The LV stroke distance (centimetres) was measured tracing the outer edge of the most dense (or brightest) portion of the spectral LVOT tracing recorded from the apical five-chamber view, with the pulsed-wave Doppler sample volume positioned ~5 mm proximal to the aortic valve. At baseline and at each stress echo level, Doppler-derived CO at the LVOT, heart rate, and arterial systolic and diastolic BP (by cuff sphygmomanometry) were measured. Mean BP (MBP) was estimated as follows: diastolic BP + 1/3 (systolic BP − diastolic BP). Stroke volume was calculated as stroke distance multiplied by LVOT area and CO as stroke volume multiplied by heart rate. Great care was taken to ensure that patients held their breath at each acquisition time and to acquire three consecutive Doppler tracings. All measures were averaged over three consecutive cycles. LV power output was calculated as the product of a constant ($K_1 = 2.22 \times 10^{-3}$) with CO (L/min) and MBP (mmHg). Power/mass (W/100 g) was obtained by multiplying LV power output by 100 divided by LV mass $= K \times$ CO (L/min) $\times$ MBP (mmHg) $\times M^{-1}$ (g); $K = 2.22 \times 10^{-1}$.[6]

Follow-up

Follow-up data were obtained from at least one of four sources: review of the patient's hospital record, personal communication with the patient's physician, review of the patient's chart, and a telephone interview with the patient's relatives conducted by trained personnel. Death certificates were obtained in case of need. Mortality was the only accepted end point. Coronary revascularization (surgery or percutaneous intervention) was also recorded. To avoid misclassification of the cause of death,[11] overall mortality was considered. Follow-up data were analysed for the prediction of survival (death).

Statistical analysis

Continuous variables are expressed as mean $\pm$ SD. Mortality rates were estimated with Kaplan–Meier curves and compared by the log-rank test. Patients undergoing coronary revascularization were censored at the time of the procedure. Survival analyses were also performed for patients who received revascularization or were treated medically. A receiver operating characteristic analysis was used to obtain the best prognostic predictor for peak-stress cardiac power output and peak-stress power/mass. The association of selected variables with outcome was 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, while 0.1 was the cut-off value for exclusion. Hazard ratios (HR) with the corresponding 95% confidence interval (CI) were estimated. The interobserver variabilities of peak-stress cardiac power output and of power/mass were evaluated by the Bland and Altman method in 10 patients

of the study population by the physician sonographer and by an independent observer. Statistical significance was set at $P < 0.05$. Statistical Package for the Social Sciences (SPSS release 13.0, Chicago, IL, USA) was used for analysis.

Results

In *Table 1* are listed the main clinical and echocardiographic characteristics of the study population. Mean EF increased from 35 ± 7% in resting condition to 42 ± 13% at peak of stress ($P < 0.0001$) (*Table 1*). Similarly, mean cardiac power output and power/mass rose, respectively, from 0.93 ± 0.29 to 1.75 ± 0.76 W ($P < 0.0001$), and from 0.38 ± 0.11 to 0.70 ± 0.31 W/100 g ($P < 0.0001$) (*Table 1*). Twenty-four (22%) subjects exhibited substantial viable myocardium (*Table 1*). Peak-stress maximal predicted heart rate was 67 ± 17% in the 19 patients tested on β-blockers and 79 ± 17% in the 92 patients tested off therapy ($P = 0.007$). During test, systolic BP increased in 79 (71%) patients (from 10 to 100 mmHg, mean 28 ± 18 mmHg), remained unchanged in 12 (11%) patients, and decreased in 20 (18%) patients (from 10 to 50 mmHg, mean 17 ± 13 mmHg). Peak-stress cardiac power output was 1.45 ± 0.73 W in patients on β-blockers and 1.81 ± 0.75 W in those tested off therapy ($P = 0.994$). Peak-stress power/mass was 0.60 ± 0.29 W/100 g in those who received β-blockers and 0.72 ± 0.31 W/100 g in those where these drugs were withheld or not administered ($P = 0.791$). One hypertensive and four hypotensive responses were observed at target heart rate and were not the primary cause for test interruption accordingly.

Table 1 Clinical and echocardiographic findings of the study population

Clinical findings	
Age (years)	69 ± 11
Males	91 (82%)
Prior myocardial infarction	63 (57%)
Prior CABG	13 (12%)
Prior PCI	28 (25%)
Known CAD	80 (72%)
Arterial hypertension	52 (47%)
Diabetes mellitus	39 (35%)
Resting and stress echo findings	
Left ventricular mass (g)	255 ± 60
Rest LV ejection fraction (%)	35 ± 8
Peak LV ejection fraction (%)	42 ± 13
Rest WMSI	1.96 ± 0.33
Peak WMSI	1.75 ± 0.39
Rest heart rate (bpm)	72 ± 12
Peak heart rate (bpm)	112 ± 23
Rest SP (mmHg)	129 ± 18
Peak SP (mmHg)	146 ± 28
Rest LV EDV (mL/m^2)	187 ± 69
Peak LV EDV (mL/m^2)	152 ± 74
Rest LV ESV (mL/m^2)	124 ± 55
Peak LV ESV (mL/m^2)	93 ± 64
Rest cardiac output (W)	4.44 ± 1.30
Peak cardiac output (W)	7.54 ± 3.06
Peak power/mass (W/100 g)	1.68 ± 0.70

Data presented are mean value ± SD or number (%) of patients.
CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; CAD, coronary artery disease; LV, left ventricular; WMSI, wall motion score index; SP, systolic pressure; EDV, end-diastolic volume; ESV, end-systolic volume.

Follow-up data

During a median follow-up of 29 months (inter-quartile range 16–72 months), 29 (26%) patients died. Additionally, 14 patients underwent coronary revascularization (5 surgery, 9 angioplasty) and were censored.

With a receiver operating characteristic analysis, peak-stress cardiac power output ≤1.48 W [area under the curve 0.70 (95% CI 0.60; 0.78); sensitivity 62%, specificity 71%] (*Figure 1*) and peak-stress power/mass ≤0.50 W/100 g [area under curve 0.72 (95% CI 0.63; 0.80), sensitivity 59%, specificity 80%] (*Figure 2*) were the best predictors of mortality. Peak-stress power/mass ≤0.50 W/100 g provided a better prediction of the outcome in lower strata of EF (LV EF ≤ 35%): area under curve 0.79 [95% CI 0.66; 0.88], sensitivity 79%, specificity 70%.

Univariate prognostic indicators were age, male sex, peak-stress EF, peak-stress stroke volume, peak-stress CO, peak-stress cardiac power output ≤1.48 W, and peak-stress power/mass ≤0.50 W/100 g (*Table 2*). At multivariate analysis, age (HR 1.08, 95% CI 1.04; 1.14; $P = 0.004$) and peak-stress power/mass ≤0.50 W/100 g (HR 4.05, 95% CI 1.36; 12.00; $P = 0.01$) yielded strong and independent prognostic contribution (*Table 2*).

Three-year mortality was 14% in patients with peak-stress cardiac power output >1.48 W and 40% in those with peak-stress cardiac power output ≤1.48 W (log-rank 11.5; $P < 0.0001$) (*Figure 3*); it was 14% in patients with peak-stress power/mass >0.50 W/100 g and

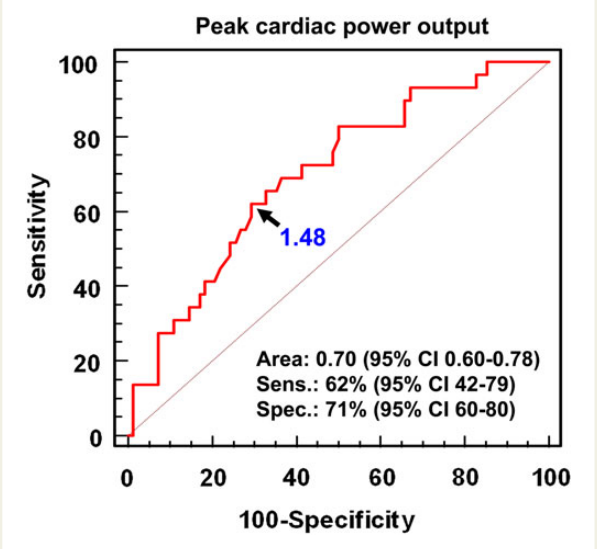

Figure 1 Receiver operating characteristic analysis, evidencing a peak-stress cardiac power output of 1.48 W as the best value for predicting mortality.

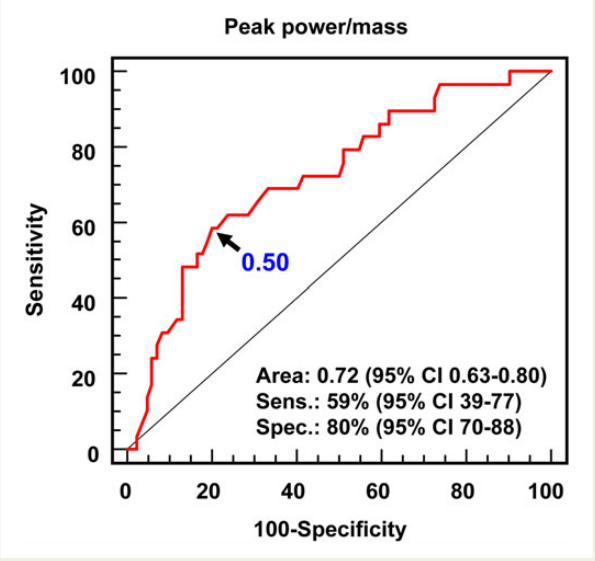

Figure 2 Receiver operating characteristic analysis, evidencing a peak-stress power/mass of 0.50 W/100 g as the best value for predicting mortality.

47% in those with peak-stress power/mass ≤0.50 W/100 g (log-rank 21.0; $P < 0.0001$) (*Figure 4*). Three-year mortality was 10% in patients with peak-stress cardiac power output >1.48 W who received revascularization, 15% in patients with cardiac power output >1.48 W who were treated medically, and 48% in patients with cardiac power output ≤1.48 W (log-rank 11.6; $P = 0.0003$); it was 0% in patients with peak-stress power/mass >0.50 W/100 g who received revascularization, 16% in those with peak-stress power/mass >0.50 W/100 g who were treated medically, and 48% in those with peak-stress power/mass ≤0.50 W/100 g (log-rank 21.1; $P < 0.0001$).

The interobserver variability showed an averaged difference of -0.018 ± 0.086 W [95% CI −0.084; 0.048; $P = 0.550$] for peak-stress cardiac power output and an averaged difference of -0.038 ± 0.185 W/100 g [95% CI −0.180; 0.104; $P = 0.557$] for peak-stress power/mass.

Discussion

We found that power/mass at peak of dobutamine stress echocardiography provides prognostically valuable information in patients with coronary artery disease and LV dysfunction.

Ischaemic cardiomyopathy is steadily increasing as a consequence of the ageing of the population and the improved survival of patients with coronary artery disease.[12] In this setting, the distinction between reversible and non-reversible LV dysfunction may be not only important but also challenging.

With dobutamine echocardiography, a positive response to the stress test is conventionally indicated by an increase of WMSI > 0.4, and this may be used to select patients in whom LV recovery and improvement of prognosis would overweigh the risk of revascularization.[13,14] Conversely, there may be other patients, that have substantial amounts of viable myocardium albeit <0.4 WMSI improvement, that are considered non-responders to the echocardiographic test of viability.[15] Finally, akinetic or severely hypokinetic segments may be classified as viable at nuclear heart imaging even if they are not able to respond to the inotropic stimulation.[16] These latter findings may be advocated as reasons why the clinical value of viability assessment has recently been questioned by the STICH trial,[17] where no significant survival benefit was demonstrated in patients who underwent revascularization classified as having myocardial viability by echocardiographic or scintigraphic techniques.

The echo-derived cardiac power output has been proposed by Marmor *et al.*[4] as a more quantitative indicator of cardiac reserve. To better elucidate the changes in the contractile state as a reflection of substantial amount of viable myocardium, we have recently proposed peak power output-to-LV mass (power/mass). With echocardiography, LV mass can be measured at baseline by M-mode, two-dimensional or three-dimensional echocardiographic methods,[11] while Doppler-derived cardiac power output can be easily attained according to the formula that incorporates BP and CO. Peak-stress power/mass is an index that allows to investigate the relationship between the recruited myocardial muscle and the power delivered by the left ventricle. The concept behind the ratio is that a stronger ventricle with a greater amount of viable myocardium will contract to a higher power output under stimulation. Patients in whom LV power at peak stress parallels the extent of LV mass likely reflect more viable myocardium, whereas a peak LV power/mass in the lower range suggests that the left ventricle has depressed cardiac reserve and therefore less viable myocardium and more fibrosis.[18,19]

In the current study, power/mass ≤0.50 W/100 g at peak of dobutamine stress emerged as a strong and independent predictor of mortality, whereas patients with a peak power/mass >0.50 W/100 g, who were either revascularized or not revascularized, exhibited a better prognosis. Interestingly enough, the ability of this index in predicting patients' survival was more accurate than that of peak stress-LV EF. Possible explanation for this may be that LV peak power/mass better reflects the myocardial energy delivery that is potentially stored in the viable myocardium. When a compromised contractile function co-exists with an increased mass, it probably means that the rate of energy delivery from the myocardium is impaired as a result of maladaptive feature of LV remodelling.[20]

Peak power/mass has advantages over other indices used to assess contractile reserve. Differently from LV elastance and EF, it does not require LV volumes identification, that it is often problematic as a result of difficulties in endocardial border detection[21] and is independent of geometric assumptions on LV shape. In addition, it also incorporates information on BP (similar to LV elastance) and LV mass index which are recognized prognostic indicators in these patients. In fact, prognosis is worse in the presence of low values of peak stress BP[22] and high values of LV mass index.[23]

Power/mass may be considered not only a measure of LV cardiac reserve but also an index of myocardial efficiency,[24] since this ratio incorporates the degree of external work per unit of time and the maximal work possible. Although the denominator of this equation cannot be estimated, it can be argued that in normal ventricles the amount of LV mass is proportional to the myocardial power delivery.

Table 2 Univariable and multivariable predictors of mortality

	Univariate analysis HR (95% CI)	*P*-value	Multivariate analysis HR (95% CI)	*P*-value
Age	1.10 (1.05; 1.16)	<0.0001	1.08 (1.03; 1.14)	0.004
Male gender	2.36 (1.06; 5.27)	0.03		
Diabetes mellitus	0.84 (0.39; 1.82)	0.66		
Hypertension	1.40 (0.67; 2.92)	0.37		
Prior myocardial infarction	1.22 (0.58; 2.55)	0.60		
Prior CABG	0.32 (0.11; 2.02)	0.32		
Prior PCI	1.81 (0.84; 3.90)	0.13		
History of CAD	1.40 (0.59; 3.31)	0.45		
LV mass	1.00 (1.00; 1.01)	0.23		
Rest LV ejection fraction	0.97 (0.93; 1.01)	0.13		
Peak LV ejection fraction	0.97 (0.95; 1.00)	0.05		
Rest LV EDV	1.00 (0.99; 1.00)	0.43		
Peak LV EDV	1.00 (1.00; 1.00)	0.50		
Rest LV ESV	1.00 (1.00; 1.00)	0.72		
Peak LV ESV	1.00 (1.00; 1.01)	0.41		
WMSI	2.27 (0.83; 6.21)	0.11		
Peak WMSI	3.52 (1.24; 9.98)	0.018		
Delta WMSI ≤ 0.2	0.74 (0.33; 1.67)	0.47		
Delta WMSI ≤ 0.4	0.48 (0.17; 1.40)	0.18		
Rest cardiac power output	1.10 (0.33; 3.64)	0.88		
Peak cardiac power output	0.42 (0.24; 0.73)	0.002		
Rest cardiac output	1.06 (0.82; 1.38)	0.63		
Peak cardiac output	0.83 (0.73; 0.95)	0.009		
Peak power/mass	0.84 (0.02; 0.36)	0.001		
Peak cardiac power output ≤1.48 W	3.75 (1.87; 8.41)	0.001		
Peak power/mass ≤0.5 W/100 g	5.27 (2.39; 11.62)	<0.0001	4.05 (1.36; 12.00)	0.01

Abbreviations as in *Table 1*.

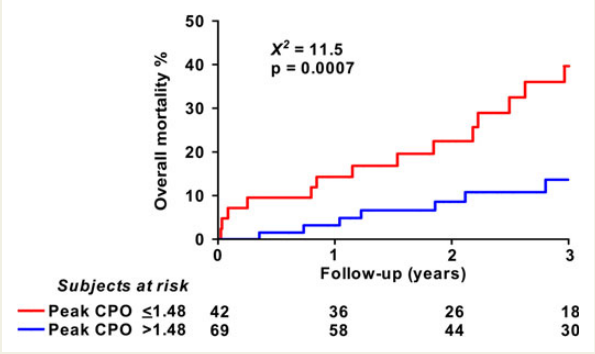

Figure 3 Mortality rate for patients with peak-stress cardiac power output (CPO) greater than and ≤1.48 W. Number of patients per year is shown.

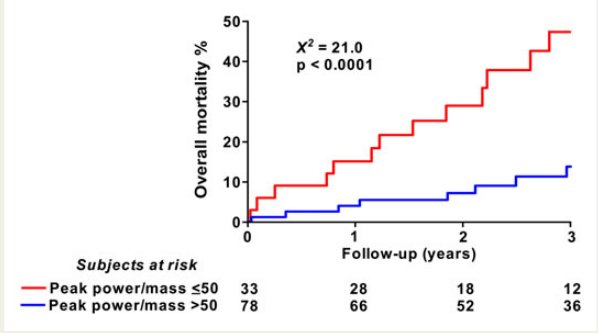

Figure 4 Mortality rate for patients with power/mass greater than and ≤0.50 W/100 g. Number of patients per year is shown.

Clinical implications

Patients with negative stress echo are a large and expanding population in stress imaging lab totaling 70–80% of all stress tests.[25] Although the risk category associated with this response is generally considered low and the prognosis benign,[26] we have learned in recent years that the prognosis in this group is heterogeneous. Relatively higher risk subsets can be identified with simple clinical and echocardiographic variables since a higher risk is associated with negativity occurring with submaximal testing[27] or in patients studied

on anti-anginal therapy.[13] Stress echo parameters include decreased coronary flow velocity reserve,[28] reduced increase in LV elastance,[29] or development of severe mitral regurgitation during stress.[30] Peak-stress power/mass adds yet another parameter to substratify this challenging population. Since power/mass represents a quantitative index of global LV function, its assessment under stress may effectively contribute to estimate the overall contractile reserve, especially in patients—like those with a blunted WMSI response to dobutamine—in whom the evaluation of viability cannot rely on a single parameter, with significant implications for the selection of patients who are most likely to benefit from coronary revascularization.

Study limitations

The present study has the inherent limitations of a retrospective analysis. Patients underwent stress echo on the basis of the clinically indications, and we could not control for the many variables potentially interfering with power/mass, such as ongoing medical therapy at time of testing or post-test interventions modifying the natural history of the disease. In addition, we focused our analysis on power/mass, although many additional echocardiographic parameters may be assessed during stress echo, such as mitral insufficiency, pulmonary hypertension, B lines, right ventricular function, and coronary velocity flow reserve, which might expand the prognostic information of the test.[30] Peak power/mass exhibited a higher variability than peak LV power output. Therefore, careful acquisition of LV mass appears necessary to minimize variability and to improve reproducibility of this measurement.

Conflict of interest: None declared.

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