Journal of Cardiology 73 (2019) 73–80

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Abnormal exercise echocardiography plus abnormal E/e′ ratio at exercise portends worse outcome in patients with dyspnea

Jesús Peteiro (MD PhD)[a,*], Alberto Bouzas-Mosquera (MD PhD)[a], Javier Broullon (MD)[b], Jose M. Larrañaga (MD)[a], Jose M. Vazquez-Rodriguez (MD PhD)[a]

[a] Department of Cardiology, Complejo Hospitalario Universitario de A Coruña (CHUAC), CIBERCV, Instituto de Investigación Biomédica de A Coruña (INIBIC) y Universidad de A Coruña, A Coruña, Spain

[b] Department of Information Technology, Complejo Hospitalario Universitario de A Coruña (CHUAC), CIBERCV, Instituto de Investigación Biomédica de A Coruña (INIBIC) y Universidad de A Coruña, A Coruña, Spain

ARTICLE INFO

Article history:
Received 11 May 2018
Received in revised form 3 July 2018
Accepted 17 July 2018
Available online 5 September 2018

Keywords:
Exercise echocardiography
Ischemia
E/e′ values

ABSTRACT

Background: The role of exercise echocardiography (ExE) for the assessment of patients with dyspnea is promising. We aimed to analyze the clinical characteristics and outcome of patients with this condition referred for ExE.

Methods: A total of 505 patients (66 ± 11 years, 57% women) referred for evaluation of dyspnea were considered. Mitral regurgitation, ratio of early left ventricular inflow wave to early diastolic annulus wave (E/e′), and wall motion abnormalities (WMAs) were measured at rest and at exercise. Considered events were overall mortality, non-fatal myocardial infarction, late revascularization, and admission for heart failure.

Results: Ischemia was observed in 102 patients (20%), whereas WMAs were already present at rest in 55 patients (11%). A percent achieved of predicted metabolic equivalents >100% was found for most of the patients (70%). During a median follow-up of 3.50 years, 66 patients had events (annualized event rate 3.5%). An E/e′ value of 13 at post-exercise was the best cut-off value to predict events. After adjustment by clinical and ExE variables, the combination of an abnormal ExE and E/e′ values at post-exercise ≥13 was an independent predictor of events (hazard ratio = 3.67, 95% confidence interval = 2.11–6.38, $p < 0.001$). The worse outcome corresponded to patients with abnormal ExE and raised E/e′ values at post-exercise (annualized event rate 17.2%). Patients with normal E/e′ values at post-exercise had better outcome irrespective of the ExE results (annualized event rate 2.2% with normal ExE and 2.9% with abnormal ExE), whereas patients with high E/e′ values at post-exercise but normal ExE results were at intermediate risk (annualized event rate 5.0%).

Conclusions: Despite favorable ExE results, event rate remains high among patients with dyspnea referred for ExE, which may have a role to predict outcome in this setting. Patients with both raised E/e′ values at post-exercise and abnormal ExE results are at the highest event risk.

Introduction

Exercise echocardiography (ExE) may be of interest for the assessment of patients with dyspnea. The number of patients with this complaint or with the suspicion of heart failure with preserved ejection fraction (HFpEF) that are referred for ExE would likely increase in the future [1]. Dyspnea on effort may be an angina-like symptom, and in this case ischemia should be ruled out, or reflect diastolic dysfunction, and in this case it would be important to demonstrate exercise-induced high left ventricular filling pressures. ExE has the capability of assessing both exercise-induced wall motion abnormalities (WMAs) and diastolic function. It has been shown that raised E/e′ ratios increase the value of ExE for assessing outcome in patients with a clinically indicated ExE [2], but its value has not been addressed in the specific group of patients with dyspnea. We aimed to assess WMAs and diastolic function (by the E/e′ ratio) during exercise in patients whose main complaint was dyspnea, in order to investigate the impact of both on outcome. We hypothesized that patients with either abnormal ExE or increased E/e′ values at post-exercise might have worse outcome.

* Corresponding author at: Department of Cardiology, Complejo Hospitalario Universitario de A Coruña (CHUAC), As Xubias, 84, 15006 A Coruña, Spain.
E-mail address: pete@canalejo.org (J. Peteiro).

https://doi.org/10.1016/j.jjcc.2018.07.003
0914-5087/

Methods

Patients

This is a prospective study of patients referred for evaluation of dyspnea by ExE. After exclusion of those with myocardiopathies, moderate or severe aortic or mitral valve disease, congenital heart disease, left ventricular systolic dysfunction as defined as a left ventricular ejection fraction (LVEF) <45%, and unfeasible/technically deficient recordings, an overall group of 505 patients was considered. All patients gave informed consent.

Exercise echocardiography

ExE was performed in a treadmill according to different protocols, adjusted to the clinical characteristics of the patients (Bruce protocol 83%, modified protocols 17%). Exercise end points included physical exhaustion, significant arrhythmia, severe hypertension [systolic blood pressure (BP) >240 mmHg or diastolic BP >110 mmHg], severe hypotensive response (decrease >20 mmHg), or symptoms during exercise. Ischemic electrocardiogram (ECG) was defined as the development of ST-segment deviation of ≥1 mm which was horizontal or downsloping away from the isoelectric line 80 ms after the J point in at least 2 leads, in patients with normal baseline ST segments. The ECG was considered non-diagnostic in the presence of left bundle branch block, preexcitation, paced rhythm, repolarization abnormalities, or treatment with digoxin. Positive exercise testing was defined as chest pain during the test and/or ischemic ECG abnormalities in patients with diagnostic ECG [3,4]. We defined dyspnea on exercise just in case of severe respiratory distress in a given patient, instead of a patient's self-reported impairment during the test. A maximal test was defined as the achievement of at least 85% of the mean age-predicted heart rate (MAPHR), otherwise the test was considered submaximal. Estimated maximal workload was assessed according to the percentage achieved of predicted metabolic equivalents (METs) estimated by age and sex. For men, we used the Veterans Affairs formula (predicted METs = 18 − [0.15 × age]) [5], and for women the St. James Take Heart Project formula (predicted METs = 14.7 − [0.13 × age]) [6]. These formulae have previously demonstrated their ability to predict outcomes [7]. Therefore, we calculated the ratio: (METs achieved/predicted METs) × 100. Patients achieving less than 100% of their age and gender predicted METs were classified as having exercise intolerance.

Echocardiography was performed in 3 apical views (long axis, 4-, and 2-chambers) and 2 parasternal views (long- and short-axis) at baseline in the table-bed, and at peak exercise on the treadmill [4,8]. Regional WMAs were evaluated with a 16-segment model of the left ventricle [9]. Each segment was graded on a 4-point scale, with normal wall-motion scoring = 1, hypokinetic = 2, akinetic = 3, and dyskinetic = 4. However, isolated hypokinesia of the basal inferior or infero-septal segments was not considered abnormal [10]. Wall motion score index (WMSI) and visually estimated LVEF [11] were calculated at rest and at peak exercise. Ischemia was defined as the development of a new WMA or as worsening of a resting WMA with exercise. A fixed WMA was defined as a resting WMA that remained the same with exercise. An abnormal ExE was defined as ischemia or fixed WMAs.

Mitral regurgitation (MR) was assessed at rest and in the immediate post-exercise period by a comprehensive approach, that integrates measurements of vena contracta, proximal isovelocity surface area, and jet area in the left atrium, as recommended [12]. However, patients with more than mild MR at rest were excluded from the study as increase in MR might affect the results. MR recordings were followed by early LV diastolic filling wave (E) and early diastolic mitral annulus wave (e′) at the septal annulus recordings, by pulsed Doppler and tissue Doppler imaging, respectively.

Also, we assessed two-dimensional image quality by a qualitative approach in 20 randomized studies, by an expert observer (JP). Excellent imaging quality was defined as complete visualization of all segments in the apical and parasternal views with clean endocardial border excursion and systolic thickening. Good quality was defined as complete visualization of all segments in the apical views with good assessment of endocardial border excursion and systolic thickening but incomplete assessment of the endocardial border excursion or thickening in at least one segment in the parasternal views. Poor quality referred to a lack of assessment of the endocardial border excursion or thickening in one segment in the different views. Bad quality was defined as a lack of assessment of endocardial border excursion or thickening in two or more segments in the different views.

Follow-up and endpoints

The inclusion period of this study extended for 11 years, from June 2006 to August 2017. All patients were followed for the considered events by review of electronic medical records which include information on hospital admissions, coronary procedures, and vital status. Mortality and cause of death was obtained from the Mortality Registry of Galicia (our community). Also, in case of doubts a telephone interview was done. No patients were lost during follow-up. Considered events were death of any cause, cardiac death, non-fatal myocardial infarction (MI), late revascularization (≥6 months), and heart failure requiring admission. Cardiac death was defined as death caused by acute MI, heart failure, life-threatening arrhythmias, or documented cardiac arrest; unexpected and unexplained sudden death was also considered of cardiac origin. MI was defined as the appearance of new symptoms of myocardial ischemia or ischemic ECG changes accompanied by increases in markers of myocardial necrosis. Heart failure was defined as symptoms and signs of congestion requiring hospital admittance.

Statistical analysis

Categorical variables were reported as % and continuous variables as mean ± 1 standard deviation. Annualized event rates were calculated by dividing the number of events by the total number of person-years at risk. Survival free of the endpoint of interest was estimated by the Kaplan–Meier method, and survival curves were compared with the log-rank test.

Univariable and multivariable associations of the different variables with outcome were assessed with Cox's proportional hazard model. Significant variables in the univariable analysis at a level of $p = 0.05$ were entered in a multivariate analysis using backward modeling. Hazard ratios (HR) with 95% confidence intervals (CI) were estimated. To choose the best cut-off E/e′ value to predict events we studied a derivation set formed by the first 180 patients included (30 events) and a validation set formed by the last 325 patients included (36 events). The area under the curve (AUC) of receiver operator curves for predicting events in the derivation and validation samples are provided. Statistical analysis was performed using SPSS software, version 15.0 (SPSS, Chicago, IL, USA).

Results

No patients were excluded on the basis of suboptimal two-dimensional imaging or unfeasible pulsed or tissue Doppler recordings, although technical problems with Doppler acquisition prevented the inclusion of four patients. Two-dimensional image

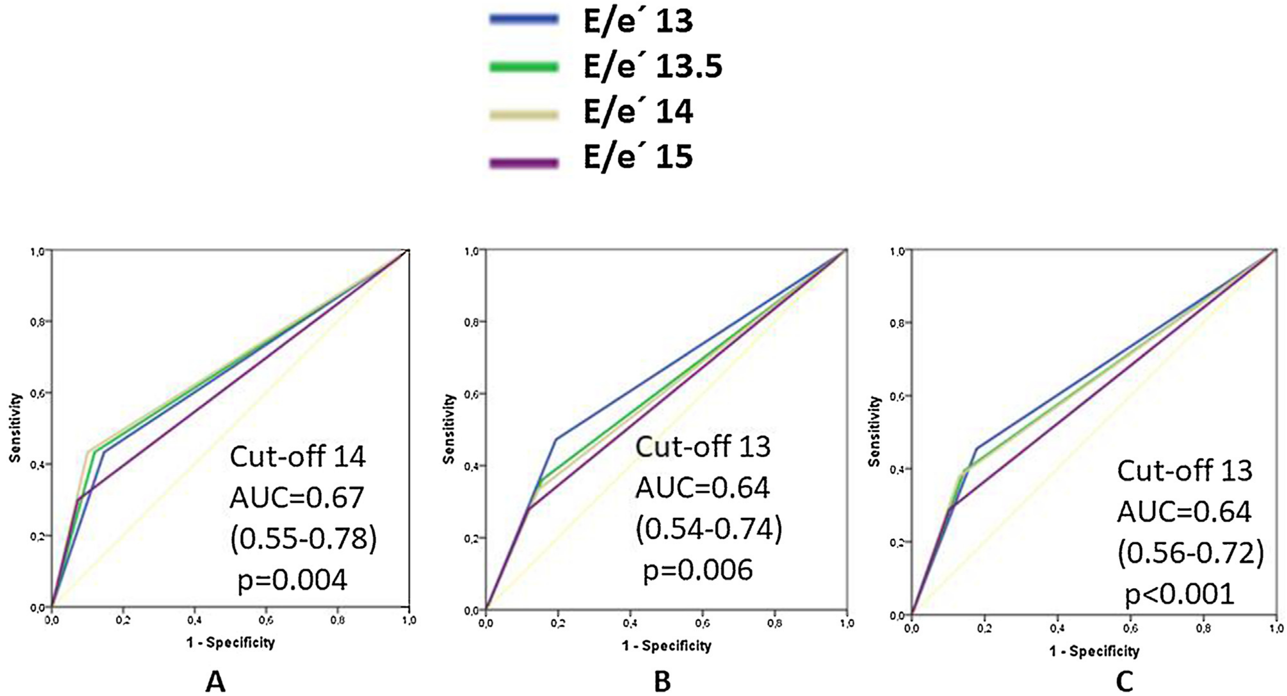


Fig. 1. Receiver operator curves of E/e′ values at post-exercise for predicting outcomes in the derivation (A), validation (B), and overall group (C). *Abbreviation*: AUC, area under the curve; E/e′, ratio of early left ventricular inflow wave to early diastolic annulus wave.

quality was considered excellent in 21% of the studies, good in 69%, poor in 8%, and bad in 2%.

Patients in the derivation group were younger than those in the validation group (64 ± 13 years vs. 67 ± 10 years, p = 0.006), and consequently achieved more METs and higher double product HR × BP (8.8 ± 3.0 vs. 8.1 ± 2.7, p = 0.009; and 23.4 ± 4.8 vs. 22.4 ± 4.9, p = 0.03, respectively), and had lower E/e′ values at post-exercise (10.3 ± 4.1 vs. 11.2 ± 4.5, p = 0.04). Also, they had less frequently resting WMAs (7% vs. 13%, p = 0.049) and abnormal ExE (19% vs. 29%, p = 0.02). The best post-exercise E/e′ cut-off value for predicting outcome in the derivation group was 14 (AUC = 0.67; 95% CI = 0.55–0.78; p = 0.004) whereas in the validation group it was 13 (AUC = 0.67; 95% CI = 0.55–0.78; p = 0.004), as it was in the overall group (AUC = 0.64; 95% CI = 0.56-0.72; $p < 0.001$). Therefore we used the value of 13 for further analyses (Fig. 1).

A percentage of predicted METs >100% was observed in 70% of the patients, although it was more frequent in women than in men (81% vs. 55%, $p < 0.001$). Also, most patients had normal E/e′ values at both rest and post-exercise (n = 351, 70%), whereas raised values at both conditions were observed in 73 (14%). In 35 patients (7%) E/e′ values increased only at post-exercise, and in 46 (9%) increased E/e′ values were detected only at rest. Fig. 2 shows the number of patients with raised E/e′ values at rest and at post-exercise, abnormal ExE results, and exercise intolerance.

During a median follow-up of 3.50 years (25–75th percentiles 1.96–5.17), there were 66 combined events (annualized event rate

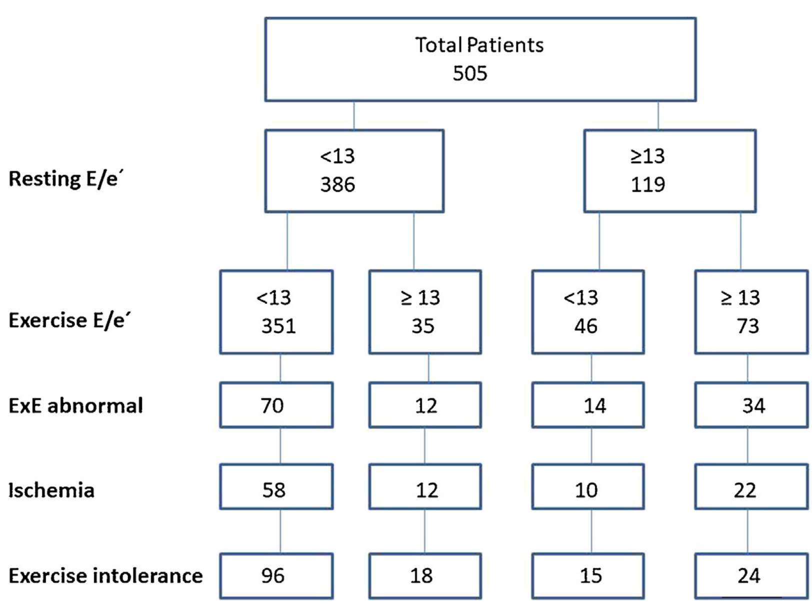
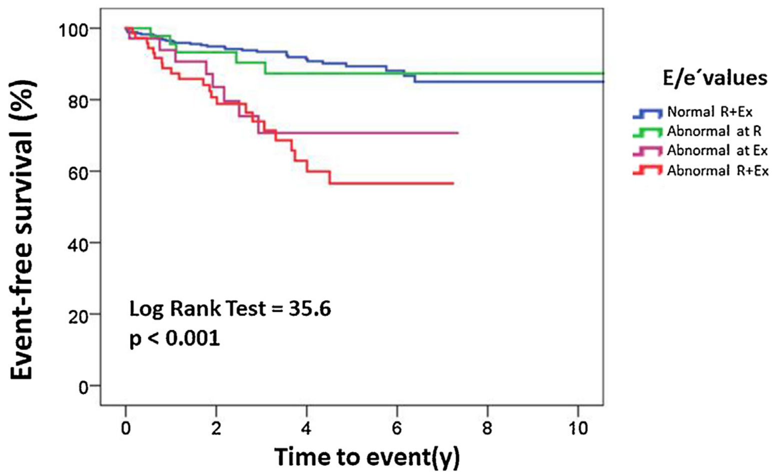


Fig. 2. Flow chart considering resting and exercise E/e′, abnormal exercise echocardiography (ExE), presence of ischemia, and exercise intolerance in the 505 patients. E/e′, ratio of early left ventricular inflow wave to early diastolic annulus wave.



Normal rest+exercise	351	275	161	64	8
Abnormal only at rest	46	34	24	11	2
Abnormal only at exercise	35	21	9	4	-
Abnormal rest+exercise	73	44	21	7	-

Fig. 3. Combined event-free survival curves for patients with normal E/e′ values at rest and exercise (<13 both), E/e′ increased only at rest, E/e′ increased only at exercise, and E/e′ increased at both rest and exercise (≥13 both). E/e′, ratio of early left ventricular inflow wave to early diastolic annulus wave.

3.5%). The first event was heart failure in 31 patients, non-fatal MI in 6, coronary revascularization in 10, and death in 19 patients. The worst survival-free of the combined event was observed in patients with increased E/e′ values at rest and at post-exercise (annualized event rate 10.3%), in comparison with patients with increased E/e′ values only at post-exercise (annualized event rate 7.7%), only at rest (2.6%), or without increase (annualized event rate 2.3%; Fig. 3).

Ischemia was observed in 102 patients (20%), whereas WMAs were already present at rest in 55 patients (11%). A total of 130 patients had abnormal ExE results (26%), divided in those with only ischemia (n = 75, 58%), those with fixed WMAs without ischemia (n = 28, 21%), and those with mixed WMAs plus ischemia in the same or different territory (n = 27, 21%). Among the 130 patients with abnormal ExE, there were 28 of the 66 combined events. The first event in this subgroup was death in 5 patients, non-fatal MI in 3, late coronary revascularization in 7, and heart failure requiring admission in 13 patients.

When information on WMAs during ExE (fixed or new WMAs) was combined with information on E/e′ values, we found that the worse outcome corresponded to patients with abnormal ExE and raised E/e′ values at post-exercise (annualized event rate 17.2%). In contrast, patients with normal E/e′ values at post-exercise had better outcome irrespectively of the ExE results (annualized event rate 2.2% with normal ExE and 2.9% with abnormal ExE). Patients with high E/e′ values at post-exercise and normal ExE were placed in an intermediate position (annualized event rate 5.0%) (Fig. 4A). Similarly, when information on new WMAs (ischemia) was added to E/e′ values at post-exercise, the worst outcome was found in patients with both ischemia and increased E/e′ values (Fig. 4B).

Tables 1 and 2 show the clinical characteristics and the ExE results in patients classified as having or not abnormal ExE and raised E/e′ values at post-exercise. A total of 180 patients in the overall group (36%) had functional respiratory tests performed at the time of the ExE, with normal results in a half (94 cases) and abnormal results in another half (83 cases), whereas the tests were unfeasible in 3 subjects. A total of 91 patients had a clinical diagnosis of pulmonary disease, which was chronic obstructive pulmonary disease or asthma for most of them (n = 69).

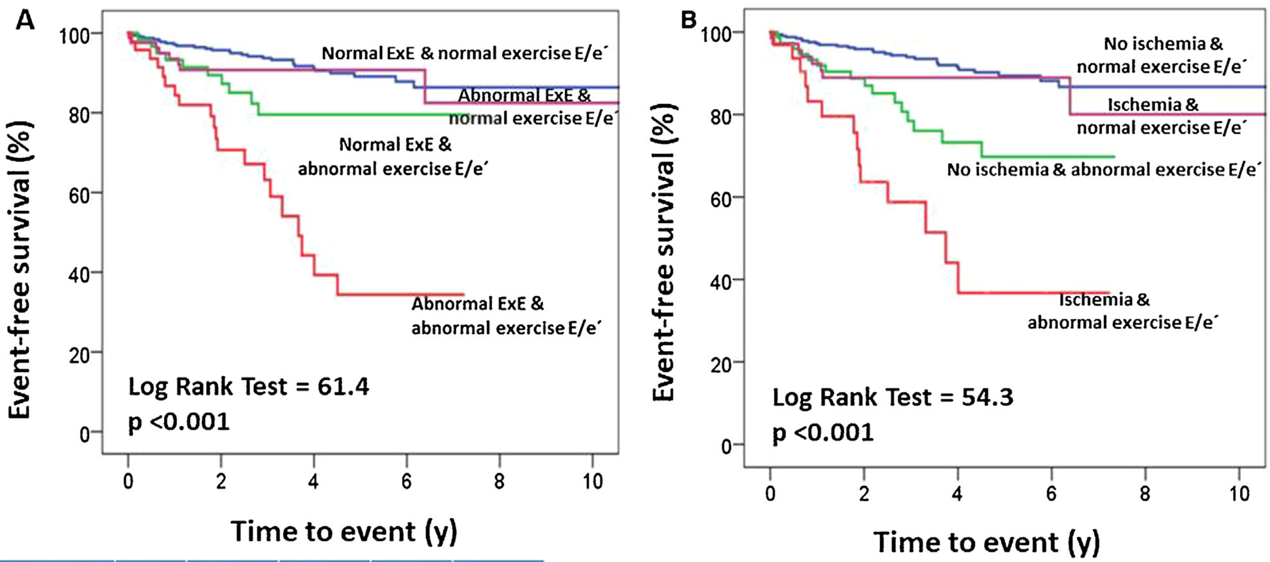
Table 3 shows univariable and multivariable predictors of the combined events. The combination of exercise-induced WMAs plus increased E/e′ values at post-exercise was predictive of events, on top of clinical variables and maximal achieved workload.

Discussion

The main finding of this study was that despite favorable ExE results in terms of functional capacity and presence of abnormal results, events during follow-up were frequent among patients with dyspnea referred for ExE. The percentage of patients with ischemia and with abnormal ExE was not higher than the 30% of the sample. However, the event rate was higher than expected in a population of these characteristics. For instance, in a previous ExE study by our group, the annualized mortality rate for patients with suspected coronary artery disease (CAD) due to mainly chest pain, with similar percentages of ischemia (19%) and resting WMAs (13%), and a similar achieved maximal workload of 7–9 METs, was just 2.2% [13]. In another study on patients with either angina or dyspnea referred for ExE, cardiac events were also more than double in those with dyspnea [14]. In that study the event rate for patients with dyspnea was 6.3% in 3 years of mean follow-up for cardiac death plus non-fatal MI, whereas in our current study the rate of combined events was 3.5% for a median follow-up of 3.5 years.

A metaanalysis on patients with either angina or dyspnea referred for functional imaging also found that patients with dyspnea had worse outcome, even though the percentage of abnormal tests was lower than in patients with angina [15]. A plausible explanation for these findings is therefore that other factors that lead to poor outcome, apart from CAD, might account for patients who complain of dyspnea.

On the other hand we have observed that our protocol is valid for the assessment of systolic and diastolic LV function. Combined data on abnormal regional function suggesting CAD plus abnormal LV diastolic function provided significant prognostic information. Patients with these characteristics had the worse outcome, portending a more than three-times increased risk of events.



Normal ExE & normal exercise E/e´	315	256	157	63	6
Normal ExE & abnormal exercise E/e´	60	41	9	-	-
Abnormal ExE & normal exercise E/e´	82	53	28	12	4
Abnormal ExE & abnormal exercise E/e´	48	24	9	2	-

No ischemia & normal exercise E/e´	327	266	161	64	6
No ischemia & abnormal exercise E/e´	76	50	24	9	-
Ischemia & normal exercise E/e´	70	43	24	11	4
Ischemia& abnormal exercise E/e´	32	15	6	-	-

Fig. 4. Combined event-free survival curves for patients grouped according to the presence or absence of wall motion abnormalities during exercise echocardiography (ExE) and of the presence or absence of a raised E/e′ value (≥13) at exercise (A), and for patients grouped according to the presence or absence of ischemia and of the presence or absence or a raised E/e′ value (≥13) at exercise (B). E/e′, ratio of early left ventricular inflow wave to early diastolic annulus wave.

Table 1
Clinical baseline characteristics and medications by group.

	ExE (−) plus Exercise E/e′ <13 (*n* = 315)	ExE (−) plus Exercise E/e′ ≥13 (*n* = 60)	ExE (+) plus Exercise E/e′ <13 (*n* = 82)	ExE (+) plus Exercise E/e′ ≥13 (*n* = 48)	*p*-value
Male gender, *n* (%)	130 (41)	18 (30)	48 (59)	22 (46)	**0.005**
Age (y)	65 ± 12	69 ± 10	66 ± 10	70 ± 10	**0.002**
Diabetes mellitus, *n* (%)	67 (21)	24 (40)	16 (20)	17 (35)	**0.003**
Hypertension, *n* (%)	186 (59)	46 (77)	53 (65)	38 (79)	**0.006**
Smoking, *n* (%)	43 (14)	7 (12)	14 (17)	8 (17)	0.80
Hypercholesterolemia, *n* (%)	165 (52)	31 (52)	53 (65)	29 (60)	0.19
Body mass index	31 ± 6	33 ± 3	33 ± 7	32 ± 7	0.57
Pulmonary disease, *n* (%)	59 (19)	15 (25)	11 (13)	6 (13)	0.23
Atrial fibrillation, *n* (%)	17 (5)	2 (3)	4 (5)	5 (10)	0.42
Abnormal resting ECG, *n* (%)	26 (8)	12 (20)	16 (20)	17 (35)	<**0.001**
History of CAD[a], *n* (%)	27 (9)	5 (8)	34 (41)	21 (44)	<**0.001**
Typical or atypical angina	63 (20)	19 (32)	23 (28)	10 (21)	0.46
Medications					
Beta-blockers[b], *n* (%)	22 (7)	11 (18)	14 (17)	15 (31)	<**0.001**
Calcium channel blockers, *n* (%)	45 (14)	10 (17)	12 (15)	4 (8)	0.64
Nitrites, *n* (%)	21 (7)	7 (12)	8 (10)	5 (10)	0.47
AECI/ARAs, *n* (%)	124 (39)	40 (67)	45 (55)	29 (60)	<**0.001**
Digoxin, *n* (%)	3 (1)	0 (0)	0 (0)	1 (2)	0.50
Diuretics, *n* (%)	17 (5)	10 (17)	4 (5)	4 (8)	**0.01**

Bold values represent *p* significance at a level of < 0.05.
ACEI, angiotensin-converting enzyme inhibitors; ARA, angiotensin receptor antagonists; CAD, coronary artery disease; ECG, electrocardiogram; ExE, exercise echocardiography.
[a] Either previous myocardial infarction, coronary revascularization, or non-revascularized coronary lesions.
[b] At the time of the ExE.

Table 2
Exercise echocardiography results by group.

	ExE (−) plus Exercise E/e′ <13 (n = 315)	ExE (−) plus Exercise E/e′ ≥13 (n = 60)	ExE (+) plus Exercise E/e′ <13 (n = 82)	ExE (+) plus Exercise E/e′ ≥13 (n = 48)	p-value
Symptoms during exercise testing, n (%)					
Any symptom	68 (22)	21 (35)	24 (29)	12 (25)	0.11
Dyspnea	51 (16)	18 (30)	11 (13)	7 (15)	**0.04**
Positive ECG, n (%)	30 (10)	3 (5)	15 (18)	6 (13)	0.06
Either symptoms or (+) ECG	92 (29)	24 (40)	31 (38)	16 (33)	0.24
Maximal achieved workload (METs)	8.7 ± 2.9	7.3 ± 2.2	8.3 ± 2.7	6.9 ± 2.4	<**0.001**
Heart rate (bpm)					
Rest	80 ± 14	74 ± 10	76 ± 15	75 ± 12	**0.001**
Exercise	146 ± 19	131 ± 18	145 ± 20	135 ± 18	<**0.001**
Submaximal test, n (%)[a]	54 (17)	24 (40)	14 (17)	16 (33)	<**0.001**
Blood pressure (mmHg)					
Rest	129 ± 20	132 ± 19	130 ± 18	134 ± 18	0.34
Exercise	160 ± 24	159 ± 27	158 ± 25	152 ± 23	0.18
Double product (mmHg × lpm × $10^{(3)}$)					
Rest	10.3 ± 2.3	9.7 ± 1.9	10.0 ± 2.7	10.0 ± 2.0	0.24
Exercise	23.5 ± 4.9	20.8 ± 4.4	22.9 ± 4.7	20.5 ± 4.2	<**0.001**
LV ejection fraction (%)					
Rest	61 ± 4	61 ± 4	58 ± 5	55 ± 6	<**0.001**
Exercise	69 ± 4	68 ± 5	58 ± 8	53 ± 8	<**0.001**
Wall motion score index					
Rest	1 (1-1)	1 (1-1)	1.09 ± 0.15	1.23 ± 0.29	<**0.001**
Exercise	1 (1-1)	1 (1-1)	1.35 ± 0.29	1.48 ± 0.29	<**0.001**
LV hypertrophy, n (%)	101 (32)	26 (43)	28 (34)	23 (48)	0.09
Pulmonary artery pressure, mmHg					
Rest (n)	40 ± 11 (47)	40 ± 10 (18)	39 ± 4 (13)	45 ± 10 (13)	0.38
Exercise (n)	61 ± 15 (41)	63 ± 16 (17)	59 ± 14 (12)	63 ± 13 (11)	0.82
Moderate or severe MR at exercise, n (%)	1 (0.3)	0 (0)	1 (1)	3 (6)	**0.001**
E/e′					
Rest	9.6 ± 2.6	14.5 ± 5.2	10.0 ± 2.9	15.9 ± 6.1	<**0.001**
Exercise	9.0 ± 1.8	16.9 ± 5.3	9.8 ± 1.8	17.4 ± 5.3	<**0.001**

Bold values represent p significance at a level of < 0.05.
ECG, electrocardiogram; E/e′, ratio of early left ventricular inflow wave to early diastolic annulus wave; MR, mitral regurgitation.
[a] <85% of the maximal age-predicted heart rate.

Our approach consisted of peak imaging on the treadmill for assessment of regional and global LV systolic function, and therefore for ruling in or ruling out ischemic CAD, followed by post-exercise imaging on the table bed for diastolic function assessment. Thus, E/e′ was measured in the same position at rest and at post-exercise. The best post-exercise E/e′ cut-off value for predicting outcome using septal measurements was 13. This value is in agreement with previous studies in which the best cut-off values oscillated between 12 and 15 [16–19]. In a recent study on patients with demonstrated heart failure with preserved ejection fraction a post-exercise E/e′ higher than 14 was the best cut-off value for diagnosing the disease, with sensitivity of 90% and specificity of 71%, whereas current guidelines had sensitivities ranging from 34% to 60% [20]. In contrast, in normal individuals the upper limit of normality ranges between 10.2 and 11.6 [18,21].

Previous studies assessing E/e′ during exercise echocardiography

Holland et al. studied ischemia, E/e′, and functional capacity by ExE in patients with dyspnea and criteria of heart failure with preserved LVEF at rest [19]. They found increased E/e′ values with exercise (E/e′ >13) in 21% of their 436 patients and ischemia in 27%; the corresponding figures in our study were 21% for E/e′ >13 and 20% for ischemia. Therefore these numbers are similar. Regarding exercise tolerance using the same scales of Morris [5] and Gulati [6] in both studies, they showed low functional capacity in 14% of their patients in contrast to 30% in our study. However, mean age was 9 years higher in our study and the percentage of women and diabetics was also higher (57% vs. 43%, and 25% vs. 16%, respectively).

In another study by the same group but this time dealing with patients who had different clinical indications for an ExE [2], they found that both ischemia and elevated E/e′ at post-exercise (>14.5) were independent predictors of outcome. Similar to our results in patients referred for evaluation of dyspnea as the main or only complaint, the worse outcome was observed in those with both WMAs and raised E/e′ at post-exercise. However, the event rate was formed by softer events than in our study, such as hospitalizations, and no deaths were registered during a median follow-up of 1 year.

Limitations

Dyspnea may have a multifactorial origin in many patients, particularly in older subjects, and this fact could have impacted outcome. A non-insignificant number of patients were obese, and 18% of subjects were studied by respiratory tests at the time of the ExE. Whether respiratory tests and ExE should be performed in any patient with complaints of dyspnea and in which order is beyond the scope of this study.

We used the septal e′ in order to simplify the protocol, as the time window for imaging is limited with exercise on a treadmill. The septal e′ measurement could have led to diminished values in patients with WMAs at this level. However, this approach has also been used in other ExE studies [2–19], so it might be useful for comparisons. Besides E/e′ values, assessment of pulmonary artery pressures by Doppler at the tricuspid level may be valuable for studying these patients. Unfortunately, it was only feasible in a small percentage of the subjects.

Patients were followed by their responsible clinicians taking into consideration the results of the ExE. Although a state-of-the

Table 3
Univariable and multivariable predictors of combined events.

	Univariable			Multivariable		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Clinical variables						
Age (per year)	1.09	1.05–1.13	<0.001	1.06	1.03–1.10	<0.001
Male gender	1.93	1.18–3.13	0.009	2.18	1.33–3.58	0.02
Diabetes mellitus	3.36	2.08–5.42	<0.001	2.38	1.46–3.88	0.001
Atrial fibrillation	2.46	1.12–5.41	0.03			
History of CAD	2.66	1.58–4.47	<0.001			
Nitrites	2.42	1.27–4.64	0.007			
Ca^{++} antagonists	2.15	1.22–3.77	0.008			
Resting echocardiography						
Resting WMSI	8.54	2.92–25.03	<0.001			
Resting LVEF	0.93	0.89–0.97	0.002			
E/e′ at rest	1.09	1.05–1.13	<0.001			
Exercise testing						
METs	0.76	0.69–0.83	<0.001	0.85	0.77–0.95	0.001
Δ in double product	0.86	0.81–0.92	<0.001			
Peak double product	0.88	0.83–0.93	<0.001			
% achieved of the MAPHR	0.07	0.00–0.62	0.02			
Any symptoms during ExE	2.26	1.38–3.69	0.001			
Dyspnea during ExE	1.72	1.00–2.96	0.049			
Positive exercise testing[a]	2.34	1.44–3.79	0.001			
ExE						
Exercise LVEF	0.94	0.92–0.97	<0.001			
Δ LVEF	0.94	0.91–0.97	<0.001			
Δ WMSI	4.97	2.26–10.92	<0.001			
Exercise WMSI	6.67	3.39–13.11	<0.001			
Abnormal ExE	2.77	1.70–4.52	<0.001			
Ischemia	2.54	1.52–4.24	0.001			
E/e′ at exercise	1.09	1.06–1.13	<0.001			
Exercise E/e′ ≥13	3.87	2.38–6.29	<0.001			
Moderate or severe MR at exercise	12.16	4.38–33.81	<0.001			
Abnormal ExE + Exercise E/e′ ≥13	6.74	3.49–13.00	<0.001	3.67	2.11–6.38	<0.001

CAD, coronary artery disease; E/e′, ratio of early left ventricular inflow wave to early diastolic annulus wave; ExE, exercise echocardiography; LVEF, left ventricular ejection fraction; MAPHR, maximal age-predicted heart rate; METs, metabolic equivalents; MR, mitral regurgitation; WMSI, wall motion score index.
Other non-significant analyzed variables were hypertension, hypercholesterolemia, family history of CAD, smoking, pulmonary disease, obesity, resting rate-pressure product, treatment with beta-blockers, treatment with diuretics, treatment with digoxin, treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists, typical or atypical angina along with dyspnea, abnormal resting ECG, and positive exercise ECG.
[a] Positive exercise testing was defined as symptoms *or* ST segment changes during exercise, irrespective of the ExE results.

art treatment including coronary angiography for patients with a positive ExE was probably frequent, therapeutic options for patients without WMAs during an ExE but with raised E/e′ values are less established. Unfortunately, we do not have data on treatments used during follow-up. Also, the relatively low number of events and short follow-up may have limited the value of our multivariable analysis.

Current study and clinical implications

Our research confirms and extends previous reports on the adverse outcome conferred by an E/e′ raised at post-exercise in patients with suspicion of heart failure with preserved ejection fraction. Interestingly, a non-insignificant number of subjects were found to have abnormal E/e′ values at rest but not at post-exercise, and these subjects had a favorable outcome. On the other hand, outcome was similar in patients with abnormal E/e′ values at rest and at post-exercise or only at post-exercise. The fact that the worse outcome was found in patients with raised E/e′ at post-exercise, particularly in the presence of WMAs, enhances the potential of ExE for the assessment of patients with dyspnea. These patients have likely greater ischemic burden that may be associated with LV diastolic dysfunction, and therefore outcome is expected to be significantly worse.

Conflict of interest

There is no conflict of interest.

Funding

There is no funding for this research.

References

[1] Bouzas-Mosquera A, Peteiro J, Broullón FJ, Calviño-Santos R, Mosquera VX, Sánchez-Fernández G, et al. Temporal changes in the use and results of exercise echocardiography. Eur Heart J Cardiovasc Imaging 2015;16:1207–12.
[2] Holland DJ, Prasad SB, Marwick TH. Prognostic implications of left ventricular filling pressure with exercise. Circ Cardiovasc Imaging 2010;3:149–56.
[3] Arós F, Boraita A, Alegría E, Alonso AM, Bardají A, Lamiel R, et al. Guidelines of the Spanish Society of Cardiology for clinical practice in exercise testing. Rev Esp Cardiol 2000;53:1063–94.
[4] Bouzas-Mosquera, Peteiro J, Alvarez-Garcia N, Broullon FJ, Mosquera VX, Garcia-Bueno L, et al. Prediction of mortality and major cardiac events by exercise echocardiography in patients with normal exercise electrocardiographic testing. J Am Coll Cardiol 2009;53:1981–90.
[5] Morris CK, Myers J, Froelicher VF, Kawaguchi T, Ueshima K, Hideg A. Nomogram based on metabolic equivalents and age for assessing aerobic exercise capacity in men. J Am Coll Cardiol 1993;22:175–82.
[6] Gulati M, Pandey DK, Arnsdorf MF, Lauderdale DS, Thisted RA, Wicklund RH, et al. Exercise capacity and the risk of death in women: the St James Women Take Heart Project. Circulation 2003;108:1554–9.
[7] Kim ES, Ishwaran H, Blackstone E, Lauer MS. External prognostic validations and comparisons of age- and gender-adjusted exercise capacity predictions. J Am Coll Cardiol 2007;50:1867–75.
[8] Peteiro J, Bouzas-Mosquera A, Broullón FJ, Garcia-Campos A, Pazos P, Castro-Beiras A. Prognostic value of peak and post-exercise treadmill exercise echocardiography in patients with known or suspected coronary artery disease. Eur Heart J 2010;31:187–95.
[9] Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the

European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28. 1–39.e14.

[10] Hoffmann R, Lethen H, Marwick T, Rambaldi R, Fioretti P, Pingitore A, et al. Standardized guidelines for the interpretation of dobutamine echocardiography reduce interinstitutional variance in interpretation. Am J Cardiol 1998;82:1520–4.

[11] Stamm RB, Carabello BA, Mayers DL, Martin RP. Two-dimensional echocardiographic measurement of left ventricular ejection fraction: prospective analysis of what constitutes an adequate determination. Am Heart J 1982;104:136–44.

[12] Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr 2017;30:303–71.

[13] Peteiro J, Broullón F, Martinez D, Yañez J, Castro-Beiras A. Value of an exercise workload ≥10 metabolic equivalents for predicting inducible myocardial ischemia. Circ Cardiovasc Imaging 2013;6:899–907.

[14] Bergeron S, Ommen SR, Bailey KR, Oh JK, McCully RB, Pellikka PA. Exercise echocardiographic findings and outcome of patients referred for evaluation of dyspnea. J Am Coll Cardiol 2004;43:2242–6.

[15] Argulian E, Agarwal V, Bangalore S, Chatterjee S, Makani H, Rozanski A, et al. Meta-analysis of prognostic implications of dyspnea versus chest pain in patients referred for stress testing. Am J Cardiol 2014;113:559–64.

[16] Peteiro J, Pazos P, Bouzas A, Piñon P, Estevez R, Castro-Beiras A. Assessment of diastolic function during exercise echocardiography: annulus mitral velocity or transmitral flow pattern? J Am Soc Echocardiogr 2008;21:178–84.

[17] Burgess MI, Jenkins C, Sharman JE, Marwick TH. Diastolic stress echocardiography: hemodynamic validation and clinical significance of estimation of ventricular filling pressure with exercise. J Am Coll Cardiol 2006;47:1891–900.

[18] Ha JW, Lulic F, Bailey KR, Pellikka PA, Seward JB, Tajik AJ, et al. Effects of treadmill exercise on mitral inflow and annular velocities in healthy adults. Am J Cardiol 2003;91:114–5.

[19] Holland DJ, Prasad SB, Marwick TH. Contribution of exercise echocardiography to the diagnosis of heart failure with preserved ejection fraction (HfpEF). Heart 2010;96:1024–8.

[20] Obokata M, Kane GC, Reddy YN, Olson TP, Melenovsky V, Borlaug BA. Role of diastolic stress testing in the evaluation for heart failure with preserved ejection fraction: a simultaneous invasive-echocardiographic study. Circulation 2017;135:825–38.

[21] Schiano-Lomoriello V, Santoro C, de Simone G, Trimarco B, Galderisi M. Diastolic bicycle stress echocardiography: normal reference values in a middle age population. Int J Cardiol 2015;191:181–3.