Journal of the American College of Cardiology
© 2006 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 47, No. 9, 2006
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2006.02.042

EXPEDITED REVIEW

Diastolic Stress Echocardiography: Hemodynamic Validation and Clinical Significance of Estimation of Ventricular Filling Pressure With Exercise

Malcolm I. Burgess, MD, MRCP, Carly Jenkins, BSc, James E. Sharman, PhD, Thomas H. Marwick, MD, PhD, FACC

Brisbane, Australia

OBJECTIVES Our study attempted to validate a Doppler index of diastolic filling (E/E') during exercise with simultaneously measured left ventricular diastolic pressure (LVDP), investigate its association with exercise capacity, and understand which patients to select for testing.

BACKGROUND The ratio of early diastolic transmitral velocity to early diastolic tissue velocity approximates LVDP at rest, but there is limited validation of exercise E/E' with invasive hemodynamic measurement, and its clinical implications are unclear.

METHODS The ratio of early diastolic transmitral velocity to early diastolic tissue velocity was measured at rest and during supine cycle ergometry in 37 patients undergoing left heart catheterization. In addition to correlation between invasive and estimated LVDP, the accuracy of different cutoffs for identification of elevated LVDP (>15 mm Hg) was determined at both rest and exercise. Doppler index of diastolic filling was also measured at rest and immediately after maximal treadmill exercise in 166 patients to investigate the association between exercise E/E' and exercise capacity (<8 metabolic equivalents [METs]).

RESULTS In patients undergoing invasive measurement, nine (24%) had elevation of LVDP only during exercise. There was a good correlation between E/E' and LVDP at rest ($r = 0.67$) and during exercise ($r = 0.59$), and the regressions at rest and exercise corresponded closely. Receiver-operator curve analysis indicated that a cutoff value of 13 for exercise E/E' identified patients with an elevated LVDP during exercise. A post-exercise E/E' >13 was highly specific (90%) for reduced exercise capacity, and even after classification of resting E/E', exercise E/E' permitted classification of patients with exercise capacity <8 METs or ≥8 METs.

CONCLUSIONS The ratio of early diastolic transmitral velocity to early diastolic tissue velocity correlates with invasively measured LVDP during exercise. It can be used to reliably identify patients with elevated LVDP during exercise and reduced exercise capacity. (J Am Coll Cardiol 2006;47: 1891–900) © 2006 by the American College of Cardiology Foundation

An increase in left ventricular diastolic pressure (LVDP) is an important cardiac cause of exertional dyspnea (1). These symptoms often occur in patients with early myocardial abnormalities such as those seen in hypertensive and diabetic heart disease (2,3) and are independent of the influence of exercise-induced ischemia. Ejection fraction is characteristically preserved in these patients, but although such patients may be labeled as having diastolic heart failure (4–7), resting diastolic filling patterns may be normal, even in the presence of demonstrable myocardial structural abnormalities. Guidelines on the diagnosis of diastolic heart failure, other than alluding to the changes occurring in relation to ischemia, make no reference to the use of physical exercise to provide supplementary information (8).

Previous work has shown that, under resting conditions, LVDP can be estimated noninvasively by Doppler techniques (9). The ratio of early diastolic transmitral velocity to tissue velocity (E/E') correlates with LVDP, and an E/E' of >15 has been found to be a reliable means of predicting an elevated LVDP (10). Approximations of resting filling pressure from this method have been shown to correlate with exercise capacity in unselected patients, many of whom had ventricular hypertrophy and Doppler evidence of impaired relaxation (11). However, considering that in many cases it is only under conditions of cardiovascular stress that LVDP increases and exercise-limiting symptoms develop, it is not surprising that resting estimation of LVDP gives incomplete information. Therefore, measurement of E/E' during physical exercise may give a more clinically relevant assessment of the effects of changes in LVDP on exercise capacity.

Although the feasibility of non-invasive estimation of LVDP during tachycardia (12) and exercise (13) has been confirmed, there are limited data on the validation of exercise E/E' with invasively determined pressure or its clinical relevance. Accordingly, we designed a study with two components. The first was an invasive hemodynamic validation of E/E' at rest and during exercise with simultaneous invasive measurement of LVDP where we sought the sensitivity and specificity of different E/E' cutoffs for iden-

From the Department of Medicine, University of Queensland, Princess Alexandra Hospital, Brisbane, Australia.

Manuscript received December 23, 2005; revised manuscript received February 27, 2006, accepted February 28, 2006.

Abbreviations and Acronyms

A velocity	= late diastolic transmitral velocity
E velocity	= early diastolic transmitral velocity
E'	= early diastolic tissue velocity
E/E'	= ratio of early diastolic transmitral velocity to early diastolic tissue velocity
LV	= left ventricle/ventricular
LVDP	= left ventricular diastolic pressure
MET	= metabolic equivalent
ROC	= receiver-operator characteristic

tifying patients with high LVDP during exercise. The second component, a parallel non-invasive study in the exercise echocardiography laboratory, was designed to investigate an association between exercise E/E' and exercise capacity and attempt to determine a cutoff value of exercise E/E' that could identify patients with reduced exercise capacity due to elevated LVDP. We also examined the relationship between exercise E/E' and exercise capacity according to the resting diastolic filling pattern in an attempt to identify a specific subgroup of patients in whom measurement of exercise E/E' was most useful.

METHODS

Study design. For the invasive study, E/E' was calculated by Doppler echocardiography in 37 unselected patients undergoing clinically indicated left heart catheterization, which allowed simultaneous invasive measurement of LVDP. We included only patients who were in sinus rhythm, and patients with unstable coronary syndromes, valvular disease, or valve surgery were excluded. Doppler recordings were made at rest and after 3 to 5 min of supine cycle exercise. The study protocol was approved by the hospital research ethics committee, and all patients gave written informed consent.

In the noninvasive study, the same Doppler recordings were made before and immediately after symptom-limited treadmill exercise in 166 consecutive patients. The investigations were again performed for routine clinical indications, and the same inclusion criteria applied.

Echocardiography. For the invasive study, transthoracic imaging was performed with the patient lying supine on the cardiac catheter laboratory table using a Vingmed Vivid system 5 or 7 (General Electric-Vingmed, Milwaukee, Wisconsin) machine and a 3.5-MHz transducer. Studies were performed by a single experienced operator (M.B.). The transmitral flow velocity profile was recorded in the apical four-chamber view with the sample volume positioned in the direction of antegrade flow at the level of the mitral valve tips in diastole. The early diastolic tissue (E') velocity was recorded in the same view with the sample volume (5 mm) positioned at the septal mitral annulus (10). Gain and filter settings were adjusted to optimize the quality of the trace and minimize spectral broadening. The same recordings were made during exercise after there had been a significant increment in heart rate. When possible, the recordings were made in end-expiratory apnea. Studies were recorded digitally for subsequent off-line analysis (Fig. 1), by an observer unaware of the invasive hemodynamic findings.

For the noninvasive study, images were acquired both before and after symptom-limited exercise with the patient in the left lateral decubitus position using a Philips Sonos 7500 or IE33 (Andover, Massachusetts) machine and a

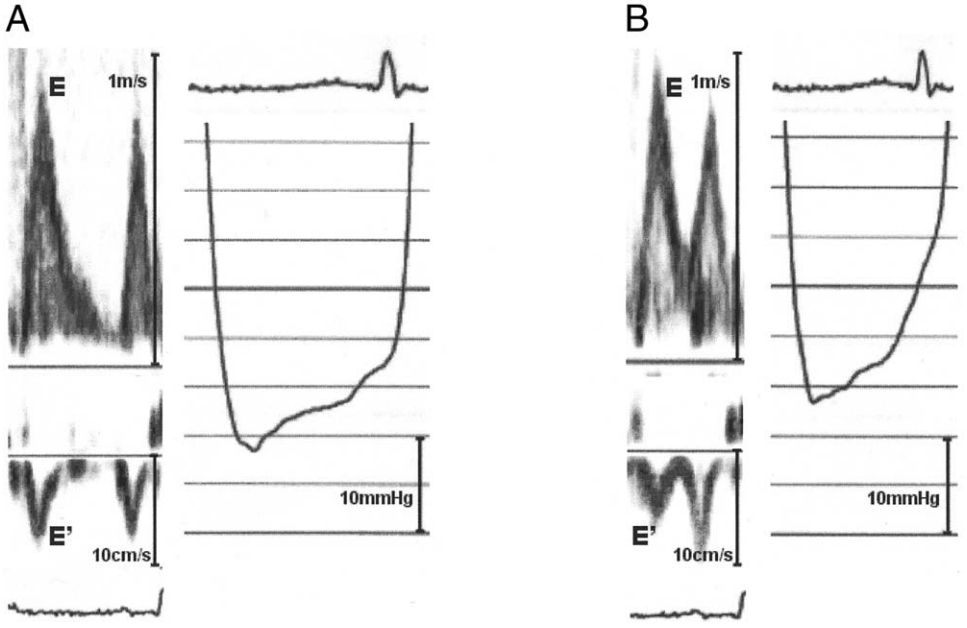

Figure 1. Representative hemodynamic and Doppler traces of a patient with normal left ventricular diastolic pressure (LVDP) at rest **(A)** and an increase in LVDP with exercise **(B)**. At rest, the mean LVDP is 13.2 mm Hg and the ratio of early diastolic transmitral velocity to early diastolic tissue velocity (E/E') is 12.1. With exercise, the mean LVDP increases to 18.0 mm Hg and the E/E' increases to 17.1.

3.5-MHz transducer. For the post-exercise imaging, recording of the Doppler traces was performed after the acquisition of the two-dimensional digital loops for assessment of regional wall motion. Images were recorded on videotape and in digital format and analyzed off-line. Studies were performed and interpreted by separate experienced operators.

Wall motion was reported using a conventional 16-segment model (14). An ischemic response was defined as the development of a stress-induced wall motion abnormality in a segment with normal resting wall motion. For both studies, measurements of modal E and E' velocities were averaged over at least three cardiac cycles. Ectopic and post-ectopic beats were disregarded. Left atrial area was measured by planimetry in the apical four-chamber view. To determine the influence of the resting diastolic filling pattern on the relationship between exercise E/E' and exercise capacity, patients were divided into three groups based on E/E', left atrial size, and age- and gender-specific normal ranges of mitral deceleration time (15). The group with *normal filling* was characterized by a normal mitral deceleration time combined with an E/E' <8, or if the E/E' was indeterminate (8–15), a normal left atrial area ≤24 cm^2. The second group was defined as having *delayed relaxation* on the basis of an increased mitral deceleration time, but E/E' ≤15. The third group with *elevated filling pressure* (pseudo-normal and restrictive filling) had an E/E' >15 or an E/E' of 8 to 15 and left atrial area >24 cm^2.

Invasive hemodynamic assessment. During left heart catheterization, a fluid-filled 6-F pigtail catheter was positioned in the mid-left ventricular (LV) cavity using fluoroscopic screening. Transducers were balanced before the study with the zero level at the mid-axillary line. Studies were performed after diagnostic coronary angiography but before LV angiography. Digital records of rapid acquisition LV pressure tracings were recorded. Measurements were made offline from the digitized recordings by an independent observer. Mean (16) LVDP was calculated. Values were averaged over five cardiac cycles, and ectopic or post-ectopic beats disregarded. A value of >15 mm Hg was chosen as a definition of significant elevation of mean LVDP.

Exercise stress protocol. For the invasive study, after collection of the resting echocardiographic and hemodynamic data, the patient exercised for 3 to 5 min. This was achieved with single-leg supine cycle ergometry using the opposite leg to that used for arterial access. Exercise was submaximal. The number of watts of exercise and the Borg score (17) were recorded. Patients were not asked to discontinue beta-blocking agents for the purpose of the study.

In the noninvasive study, symptom-limited maximal treadmill exercise was performed with the standard Bruce protocol. A physician was present to encourage maximal exercise. Patients were asked to discontinue beta-blocking agents on the day of the test. Patients had Doppler recordings made pre-exercise and immediately post-exercise. The primary end point was maximal exercise tolerance defined as the number of metabolic equivalents (METs) achieved. The primary reason for discontinuing the exercise test included limiting dyspnea, chest pain, peripheral muscle fatigue, severe ST-segment depression, or recorded arrhythmia.

Statistical analysis. Continuous variables are expressed as mean ± SD. Comparisons between continuous patient data is made using the unpaired *t* test and comparisons of within patient data by the paired *t* test. Multiple comparisons were made with analysis of variance with Bonferroni correction. Categorical data was compared by the chi-square test. For the invasive data, the correlation between mean LVDP and echocardiographic variables was analyzed by the Pearson correlation coefficient. Receiver-operator characteristic (ROC) curves were plotted to determine the sensitivity and specificity of different exercise E/E' values to predict an elevation of mean LVDP >15 mm Hg at rest and during exercise. The optimal cutoff value of E/E' was determined from the derived curve. For the non-invasive data, the correlation between exercise capacity (METs) and echocardiographic variables was analyzed by the Pearson correlation coefficient. Identification of clinical and echocardiographic predictors of a significantly reduced exercise capacity (<8 METs) was determined by logistic regression analysis. In patients without inducible ischemia, ROC curves were plotted to determine the sensitivity and specificity of different exercise E/E' values to predict reduced exercise capacity and determine cutoff values. Because there is an optimistic bias associated with developing and evaluating a discriminant rule using the same dataset, cross-validation was used as an unbiased approach to verify the reliability of the derived cutoff value. Half of the cases were randomly chosen as the development set and half as the validation set. Ninety-five percent confidence intervals are quoted throughout and are expressed as mean ± SD. A statistical significance level of 0.05 was used throughout. Statistical analysis was performed using standard software (version 12.0, SPSS Inc., Chicago, Illinois).

RESULTS

Patient characteristics. The characteristics of the patients included in the invasive study are shown in Table 1. Mean age was 61 years and 73% were men. Three quarters of patients had significant obstructive epicardial disease (>50% diameter stenosis) at coronary angiography. A similar proportion was receiving beta-blocker therapy. Table 2 shows the characteristics of the patients in the noninvasive study. Patients were of a similar age as the invasive study (59 ± 11 years). Assessment of chest pain or functional significance of ischemia was the primary indication for the exercise test in the majority of patients. There was an ischemic response in 53 (32%) patients. In the invasive

Table 1. Clinical Data of Patients in the Invasive Hemodynamic Study

	All Patients (n = 37)	LVDP Normal (n = 20)	LVDP High Only With Exercise (n = 9)	LVDP High at Rest (n = 8)
Demographics				
Age (yrs)	61 ± 9	59 ± 9	63 ± 9	63 ± 9
Male (%)	27 (73%)	17 (85%)	5 (56%)	5 (63%)
BMI (kg/m^2)	29 ± 4	28 ± 3	29 ± 4	30 ± 3
Previous MI	11 (30%)	5 (20%)	4 (44%)	2 (25%)
Hypertension	19 (51%)	8 (40%)	7 (78%)	4 (50%)
Diabetes	11 (30%)	5 (25%)	3 (33%)	3 (38%)
Smoking history	18 (49%)	8 (40%)	6 (67%)	4 (50%)
Coronary disease	28 (76%)	15 (75%)	6 (67%)	7 (88%)
NYHA functional class	1.5 ± 0.7	1.3 ± 0.4	1.9 ± 0.8*	1.9 ± 0.8*
Drug therapy:				
Beta-blocker	28 (76%)	13 (65%)	8 (89%)	7 (88%)
ACEI/ARB	24 (65%)	14 (70%)	4 (44%)	6 (75%)
Calcium channel blocker	7 (19%)	3 (15%)	2 (22%)	2 (25%)
Nitrate	8 (22%)	2 (10%)	3 (33%)	3 (38%)

Continuous data compared with analysis of variance applying Bonferroni correction. *$p < 0.05$ compared to patients with normal resting and exercise LVDP.

ACE = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; LVDP = left ventricular diastolic pressure; MI = myocardial infarction; NYHA = New York Heart Association.

study, there were six (16%) patients with an LV ejection fraction <45%. Patients in the noninvasive study had preserved LV systolic function (resting wall motion score index 1.0 ± 0.1).

Hemodynamics and echocardiographic variables at rest and during exercise. Echocardiographic measurement of E/E' could be made both at rest and during exercise in all patients. With exercise, heart rate increased significantly

Table 2. Clinical, Stress, and Echocardiographic Data of Patients in the Noninvasive Study

	All Patients (n = 166)	Exercise E/E' ≤13 (n = 126)	Exercise E/E' >13 (n = 40)	p
Demographics				
Age (yrs)	59 ± 11	57 ± 11	65 ± 7	<0.001
Male (%)	109 (66%)	88 (70%)	21 (53%)	0.044
Indication				
Chest pain, suspected ischemia	144 (87%)	111 (88%)	33 (83%)	ns
Dyspnea	16 (9%)	11 (9%)	5 (12%)	ns
Other	6 (4%)	4 (3%)	2 (5%)	ns
Stress response				
Heart rate rest (beats/min)	80 ± 14	81 ± 15	75 ± 10	0.002
Systolic BP rest (mm Hg)	130 ± 20	129 ± 20	133 ± 20	ns
Heart rate stress (beats/min)	152 ± 23	156 ± 23	140 ± 16	<0.001
Systolic BP stress (mm Hg)	176 ± 23	176 ± 24	172 ± 23	ns
Echocardiography				
Resting WMSI	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	ns
Stress WMSI	1.1 ± 0.2	1.1 ± 0.1	1.1 ± 0.2	ns
Ischemic response	53 (32%)	39 (31%)	14 (35%)	ns
Left atrial area (cm^2)	21 ± 4	20 ± 4	22 ± 4	0.015
E velocity rest (cm/s)	71 ± 17	68 ± 16	78 ± 18	0.001
E velocity stress (cm/s)	96 ± 23	89 ± 20	116 ± 21	<0.001
A velocity rest (cm/s)	77 ± 17	73 ± 15	88 ± 17	<0.001
A velocity stress (cm/s)	93 ± 22	90 ± 18	104 ± 28	0.007
E/A ratio rest	0.95 ± 0.28	0.96 ± 0.30	0.90 ± 0.23	ns
E/A ratio stress	1.06 ± 0.38	1.02 ± 0.31	1.20 ± 0.52	0.045
Deceleration time rest (ms)	214 ± 53	211 ± 53	226 ± 51	ns
Deceleration time stress (ms)	171 ± 42	173 ± 42	162 ± 39	ns
E' rest (cm/s)	6.7 ± 1.9	7.1 ± 1.8	5.5 ± 1.5	<0.001
E' stress (cm/s)	9.4 ± 2.8	10.2 ± 2.7	7.2 ± 1.8	<0.001
E/E' rest	11.2 ± 4.0	9.9 ± 2.4	15.1 ± 5.2	<0.001
E/E' stress	11.0 ± 4.5	9.2 ± 2.1	16.9 ± 4.8	<0.001

A velocity = late diastolic transmitral velocity; BP = blood pressure; E velocity = early diastolic transmitral velocity; E/E' = ratio of early diastolic transmitral velocity to early diastolic tissue velocity; WMSI = wall motion score index.

Table 3. Stress and Echocardiographic Data in the Invasive Hemodynamic Study

	All Patients (n = 37)	LVDP Normal (n = 20)	LVDP High Only With Exercise (n = 9)	LVDP High at Rest (n = 8)
Stress response				
Heart rate rest (beats/min)	63 ± 10	61 ± 10	69 ± 10	62 ± 9
Heart rate stress (beats/min)	83 ± 11	82 ± 12	87 ± 9	81 ± 8
LVSP rest (mm Hg)	147 ± 24	143 ± 24	146 ± 27	161 ± 20
LVSP stress (mm Hg)	161 ± 27	156 ± 26	167 ± 35	168 ± 23
Mean LVDP rest (mm Hg)	11.2 ± 6.6	8.3 ± 4.2	8.9 ± 5.3	20.8 ± 3.4†§
Mean LVDP stress (mm Hg)	14.5 ± 7.9	9.1 ± 4.3	21.5 ± 7.0†	20.4 ± 5.4†
Echocardiography				
LV mass index (g/m^2)	105 ± 26	105 ± 19	113 ± 39	93 ± 20
LV ejection fraction (%)	58 ± 12	59 ± 6	56 ± 20	58 ± 15
Left atrial area (cm^2)	20 ± 4	19 ± 3	21 ± 3	22 ± 7
E velocity rest (cm/s)	82 ± 18	76 ± 17	80 ± 18	100 ± 10†‡
E velocity stress (cm/s)	90 ± 18	84 ± 16	90 ± 18	105 ± 16*
A velocity rest (cm/s)	76 ± 18	74 ± 16	78 ± 15	79 ± 27
A velocity stress (cm/s)	89 ± 22	90 ± 17	78 ± 21	96 ± 31
E/A ratio rest	1.14 ± 0.38	1.06 ± 0.27	1.05 ± 0.24	1.42 ± 0.59
E/A ratio stress	1.07 ± 0.39	0.96 ± 0.22	1.18 ± 0.34	1.23 ± 0.65
Deceleration time rest (ms)	203 ± 47	214 ± 54	197 ± 29	183 ± 41
Deceleration time stress (ms)	179 ± 43	194 ± 47	167 ± 23	160 ± 38
E' rest (cm/s)	7.5 ± 1.7	8.0 ± 1.6	7.3 ± 1.6	6.5 ± 1.5
E' stress (cm/s)	7.4 ± 1.9	8.3 ± 1.5	6.1 ± 1.8†	6.5 ± 1.9
E/E' rest	11.7 ± 4.4	9.8 ± 2.4	11.8 ± 4.7	16.3 ± 4.9†
E/E' stress	13.4 ± 6.2	10.3 ± 2.1	16.1 ± 6.7*	18.1 ± 8.6†

Data compared with analysis of variance applying Bonferroni correction. *$p < 0.05$ compared to patients with normal resting and exercise LVDP. †$p < 0.01$ compared to patients with normal resting and exercise LVDP. ‡$p < 0.05$ compared to patients with high LVDP only during exercise. §$p < 0.01$ compared to patients with high LVDP only during exercise.
LV = left ventricular; LVSP = left ventricular systolic pressure; other abbreviations as in Tables 1 and 2.

from 63 ± 10 beats/min to 83 ± 11 beats/min (Table 3). Patients completed 88 ± 10 W of exercise. The Borg score was 4.6 ± 1.0. In the invasive study, a resting E/E' of <8 was seen in seven patients. The mean LVDP was 6.0 ± 3.6 mm Hg in this group. Mean LVDP was 11.2 ± 5.9 in the 23 patients with a resting E/E' of 8 to 15 and 16.3 ± 7.8 in the 7 patients with a resting E/E' >15 ($p = 0.01$ for difference between groups). Of the 37 patients, mean LVDP was normal (≤15 mm Hg) in 29 patients at rest. In 20 of these patients, it remained normal during exercise, and in 9 patients it became elevated (>15 mm Hg). The remaining eight patients had elevated mean LVDP at rest. Figure 2 shows the changes in E/E' from rest to exercise according to the mean LVDP. Patients with a normal mean LVDP at both rest and exercise had the lowest E/E' with no significant change with exercise. Patients with an elevated mean LVDP only during exercise had a significant

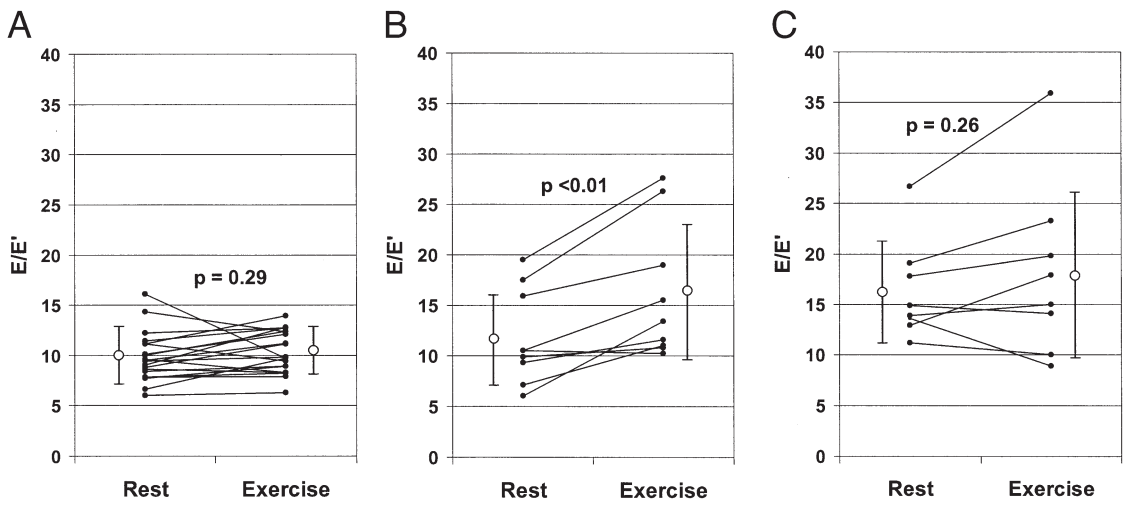

Figure 2. (A) Changes in the ratio of early diastolic transmitral velocity to early diastolic tissue velocity (E/E') between rest and exercise in patients with normal mean left ventricular diastolic pressure (LVDP) at both rest and exercise. **(B)** Changes in E/E' between rest and exercise in patients with an elevated mean LVDP only during exercise. **(C)** Changes in E/E' between rest and exercise in patients with an elevated mean LVDP at rest.

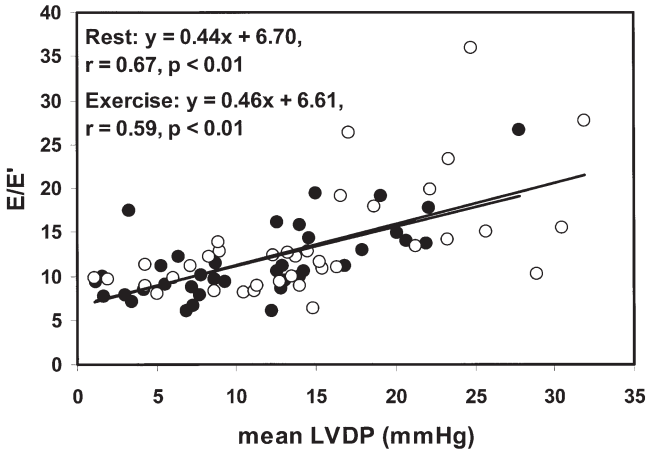

Figure 3. Correlation, both at rest and during exercise, between mean left ventricular diastolic pressure (LVDP) and ratio of early diastolic transmitral velocity to early diastolic tissue velocity (E/E'). **Solid circles** = resting data; **open circles** = exercise data.

increase in E/E' from rest to exercise. Patients with an elevated mean LVDP at rest had a high resting E/E' with no significant change with exercise.

There was a good correlation between E/E' and mean LVDP at rest ($r = 0.67$, $p < 0.01$) (Fig. 3). The correlation was less strong during exercise ($r = 0.59$, $p < 0.01$) mainly due to greater scatter at the higher levels of mean LVDP. There was almost complete overlap of the resting and exercise regression lines. The ROC analysis for prediction of an elevated mean LVDP showed an area under the curve of 0.89. An exercise E/E' >13 had a sensitivity of 73% and a specificity of 96% for identification of an elevated exercise mean LVDP. Applying this cutoff value of 13 to the data on the scatterplot indicated that only 6 (16%) patients were misclassified based on E/E' assessment of mean LVDP at exercise.

Relationship between echocardiographic variables and exercise capacity. In the non-invasive study, measurement of E/E' could be made both at rest and post-exercise in all patients; if the mitral inflow profile initially showed fusion due to tachycardia, the measurement was repeated after the heart rate fell. The heart rate increased from 80 ± 14 beats/min at rest to 152 ± 23 beats/min with exercise (Table 2), and 83% of patients reached at least 85% of age-predicted maximal heart rate. Exercise was limited by chest pain in 14 (8%) patients, by dyspnea in 56 (34%) patients, by peripheral muscle fatigue in 80 (48%) patients, and by development of arrhythmia in 2 (1%) patients. ST-segment depression developed in 35 (22%) patients, but in no patient was it severe enough to discontinue exercise.

Of the conventional transmitral flow variables, resting but not exercise A velocity, E/A ratio, and deceleration time correlated significantly with exercise capacity (Table 4); E' and E/E' had a better correlation with exercise capacity (Fig. 4A). For both these variables, the correlation was slightly better for exercise than resting measurements ($r = 0.45$ and 0.41, respectively, for E' and $r = -0.44$ and -0.37, respectively, for E/E'). Removal of patients with inducible ischemia did not influence the correlations significantly.

A cutoff value of 13 for exercise E/E' derived from the invasive study was highly specific (90%) for prediction of reduced exercise capacity but lacked sensitivity (48%). An exercise capacity of <8 METs is often used to signify prognostically important impairment of exercise capacity in the typical patient with cardiac symptoms, corresponding to the group studied here. In 113 patients with no ischemia, the ROC analysis for prediction of exercise capacity <8 METs using exercise E/E' demonstrated an area under the curve of 0.77. The optimal exercise E/E' cutoff value (>10) had a sensitivity of 71% and a specificity of 69% for prediction of a reduced exercise capacity; cross-validation demonstrated similar sensitivity (72%) and specificity (68%) in the 56 patients in a development set and the 57 patients in the validation set (71% and 70%, respectively) indicating that this discriminant rule was developed without significant bias. While this area under the curve was not superior to that for resting E/E' (0.74) (Fig. 4B), some findings support the value of exercise E/E' as a correlate of reduced exercise capacity. First, except in patients without ischemia who had resting E/E' >10, exercise capacity was significantly different in patients who did and did not manifest an increase in E/E' with exercise irrespective of resting E/E' (Table 5). Second, exercise E/E' was higher in patients who experienced limiting dyspnea than it was in those who discontinued exercise for other reasons (12.2 ± 4.6 vs. 10.4 ± 4.3, respectively, $p = 0.02$).

Table 4. Correlation Between Exercise Capacity and Echocardiographic Variables in the Noninvasive Study

	All patients (n = 166)		Patients With No Ischemia (n = 113)	
Variable	**r**	**p**	**r**	**p**
E				
Rest	−0.05	0.53	−0.11	0.24
Stress	−0.16	0.04	−0.18	0.05
A				
Rest	−0.44	<0.001	−0.50	<0.001
Stress	−0.14	0.08	−0.21	0.03
E/A				
Rest	0.32	<0.001	0.35	<0.001
Stress	−0.03	0.70	0	0.98
Deceleration time				
Rest	−0.25	0.01	−0.28	<0.01
Stress	−0.13	0.13	−0.14	0.18
E'				
Rest	0.41	<0.001	0.37	<0.001
Stress	0.45	<0.001	0.41	<0.001
E/E'				
Rest	−0.37	<0.001	−0.37	<0.001
Stress	−0.44	<0.001	−0.39	<0.001
WMSI				
Rest	−0.04	0.61	−0.03	0.74
Stress	−0.18	0.02	−0.01	0.96
Left atrial area	−0.08	0.30	−0.11	0.26

Abbreviations as in Table 2.

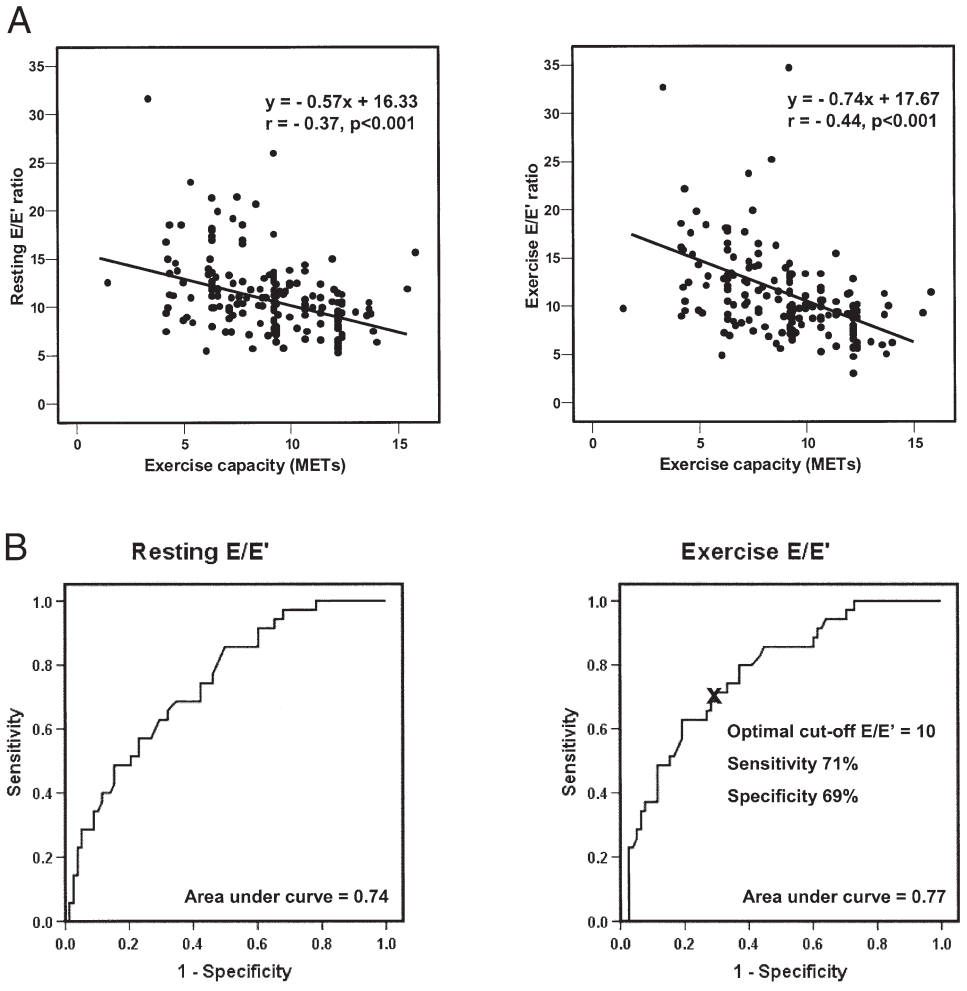

Figure 4. **(A)** Correlation between exercise capacity (metabolic equivalents [METs]) and the ratio of early diastolic transmitral velocity to early diastolic tissue velocity (E/E') both at rest **(left)** and with exercise **(right)**. **(B)** Receiver-operator characteristic curve showing sensitivity and specificity of different E/E' values both at rest **(left)** and with exercise **(right)** to predict exercise capacity (<8 METs).

Implications of resting diastolic indexes for exercise capacity. Forty-four (46%) of the 95 patients with normal filling at rest manifested an E/E'>10 with exercise. These patients had lower exercise capacity than patients with an exercise E/E' ≤10 (8.6 ± 2.4 METs vs. 10.1 ± 2.6 METs, respectively, p = 0.006) (Fig. 5). Exercise capacity was also lower in the 13 (34%) of the 38 patients with delayed relaxation at rest who manifested an exercise E/E'>10 than it was in patients with an exercise E/E'≤10 (7.0 ± 2.5 METs vs. 9.6 ± 2.6 METs, respectively, p = 0.004). Of the 33 patients with elevated filling pressure at rest, 24 (73%) patients with an exercise E/E'>10 had a reduced exercise capacity compared with 9 patients who had an exercise E/E' ≤10 (7.4 ± 2.5 METs vs. 9.3 ± 2.2 METs, respectively, p = 0.045). It was noted in patients with elevated filling pressure at rest that, although the majority of patients had

Table 5. Exercise Capacity According to Resting E/E' and Subsequent Change in E/E' With Exercise

Group	Resting E/E'	Change in E/E' With Exercise	Exercise Capacity (METs)	p
All patients (166)	≤10 (75)	No increase (31)	10.6 ± 2.4	0.01
		Increase (44)	9.1 ± 2.5	
	>10 (91)	No increase (58)	8.9 ± 2.7	<0.01
		Increase (33)	7.2 ± 2.1	
Patients with no inducible ischemia (113)	≤10 (50)	No increase (23)	11.4 ± 1.4	<0.01
		Increase (27)	9.1 ± 2.5	
	>10 (63)	No increase (43)	8.9 ± 2.7	0.06
		Increase (20)	7.7 ± 1.9	

Numbers in parentheses represent number of patients in each group/subgroup.
E/E' = ratio of early diastolic transmitral velocity to early diastolic tissue velocity.

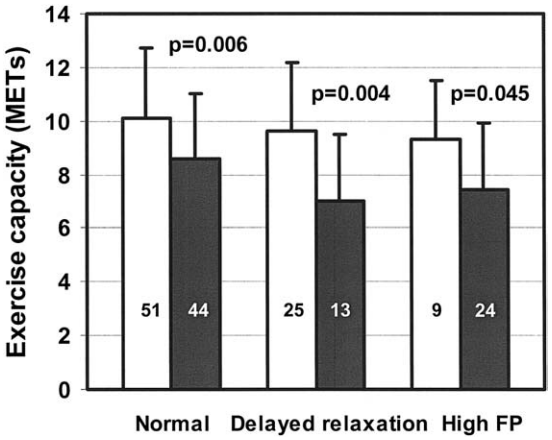

Figure 5. Differences in exercise capacity by exercise ratio of early diastolic transmitral velocity to early diastolic tissue velocity according to resting pattern of diastolic filling. The **numbers inside the bars** indicate the number of patients in that subgroup. **Open bars** = exercise E/E' ≤10; **solid bars** = exercise E/E' >10. FP = filling pressure; METs = metabolic equivalents.

an exercise E/E' >10, E/E' decreased with exercise in 21 cases (in 6 patients it decreased by more than 5).

Predictors of a reduced exercise capacity. Regression analysis in the 113 patients with no ischemia demonstrated that a number of clinical and echocardiographic variables were predictive of reduced exercise capacity (Table 6). Age, limiting dyspnea, and both rest and exercise E' and E/E' were among the univariate correlates. Multivariate analysis revealed important roles for age and limiting dyspnea in predicting reduced exercise capacity.

DISCUSSION

The results of this study have shown that the correlation of LV filling pressure with E/E' at exercise corresponds closely to its relationship at rest. The ROC analysis suggests that a cutoff value of 13 identifies patients with an LVDP of >15 mm Hg, allowing the accurate classification of patients into those with high and low filling pressure during exercise, independent of the presence of myocardial ischemia. Moreover, a cutoff value of 10 for post-exercise E/E' identifies those who cannot complete 8 METs of exercise. Post-exercise E/E' was higher in patients who experienced limiting dyspnea than it was in those who discontinued exercise for other reasons implicating a likely increase in filling pressure as the cause of reduced exercise capacity in these patients. Finally, increased E/E' during exercise identified worse functional status, not only in those with delayed relaxation but also in those with normal filling at rest.

Investigation of exertional dyspnea. Exertional dyspnea is a common symptom with a wide range of etiologies, and difficulties are frequently encountered in distinguishing cardiac from non-cardiac causes. Although the use of brain natriuretic peptide may help identify cardiac causes in certain clinical situations, this may not clarify the etiology of dyspnea when this occurs only with activity, and when filling pressure is normal at rest (18,19). The development of Doppler indexes such as E/E' may contribute useful diagnostic information by indicating an elevated LVDP and, by implication, a predominant cardiac contribution to the problem. Numerous studies have validated the use of E/E' to reliably identify patients with elevated LVDP in a number of different clinical circumstances (9,10,12,20).

Although non-invasive assessment of LVDP has conventionally been made in the resting state, because symptoms develop during physical activity it may be more relevant to make measurements during or after exercise. The same concept underlies the detection of ischemia and the functional evaluation of mitral valve disease and pulmonary hypertension. In our invasive study, we demonstrated that one quarter of the patients manifested an elevated mean LVDP only during exercise, and the non-invasive study showed that an abnormal exercise E/E' occurred in over a third of patients with normal filling and delayed relaxation at rest. This increase in filling pressure is a recognized phenomenon in a significant proportion of patients complaining of dyspnea (21) and supports a cardiac cause of dyspnea.

Specific potential difficulties with measurement of E/E' during or post-exercise include merging of passive and active components of both tissue and blood-pool Doppler signals and the effects of hyperventilation with swinging of the heart during respiration and consequent difficulties with sample volume positioning. However, these theoretical concerns do not pose insurmountable problems either in our experience or in previous studies (12,13).

Like other investigators, we found a good correlation between E/E' and mean LVDP at rest. Interestingly, this correlation was almost identical during supine cycle ergometry, indicating that E/E' can be used reliably as a convenient non-invasive means of estimating LVDP during physical exercise. The correlation during exercise was best at low filling pressures, and, although there was more scatter at higher levels of LVDP, patients could still be classified into those with and without an elevation of LVDP with good

Table 6. Regression Analysis of Clinical and Echocardiographic Variables to Predict Reduced Exercise Capacity (<8 METs) in Patients Without Evidence of Ischemia

Variable	Univariate		Multivariate	
	β	p	β	p
Clinical				
Age (yrs)	0.416	<0.001	0.279	0.004
Limiting dyspnea	0.370	0.001	0.258	0.003
Echocardiographic				
Left atrial area (cm^2)	0.147	0.126		
E velocity rest (cm/s)	0.135	0.153		
E velocity stress (cm/s)	0.214	0.023	0.165	0.054
E' rest (cm/s)	−0.338	<0.001		
E' stress (cm/s)	−0.342	<0.001	−0.182	0.061
E/E' rest	0.365	<0.001		
E/E' stress	0.343	<0.001		
Exercise increase E/E'	0.042	0.662		

METs = metabolic equivalents; other abbreviations as in Table 2.

sensitivity and specificity. The additional information provided by the non-invasive data is the demonstration that a high exercise E/E' is associated with a reduced exercise capacity. The correlation between E/E' and exercise capacity was modest, not surprisingly, given the complexities in the pathophysiology of exertional dyspnea, which is often multifactorial (22,23). Furthermore, influences from higher centers act to modify the subjective perception of the level of limitation in exercise capacity.

Study limitations. Application of these findings to clinical practice should take account of the multifactorial nature of exertional dyspnea in many patients. It was not possible for us to quantify the limitation in exercise capacity imposed by non-cardiac causes; in particular, the influence of pulmonary disease is recognized as being difficult to assess.

The protocol for cardiovascular stress was not the same in the invasive and the non-invasive studies. We were limited by the use of single-leg exercise with restrictions in body movement during cardiac catheterization from the femoral approach as well as the effects of beta-blockade (beta-blocking agents were omitted on the day of the test in the noninvasive study). Although a higher heart rate might have increased the proportion of patients with a high exercise LVDP, the proportion showing this response was similar in both groups. In any event, this aspect of the study was aimed at establishing the correlation between E/E' and LVDP during exercise rather than determining the prevalence of a high LVDP during exercise, and, for the same reason, we feel that the use of fluid-filled rather than solid-state catheters did not have a great influence on the results. Also, Doppler recordings were made *during exercise* in the invasive study and *post-exercise* in the non-invasive study.

Finally, the determination of a precise cutoff value of E/E' to clearly classify patients into two discrete groups is undoubtedly simplistic. Nonetheless, the association between high exercise E/E' and reduced exercise capacity is reassuring in that the detection of high or low E/E' post-exercise is physiologically meaningful.

Clinical implications. The confirmation of a cardiac etiology for exertional dyspnea has potential therapeutic (24) and prognostic implications (25–28). While resting tissue Doppler measures have recently been shown to provide prognostic information in patients with a range of cardiac diseases (29,30), the prognostic implications of elevated exercise E/E' remain to be defined. Nonetheless, the findings of this study validate exercise E/E' as a marker of ventricular filling pressure, and suggest that its measurement may explain functional impairment in patients with normal or mildly abnormal diastolic parameters at rest.

Reprint requests and correspondence: Dr. Malcolm Burgess, University of Queensland Department of Medicine, Level 4, Princess Alexandra Hospital, Ipswich Road, Brisbane QLD 4102, Australia. E-mail: mburgess@soms.uq.edu.au.

REFERENCES

1. Kitzman DW, Higginbotham MB, Cobb FR, et al. Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism. J Am Coll Cardiol 1991;17:1065–72.
2. Maurer MS, Spevack D. Diastolic dysfunction: can it be diagnosed by Doppler echocardiography? J Am Coll Cardiol 2004;44:1543–9.
3. Klapholz M, Maurer M, Lowe AM, et al. Hospitalization for heart failure in the presence of a normal left ventricular ejection fraction: results of the New York Heart Failure registry. J Am Coll Cardiol 2004;43:1432–8.
4. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure—abnormalities in active relaxation and passive stiffness of the left ventricle. N Engl J Med 2004;350:1953–9.
5. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure. Part I: diagnosis, prognosis and measurements of diastolic function. Circulation 2002;105:1387–93.
6. Burkhoff D, Maurer MS. Heart failure with a normal ejection fraction: is it really a disorder of diastolic function? Circulation 2003;107:656–8.
7. Vasan RS, Benjamin EJ, Levy D. Prevalence, clinical features and prognosis of diastolic heart failure: an epidemiological perspective. J Am Coll Cardiol 1995;26:1565–74.
8. European Study Group on Diastolic Heart Failure. How to diagnose diastolic heart failure. Eur Heart J 1998;19:990–1003.
9. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol 1997;30:1527–33.
10. Ommen SR, Nishimura RA, Appleton CP, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures. A comparative simultaneous Doppler-catheterization study. Circulation 2000;102:1788–94.
11. Skaluba SJ, Litwin SE. Mechanisms of exercise intolerance: insights from tissue Doppler imaging. Circulation 2004;109:972–7.
12. Nagueh SF, Mikati I, Kopelen HA, Middleton KJ, Quinones MA, Zoghbi WA. Doppler estimation of left ventricular filling pressure in sinus tachycardia: a new application of tissue Doppler imaging. Circulation 1998;98:1644–50.
13. Ha J, Lulic F, Bailey KR, et al. Effects of treadmill exercise on mitral inflow and annular velocities in healthy adults. Am J Cardiol 2003;91:114–5.
14. Armstrong WF, Pellikka PA, Ryan T, Crouse L, Zoghbi WA. Stress echocardiography: recommendations for performance and interpretation of stress echocardiography. Stress Echocardiography Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. J Am Soc Echocardiogr 1998;11:97–104.
15. Klein AL, Burstow DJ, Tajik AJ, Zachariah PK, Bailey KR, Seward JB. Effects of age on left ventricular dimensions and filling dynamics in 117 normal persons. Mayo Clin Proc 1994;69:212–24.
16. Yamamoto K, Nishimura RA, Redfield MM. Assessment of mean left atrial pressure from the left ventricular pressure tracing in patients with cardiomyopathies. Am J Cardiol 1996;78:107–10.
17. Borg GAV. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982;14:377–81.
18. Mottram PM, Leano R, Marwick TH, et al. Usefulness of B-type natriuretic peptide in hypertensive patients with exertional dyspnea and normal left ventricular ejection fraction and correlation with new echocardiographic indexes of systolic and diastolic function. Am J Cardiol 2003;92:1434–8.
19. Joung B, Ha JW, Young GK, et al. Can pro-brain natriuretic peptide be used as a noninvasive predictor of elevated left ventricular diastolic pressures in patients with normal systolic function? Am Heart J 2005;150:1213–9.
20. Bruch C, Grude M, Muller J, Breithart G, Wichter T. Usefulness of tissue Doppler imaging for estimation of left ventricular filling pressures in patients with systolic and diastolic heart failure. Am J Cardiol 2005;95:892–5.
21. Talreja D, Nishimura R, Oh J. Non-invasive parameters of diastolic function reflect invasively measured filling pressures during exercise (abstr). Circulation 2004;110 Suppl:III474.

22. Altose MD. Assessment and management of breathlessness. Chest 1985;88 Suppl 2:77S–83S.
23. Gillespie DJ, Staats BA. Unexplained dyspnea. Mayo Clin Proc 1994;69:657–63.
24. Mehta SK, Holliday C, Hayduk L. Effect of regular exercise after third decade on Doppler-derived left ventricular filling. Am J Cardiol 2004;94:1595–7.
25. Abidov A, Rozanski A, Hachamovitch R, et al. Prognostic significance of dyspnea in patients referred for cardiac stress testing. N Engl J Med 2005;353:1889–98.
26. 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.
27. Jones RC, Pothier CE, Blackstone EH, Lauer MS. Prognostic importance of presenting symptoms in patients undergoing exercise testing for evaluation of known or suspected coronary disease. Am J Med 2004;117:380–9.
28. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med 2002;346:793–801.
29. Wang M, Yip GW, Wang AY, et al. Tissue Doppler imaging provides incremental prognostic value in patients with systemic hypertension and left ventricular hypertrophy. J Hypertens 2005;23:183–91.
30. Hillis GS, Moller JE, Pellikka P, et al. Noninvasive estimation of left ventricular filling pressure by E/e' is a powerful predictor of survival after acute myocardial infarction. J Am Coll Cardiol 2004;43:360–7.