

Prognostic Implications of Left Ventricular Filling Pressure With Exercise

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Background—The estimation of left ventricular (LV) filling pressure from the ratio of transmitral and annular velocities (E/e') after exercise echocardiography may identify diastolic dysfunction in patients who complain of exertional dyspnea. This study sought to determine the relative contributions of exercise E/e' and ischemia to outcomes in patients referred for exercise echocardiography.

Methods and Results—Rest and exercise E/e' were obtained in 522 patients referred for exercise echocardiography, who were followed for cardiovascular death and hospitalization over a median of 13.2 months. Exercise $E/e' > 2$ SD from normal was used to denote raised LV filling pressure with stress ($n=75$), and ischemia ($n=250$) was identified by inducible wall motion abnormalities. There were 65 cardiovascular hospitalizations during the follow-up period. Survival analysis showed patients without ischemia and with normal exercise E/e' to have a better prognosis than those with ischemia, with or without raised exercise E/e' ($P=0.003$) and the outcomes of patients with isolated raised exercise E/e' and isolated ischemia to be similar. Exercise E/e' was most valuable in patients with normal resting E/e' ; those with elevation with exercise had a worse outcome than those with normal exercise E/e' ($P=0.014$). Exercise capacity (hazard ratio, 0.893; $P=0.008$), exercise wall motion score index (hazard ratio, 1.507; $P<0.001$), and exercise $E/e' > 14.5$ (hazard ratio, 2.988; $P=0.002$) were independent predictors of outcome. The addition of exercise E/e' to exercise capacity and wall motion score index resulted in an increment in model power to predict adverse outcome ($P=0.006$).

Conclusions—Exercise E/e' is associated with cardiovascular hospitalization, independent of and incremental to inducible ischemia. (*Circ Cardiovasc Imaging*. 2010;3:149-156.)

Key Words: exercise ■ echocardiography ■ diastole ■ ischemia ■ prognosis

The exclusion of ischemia at exercise echocardiography (ExE) is prognostically very meaningful, the event rate associated with a negative test being $<1\%$ per year.¹⁻³ The risk associated with a positive test is quite variable and depends on the extent of ischemia and ischemic threshold, among other features.³⁻⁵ In both positive and negative test settings, risk is related to underlying clinical status, with important contributions of age, diabetes mellitus, and exercise capacity.^{1,6}

Clinical Perspective on p 156

Dyspnea during stress testing has important clinical and prognostic significance in patients both with and without a history of coronary artery disease (CAD).⁷⁻⁹ Although this contribution has been linked to silent ischemia,¹⁰ diastolic dysfunction is an important contributor to dyspnea that may be pertinent. Diastolic dysfunction is already recognized as a predictor of outcome, but this assessment is performed at rest,¹¹⁻¹⁴ and, in some patients, symptoms (and raised filling pressure) may only be unmasked with

exercise. ExE permits the determination of E/e' with stress¹⁵⁻¹⁷; validation of this in >50 patients suggests that it is analogous to that obtained at rest.^{15,18} However, the contribution of diastolic dysfunction to the prognostic implications of ExE is undefined. In this study, we sought whether an abnormal exercise E/e' predicted adverse outcome, independent of ischemia.

Methods

Patient Selection

We studied 538 consecutive patients undergoing clinically indicated ExE with normal systolic function (ejection fraction $\geq 50\%$), in sinus rhythm, and without valvular disease of greater than mild severity.

Resting Echocardiography Protocol

Echocardiography was performed by experienced sonographers on a standard cardiac ultrasound machine (ie33 or Philips 7500, Philips, Andover, Mass) using a 3.5-MHz transducer. Transthoracic images were digitally recorded for off-line analysis. Mitral inflow velocities were measured in the apical 4-chamber view during early (E), and late (A) diastole, with the sample volume placed at the level of the

Received September 11, 2009; accepted January 13, 2010.

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Circ Cardiovasc Imaging is available at <http://circimaging.ahajournals.org>

DOI: 10.1161/CIRCIMAGING.109.908152

mitral valve leaflets. Similarly, tissue velocities were measured during systole (s') and early (e') and late (a') diastole in the apical 4-chamber view by pulsed-wave tissue Doppler with the sample volume positioned at the septal mitral annulus. Gain settings were optimized to minimize spectral broadening, and the E/e' ratio was measured as the average of 3 cardiac cycles, with resting $E/e' > 15$ considered raised. Left atrial (LA) enlargement was denoted as LA area $> 20 \text{ cm}^2$ measured in the apical 2- or 4-chamber view.¹⁹

Normal diastolic function was determined by normal age-specific deceleration time (DT)²⁰ with resting $E/e' < 8$, or E/e' 8 to 15 with normal LA dimensions. Patients with DT > 2 SD of normal values with $E/e' < 15$ were deemed to have impaired relaxation. Finally, patients with elevated filling pressure were identified by $E/e' > 15$ or with a nonconclusive E/e'^{8-15} with evidence of LA enlargement.

Exercise Echocardiography Protocol

Two-dimensional echocardiographic loops were obtained for the assessment of wall motion abnormalities at rest and after symptom-limited exercise using standard treadmill protocols with 12-lead ECG monitoring. Transmittal flow and tissue Doppler was measured after acquisition of these loops.¹⁵ In the event of fusion of E and A, or e' and a' Doppler signals at high heart rates, images are acquired at the earliest time point when delineation between the aforementioned parameters is possible.

A standard segmental model was used to measure wall motion scores (WMS) for the detection of inducible ischemia, in accordance with American Society of Echocardiography guidelines.¹⁹ Segments were scored as normal (1), hypokinetic (2), severely hypokinetic (2.5), akinetic (3), or dyskinetic (4) with the average of these segments determining the wall motion score index (WMSI). Ischemia was identified by the consensus of 2 or more experienced readers when new or inducible wall motion abnormalities were detected in ≥ 1 segment. A single experienced reader (T.M.) supervised and approved all WMS reports. Postexercise diastolic measurements were made offline by 2 experienced observers.

Previously published data¹⁵ were used to determine an abnormal exercise E/e' . From these data, exercise E/e' in patients with normal left ventricular (LV) diastolic pressure during diastolic stress testing was 10.3 ± 2.1 . Therefore, $E/e' > 2$ SD from normal (ie, exercise $E/e' > 14.5$) was used to define a raised LV filling pressure response to exercise. Intraobserver and interobserver reproducibility of E/e' measurements by our group have been reported,²¹ with small mean differences (< 0.02) and high intraclass correlations (> 0.87 ; $P < 0.001$ for all) at both rest and exercise.

Patients were grouped on the basis of the E/e' response to exercise (normal, exercise $E/e' \leq 14.5$; abnormal, > 14.5) in the absence or presence of inducible ischemia. The 4 groups were (1) normal exercise E/e' with no ischemia, (2) normal exercise E/e' with inducible ischemia, (3) raised exercise E/e' with no ischemia, and (4) raised exercise E/e' with inducible ischemia. Finally, the patient cohort was divided into groups, depending on the severity of ischemia measured by the exercise WMSI. Patients without ischemia, those with a WMSI below the population mean, and those with a WMSI above the mean were divided into the respective groups: (1) no ischemia, (2) minor ischemia, and (3) major ischemia.

Angiography

Coronary angiography was performed as required on clinical grounds, according to the judgment of the responsible physician. Standard views were obtained and obstructive CAD was identified on the basis of $> 50\%$ diameter stenosis.

Follow-Up

The primary outcome for this study was cardiovascular death or hospitalization. The follow-up period was initiated on the day of exercise testing, and follow-up data were obtained from the hospital information registry. In addition to spontaneous events, we included unplanned revascularizations for worsening symptoms at least 3 months after the ExE (and were not a direct result of the ExE

Table 1. Clinical Characteristics of the Study Population and Those Lost to Follow-Up

	Study Population (n=493)	Lost to Follow-Up (n=29)	P Value
Age, y	58±11	53±13	0.051
Male, %	58	72	0.453
Ejection fraction, %	54±4	55±3	0.518
Diabetes, %	21	14	0.448
Hypertension, %	42	39	0.834
Ischemia, %	51	41	0.555
Medications			
β-blockers, %	60	41	0.310
ACE inhibitors, %	39	7	0.009
ARBs, %	12	10	0.815
Nitrates, %	32	14	0.128
Statins, %	68	38	0.118

findings). Revascularization before this was attributed to the test result and not considered as events.

Statistical Analysis

Student t tests were used to test for significant differences between 2 continuous variables, whereas the χ^2 test was used for categorical variables. Statistical significance was identified by $P < 0.05$. Cox univariate analysis was used to determine relationships between baseline and exercise parameters and outcome variables. Kaplan–Meier survival analysis with log-rank tests for significance (overall and between strata) was used to express the relationship of the dependent variables (ischemia and exercise E/e') to the cardiovascular end points.

Cox proportional hazards modeling using the backward-stepwise method was used to evaluate the incremental benefit of ExE over clinical and echocardiography parameters. Variables selected for entry into the model were those with $P < 0.1$ on Cox univariate analysis, and Akaike Information Criterion was used to select the optimal statistical model.²² Despite having univariate $P > 0.1$, both age and sex were forced into the Cox models throughout because they are important clinical variables pertinent to LV filling pressure, and their inclusion in the multivariate models improved overall model power. Exclusion of both age and sex based on univariate significance did not alter the model outcome. The final step of the model was to include the detection of ischemia or raised E/e' with exercise. To allow direct comparison of hazards ratios, variables were assessed per unit of their standard deviation. All statistical analysis was performed using a standard statistical software package (SPSS version 17.0, SPSS, Inc, Chicago, Ill).

Results

Clinical Characteristics

Clinical characteristics of the 522 patients (of 538) with measurable E/e' are presented in Table 1. Follow-up was available in 493 of these patients; those lost to follow-up (n=29, 5.6%) had lower resting E/e' (9.1 ± 3.2 versus 10.7 ± 3.7 ; $P = 0.027$) and had a higher exercise capacity (11.5 ± 3.1 versus 9.7 ± 3.1 METs; $P = 0.002$). Correction of resting E/e' for age, which was of borderline significance between groups, removed the statistical difference in resting E/e' ($P = 0.06$).

Table 2. Clinical, Echocardiographic, and Prognostic Data of the Study Groups

Group	1 (n=204)	2 (n=214)	3 (n=39)	4 (n=36)	ANOVA P Value
	Normal E/e' No Ischemia	Normal E/e' Ischemia	↑ E/e' No Ischemia	↑ E/e' Ischemia	
Clinical					
Age, y	58.9±10.3	55.2±12.1	59.2±11.6	62.1±10.9	<0.001
Male, %	58.3	60.0	52.6	52.8	0.646
Ejection fraction, %	54±4	54.2±4	55±4	54±3	0.713
Echocardiography					
Rest					
E/e'	10.2±2.8	9.5±2.4	15.7±4.6	15.3±4.8	<0.001
WMSI	1.04±0.09	1.12±0.20	1.03±0.10	1.073±0.15	<0.001
Heart rate, bpm	79±16	78±15	74±15	78±16	0.517
Systolic blood pressure, mm Hg	133±20	131±18	132±24	143±21	0.038
Exercise					
E/e'	9.8±2.3	10.0±2.2	18.2±4.1	18.2±3.5	<0.001
ΔE/e'	-0.15±2.9	0.70±2.9	2.9±4.2	2.8±3.2	<0.001
WMSI	1.04±0.09	1.43±0.31	1.03±0.09	1.43±0.35	<0.001
ΔWMSI	-0.00±0.03	0.30±0.27	-0.00±0.03	0.34±0.30	<0.001
Heart rate, bpm	150±23	148±22	144±27	147±26	0.586
Systolic blood pressure, mm Hg	173±25	170±24	175±23	170±23	0.373
Exercise capacity, METs	9.8±3.0	9.8±3.2	9.3±2.6	8.0±3.1	0.007
Prognostic					
No. of events	15	37	5	8	
Median follow-up, d	406	351	467	457	0.865

Data are mean±SD unless stated.

Exercise Testing

Of 493 patients with follow-up, more than half (n=250) developed ischemia with stress, in whom the resting WMSI increased from 1.11±0.19 to 1.43±0.32 with exercise. Patients with ischemia were younger (P=0.007) and had a lower resting E/e' (P=0.08). There was no difference in exercise E/e' for patients with ischemia compared with those without (P=0.92). There were no correlations between indices of exercise-induced ischemia and E/e' at rest or exercise. Finally, the WMSI was similar in patients with ischemia and normal exercise E/e' compared with those with a combination of both (P=0.97). Table 2 displays results from resting and exercise imaging.

LV Filling Pressure

Fifty-seven patients had E/e' >15 at rest (Table 3), in whom the proportion of patients with (n=25) and without (n=32) ischemia was similar to those with E/e' <15 (P=0.26). There were 75 patients in total with an abnormal E/e' response to exercise (E/e' >14.5), in whom half (n=36) had inducible ischemia. In patients with raised resting E/e', 34 (60%) had

raised E/e' with exercise. There were an additional 41 patients (20 with inducible ischemia) with normal E/e' at rest, who had raised E/e' with exercise. Exercise was terminated because of dyspnea and/or fatigue in two thirds (n=30) of patients with raised exercise E/e', among whom 18 (60%) had no ischemia.

Outcomes

The median (25% to 75% range) follow-up period was 13.2 (2.2 to 29.2) months, during which there were 65 cardiovascular hospitalizations but no cardiovascular deaths. Most events were ischemic (26 with acute coronary syndromes and 6 with acute myocardial infarction), late coronary revascularization (n=21), dyspnea, or heart failure (n=11) and stroke (n=1).

Contributions of Exercise E/e' and Ischemia to Events

Patients with normal exercise E/e' who were also free of ischemia had the most favorable prognosis compared with patients with ischemia, with or without raised exercise E/e' (P=0.003 for both, Figure 1). Importantly, prognosis was similar in patients with isolated raised exercise E/e' and those with ischemia and normal E/e' (P=0.46).

Association of the Extent of Ischemia With Outcome

This association was assessed by comparing prognosis in patients with normal and raised exercise E/e', respectively.

Table 3. LV Filling Pressure Response to Exercise

	Normal Resting E/e'	Raised Resting E/e'	Total
Normal exercise E/e'	395	23	418
Raised exercise E/e'	41	34	75
Total	436	57	493

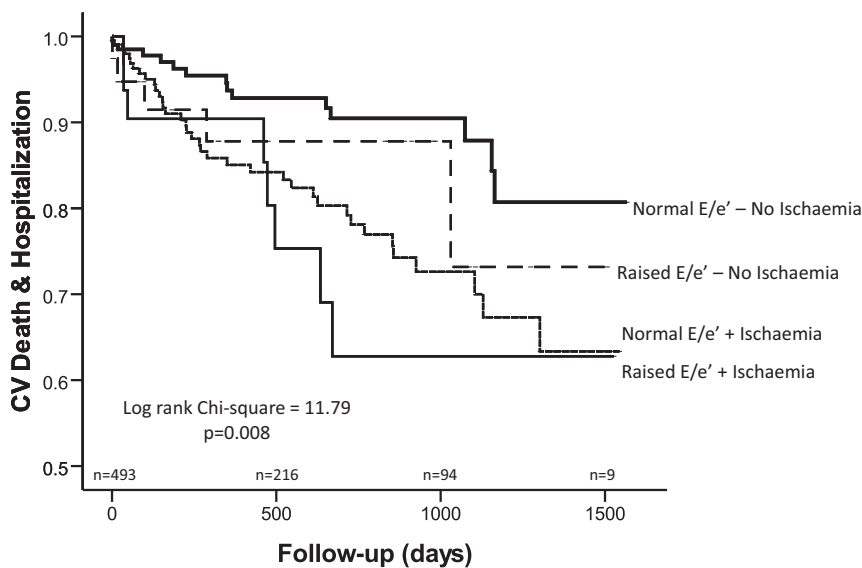


Figure 1. Kaplan–Meier survival curves depicting the prognosis associated with the 4 groups of classification based on ischemia and exercise E/e'. Patients are grouped by normal or raised exercise E/e', in the absence or presence of ischemia. Numbers of patients at risk are labeled on the x-axis. Patients with isolated ischemia or ischemia and raised E/e' have worse outcome than those with neither ($P=0.003$ for both). There was no difference in outcome between patients with isolated ischemia or isolated raised E/e' ($P=0.46$).

The average WMSI in patients with inducible ischemia was 1.40. The study population was, therefore, classified as (1) no ischemia, WMSI=1.00, (2) minor ischemia, WMSI <1.40, and (3) major ischemia, WMSI >1.40. In patients with normal exercise E/e' (Figure 2A), the severity of ischemia appeared to contribute incremental value when compared with those with no ischemia (minor ischemia, $P=0.062$; major ischemia, $P<0.001$). In patients with raised exercise E/e' (Figure 2B), however, the influence of ischemia, regardless of severity, did not affect the outcome ($P>0.05$ for all).

Severity of Diastolic Dysfunction and Outcome

The role of exercise E/e' and ischemia to outcomes was also explored in patients with mild diastolic dysfunction, defined by DT >2 SD from age-specific normal values.²⁰ In patients with normal DT, the results were similar to those in unselected patients, shown in Figure 1, where ischemia and

ischemia plus raised exercise E/e' had worse prognostic outcome than those with neither ($P<0.05$ for both). When patients with mild diastolic dysfunction were assessed, there was no difference in outcome between the individual groups ($P>0.3$ for all).

Change of E/e' From Rest to Exercise

This analysis sought to identify subgroups of patients in whom the measurement of exercise E/e' would be of most value. The subgroups were (1) normal resting E/e', with either (1a) normal exercise E/e' or (1b) raised exercise E/e', and (2) raised resting E/e' (>15). In patients with elevation of E/e' at baseline, the additional prognostic information afforded by exercise E/e' did not reach statistical significance ($P>0.05$ for the difference between all groups). In patients with normal E/e' at rest, those with elevation with exercise had a significantly worse outcome than those with normal

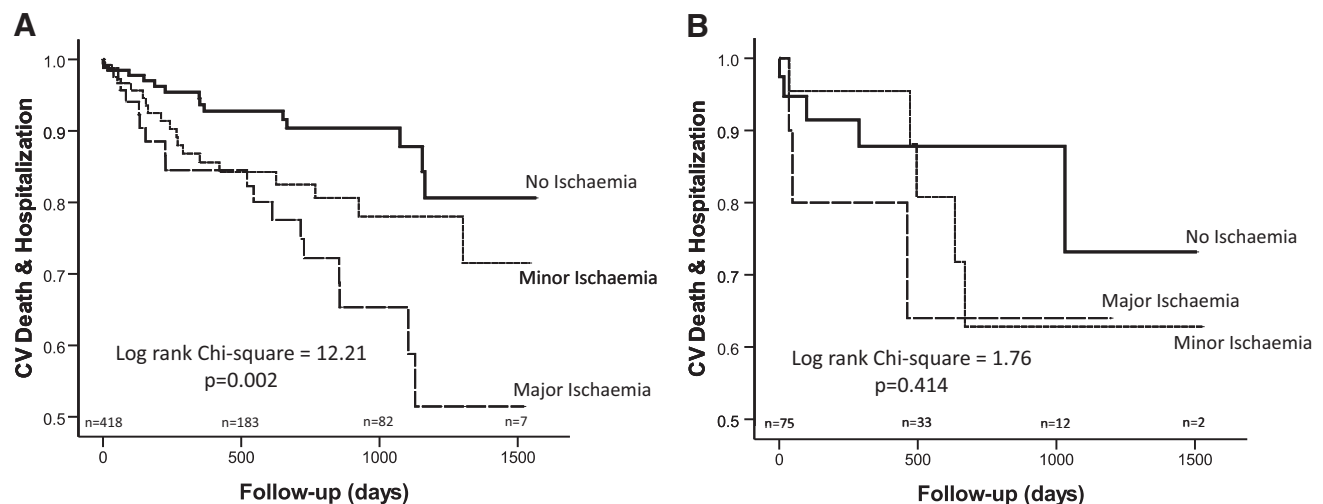


Figure 2. Kaplan–Meier survival curves showing the prognosis associated with the degree of ischemia in patients with normal exercise E/e' (A), and raised exercise E/e' (B). No ischemia indicates no inducible wall motion abnormalities (n=243); minor ischemia, exercise WMSI <1.40 (n=154); major ischemia, exercise WMSI >1.40 (n=96). In patients with normal E/e', those with ischemia have worse outcome than those with no ischemia (major ischemia, $P<0.001$; minor ischemia, $P=0.062$). In patients with raised exercise E/e', there is no difference in outcome regardless of the extent of ischemia ($P>0.3$ for all).

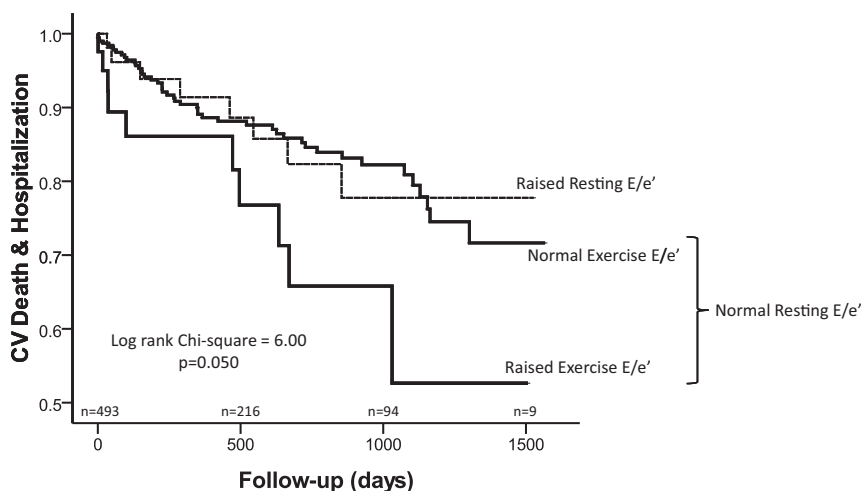


Figure 3. Kaplan–Meier curves showing the prognosis associated with the change in resting E/e' with exercise. In patients with normal E/e' at rest, outcome is worse in those with raised exercise E/e' (P=0.014). Raised exercise E/e' appeared to have little incremental value in patients with raised E/e' at rest (P=0.11 for the comparison with normal resting E/e').

exercise E/e' (P=0.014, Figure 3). Similarly, in patients with normal resting E/e' without inducible ischemia, those with elevation of E/e' with exercise had a significantly worse prognosis than those with normal exercise E/e' (P=0.033). Among the 41 patients with an increased E/e' response to exercise, the event rate was 20% in the 20 without ischemia and 29% in those with ischemia.

Independent and Incremental Association of E/e' With Outcome

Cox proportional hazards models were constructed to assess the role of exercise E/e' to outcomes in patients with normal E/e' at rest (Figure 4). On univariate analysis, resting and exercise WMSI, ischemia, exercise capacity, and exercise E/e' >14.5 were significant predictors of outcome. Using the Akaike Information Criterion for model selection, Cox multivariate predictors of outcome were exercise capacity (hazard ratio, 0.893; P=0.008), exercise WMSI (HR: 1.507;

P<0.001), and exercise E/e' >14.5 (hazard ratio, 2.988; P=0.002).

Using significant multivariate predictors of outcome, Cox nested models were constructed to assess the incremental value of exercise E/e' over standard clinical characteristics and ExE protocols (Figure 4). First, an objective measure of exercise capacity (treadmill METs) was added to clinical characteristics (age, sex). The exercise WMSI was subsequently added to exercise capacity, resulting in a significant increase of model power, as represented by the model χ^2 (P=0.001). With the addition of exercise E/e' >14.5 to these standard ExE measurements, there was an incremental, step-wise increase in power of the model (P=0.006).

Angiography

ExE is an imperfect test for the detection of CAD. An audit of angiography studies was conducted to address the sensitivity of ExE to detect significant CAD in the study popula-

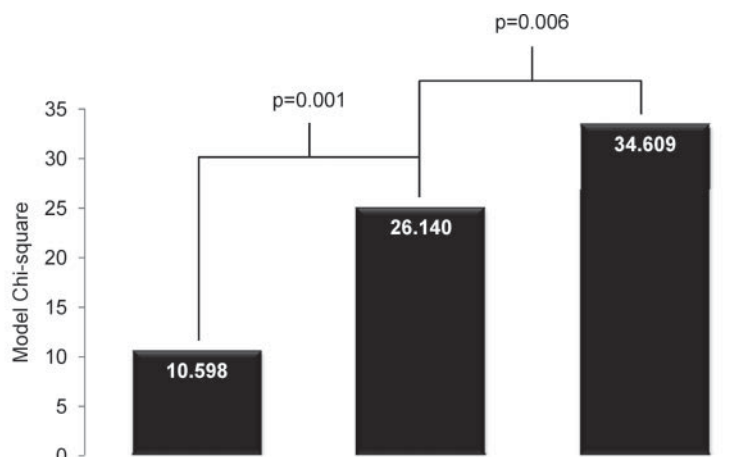


Figure 4. Cox proportional hazards model showing the incremental benefit of exercise E/e' to standard exercise echocardiography protocols. The addition of exercise E/e' to standard information obtained during exercise echocardiography (exercise capacity, inducible wall motion abnormalities) results in a significant increase of model power to predict adverse outcome.

	Age + Sex + METs		+ Ex WMSI		+ Ex E/e' >14.5	
	HR	Sig.	HR	Sig.	HR	Sig.
Age	1.027	0.867	1.124	0.455	1.139	0.413
Sex	0.567	0.066	0.652	0.166	0.589	0.088
Exercise Capacity	0.686	0.013	0.737	0.041	0.739	0.044
Exercise WMSI			1.478	<0.001	1.526	<0.001
Exercise E/e' >14.5					3.023	0.002

Table 4. Angiography Results

Group	No.	Angiography (n)	Stenosis >50% (n)
1			
Normal E/e', no ischemia	204	29	11 (38%)
2			
Normal E/e', ischemia	214	62	51 (82%)
3			
Raised E/e', no ischemia	39	4	2 (50%)
4			
Raised E/e', ischemia	36	10	8 (80%)

tion. Of 493 patients with follow-up, 105 underwent angiography within 6 months of the ExE (Table 4). In patients with ischemia, 72 (29%) underwent cardiac catheterization, in whom 82% had angiographically significant CAD, defined by a stenosis >50% in at least 1 coronary vessel. There were 33 patients with the absence of inducible WMA on ExE who underwent angiography, 4 of whom had raised exercise E/e'. In this group of patients without echocardiographic evidence of myocardial ischemia (n=33), 13 (39%) had angiographically significant CAD.

Discussion

The results of this study show that the identification of raised LV filling pressures during exertion is associated with adverse cardiovascular outcomes. These findings are important from 2 aspects. First, the study suggests that the measurement of exercise E/e' for the recognition of diastolic dysfunction when exertional symptoms are present is clinically significant. Second, although these findings are independent of detectable ischemia, they are nonetheless associated with ischemic as well as heart failure events in follow-up.

Assessment of LV Filling Pressure

The finding of diastolic dysfunction at resting echocardiography is known to hold prognostic value.^{14,23–26} Redfield et al²³ showed that diastolic dysfunction was common, and data from this and other studies²⁴ indicated that many patients with severe diastolic dysfunction may be asymptomatic. Although this study showed that the prognosis associated with any form of dysfunction was significantly worse than those with normal diastolic function, the prognosis associated with mild diastolic dysfunction, in the absence of raised LV filling pressure, is controversial.²⁶

The potential role of exercise E/e' was explored because patients with normal filling pressure (either a normal filling pattern or delayed relaxation) may experience symptoms and elevation of E/e' only during exertion.^{16,27} We have previously reported that patients with raised LV filling pressure at rest often maintain high pressures with exercise.¹⁵ In patients with such obvious diastolic filling abnormalities evidenced by raised LV filling pressure at rest, the incremental benefit of ExE may be limited. In this study, however, 55% (41 of 75) of patients with elevation of E/e' with exercise had a normal (<8), or nonconclusive resting E/e' (8 to 15), indicating the limited sensitivity for resting echocardiography to identify those at risk when resting measures are not convinc-

ing. These patients may benefit most from detection of raised LV filling pressure with exercise, especially in the investigation of cardiac causes of dyspnea.

Ischemia

The detection of inducible myocardial ischemia is often the primary purpose for ExE, and this information holds significant, independent prognostic value.^{2–6} Despite the sinister outcomes associated with LV dysfunction related to ischemia, many epidemiological studies investigating the prevalence and prognosis associated with diastolic dysfunction fail to account for the influence of ischemia. Furthermore, ischemia has the propensity to influence LV filling pressure, particularly with stress.²⁸ For these reasons, the current study is unique in demonstrating the independent prognostic value of exercise E/e' after accounting for the influence of inducible ischemia.

Study Limitations

Follow-up was obtained on 95% of patients who underwent baseline testing. Although there were differences between those who remained in the study and those lost to follow-up, the differences probably represent clinical outpatient practice in which younger and more active patients do not typically require further hospital contact. In addition, age appears to influence E/e' at rest,²⁹ which may affect the threshold for detecting raised LV filling pressure. However, the mean age of patients enrolled in the original validation study of exercise E/e' was similar to our population, and, because there are no data describing changes in exercise E/e' with age, we have not adopted an age-dependent correction.

The accuracy of ExE for detecting angiographically “significant” stenoses is imperfect. In this study, the results of ExE were comparable with published data for the detection of CAD (sensitivity, 88%; specificity, 79%),³⁰ but echocardiographic contrast agents—which were not available to us during this study—could have improved these results. Inducible ischemia is a possible cause of disturbed LV filling and therefore elevated filling pressure in patients with an ischemic response. However, the extent of ischemia was comparable in patients with and without an increased exercise E/e', supporting the contention that an increased E/e' response to exercise is independent of ischemia. The numbers of patients with increased E/e' was relatively small, and the study was not powered to make definitive conclusions about the prognosis of this subgroup.

Clinical Implications

The detection and adequate treatment of patients with ischemia has been associated with improved outcome.³¹ However, although the identification of raised LV filling pressure with exercise appears to be of similar importance, the therapeutic implications of these findings are currently unclear. Epidemiological data suggest that control of hypertension may be effective in reducing the risk of patients with diastolic dysfunction.²³ Mechanistic studies also support the hypothesis that ventricular-vascular stiffening, possibly caused by the chronic effects of hypertension, is an important contributor to the development of heart failure with preserved ejection

fraction.^{32,33} In patients without ischemia who display evidence of raised LV filling pressure with exercise, studies of careful control of hypertension and improvement of ventricular-vascular interaction may demonstrate an improvement of the LV filling pressure response to exercise and therefore improve outcomes. Finally, although statistical modeling separates the predictive power of ischemia and exercise E/e' , raised LV filling with exercise may be a subclinical expression of myocardial ischemia, not visibly detected by wall motion assessment. Further studies are required to test this hypothesis.

Conclusion

In addition to permitting the detection of inducible myocardial ischemia, exercise echocardiography identifies a small group of patients who demonstrate an increase of E/e' with exercise. The finding of raised exercise E/e' is independently associated with subsequent cardiovascular hospitalization.

Sources of Funding

This study was supported by a project grant (456139) from the National Health and Research Council, Canberra, Australia.

Disclosures

None.

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CLINICAL PERSPECTIVE

Evidence of raised left ventricular filling pressure (based on the ratio of transmitral and annular velocities, E/e' ratio) during resting echocardiography holds important prognostic value. However, many patients with normal resting left ventricular filling pressure complain of exertional symptoms, and some of these demonstrate an increment of E/e' ratio with stress. The prognostic implications of this response, especially in relation to other prognostic markers such as ischemia, are undefined. This may be particularly important because many studies have failed to account for the influence of ischemia on diastolic function. This study demonstrates the adverse outcome associated with raised E/e' during exercise echocardiography. Importantly, more than half of the patients with raised E/e' with exercise had normal filling pressure at rest indicating the incremental information provided by exercise. This study shows that the prognostic value of exercise E/e' is independent of ischemia. Despite the similar outcomes associated with raised exercise E/e' and ischemia, treatment options for raised filling pressure are not known, and objective identification of those at risk may assist in the investigation of appropriate therapies.