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Exercise Echocardiographic Findings and Outcome of Patients Referred for Evaluation of Dyspnea

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OBJECTIVES The purpose of this study was to characterize the outcome of patients referred for exercise echocardiographic evaluation of dyspnea.

BACKGROUND Little information exists regarding outcome of patients with dyspnea.

METHODS We identified 443 patients with unexplained dyspnea, 2,033 with chest pain, and 587 with both symptoms referred for exercise echocardiography.

RESULTS Compared to those with chest pain alone, patients referred for dyspnea alone were older, predominately men, and had lower workload, lower ejection fraction (EF), more prior myocardial infarction (MI), and abnormal rest electrocardiograms. Patients with both symptoms were similar to those with dyspnea, but more had prior revascularization. Exercise echocardiography showed ischemia in 42% of patients with dyspnea, 19% with chest pain, and 58% with both symptoms. During 3.1 ± 1.8 years follow-up, cardiac death (5.2% vs. 0.9%, $p < 0.0001$) and nonfatal MI (4.7% vs. 2.0%, $p < 0.0001$) occurred more often in patients with dyspnea. Events in patients with both symptoms were similar to those with dyspnea, except for revascularization (20% vs. 13%, $p = 0.0004$). For patients with dyspnea, independent predictors of events were previous MI (hazard ratio [HR] 3.35, $p < 0.0001$), male gender (HR 1.94, $p = 0.0252$), EF (HR 0.95/10% increment, $p < 0.0001$), and increase in wall motion score index with exercise (HR 4.19/0.25 U, $p < 0.0001$), but not chest pain.

CONCLUSIONS Patients with unexplained dyspnea have a high likelihood of ischemia and an increased incidence of cardiac events. Exercise echocardiography provides independent information for identifying patients at risk. In patients with known or suspected coronary artery disease, dyspnea is a symptom requiring investigation. (J Am Coll Cardiol 2004;43:2242–6) © 2004 by the American College of Cardiology Foundation

Dyspnea is a complex sensation that arises from multiple stimuli and clinical etiologies (1). When a cardiac etiology is suspected, exercise stress testing and echocardiography are often utilized to predict cardiovascular morbidity and mortality (2,3).

Exercise echocardiography permits combined assessment of exercise capacity, left ventricular systolic function, and exercise-induced ischemia, and has been validated as a predictor of cardiac events. Its prognostic value has been assessed in multiple large populations (4–6); however, these studies included little or no information about dyspnea as the primary referral symptom. Similarly, studies involving exercise electrocardiography have not provided subset analysis of patients with dyspnea (7,8). In a large nuclear perfusion study, dyspnea was an independent predictor of cardiac death; however, this symptom was present in only 10% of the population (9).

The purpose of this study was to characterize the results of exercise echocardiography in patients referred for evaluation of dyspnea, and the outcome of this group. For reference, we compared this group to patients referred for evaluation of chest pain and patients referred for evaluation of both chest pain and dyspnea.

METHODS

Patients. The study was approved by the institutional review board. From 1990 to 1995, 6,421 patients were referred for exercise echocardiography. Of these, 254 had inadequate echocardiographic images and 136 refused to participate in research. Of the remaining 6,031 patients, we identified 3,260 patients referred for evaluation of chest pain or dyspnea. Chest pain was classified as typical or atypical (10). We excluded 73 patients because of moderate or severe valvular heart disease and 58 because of previously established explanations of noncardiac dyspnea (31 with severe chronic obstructive pulmonary disease, 22 with other pulmonary pathology, and 5 with hemoglobin <9 g/dl). Of the remaining 3,129 patients, survival status was ascertained in 3,063 (98%). These constitute the population studied.

Exercise echocardiography. All patients underwent symptom-limited treadmill exercise echocardiography according to previously described methods (4). Exercise was performed according to the Bruce protocol in 2,734 patients, Naughton in 150 patients, and modified Bruce in 179 patients.

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Abbreviations and Acronyms

CAD = coronary artery disease
EF = ejection fraction
HR = hazard ratio
MI = myocardial infarction
NYHA = New York Heart Association
WMSI = wall motion score index

Wall motion was scored according to a 16-segment model, in which 1 = normal or hyperdynamic, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic, and 5 = aneurysm (11). Wall motion score index (WMSI) was calculated at rest and with exercise as the sum of segmental scores divided by number of segments. New or worsening wall motion with exercise was considered indicative of myocardial ischemia. Wall motion abnormalities present at rest and unchanged with exercise were classified as fixed. Exercise echocardiography was considered abnormal if ischemia or fixed wall motion abnormalities were present.

Follow-up. The Social Security Agency Death Index was used to ascertain survival status. Additionally, follow-up for cardiac events (4) was available in 1,016 of 1,030 (99%) patients with dyspnea and 1,966 of 2,033 (97%) patients with chest pain.

End points were cardiac events, including nonfatal myocardial infarction (MI) and cardiac death, and all-cause mortality. Patients who had coronary revascularization before other events were censored at the time of revascularization for the cardiac event analysis. No censoring was performed for analysis of all-cause mortality.

Statistical analysis. Continuous variables were reported as mean ± SD; comparisons between groups were based on the Wilcoxon rank-sum test. Group comparisons were based on the chi-square test. Survival was estimated by the Kaplan-Meier method. Univariable and multivariable associations of clinical and exercise echocardiographic variables with cardiac events were assessed in the Cox proportional hazards framework. Variables were selected in a stepwise forward selection manner with entry and retention set at a significance level of 0.05. Parameters with univariate significance were considered for multivariate analysis.

RESULTS

Study group. There were 443 patients with dyspnea alone, 587 with dyspnea and chest pain (typical in 75% and atypical in 25%), and 2,033 patients with chest pain alone (typical in 33% and atypical in 67%). Clinical characteristics are presented in Table 1. Among patients with dyspnea, symptoms were New York Heart Association (NYHA) functional class I in 415 (40%) patients, class II in 564 (55%) patients, and class III in 51 (5%) patients. Exercise echocardiographic parameters are summarized in Table 2.

Outcomes. Table 3 shows cardiac events, coronary revascularization, and mortality based on presenting symptoms during a median follow-up of 3.1 ± 1.8 years. Dyspnea was associated with a higher occurrence of each event compared to chest pain alone. The outcome for patients with both symptoms was similar to that of patients with dyspnea alone, except for a higher rate of revascularization. For all-cause mortality, the estimated one-, three-, and five-year survival rates were significantly worse for patients with dyspnea alone (97%, 92%, and 86%, respectively) than for those with chest pain (99.6%, 99%, and 96%, respectively) (Fig. 1). Similarly, the estimated cardiac event-free survival for patients with dyspnea was 98%, 95%, and 92% at one, three, and five years compared to 99.5%, 99%, and 96% for those with chest pain (Fig. 2).

Table 1. Clinical Characteristics

Characteristics	Dyspnea Alone (n = 443) Group 1	Chest Pain Alone (n = 2033) Group 2	Dyspnea and Chest Pain (n = 587) Group 3	p Value Group 1 vs. 2	p Value Group 1 vs. 3	p Value Group 2 vs. 3
Clinical characteristics, n (%)						
Age (mean, yrs)	64.5 ± 11.0	58.7 ± 12.8	63.9 ± 11.5	<0.0001	0.5238	<0.0001
Male gender	237 (54)	926 (46)	309 (53)	0.0024	0.7847	0.0024
Current smoking	52 (12)	277 (14)	77 (13)	0.2973	0.5252	0.7388
Diabetes mellitus	45 (10)	167 (8)	69 (12)	0.1809	0.4333	0.0088
Prior MI	53 (12)	145 (7)	97 (17)	0.0007	0.0389	<0.0001
Revascularization	42 (10)	165 (8)	110 (19)	0.3470	<0.0001	<0.0001
Hypertension	231 (52)	848 (42)	289 (49)	<0.0001	0.3549	0.0012
Hypercholesterolemia	223 (50)	1,078 (53)	349 (60)	0.3286	0.0041	0.0059
Beta-blocker therapy	71 (16)	408 (20)	163 (28)	0.0528	<0.0001	<0.0001
Mild lung disease	8 (2)	36 (2)	42 (7)	0.9596	<0.0001	<0.0001
Body mass index (kg/m^2)						
Mean	27.7 ± 4.8	27.5 ± 7.1	27 ± 4.7	0.0982	0.2036	0.3105
> 30	113 (26)	453 (22)	123 (21)	0.4369	0.1430	0.6787
Baseline ECG, n (%)						
Normal	190 (43)	1,152 (57)	250 (43)	<0.0001	0.9357	<0.0001
Q-wave	61 (14)	169 (8)	82 (14)	0.0210	0.7539	0.0298
ST/T abnormalities	182 (42)	663 (31)	247 (42)	0.1006	0.5941	0.2463

ECG = electrocardiogram; MI = myocardial infarction.

Table 2. Exercise Echocardiographic Parameters

Characteristics (Mean ± SD or Number [%])	Dyspnea Alone (n = 443) Group 1	Chest Pain Alone (n = 2,033) Group 2	Dyspnea and Chest Pain (n = 587) Group 3	p Value Group 1 vs. 2	p Value Group 1 vs. 3	p Value Group 2 vs. 3
Workload (METs)	7.3 ± 2.7	8.7 ± 3.5	7.5 ± 2.5	<0.0001	0.2106	<0.0001
Exercise heart rate (beats/min)	141 ± 25	150 ± 24	140 ± 25	<0.0001	0.4067	<0.0001
Exercise electrocardiogram						
Positive (%)	88 (20)	317 (16)	186 (32)	0.0272	<0.0001	<0.0001
Negative (%)	240 (54)	1,364 (67)	280 (48)	<0.0001	0.0395	<0.0001
Nondiagnostic (%)	112 (25)	342 (17)	118 (20)	0.0002	0.0481	0.0658
Ejection fraction	56 ± 11	59 ± 6	57 ± 8	<0.0001	0.7028	<0.0001
Rest WMSI	1.18 ± 0.37	1.07 ± 0.21	1.18 ± 0.31	<0.0001	0.1455	<0.0001
Exercise WMSI	1.31 ± 0.46	1.12 ± 0.28	1.38 ± 0.4	<0.0001	<0.0001	<0.0001
Change in WMSI	0.13 ± 0.27	0.05 ± 0.18	0.20 ± 0.29	<0.0001	<0.0001	<0.0001
Exercise RPP	24,944 ± 6,757	26,850 ± 6,075	24,530 ± 7428	<0.0001	0.2025	<0.0001
Ischemia by exercise echocardiography (%)	186 (42)	394 (19)	338 (58)	<0.0001	<0.0001	<0.0001
Abnormal exercise echocardiography (%)	263 (59)	589 (29)	442 (72)	0.0024	0.7847	<0.0001
Percentage of ischemic segments	12.4 ± 20.13	5.5 ± 13.5	19.0 ± 22.4	<0.0001	<0.0001	<0.0001
Percentage of abnormal segments with exercise	22.5 ± 30.5	8.8 ± 19.0	27.1 ± 28.3	<0.0001	<0.0001	<0.0001

METs = metabolic equivalents; RPP = rate-pressure product; WMSI = wall motion score index.

A separate analysis was performed to compare patients with isolated dyspnea to the 671 patients with typical chest pain. Patients with dyspnea had a higher occurrence of cardiac events (6.3% vs. 3.0%, $p = 0.0081$), cardiac death (5.2% vs. 1.5%, $p = 0.0004$), and all-cause mortality (11.7 % vs. 4.1 %, $p < 0.0001$).

Predictors of cardiac events for patients with dyspnea. Univariate and multivariate predictors of cardiac events in dyspneic patients are presented in Table 4. Ejection fraction (EF) and change in WMSI were independently predictive of cardiac events. Chest pain, typical angina, hypertension, hypercholesterolemia, diabetes mellitus, mild lung disease, smoking, and NYHA functional class were not predictive.

DISCUSSION

Among patients referred for exercise echocardiography, those with the primary symptom of dyspnea were at high risk of having coronary artery disease (CAD). Indeed, among patients with dyspnea but no chest pain, 42% had echocardiographic evidence of ischemia and 59% had an abnormal exercise echocardiogram. During 3.1 ± 1.8 years follow-up, MI, coronary revascularization, or death occurred in 23% of these patients.

Compared to those with chest pain, patients with dyspnea alone had twice the incidence of positive (42% vs. 19%) and abnormal exercise echocardiography (59% vs. 29%). During follow-up, patients with dyspnea alone had a higher incidence of MI (4.7% vs. 2.0%), cardiac death (5.2% vs. 0.9%), and all-cause mortality (11.7% vs. 2.3%). Patients with both chest pain and dyspnea were more likely to have positive exercise echocardiography or revascularization, but had other event rates similar to those with dyspnea alone.

It is accepted that the probability of CAD among patients with chest pain depends on the quality of the symptom (10,12). Therefore, we compared the group with dyspnea alone to those with typical angina. Patients with dyspnea remained at increased risk, with an event rate double that of patients with typical angina.

Results of exercise echocardiography were independently

Table 3. Outcome for Patients With Dyspnea Compared With Those Having Chest Pain

Cardiac Events, n (%)	Dyspnea Alone n = 443 Group 1	Chest Pain Alone n = 2,033 Group 2	Dyspnea and Chest Pain n = 587 Group 3	p Value Group 1 vs. 2	p Value Group 1 vs. 3	p Value Group 2 vs. 3
MI or cardiac death	28 (6.3)	46 (2.3)	35 (6.0)	<0.0001	0.8124	<0.0001
MI	21 (4.7)	40 (2.0)	31 (5.3)	<0.0001	0.6948	<0.0001
Cardiac death	23 (5.2)	19 (0.9)	24 (4.1)	<0.0001	0.4009	<0.0001
Noncardiac death	29 (6.5)	28 (1.4)	38 (6.5)	<0.0001	0.9627	0.0006
All-cause mortality	52 (11.7)	47 (2.3)	62 (10.6)	<0.0001	0.5515	<0.0001
Coronary revascularization	57 (12.9)	116 (5.7)	115 (19.6)	<0.0001	0.0042	<0.0001
Any event	103 (23.3)	171 (8.4)	170 (29.0)	<0.0001	0.0398	<0.0001

MI = myocardial infarction.

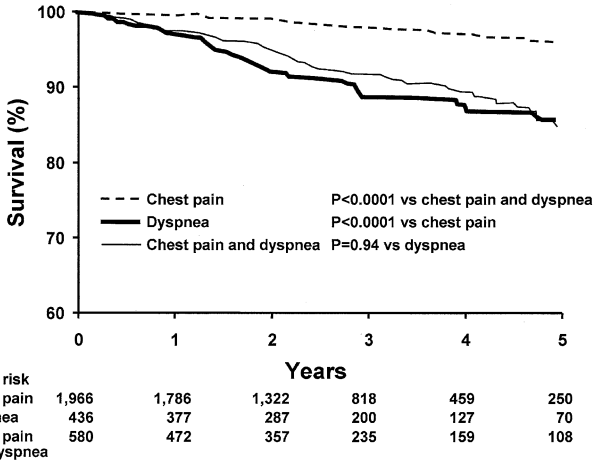

Figure 1. Survival among patients referred for dyspnea, with or without chest pain, was significantly worse than that of patients referred for evaluation of chest pain.

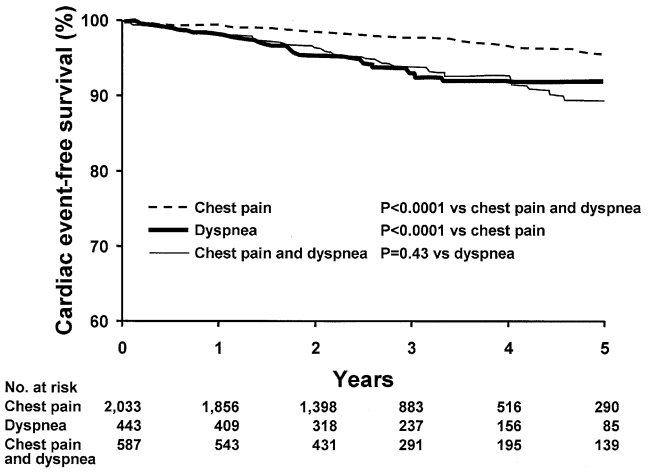

Figure 2. Cardiac event-free survival among patients referred for dyspnea, with or without chest pain, was significantly worse than that of patients referred for evaluation of chest pain.

predictive of cardiac events among dyspneic patients. Multivariate analysis showed that exercise-induced change in WMSI, an indicator of extent and severity of ischemia, was associated with worse outcome. Male gender, EF, and history of MI were also independent predictors of cardiac events.

Dyspnea is a subjective symptom with multiple potential etiologies. Smoking, a contributor to lung and heart disease, was not predictive of events in our patients. The relationship of dyspnea to functional capacity is imperfect (13), yet workload was independently predictive of mortality. Although symptoms during exercise testing do not correlate well with the severity of ventricular dysfunction (14), EF was an independent predictor of cardiac events and all-cause mortality. Dyspnea may be a manifestation of increased filling pressures or heart failure, which is generally associated with a poor prognosis, even when symptoms are mild (15). Lastly, dyspnea may represent a more advanced state of heart disease. Silent ischemia and dyspnea as an anginal equivalent are well described in patients with diabetes mellitus or after coronary artery bypass grafting, but also occur in others (16).

Diastolic function was not assessed in our patients and may have accounted for symptoms or events as recent data have demonstrated increased mortality in subjects with diastolic dysfunction (17,18). Assessment of diastolic function during exercise has been shown to be feasible (19) and may be beneficial in dyspneic patients

Study limitations. Patients with lung disease precluding satisfactory echocardiographic images or with recognized noncardiac explanation for dyspnea were excluded. This may have resulted in a concentration of cardiac explanations for dyspnea in this population. However, screening for underlying lung disease was not standardized, so it is probable that patients with noncardiac causes of dyspnea were included. Lastly, all patients were able to perform exercise testing, and most were NYHA functional class I to

Table 4. Predictors of Cardiac Death or MI for Patients With Dyspnea

Variable	Univariate Predictors			Multivariate Predictors		
	Hazard Ratio	95% CI	p Value	Hazard Ratio	95% CI	p Value
Age*	1.34	1.06–1.70	0.0131			
Male gender	2.82	1.60–4.98	0.0004	1.94	1.09–3.46	0.0252
Prior MI	3.45	2.02–5.89	<0.0001	3.35	1.92–5.84	<0.0001
Prior revascularization	1.93	1.08–3.46	0.0276			
Known CAD	4.41	2.55–7.64	<0.0001			
Normal rest electrocardiogram	0.35	0.19–0.64	0.0006			
Ejection fraction†	0.94	0.92–0.96	<0.0001	0.95	0.933–0.974	<0.0001
Workload, METs§	0.91	0.82–1.00	0.0664			
Positive exercise electrocardiogram	2.10	1.25–3.52	0.0049			
Rest WMSI‡	4.20	2.60–6.78	<0.0001			
Change in WMSI‡	3.84	1.91–7.69	0.0002	4.19	2.06–8.56	<0.0001
Percentage of abnormal segments with exercise†	1.02	1.02–1.03	<0.0001			
Percentage of ischemic segments†	1.02	1.01–1.03	0.0005			

*Per decade; †per 10% increment; ‡per 0.25 increment or 4 of 16 segments; §per 1 MET change.
CAD = coronary artery disease; CI = confidence interval; METs = metabolic equivalents; MI = myocardial infarction; WMSI = wall motion score index.

II. The significance of dyspnea that prevents exercise testing may be different.

Conclusion. Patients with dyspnea have a high likelihood of ischemia and a high incidence of cardiac events during follow-up. Exercise echocardiography provides independent information for identifying patients at risk of cardiac events. In patients with known or suspected CAD, dyspnea is a serious symptom that requires investigation.

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