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Prognostic Significance of Dyspnea in Patients Referred for Cardiac Stress Testing

Aiden Abidov, M.D., Ph.D., Alan Rozanski, M.D., Rory Hachamovitch, M.D.,
Sean W. Hayes, M.D., Fatma Aboul-Enein, M.D., Ishac Cohen, Ph.D.,
John D. Friedman, M.D., Guido Germano, Ph.D., and Daniel S. Berman, M.D.

ABSTRACT

BACKGROUND

Although dyspnea is a common symptom, there has been only limited investigation of its prognostic significance among patients referred for cardiac evaluation.

METHODS

We studied 17,991 patients undergoing myocardial-perfusion single-photon-emission computed tomography during stress and at rest. Patients were divided into five categories on the basis of symptoms at presentation (none, nonanginal chest pain, atypical angina, typical angina, and dyspnea). Multivariable analysis was used to assess the incremental prognostic value of symptom categories in predicting the risk of death from cardiac causes and from any cause. In addition, the prognosis associated with various symptoms at presentation was compared in subgroups selected on the basis of propensity analysis.

RESULTS

After a mean (\pm SD) follow-up of 2.7 ± 1.7 years, the rate of death from cardiac causes and from any cause was significantly higher among patients with dyspnea (both those previously known to have coronary artery disease and those with no known history of coronary artery disease) than among patients with other or no symptoms at presentation. Among patients with no known history of coronary artery disease, those with dyspnea had four times the risk of sudden death from cardiac causes of asymptomatic patients and more than twice the risk of patients with typical angina. Dyspnea was associated with a significant increase in the risk of death among each clinically relevant subgroup and remained an independent predictor of the risk of death from cardiac causes ($P<0.001$) and from any cause ($P<0.001$) after adjustment for other significant factors by multivariable and propensity analysis.

CONCLUSIONS

In a large series of patients, self-reported dyspnea identified a subgroup of otherwise asymptomatic patients at increased risk for death from cardiac causes and from any cause. Our results suggest that an assessment of dyspnea should be incorporated into the clinical evaluation of patients referred for cardiac stress testing.

From the Department of Imaging, Division of Nuclear Medicine, and the Department of Medicine, Division of Cardiology, Cedars-Sinai Medical Center, Los Angeles (A.A., S.W.H., F.A.-E., I.C., J.D.F., G.G., D.S.B.); the Department of Medicine, St. Joseph Mercy Oakland Medical Center, Pontiac, Mich. (A.A.); the Division of Cardiology, St. Luke's-Roosevelt Hospital Center, New York (A.R.); the Cardiovascular Division, Department of Medicine, Keck School of Medicine, University of Southern California, Los Angeles (R.H.); and the Department of Medicine, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles (J.D.F., G.G., D.S.B.). Address reprint requests to Dr. Berman at the Department of Imaging, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Los Angeles, CA 90048, or at bermand@cshs.org.

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A NUMBER OF CLINICAL VARIABLES HAVE been used to assess prognosis in patients with known or suspected coronary artery disease, including age, sex, coronary risk factors, and the presence or absence and character of chest pain.^{1,2} Although other somatic symptoms may also be associated with coronary artery disease, including fatigue, dyspnea, and palpitations, they have not been routinely integrated into models predicting the risk of cardiac events. Among commonly cited symptoms, dyspnea is of particular interest, since it may be a sign of occult left ventricular dysfunction or noncardiac disease (especially pulmonary disorders such as chronic bronchitis or emphysema) or, possibly, an exertional “anginal equivalent.”³ Some studies have suggested that patients with dyspnea are at increased risk for angina or adverse cardiac events,⁴⁻⁷ but systematic epidemiologic study among populations with known or suspected cardiac disorders has been lacking.

For years, we have included a single questionnaire item concerning dyspnea in the assessment of all patients undergoing myocardial-perfusion single-photon-emission computed tomography (SPECT) at rest and during stress. Follow-up survival data have been obtained in a large cohort of these patients. We analyzed the value of dyspnea as a predictor of death from cardiac causes and from any cause.

METHODS

STUDY DESIGN

We evaluated consecutive patients free of known cardiomyopathy or valvular disease who underwent separate-acquisition dual-isotope myocardial-perfusion SPECT at rest with the use of thallium-201 as a tracer and during exercise-induced or vasodilator-induced stress with the use of technetium-99m (sestamibi) between January 1991 and May 2000. All patients were prospectively enrolled in a registry, and follow-up data were obtained for at least one year after testing. Each patient provided written informed consent (including consent to participate in our registry) at the time of exercise testing. The study was approved by the institutional review board of Cedars-Sinai Medical Center in Los Angeles. Funding for the follow-up aspects of this study was provided by grants from Bristol-Myers Squibb Medical Imaging and Fujisawa Healthcare. The sponsors had no role in the conception and design of the study, the collection, analysis, and interpre-

tation of the data, and the drafting and revision of the manuscript.

Patients were divided into five categories according to their self-reported symptoms of chest pain and dyspnea at the time of testing. Typical angina was defined as chest pain that was substernal, occurred during stress, and resolved within 10 minutes after rest or the receipt of nitroglycerin.⁸ Chest pain was classified as atypical angina if two of these features were present and as nonanginal if one or none of these features were present. Among patients without chest discomfort, those who responded affirmatively to the question “Do you experience shortness of breath?” were classified as having dyspnea; the remainder were classified as asymptomatic. Dyspnea was not coded in patients with chest pain.

STRESS TESTING

Patients underwent resting and stress myocardial-perfusion SPECT as previously described^{9,10} with the use of symptom-limited stress induced by exercise on a treadmill or by a vasodilator.^{9,10} The response of the heart rate to stress was considered abnormal if the heart-rate reserve — calculated as follows: (the peak heart rate—the resting heart rate) ÷ ((220—age)—the resting heart rate) — was less than 80 percent during exercise-induced stress¹¹ or if the ratio of the peak heart rate to the resting heart rate during vasodilator-induced stress was 1.12 or less.¹⁰

MYOCARDIAL-PERFUSION SPECT

Myocardial-perfusion SPECT was performed with the use of 180-degree acquisition and standard energy windows.⁹ Projection data were reconstructed into transaxial tomograms and automatically reoriented into short-axis images. In patients studied after 1994, eight-frame gated myocardial-perfusion SPECT was performed to assess the left ventricular ejection fraction and end-diastolic volume after stress with the use of an automatic program.¹²

Experienced observers used a five-point scoring system to evaluate 20 segments of each myocardial-perfusion SPECT.^{9,13} An abnormal result was defined as one in which at least 5 percent of myocardium was abnormal during stress. Ischemia was defined by the presence of reversible defects in at least 5 percent of myocardium,¹³ and a fixed defect was defined by the finding that at least 5 percent of myocardium was abnormal at rest.

FOLLOW-UP

Deaths were identified through our hospital-based patient-information system (WebVS) and the Social Security Death Index. To ascertain the cause of death, the information provided by WebVS and the death certificates obtained for all who died in Los Angeles County were reviewed consensually in a blinded fashion by two experienced cardiologists. Death from any cause was defined as any death during follow-up. Death from cardiac causes was defined as death from any cardiac cause (e.g., lethal arrhythmia, myocardial infarction, or pump failure). Follow-up in the remaining patients was sought through a mailed questionnaire or a scripted telephone interview performed in a blinded fashion with patients who did not respond to the questionnaire, followed by the use of WebVS. Patients who were not confirmed to have died and who had no follow-up information (obtained by means of the mailed questionnaire or telephone interview or at least one year of data in WebVS) were considered to be lost to follow-up.

STATISTICAL ANALYSIS

We compared available clinical, historical, myocardial-perfusion SPECT, and outcome data among the patients in each of the five symptom categories. Unadjusted means for continuous variables were compared with use of Student's *t*-test. Categorical variables were compared with use of a chi-square test. We used Bonferroni's test for adjusted pairwise comparisons by multiplying the ordinary, unadjusted pairwise *P* values by the number of comparisons in the family.¹⁴ All reported *P* values are two-sided.

A Cox proportional-hazards regression model¹⁵ was used to evaluate adjusted and unadjusted predictive values for death from cardiac causes and death from any cause according to the symptom category and to assess the incremental prognostic value of dyspnea over other clinical information. Survival was measured from the time of the original stress test. We used the date of last contact for patients who were not known to be deceased to calculate survival in the Cox survival analysis. For the Cox analysis of death from cardiac causes, we regarded deaths from other or unknown causes as censored observations. A significant increase in the global chi-square value after the addition of a variable indicated incremental prognostic value. Kaplan-Meier analysis was used to depict risk-adjusted cumulative survival curves comparing patients with symptoms with those who were asymptomatic at the time of testing.

Study end points were also analyzed in subgroups matched for propensity scores according to methods described elsewhere.¹⁶⁻¹⁸ We defined one subgroup that compared asymptomatic patients with patients with dyspnea and another that compared asymptomatic patients with those with typical angina. Logistic-regression modeling was used to generate a propensity score for having either dyspnea or angina. For this purpose, we used a nonparsimonious model, including all the available clinical variables, demographic variables, and variables associated with myocardial-perfusion SPECT. We applied Cox analysis to compare survival within these propensity-matched subgroups.

RESULTS

A total of 20,572 patients were evaluated for inclusion in the study. The 1735 patients who underwent coronary revascularization within 60 days after testing were excluded, as were 846 patients (4.4 percent) lost to follow-up, resulting in a study population of 17,991 patients, of whom 11,888 (66.1 percent) underwent myocardial-perfusion SPECT with exercise-induced stress and 6103 (33.9 percent) underwent myocardial-perfusion SPECT with vasodilator-induced stress. In 5804 patients studied after 1994, eight-frame gated myocardial-perfusion SPECT was used to assess the left ventricular ejection fraction and end-diastolic volume after stress, as noted above.¹²

Table 1 shows the patients' clinical characteristics and the results of myocardial-perfusion SPECT, according to the symptoms at presentation. The distribution of symptoms at presentation and the distribution of results of myocardial-perfusion SPECT among the patients who were lost to follow-up were very similar to those among patients who were included in the analysis. Among those known to have coronary artery disease, as well as among those not known to have coronary artery disease, patients with dyspnea were older and had a higher rate of left ventricular enlargement on myocardial-perfusion SPECT than did the other four groups of patients. Patients with dyspnea also had higher rates of atrial fibrillation and left ventricular hypertrophy on electrocardiography ($P < 0.05$) (data not shown). Patients with dyspnea had significantly higher rates of diabetes and hypertension than did asymptomatic patients, patients with nonanginal chest pain, and patients with atypical angina. As compared with asymptomatic patients, patients with dyspnea had similar levels of inducible ischemia in

Table 1. Clinical Characteristics and Results of Myocardial-Perfusion SPECT.*

Characteristic or Result	Total No. of Patients	Asymptomatic Patients	Patients with Nonanginal Chest Pain	Atypical Angina	Patients with Typical Angina	Patients with Dyspnea
No known coronary artery disease 12,279						
No. of patients		3818	2917	3589	1267	688
Age (yr)		63±12	62±13	63±13	66±12†	70±13‡
Female sex (%)		32.2‡	51.3	56.6	52.8	59.5
History of diabetes (%)		11.7	10.3	12.1	16.7†	17.6†
History of hypertension (%)		42.3	41.6	49.4	52.4†	56.7†
History of hypercholesterolemia (%)		40.4	41.6	43.5	46.9‡	37.5
Smoker (%)		12.3	13.6	12.3	13.5	13.6
Results of myocardial-perfusion SPECT						
SPECT abnormal during stress (%)		16.7	12.4	15.0	30.1‡	19.4†
Percent myocardium ischemic		2.2±5.0	1.6±4.2	2.0±4.9	4.4±7.6‡	2.4±5.3
Left ventricular enlargement at rest (%)		5.4	4.0	3.9	4.9	8.3‡
Known coronary artery disease 5,712						
No. of patients		1726	843	1571	1169	403
Age (yr)		68±11	68±12	68±12	68±11	73±10‡
Female sex (%)		18.2‡	29.8	35.5	29.6	34.2
History of diabetes (%)		15.8	19.9	19.5	23.8†	26.3†
History of hypertension (%)		44.7	49.0	54.4§	55.1§	56.6§
History of hypercholesterolemia (%)		50.3	52.2	52.7	56.0	44.7‡
Smoker (%)		11.2	10.8	13.1	11.9	13.4
Results of myocardial-perfusion SPECT						
SPECT abnormal during stress (%)		68.8	65.7	63.4	75.9†	79.7†
Percent myocardium ischemic		2.4±1.7	1.7±4.3	2.1±5.1	4.7±7.8‡	2.9±5.7†
Left ventricular enlargement at rest (%)		21.4	20.3	19.7	23.8	44.7‡

* Plus–minus values are means ±SD. P values were adjusted for multiple comparisons.

† P<0.05 for the comparison with patients with no symptoms, those with nonanginal chest pain, and those with atypical angina.

‡ P<0.05 for the comparison with all other groups.

§ P<0.05 for the comparison with patients with no symptoms and those with nonanginal chest pain.

the absence of known coronary artery disease and slightly higher levels in the presence of known heart disease. But in both patients with and those without known heart disease, the level of inducible ischemia among patients with dyspnea was substantially less than that among patients with typical angina.

During a mean (±SD) follow-up of 2.7±1.7 years, 786 patients without apparent coronary artery disease died, 224 of them of cardiac causes, and 720

patients who were known to have coronary artery disease died, 347 of them of cardiac causes. Patients with dyspnea had a substantially higher rate of both death from cardiac causes and death from any cause than those with other or no symptoms at presentation (Table 2). In contrast, patients with typical angina did not have a higher rate of death from cardiac causes or death from any cause than asymptomatic patients (Table 2). Table 3 shows the analysis of dyspnea as a predictor of mortality in vari-

Table 2. Frequency of Adverse Events.

Adverse Event	Total No. of Patients	Asymptomatic Patients	Patients with Nonanginal Chest Pain	Patients with Atypical Angina	Patients with Typical Angina	Patients with Dyspnea
No known coronary artery disease	12,279					
Death from any cause	786	261	154	178	78	115
Annualized rate (%/yr)		2.5	2.0	1.9	2.3	6.2*
Death from cardiac causes	224	55	35	60	32	42
Annualized rate (%/yr)		0.5	0.4	0.6	0.9	2.3*
Known coronary artery disease	5,712					
Death from any cause	720	190	81	178	144	127
Annualized rate (%/yr)		4.1	3.6	4.2	4.6	11.7*
Death from cardiac causes	347	81	41	80	75	70
Annualized rate (%/yr)		1.7	1.8	1.9	2.4	6.4*

* $P < 0.001$ for the difference across the other four groups.

ous clinical subgroups. For each subgroup, dyspnea was associated with a substantially higher rate of both death from cardiac causes and death from any cause.

Dyspnea remained an independent and incremental predictor of both death from cardiac causes and death from any cause on multivariable analysis, after adjustment for the other significant predictors of outcome, for patients with and patients without known coronary artery disease. Figure 1 shows the adjusted Kaplan–Meier estimates of the probability of freedom from death from cardiac causes for each presenting symptom for patients with and those without known coronary artery disease. In patients with dyspnea, the hazard ratios for death from cardiac causes in these multivariable analyses were 1.9 (95 percent confidence interval, 1.5 to 2.4) and 2.9 (95 percent confidence interval, 1.7 to 5.1), respectively. The findings for the adjusted probability of freedom from death from any cause were similar (data not shown). The hazard ratios for this end point were 1.9 (95 percent confidence interval, 1.5 to 2.4) among patients with a known history of coronary artery disease and 1.9 (95 percent confidence interval, 1.3 to 2.6) among patients with no known history of coronary artery disease.

Of 1091 patients with dyspnea, 984 (88 percent) were matched for all available variables with 984 asymptomatic patients. A similar successful matching was performed for patients with typical angina and asymptomatic patients. This propensity analysis also revealed dyspnea, as compared with the absence of symptoms, to be an independent predic-

tor of both death from any cause and death from cardiac causes (Table 4). By contrast, differences in outcome among patients with typical angina as compared with those who were asymptomatic did not achieve statistical significance by propensity analysis (Table 4).

DISCUSSION

In our study, patients with dyspnea, both those with and those without known coronary artery disease, had increased rates of death from cardiac causes and death from any cause. Among the latter, patients with dyspnea had four times the risk of death from cardiac causes of asymptomatic patients and more than twice the risk of patients with typical angina.

One potential explanation for these findings is that dyspnea reflects underlying cardiovascular disease. Along these lines, it is widely assumed that dyspnea can represent ischemia (an anginal equivalent).³ However, in our study, the level of inducible ischemia was similar among patients with dyspnea and asymptomatic patients without known coronary artery disease. Moreover, although patients with known coronary artery disease who reported dyspnea had a higher level of inducible ischemia than asymptomatic patients, the magnitude of the increase was substantially less than that among patients with typical angina. Nevertheless, patients with dyspnea had higher event rates than did patients with angina. Thus, our results do not provide objective evidence that dyspnea was associated with increased risk because it is an anginal equivalent.

Table 3. Annualized Event Rates in Different Clinical Subgroups, According to the Presence or Absence of Dyspnea.

Clinical Subgroup*	No. of Patients	Death from Cardiac Causes			Death from Any Cause		
		No Dyspnea percent	Dyspnea percent	P Value	No Dyspnea percent	Dyspnea percent	P Value
Overall population							
Age							
≤70 yr	11,174	0.4	2.4	<0.001	1.6	4.7	<0.001
>70 yr	6,817	1.8	4.8	<0.001	4.7	10.6	<0.001
Sex							
Female	7,341	0.9	2.9	<0.001	2.7	7.3	0.006
Male	10,650	1.1	4.7	<0.001	2.7	11.8	<0.001
Diabetes							
No	15,304	0.9	3.3	<0.001	2.4	7.4	<0.001
Yes	2,687	1.9	5.7	<0.001	5.1	11.2	<0.001
Smoking history							
No	15,709	1.0	3.7	<0.001	2.7	7.9	<0.001
Yes	2,282	1.0	3.9	<0.001	2.9	10.1	<0.001
Hypertension							
No	9,367	0.9	3.8	<0.001	2.4	8.1	<0.001
Yes	8,624	1.1	3.8	<0.001	3.1	8.3	<0.001
Left ventricular hypertrophy							
No	17,360	1.0	3.7	<0.001	2.7	8.0	<0.001
Yes	631	1.3	6.7	<0.001	4.0	11.9	<0.001
Left ventricular enlargement							
No	15,911	0.7	2.1	<0.001	2.3	6.7	<0.001
Yes	2,080	3.6	8.9	<0.001	6.4	12.8	<0.001
Atrial fibrillation							
No	17,528	1.0	3.8	<0.001	2.6	7.9	<0.001
Yes	463	3.2	4.3	0.434	7.9	12.0	0.04
Q waves							
No	14,874	0.8	3.5	<0.001	2.4	4.5	<0.001
Yes	3,117	2.0	5.1	<0.001	7.9	9.4	<0.001
Heart rate at rest							
Normal	17,463	1.0	3.7	<0.001	2.7	8.0	<0.001
Tachycardia	528	1.8	5.1	0.007	5.5	11.7	<0.001
Stress							
Induced by exercise	11,888	0.4	2.2	<0.001	1.3	3.7	<0.001
Induced by vasodilator	6,103	1.7	5.4	<0.001	5.9	11.7	<0.001
Stressed-induced ischemia							
No	12,949	0.6	2.9	<0.001	2.2	4.3	<0.001
Yes	5,042	2.0	5.8	<0.001	7.0	11.0	<0.001
Myocardial-perfusion SPECT							
Normal	11,474	0.3	2.2	<0.001	1.8	5.7	<0.001
Abnormal	6,517	1.6	6.2	<0.001	4.6	11.0	<0.001
Population undergoing gated myocardial-perfusion SPECT							
Left ventricular ejection fraction							
≥45%	4,952	0.5	1.8	<0.001	2.3	6.4	<0.001
<45%	852	4.6	7.7	0.009	8.7	12.7	0.008
End-diastolic volume of left ventricle							
≤120 ml	4,783	0.5	2.1	<0.001	2.3	7.3	<0.001
>120 ml	1,021	3.3	7.5	<0.001	6.2	11.1	<0.001

* SPECT denotes single-photon-emission computed tomography.

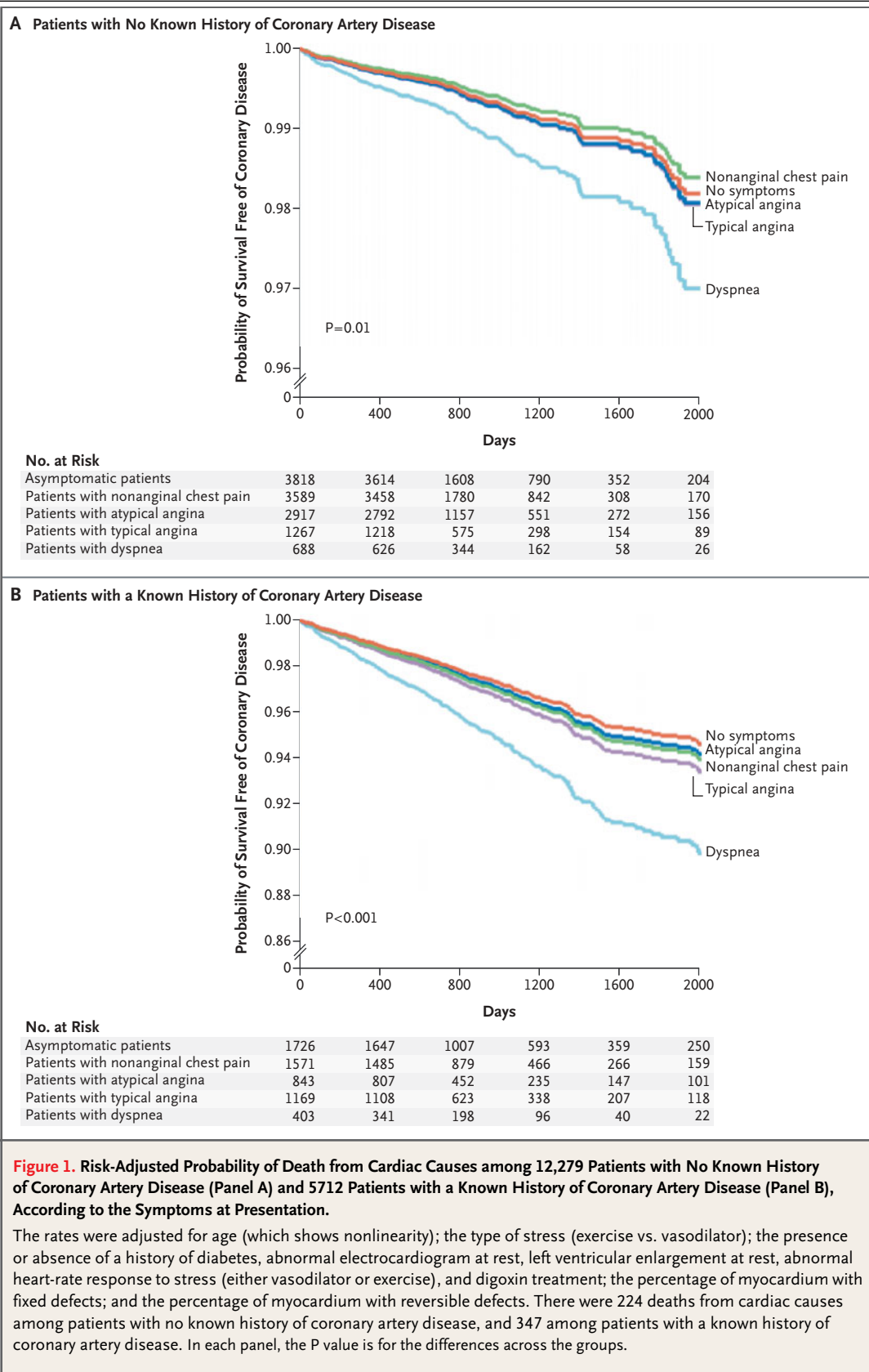


Table 4. Results of Univariable and Multivariable Cox Proportional-Hazards Survival Analysis in Propensity-Matched Population.

Cohort	No. of Patients	Hazard Ratio with Dyspnea or Typical Angina (95% CI)	P Value
Dyspnea and asymptomatic	1968*		
Death from any cause	356		
Univariable		1.39 (1.13–1.72)	0.002
Multivariable†		1.36 (1.10–1.68)	0.005
Death from cardiac causes	149		
Univariable		1.82 (1.30–2.55)	<0.001
Multivariable‡		1.76 (1.25–2.47)	0.001
Typical angina and asymptomatic	3202§		
Death from any cause	323		
Univariable		1.25 (1.01–1.56)	0.05
Multivariable†		1.21 (0.97–1.52)	0.09
Death from cardiac causes	136		
Univariable		1.33 (0.92–1.82)	0.13
Multivariable‡		1.34 (0.95–1.90)	0.09

* A total of 984 patients with dyspnea were matched with 984 asymptomatic patients. CI denotes confidence interval.

† Values were adjusted for age (which was nonlinear); the heart rate at rest; the presence or absence of a known history of coronary artery disease, history of diabetes, abnormal resting electrocardiogram, vasodilator stress, abnormal heart-rate response to stress, preoperative assessment as a reason for testing, and left ventricular enlargement at rest; the percentage of myocardium with fixed defects; and the percentage of myocardium with ischemia.

‡ Values were adjusted for age (which was nonlinear); the heart rate at rest; the presence or absence of a known history of coronary artery disease, history of diabetes, abnormal resting electrocardiogram, vasodilator stress, abnormal heart-rate response to stress, and left ventricular enlargement at rest; the percentage of myocardium with fixed defects, and the percentage of myocardium with ischemia.

§ A total of 1601 patients with typical angina were matched with 1601 asymptomatic patients.

We cannot rule out the possibility, however, that patients with dyspnea had an increased event rate in part because they had “balanced” ischemia undetected by SPECT.

Left ventricular systolic dysfunction is another cardiac abnormality that could explain the association between dyspnea and mortality. We used three separate scintigraphic variables to rule out various relevant cardiac abnormalities: perfusion defects at rest, left ventricular enlargement at rest, and gated left ventricular ejection fraction. Among patients with no abnormalities on each of these assessments (normal function, normal left ventricular volume, or no scarring), there was still a tripling of cardiac event rates among those with dyspnea. The added

prognostic value of dyspnea was most apparent in patients without a perfusion defect and those with a normal left ventricular ejection fraction on myocardial-perfusion SPECT.

We did not have data to assess diastolic function in our patients. Diastolic dysfunction may be an important contributor to heart failure, even in the presence of normal systolic function.^{19,20} Although patients with dyspnea had a greater incidence of both hypertension and left ventricular hypertrophy than other patients, dyspnea was still a significant determinant of outcome after adjustment for these variables.

Among noncardiac disorders, pulmonary disease would be a leading candidate to explain our findings. We did not have information in our database regarding the presence or absence of a history of chronic lung disease, but the relationship between dyspnea and clinical events was nearly identical among our 2282 smokers and 15,709 nonsmokers. Anemia and psychogenic causes of dyspnea were not evaluated.

It is not readily apparent why dyspnea is associated with a poorer prognosis among patients without underlying left ventricular systolic dysfunction after adjustment for the extent of myocardial ischemia, but recent data indicate several possible explanations. Many patients with coronary artery disease have paradoxical peripheral vasoconstriction during exercise rather than the vasodilation that constitutes the normal peripheral thermoregulatory vascular response to exercise.^{21,22} Could impaired heat regulation in patients with peripheral vasoconstriction cause impaired exercise tolerance and sensations of dyspnea? Alternatively, the development of coronary artery disease is associated with inflammatory proteins that can potentially induce somatic symptoms, such as malaise and fatigue.²³ Perhaps a subjective sense of dyspnea can sometimes accompany such somatic symptoms.

There is only a sparse literature concerning the prognostic significance of dyspnea in patients with known or suspected cardiac disease. A few older studies are supportive of the findings of our study.⁴⁻⁷ By contrast, in one recent study,¹⁸ the differences in outcome between asymptomatic patients and patients with dyspnea disappeared after propensity analysis was applied to adjust for differences in patients' characteristics. Comparison of this study to our own is difficult because of differences in exclusion criteria between the two studies, differences in the designation of dyspnea (reported by the

patient or identified by the referring physician), and differences in the variables used for propensity analysis, such as our inclusion of covariates based on myocardial-perfusion SPECT that reflect the percentage of ischemic and scarred myocardium. In addition, experience has demonstrated that differences in “pretest referral biases” (i.e., differences in the clinical characteristics of referral populations)^{24,25} can markedly influence the perceived prognostic accuracy of clinical variables among studies. Accordingly, there is a need to assess the extent to which the prognostic significance of dyspnea is influenced by pretest referral bias across various patient populations.

Our study has a number of limitations. Ventricular function was not assessed in all the patients, since gated myocardial-perfusion SPECT, required for its assessment, was not routinely performed until 1995. We used only a single dichotomous question concerning dyspnea, which did not grade the severity or precipitants of the symptom. By comparison, the American Thoracic Society uses a five-point scale for dyspnea.²⁶ Paradoxically, this limitation underscores the strength of our data, since dichotomously evaluated test variables generally convey less inherent information than variables that are classified in more strata.²⁷ Since we only coded dyspnea among patients without chest pain, we could not evaluate the potential interaction between dyspnea and symptoms of chest pain. We also did not evaluate the reproducibility of the self-reported symptoms. Historical or testing information regarding lung disease would have been useful. In addition, since our study patients represent a referral population for myocardial-perfusion SPECT, caution should be exercised in extrapolating our findings to the general population.

The most important limitation of our study is that, because dyspnea is closely associated with a variety of both cardiovascular and noncardiovascular disorders, it may not have been possible to account for all of the important resulting interactions. However, given the fact that the association between dyspnea and the outcome persisted after extensive assessment of the effect of other factors, it is an important observation that dyspnea as a presenting symptom in patients undergoing noninvasive testing is associated with an increased risk of death from any cause and from cardiac causes, perhaps for other reasons in addition to those commonly recognized.

In our population, asymptomatic patients without dyspnea had a rate of adverse events that was similar to the rate among those with chest pain. Similar findings have been noted by Christopher Jones et al.¹⁸ These observations may be due in part to the tendency to designate as “asymptomatic” patients with known or suspected cardiac disease who have symptoms other than chest pain that have been noted to be associated with an increased incidence of adverse events, such as a sense of exhaustion,²⁸ difficulty in relaxing,²⁹ depressive symptoms,³⁰ and sleeplessness.³¹ For instance, in a follow-up of 5053 male college alumni, those responding “frequently” to the question “how often do you experience exhaustion (except after exercise)” had twice the rate of death from cardiac causes as did other respondents over a 12-year follow-up.²⁸ Given our findings regarding dyspnea, these other somatic symptoms may also deserve further study relative to their prognostic significance in cardiac populations.

Our results indicate that dyspnea is an important symptom among patients with suspected and known coronary artery disease and imply that when dyspnea is present, the likelihood of death from cardiac causes and from any cause is increased. On the basis of our results, it may be appropriate to include an evaluation of dyspnea in the clinical assessment of patients referred for cardiac stress testing. It may also be appropriate to include an evaluation of dyspnea in future efforts to refine algorithms (such as the Duke Treadmill Score) that are used to assess the prognosis of coronary artery disease.

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REFERENCES

1. Morise AP, Jalisi F. Evaluation of pretest and exercise test scores to assess all-cause mortality in unselected patients presenting for exercise testing with symptoms of suspected coronary artery disease. *J Am Coll Cardiol* 2003;42:842-50.
2. Diamond GA, Staniloff HM, Forrester JS, Pollock BH, Swan HJ. Computer-assisted diagnosis in the noninvasive evaluation of patients with suspected coronary artery disease. *J Am Coll Cardiol* 1983;1:444-55.
3. Pepine CJ, Wiener L. Relationship of anginal symptoms to lung mechanics during myocardial ischemia. *Circulation* 1972;46:863-9.
4. Hagman M, Wilhelmsen L. Relationship between dyspnea and chest pain ischemic heart disease. *Acta Med Scand Suppl* 1981;644:16-8.
5. Hagman M, Wilhelmsen L, Wedel H, Pennert K. Risk factors for angina pectoris in a population study of Swedish men. *J Chronic Dis* 1987;40:265-75.
6. Wilhelmsen L, Wedel H, Tibblin G. Multivariate analysis of risk factors for coronary heart disease. *Circulation* 1973;48:950-8.
7. Cook DG, Shaper AG. Breathlessness, lung function and the risk of heart attack. *Eur Heart J* 1988;9:1215-22.
8. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. *N Engl J Med* 1979;300:1350-8.
9. Berman DS, Kiat H, Friedman JD, et al. Separate acquisition rest thallium-201/stress technetium-99m sestamibi dual-isotope myocardial perfusion single-photon emission computed tomography: a clinical validation study. *J Am Coll Cardiol* 1993;22:1455-64.
10. Abidov A, Hachamovitch R, Hayes SW, et al. Prognostic impact of hemodynamic response to adenosine in patients older than age 55 years undergoing vasodilator stress myocardial perfusion study. *Circulation* 2003;107:2894-9.
11. Azarbal B, Hayes SW, Lewin HC, Hachamovitch R, Cohen I, Berman DS. The incremental prognostic value of percentage of heart rate reserve achieved over myocardial perfusion single-photon emission computed tomography in the prediction of cardiac death and all-cause mortality: superiority over 85% of maximal age-predicted heart rate. *J Am Coll Cardiol* 2004;44:423-30.
12. Germano G, Kiat H, Kavanagh PB, et al. Automatic quantification of ejection fraction from gated myocardial perfusion SPECT. *J Nucl Med* 1995;36:2138-47.
13. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* 2003;107:2900-7.
14. Montgomery DC. Design and analysis of experiments. New York: Wiley, 1984.
15. Cox DR. Regression models and life-tables. *J R Stat Soc [B]* 1972;34:187-202.
16. Rubin DB, Thomas N. Matching using estimated propensity scores: relating theory to practice. *Biometrics* 1996;52:249-64.
17. Gum PA, Thamilarasan M, Watanabe J, Blackstone EH, Lauer MS. Aspirin use and all-cause mortality among patients being evaluated for known or suspected coronary artery disease: a propensity analysis. *JAMA* 2001;286:1187-94.
18. Christopher Jones R, 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.
19. Vasan RS, Benjamin EJ, Levy D. Prevalence, clinical features and prognosis of diastolic heart failure: an epidemiologic perspective. *J Am Coll Cardiol* 1995;26:1565-74.
20. Bonow RO, Udelson JE. Left ventricular diastolic dysfunction as a cause of congestive heart failure: mechanisms and management. *Ann Intern Med* 1992;117:502-10.
21. Rozanski A, Qureshi E, Bauman M, Reed G, Pillar G, Diamond GA. Peripheral arterial responses to treadmill exercise among healthy subjects and atherosclerotic patients. *Circulation* 2001;103:2084-9.
22. Qureshi E, Diamond GA, Chouraqi P, et al. Usefulness of finger blood flow during exercise as a marker of functionally significant coronary heart disease. *Am J Cardiol* 2002;90:756-9.
23. Anisman H, Merali Z. Cytokines, stress, and depressive illness. *Brain Behav Immun* 2002;16:513-24.
24. Rozanski A, Diamond GA, Berman D, Forrester JS, Morris D, Swan HJ. The declining specificity of exercise radionuclide ventriculography. *N Engl J Med* 1983;309:518-22.
25. Rozanski A, Diamond GA, Forrester JS, Berman DS, Morris D, Swan HJ. Alternative referent standards for cardiac normality: implications for diagnostic testing. *Ann Intern Med* 1984;101:164-71.
26. Dyspnea — mechanisms, assessment, and management: a consensus statement. American Thoracic Society. *Am J Respir Crit Care Med* 1999;159:321-40.
27. Diamond GA, Hirsch M, Forrester JS, et al. Application of information theory to clinical diagnostic testing: the electrocardiographic stress test. *Circulation* 1981;63:915-21.
28. Cole SR, Kawachi I, Sesso HD, Paffenbarger RS, Lee IM. Sense of exhaustion and coronary heart disease among college alumni. *Am J Cardiol* 1999;84:1401-5.
29. Suadicani P, Hein HO, Gyntelberg F. Are social inequalities as associated with the risk of ischaemic heart disease a result of psychosocial working conditions? *Atherosclerosis* 1993;101:165-75.
30. Rozanski A, Blumenthal JA, Davidson KW, Saab PG, Kubzansky L. The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: the emerging field of behavioral cardiology. *J Am Coll Cardiol* 2005;45:637-51.
31. Leineweber C, Kecklund G, Janszky I, Akerstedt T, Orth-Gomer K. Poor sleep increases the prospective risk for recurrent events in middle-aged women with coronary disease: the Stockholm Female Coronary Risk Study. *J Psychosom Res* 2003;54:121-7.

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