Published in final edited form as:
Am J Cardiol. 2007 June 15; 99(12): 1643–1647. doi:10.1016/j.amjcard.2007.01.041.

Prevalence and Prognosis of Asymptomatic Left Ventricular Diastolic Dysfunction in Ambulatory Patients With Coronary Heart Disease

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Abstract

The association of asymptomatic left ventricular (LV) diastolic dysfunction with cardiovascular outcomes in ambulatory patients with coronary heart disease (CHD) and no history of heart failure (HF) was examined. LV diastolic HF predicts adverse cardiovascular outcomes. However, the prevalence and prognosis of asymptomatic LV diastolic dysfunction in patients with established CHD in the absence of clinical HF is unknown. Six hundred ninety-three patients with stable CHD, normal systolic function (LV ejection fraction ≥50%), and no history of HF were evaluated. Echocardiography was used to classify LV diastolic function, and Cox proportional hazards models were used to evaluate the association of LV diastolic dysfunction with cardiovascular outcomes during 3 years of follow-up. Of 693 subjects with normal systolic function and no history of HF, 455 (66%) had normal LV diastolic function, 166 (24%) had mild LV diastolic dysfunction, and 72 (10%) had moderate to severe LV diastolic dysfunction. After multivariable adjustment, the presence of moderate to severe LV diastolic dysfunction was strongly predictive of incident hospitalization for HF (hazard ratio 6.3, 95% confidence interval 2.4 to 16.1, p = 0.0003) and death from heart disease (HR 3.9, 95% confidence interval 1.0 to 14.8, p = 0.05). In conclusion, moderate to severe LV diastolic dysfunction was present in 10% of patients with stable CHD with normal ejection fraction and no history of HF and predicts subsequent hospitalization for HF and death from heart disease. Patients with asymptomatic LV diastolic dysfunction may benefit from more aggressive therapy to prevent or delay the development of HF.

Left ventricular (LV) diastolic heart failure (HF) accounts for nearly half of all HF diagnoses and is associated with increased morbidity and mortality.[1–3] The prevalence and prognosis of asymptomatic LV diastolic dysfunction is unclear because most studies of the association between LV diastolic dysfunction and adverse outcomes examined patients with clinical HF.[1–3] One previous study examined the association of LV diastolic dysfunction with cardiovascular outcomes in patients without known heart disease,[4] but the prevalence and

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prognosis of asymptomatic LV diastolic dysfunction in outpatients with stable coronary heart disease (CHD) is unknown. We evaluated the prevalence and prognosis of asymptomatic LV diastolic dysfunction in ambulatory patients with CHD with preserved systolic function and no history of HF. We hypothesized that asymptomatic LV diastolic dysfunction would be an independent predictor of adverse cardiovascular outcomes in these patients.

Methods

Patients

Patients were enrolled in the Heart and Soul Study, a prospective cohort study investigating the influence of psychosocial factors on cardiovascular events. Methods were described previously.[5] Administrative databases were used to identify outpatients with documented coronary artery disease at 2 Department of Veterans Affairs medical center databases (San Francisco and Palo Alto, California), 1 university-based medical center (University of California Medical Center–San Francisco), and 9 public health clinics in the Community Health Network of San Francisco, California. Criteria for enrollment included 1 of (1) history of myocardial infarction, (2) angiographic evidence of ≥50% stenosis in ≥1 coronary vessel, (3) previous evidence of exercise-induced ischemia using treadmill electrocardiogram or stress nuclear perfusion imaging, or (4) history of coronary revascularization. Patients were excluded if they deemed themselves unable to walk 1 block, experienced an acute coronary syndrome in the previous 6 months, or were planning to move out of the local area within 3 years.

From September 2000 to December 2002, a total of 1,024 patients were enrolled in the Heart and Soul Study. We excluded 168 who had an LV ejection fraction <50% using echocardiography. We also excluded 51 patients for whom LV diastolic function could not be determined because of non–sinus rhythm, LV pacing, heart rate >100 beats/min, severe mitral valve disease, or technical reasons. This resulted in an analytic sample of 805 patients, of whom 693 had no history of HF. The study protocol was approved by the institutional review boards at each participating site, and all patients provided written informed consent.

Diastolic function

We performed echocardiography in the standard left lateral recumbent and supine positions using a commercially available ultrasound system with harmonic imaging (Acuson Sequoia, Siemens Corp, Mountain View, California). From the standard apical 4-chamber view, spectral Doppler signals of mitral inflow and pulmonary vein flow were obtained according to guidelines of the American Society of Echocardiography.[6] Patterns of LV diastolic dysfunction were based on mitral inflow E/A ratios of peak velocities at early rapid filling (E) and late filling due to atrial contraction (A) and systolic or LV diastolic dominant pulmonary venous flow using velocity time integral. Based on previously published criteria,[4] normal LV diastolic pattern was defined as E/A ratio of 0.75 to 1.5 and systolic dominant pulmonary venous flow. Impaired relaxation pattern (mild LV diastolic dysfunction) was defined as E/A ratio ≤0.75 and systolic dominant pulmonary venous flow. Pseudonormal pattern (moderate LV diastolic dysfunction) was defined as E/A ratio of 0.75 to 1.5 and LV diastolic dominant pulmonary venous flow. Restrictive pattern (advanced LV diastolic dysfunction) was defined as E/A ratio >1.5 and LV diastolic dominant pulmonary venous flow. We did not differentiate between reversible and irreversible restrictive patterns. Because <5% of the study sample had restrictive filling, pseudonormal and restrictive groups were combined for analysis.

Cardiovascular outcomes

We evaluated all-cause mortality, nonfatal myocardial infarction, incident hospitalization for HF, or death from heart disease during 3 years (range 2 to 4) of follow-up. We conducted annual telephone follow-up interviews with patients (or their proxies) to ask about death or

hospitalization for "heart trouble." For any reported event, medical records, electrocardiograms, death certificates, and coroner's reports were retrieved and reviewed by 2 independent and blinded adjudicators. If the adjudicators agreed on the outcome classification, their classification was binding. In the event of disagreement, the adjudicators conferred, reconsidered their classification, and requested consultation from a third blinded adjudicator.

All-cause mortality was determined using review of death certificates. Nonfatal myocardial infarction was defined using standard diagnostic criteria.[7] Death was considered caused by CHD if the patient (1) died during the same hospitalization in which an acute myocardial infarction was documented or (2) experienced sudden CHD death defined as an unexpected otherwise unexplained fatality within 1 hour of the onset of terminal symptoms.

HF was defined as hospitalization for a clinical syndrome involving ≥2 of paroxysmal nocturnal dyspnea, orthopnea, increased jugular venous pressure, pulmonary rales, third heart sound, cardiomegaly on chest x-ray, or pulmonary edema on chest x-ray. These clinical signs and symptoms must have represented a clear change from the normal clinical state of the patient and been accompanied by either failing cardiac output, determined as peripheral hypoperfusion (hypotension in the absence of other causes, such as sepsis or dehydration) or peripheral or pulmonary edema. Supportive documentation of decreased cardiac index, increasing pulmonary capillary wedge pressure, decreasing oxygen saturation, and end-organ hypoperfusion, if available, were included in adjudication.

Other characteristics

Each patient completed a detailed questionnaire that included age, gender, race, medical history, level of physical activity, current smoking, and level of alcohol consumption. Study personnel recorded all current medications and measured height, weight, and blood pressure. Medication categories were categorized using Epocrates Rx (San Mateo, CA). LV ejection fraction was measured quantitatively using the 2-dimensional echocardiography biplane method of discs.[8,9] We defined LV hypertrophy as LV mass index >90 g/m^2 based on the 2-dimensional echocardiography truncated ellipse method.[10] A symptom-limited graded exercise treadmill test was performed, and we used stress echocardiography to seek inducible ischemia, defined as the presence of cardiac wall motion abnormality at peak exercise that was not present at rest. A single cardiologist (NBS) blinded to clinical and laboratory information evaluated all echocardiograms. Total, low-density lipoprotein, and high-density lipoprotein cholesterol were measured from fasting serum samples. Creatinine clearance was determined using 24-hour urine sample.

Statistical analysis

The goal of this study was to examine the association of asymptomatic LV diastolic dysfunction with cardiovascular outcomes. Differences in participant characteristics by category of LV diastolic function were determined using analysis of variance for continuous variables and chi-square tests for dichotomous variables. We used Cox proportional hazard models to evaluate the independent association of LV diastolic dysfunction with cardiovascular events after adjusting for all variables in Table 1. For these analyses, we report hazard ratios (HRs) with 95% confidence intervals (CIs). Analyses were performed using Statistical Analysis Software (version 9, SAS Institute Inc, Cary, North Carolina).

Results

Of 693 patients with LV ejection fraction ≥50% and no history of HF, 455 (66%) had normal LV diastolic function, 166 (24%) had impaired relaxation (mild LV diastolic dysfunction), and 72 (10%) had pseudonormal or restrictive filling (moderate to severe LV diastolic dysfunction).

Compared with patients with normal LV diastolic function, those with LV diastolic dysfunction were older; more likely to have experienced a previous myocardial infarction, stroke, or revascularization; and less likely to smoke (Table 1). Compared with patients with normal LV diastolic function, those with LV diastolic dysfunction had greater LV mass, lower LV ejection fraction, more inducible myocardial ischemia, and lower creatinine clearance (Table 1).

During an average 3 years of follow-up, patients with moderate to severe LV diastolic dysfunction were more likely than those with normal LV diastolic function to be hospitalized for HF (11% vs 3%, p <0.001) and die from heart disease (7% vs 1%, p = 0.01l Table 2). After multivariable adjustment, the presence of moderate to severe LV diastolic dysfunction remained strongly predictive of incident hospitalization for HF (HR 6.3, 95% CI 2.3 to 17.2, p = 0.0003) and death from CHD (HR 3.9, 95% CI 1.0 to 14.8, p = 0.05; Table 3). Asymptomatic LV diastolic dysfunction predicted hospitalization for myocardial infarction in unadjusted, but not adjusted, analyses (Table 3).

Having normal LV diastolic function resulted in an excellent probability of survival free of HF, whereas moderate to severe LV diastolic dysfunction resulted in a significantly decreased probability of survival free of HF. Patients with mild LV diastolic dysfunction were also more likely than those with normal LV diastolic function to be hospitalized for HF (7% vs 3%, p = 0.01) or myocardial infarction (12% vs 5%, p = 0.003). However, mild LV diastolic dysfunction was no longer associated with cardiovascular outcomes after adjustment for potential confounding variables.

Discussion

We found that moderate to severe LV diastolic dysfunction was present in 10% of outpatients with CHD who had no systolic dysfunction or history of HF. The presence of asymptomatic moderate to severe LV diastolic dysfunction predicted a more than sixfold increased risk of incident HF and an almost fourfold increased risk of death from heart disease. The increased risk of cardiovascular events associated with asymptomatic LV diastolic dysfunction was similar to that observed for patients with known HF.[2] Our results highlight the importance of asymptomatic LV diastolic dysfunction and raise the possibility that patients with LV diastolic dysfunction may benefit from more aggressive therapy to prevent or delay the development of clinical HF.

In this study, we sought to define the prevalence of asymptomatic LV diastolic dysfunction in patients with stable CHD and examine the prognosis of LV diastolic dysfunction in patients without systolic dysfunction or history of HF. One previous study examined the association of LV diastolic dysfunction with cardiovascular outcomes in patients without known heart disease,[4] but the prevalence and prognosis of asymptomatic LV diastolic dysfunction in outpatients with stable CHD is unknown. Because patients with CHD are at high risk of developing HF,[11] this group represents a relevant target population for which closer follow-up and earlier interventions to prevent HF might be considered.

We found that asymptomatic moderate to severe LV diastolic dysfunction predicted hospitalization for HF and death from heart disease at rates similar to those observed with clinically overt HF. Because LV diastolic dysfunction did not predict subsequent myocardial infarction, the association of LV diastolic dysfunction with death from heart disease was likely caused by the interim development of HF. We considered the possibility that greater LV mass, lower LV ejection fraction, more inducible ischemia, or lower creatinine clearance might explain the observed association between LV diastolic dysfunction and HF. However, even after adjusting for these factors, the association of LV diastolic dysfunction with HF remained strong.

In addition to the 10% prevalence of moderate to severe LV diastolic dysfunction in our patients, we found a 24% prevalence of mild LV diastolic dysfunction. Thus, the overall prevalence of LV diastolic dysfunction was 34%. Bursi et al[2] found that LV diastolic dysfunction was present in 44% of community-dwelling patients with HF. The lower prevalence of LV diastolic dysfunction in our study is likely explained by our study population, which consists of patients with stable CHD, but no history of HF. Although impaired relaxation predicted subsequent myocardial infarction and death from heart disease in unadjusted analyses, this association was no longer significant after adjusting for potential confounding variables. This indicates that other factors associated with impaired relaxation, such as LV hypertrophy or inducible ischemia, may have been responsible for the increased rate of adverse events. This is supported by higher incidences of LV hypertrophy and inducible ischemia in the impaired-relaxation group compared with normal patients.

American College of Cardiology/American Heart Association guidelines for the evaluation and management of chronic HF recommend specific therapies for each of 4 stages in the evolution of HF.[12] In adults at high risk of HF, but without structural heart disease or symptoms of HF (stage A), the guidelines recommend aggressive risk-factor reduction, including smoking cessation, exercise, and treatment of hypertension. In patients with structural heart disease, but without symptoms of HF (stage B), the guidelines specifically recommend therapy with angiotensin-converting enzyme inhibitors and β blockers. In our study patients with CHD, the presence of asymptomatic LV diastolic dysfunction appeared to differentiate between those with stage A HF (at risk of HF, but without structural heart disease or symptoms of HF) and those with stage B HF (structural heart disease, but without symptoms of HF). Thus, the presence of LV diastolic dysfunction identifies a subgroup of patients who may benefit from more aggressive afterload reduction with angiotensin-converting enzyme inhibitors and β blockers. However, although treatments for asymptomatic systolic dysfunction have been well established, therapies for asymptomatic LV diastolic dysfunction have yet to be evaluated in clinical trials.

Acknowledgments

This work was supported by grants from the Department of Veterans Affairs, Washington, DC; Grant No. R01 HL079235 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland; the American Federation for Aging Research (Paul Beeson Scholars Program), New York, New York; the Robert Wood Johnson Foundation (Faculty Scholars Program), Princeton, New Jersey, the Ischemia Research and Education Foundation; and the Nancy Kirwan Heart Research Fund, San Francisco, California.

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Table 1

Characteristics of 693 patients with stable coronary heart disease, normal ejection fraction, and no history of heart failure

Variable	LV Diastolic Function			p Value
	Normal (n = 455)	Impaired Relaxation (n = 166)	Pseudonormal or Restrictive (n = 72)	
Age (yrs)	65 ± 10	72 ± 9	70 ± 12	<0.0001
Men	373 (82%)	127 (77%)	61 (85%)	0.4
White	261 (57%)	98 (59%)	51 (71%)	0.2
African-American	72 (16%)	98 (59%)	51 (71%)	0.03
Asian	62 (14%)	19 (11%)	7 (10%)	0.7
Other	60 (13%)	28 (17%)	7 (10%)	0.09
Current smoker	88 (19%)	25 (15%)	10 (14%)	0.04
Habitual alcohol use	139 (31%)	50 (30%)	23 (32%)	0.5
Not physically active	159 (35%)	61 (37%)	23 (32%)	0.9
Hypertension	322 (71%)	118 (71%)	52 (72%)	0.1
Diabetes mellitus	110 (24%)	36 (22%)	22 (31%)	0.0001
History of myocardial infarction	208 (46%)	89 (54%)	33 (46%)	0.0002
Stroke	53 (12%)	21 (13%)	12 (17%)	0.001
Coronary revascularization				
Percutaneous	124 (27%)	52 (31%)	48 (68%)	<0.0001
Bypass surgery	178 (39%)	58 (35%)	27 (39%)	0.4
*β*blocker	276 (61%)	67 (40%)	49 (68%)	<0.0001
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	200 (44%)	79 (48%)	37 (51%)	0.005
Statin	290 (64%)	102 (62%)	50 (69%)	0.3
Aspirin	365 (80%)	138 (83%)	57 (79%)	0.8
LV hypertrophy	203 (45%)	95 (59%)	41 (57%)	<0.0001
LV mass index	90.7 ± 20.4	97.8 ± 24.3	92.9 ± 22.2	<0.0001
LV ejection fraction (%)	0.65 ± 0.05	0.64 ± 0.06	0.64 ± 0.07	<0.0001
Inducible myocardial ischemia	63 (15%)	45 (30%)	20 (30%)	<0.0001
Body mass index (kg/m^2)	28.5 ± 5.0	28.2 ± 4.9	28.6 ± 5.8	0.9
Total cholesterol (mg/dl)	179 ± 41	183 ± 41	173 ± 37	0.2
Low-density lipoprotein (mg/dl)	105 ± 34	110 ± 36	98 ± 27	0.04
High-density lipoprotein (mg/dl)	46 ± 14	47 ± 14	48 ± 14	0.5
Systolic blood pressure (mm Hg)	132 ± 21	138 ± 22	134 ± 24	0.05
Diastolic blood pressure (mm Hg)	75 ± 11	76 ± 11	71 ± 11	0.02
Heart rate (beats/min)	66 ± 11	72 ± 13	63 ± 11	<0.0001
Creatinine clearance	87 ± 28	74 ± 26	74 ± 28	<0.0001

Table 2

Outcomes

Variable	Normal (n = 455)	Impaired Relaxation (n = 166)	Pseudonormal or Restrictive (n = 72)	p Value
All-cause mortality	34 (7.5%)	20 (12.0%)	11 (15.3%)	0.05
Heart disease death	5 (1.1%)	6 (3.6%)	5 (6.9%)	0.01
Hospitalization for HF	13 (2.9%)	12 (7.2%)	8 (11.1%)	0.01
Hospitalization for myocardial infarction	21 (4.6%)	19 (11.4%)	8 (11.1%)	0.01

Values expressed as number (percent).

Table 3

Relative rates of cardiovascular outcomes according to the presence of isolated diastolic dysfunction or heart failure

Variable	Normal	Impaired Relaxation HR (95% CI)	p Value	Pseudonormal or Restrictive HR (95% CI)	p Value
Unadjusted					
All-cause mortality	1.0	1.3 (0.8–2.1)	0.3	1.6 (0.8–2.8)	0.1
Heart disease death	1.0	1.5 (0.6–4.1)	0.4	3.3 (1.3–8.7)	0.01
Hospitalization for HF	1.0	2.0 (1.0–3.7)	0.04	3.9 (2.0–7.5)	<0.0001
Hospitalization for myocardial infarction	1.0	2.4 (1.4–4.2)	0.003	2.0 (0.9–4.2)	0.09
Adjusted for all Table 1 variables					
All-cause mortality	1.0	0.7 (0.4–1.3)	0.3	1.2 (0.6–2.4)	0.6
Heart disease death	1.0	1.0 (0.3–3.8)	0.9	3.9 (1.0–14.8)	0.05
Hospitalization for HF	1.0	1.7 (0.7–4.5)	0.3	6.3 (2.4–16.1)	0.0001
Hospitalization for myocardial infarction	1.0	1.7 (0.8–3.7)	0.2	1.3 (0.5–3.2)	0.6