Congestive Heart Failure in Subjects With Normal Versus Reduced Left Ventricular Ejection Fraction

Prevalence and Mortality in a Population-Based Cohort

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OBJECTIVES	The purpose of this study was to assess the relative proportions of normal versus impaired left ventricular (LV) systolic function among persons with congestive heart failure (CHF) in the community and to compare their long-term mortality during follow-up.
BACKGROUND	Several hospital-based investigations have reported that a high proportion of subjects with CHF have normal LV systolic function. The prevalence and prognosis of CHF with normal LV systolic function in the community are not known.
METHODS	We evaluated the echocardiograms of 73 Framingham Heart Study subjects with CHF (33 women, 40 men, mean age 73 years) and 146 age- and gender-matched control subjects (nested case–control study). Impaired LV systolic function was defined as an LV ejection fraction (LVEF) <0.50.
RESULTS	Thirty-seven CHF cases (51%) had a normal LVEF; 36 (49%) had a reduced LVEF. Women predominated in the former group (65%), whereas men constituted 75% of the latter group. During a median follow-up of 6.2 years, CHF cases with normal LVEF experienced an annual mortality of 8.7% versus 3.0% for matched control subjects (adjusted hazards ratio = 4.06, 95% confidence interval 1.61 to 10.26). Congestive heart failure cases with reduced LVEF had an annual mortality of 18.9% versus 4.1% for matched control subjects (adjusted hazards ratio = 4.31, 95% confidence interval 1.98 to 9.36).
CONCLUSIONS	Normal LV systolic function is often found in persons with CHF in the community and is more common in women than in men. Although CHF cases with normal LVEF have a lower mortality risk than cases with reduced LVEF, they have a fourfold mortality risk compared with control subjects who are free of CHF. (J Am Coll Cardiol 1999;33:1948–55) © 1999 by the American College of Cardiology

Congestive heart failure (CHF) is a major public health problem that is associated with markedly diminished survival (1,2). Several studies have reported that a high proportion of patients with CHF have normal left ventricular systolic function (3–6), and they described a better progno-sis for these subjects (7–9) compared with those who have CHF with impaired left ventricular systolic function. These previous reports were hospital-based, used heterogeneous criteria for defining heart failure and reported widely varying prevalence and mortality rates (3–10). The reported proportion of CHF patients with normal left ventricular systolic function has ranged from 13% to 75%, and the reported annual mortality rate has varied from 1.3% to 17.5% (10). The prevalence and prognosis of CHF with normal left ventricular systolic function in the community are not known.

The objectives of this investigation were to assess the relative proportions of normal versus impaired left ventricular systolic function among persons with CHF in a community-based study sample and to examine their long-term mortality.

Abbreviations and Acronyms

CHF = congestive heart failure
CI = confidence interval
LVEF = left ventricular ejection fraction

METHODS

Study sample. The Framingham Heart Study began in 1948 with the enrollment of 5,209 men and women between the ages of 28 and 62 years. In 1971, children of the original study population and the spouses of those children (totaling 5,124) were enrolled in the Framingham Offspring Study. The selection criteria and design of these studies have been described previously (11,12). Participants in these studies were examined at intervals of 2 (original study) or 4 (Offspring Study) years to assess the occurrence of cardiovascular disease. Each examination included a medical history, physical examination, blood pressure measurements, 12-lead electrocardiogram and laboratory tests. Routine two-dimensional echocardiography was performed on study participants starting at the 18th biennial examination of the original cohort and the 3rd Offspring Study examination.

Original Framingham Heart Study subjects who attended the 18th, 19th or 20th biennial examinations (1983 to 1990) and Offspring Study participants who attended the 3rd or 4th examinations (1984 to 1991) constituted the study sample. A total of 123 subjects with CHF were alive at the time of these examinations. A diagnosis of CHF was established by the simultaneous presence of at least two major criteria, or one major plus two minor criteria (13). Of the 123 subjects with CHF, 50 subjects (40%; 22 men and 28 women) were excluded: 15 (12%; 7 men and 8 women) because they did not attend any examination during the study period, 33 (27%) because of unavailable (n = 25; 9 men and 16 women) or inadequate (n = 8; 4 men and 4 women) echocardiograms and 2 others (both men) because the episode of CHF antedated the index examination by more than 15 years. Seventy-three (60%) CHF cases had an available and adequate echocardiogram after the onset of CHF and were eligible for the present investigation.

Study design and definition of covariates. The study was designed as a nested case–control study with a prospective follow-up component. Each of the 73 CHF cases was matched with two control subjects who were of the same age and gender, were free of CHF and had an available and adequate echocardiogram at that examination. These 146 control subjects constituted a comparison group for the CHF subjects for evaluating prognosis. For the purpose of the present study, hypertension was defined as a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg or the use of antihypertensive drugs (14). Blood pressure measures used for ascertainment of hyper-

tension status were readings obtained at the examination immediately before CHF onset. All other covariates were ascertained at the index examination. Criteria for diabetes mellitus, electrocardiographic left ventricular hypertrophy, atrial fibrillation and coronary disease have been described previously (15).

Echocardiographic methods. At the index examinations, all participants routinely underwent M-mode, and two-dimensional echocardiography. All echocardiograms of the eligible participants (73 CHF cases and 146 control subjects) were analyzed by an experienced observer with a randomized sequencing of studies. The observer was blinded to all clinical information regarding the study subjects. For the CHF cases, the first echocardiogram obtained after the date of onset of CHF was selected if multiple echocardiographic studies were available. The observer visually estimated the left ventricular ejection fraction (LVEF) to the nearest 2.5% based on assessment of left ventricular contractile function in multiple echocardiographic views (16). The accuracy and reproducibility of such a visual estimate of ejection fraction has been established in several reports (17–20). For the purposes of this study, CHF subjects were divided into two groups: those with normal left ventricular systolic function (LVEF ≥0.50) and those with impaired left ventricular systolic function (LVEF <0.50); for convenience, these two groups are referred to as "normal-systolic" and "systolic" CHF, respectively. Such a division of the CHF cases resulted in the splitting of the control subjects into two groups. Thus, for systolic CHF cases and for normal-systolic CHF cases we had separate age- and gender-matched comparison groups.

Follow-up. All study subjects were routinely followed for up to 10 years. The primary end point was death due to any cause. The duration of follow-up was defined as the interval from the date of the index examination at which the echocardiogram was obtained to the date of death or the date of last contact. All deaths were reviewed by a panel of three experienced investigators who determined the cause of death by evaluating all pertinent available medical records and by communication with personal physicians and family members. Cardiovascular disease events included coronary heart disease (angina pectoris, coronary insufficiency, myocardial infarction and sudden or nonsudden death attributable to coronary heart disease), congestive heart failure, cerebrovascular disease and peripheral vascular disease. Criteria for cardiovascular and noncardiovascular disease events have been detailed previously (21).

Statistical methods. The proportions of CHF patients with normal versus reduced LVEF were determined from frequency tables, and their 95% confidence intervals (CIs) were calculated. Among the CHF cases, logistic regression analysis (22) was used to examine if select factors were associated with the presence of normal versus reduced LVEF. Survival curves for the two CHF groups and their

age- and gender-matched control subjects were estimated using the Kaplan-Meier product-limit estimator and they were compared using the log-rank test (23). Survival of CHF cases was compared with that of the matched control subjects using Cox proportional hazards regression for matched sets. Among the CHF cases, the influence of normal versus reduced LVEF on survival was examined using Cox proportional hazards regression models. Multivariable models were generated adjusting for covariates with a p value <0.20. The covariates eligible for entry in the final models included gender, age, history of coronary heart disease, history of stroke, atrial fibrillation, left ventricular hypertrophy on the electrocardiogram, diabetes, pulmonary disease, cigarette smoking, valvular disease and systolic and diastolic blood pressure. Duration of CHF was included as a covariate for analyses comparing survival in the two CHF subgroups. A p value <0.05 was considered statistically significant. All analyses were performed utilizing the SAS System (SAS Institute, Cary, North Carolina) procedures LOGISTIC, LIFETEST and PHREG (24).

RESULTS

Prevalence of normal left ventricular ejection fraction among CHF cases. The study sample consisted of 73 CHF cases (40 men, 33 women, mean age 73 years) and 146 age- and gender-matched control subjects (80 men and 66 women). The median duration of CHF at the time of echocardiographic assessment was 2.8 years (range 0.1 to 15 years) and was similar for men and women. Thirty-seven CHF cases (51%, 95% CI 40% to 62%) had normal LVEF, whereas 36 CHF cases (49%, 95% CI 38% to 60%) had reduced LVEF. Of 33 women with CHF in the study sample, only nine (27%; 95% CI 11% to 43%) had reduced LVEF. In contrast, of 40 men with CHF, 27 (67.5%; 95% CI 52% to 82%) had reduced LVEF. The distribution of values of LVEF among CHF cases is depicted in Figure 1. Among control subjects, 136 out of 146 had normal LVEF; of the 10 control subjects with reduced LVEF, eight had a history of prior myocardial infarction.

Clinical features of systolic and normal-systolic CHF. The baseline clinical characteristics of the CHF cases (with normal and reduced LVEF) and their matched control subjects are shown in Table 1. Coronary disease, atrial fibrillation, diabetes, valve disease and electrocardiographic left ventricular hypertrophy were more common in CHF cases than in control subjects. The two CHF groups did not differ with regard to the duration of CHF, smoking habits or alcohol consumption. It is noteworthy that over 40% of normal-systolic CHF cases were taking digoxin without a history of atrial fibrillation.

Among the CHF cases, multiple logistic regression analyses revealed an association of female gender with the presence of a normal LVEF (odds ratio for reduced LVEF 0.25, 95% CI
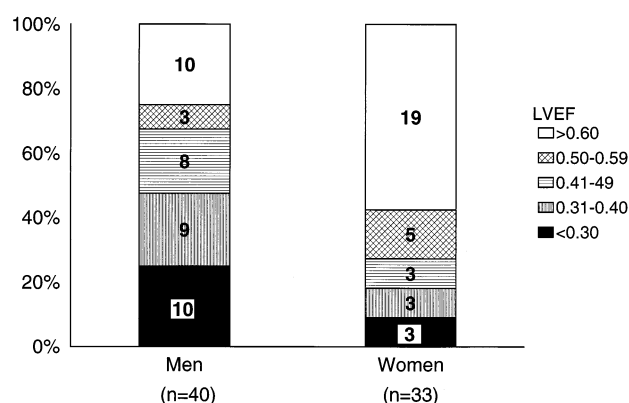

Figure 1. The distribution of left ventricular ejection fraction (LVEF) values among men and women with congestive heart failure is displayed in the figure. Twenty-seven of 40 men (67.5%) had a reduced LVEF (<0.50), compared with only nine of 33 women (27%).

0.08 to 0.77). Prior myocardial infarction was associated with an increased likelihood of having CHF with reduced LVEF (odds ratio 4.6, 95% CI 1.5 to 13.9). Diabetes mellitus, atrial fibrillation and hypertension were not associated with presence or absence of reduced LVEF among CHF cases.

Survival of CHF cases and control subjects. Heart failure cases and matched control subjects were followed for a median duration of 6.2 years (range 0.1 to 10.4 years) after the examination at which the echocardiogram was obtained. The 219 study subjects contributed 1,323 person years of observation. No subject was lost during follow-up, during which time there were 79 deaths. Seventeen of 37 normal-systolic CHF cases (46%) died, compared with 15 of the 74 matched control subjects (20%). Twenty-seven of 36 systolic CHF cases (75%) died, compared with 20 of 72 matched control subjects (28%).

Heart failure cases with reduced LVEF had an annual mortality of 18.9%, compared with an annual mortality of 4.1% in age- and gender-matched control subjects. Heart failure cases with normal LVEF experienced an annual mortality of 8.7%, compared with a mortality rate of 3.0% in matched control subjects. Figures 2 (panels A and B) and 3 (panels A and B) depict the Kaplan-Meier survival plots for the two CHF groups and their respective control subjects. In men and women survival was worse among those with CHF than in age-matched control subjects; this applied to both CHF groups. Survival plots for subjects with normal-systolic CHF compared with those with systolic CHF are presented in Figure 4. The median survival of the normal-systolic CHF group was 7.1 years, compared with a median survival of 4.3 years for the systolic CHF group.

Survival of each CHF group was also compared with that of its control group using analyses for matched sets. Compared with age- and gender-matched control subjects, and adjusting for covariates (Table 2), both normal systolic CHF and systolic CHF were associated with a fourfold

Table 1. Clinical Characteristics of Congestive Heart Failure Cases and Control Subjects*

Variable	CHF with Reduced LVEF (n = 36)	Controls for CHF with Reduced LVEF (n = 72)	CHF with Normal LVEF (n = 37)	Controls for CHF with Normal LVEF (n = 74)
Age (yr)	74 ± 7	74 ± 7	72 ± 9	72 ± 9
Male (%)	75	75	35	35
Coronary disease (%)	72	17	57	15
Myocardial infarction (%)	69	7	24	7
Angina pectoris (%)	36	13	46	14
Diabetes mellitus (%)	22	6	14	3
Atrial fibrillation (%)	36	6	35	5
Smoker (%)†	14	15	14	11
Alcohol intake (oz/week)	2.8 ± 4.6	2.9 ± 3.6	2.2 ± 4.1	2.1 ± 3.4
Valve disease (%)‡	25	6	19	8
Systolic BP (mm Hg)	138 ± 21	144 ± 19	143 ± 24	142 ± 24
Diastolic BP (mm Hg)	75 ± 10	77 ± 11	73 ± 13	76 ± 10
Hypertension (%)	71	54	75	62
ECG LVH (%)	14	4	22	3
Median CHF duration (yr)	3.2	—	2.3	—
Drug treatment (%)				
Beta blockers	11	22	32	21
Diuretics	67	33	68	38
ACE inhibitors	36	2	19	5
Calcium channel blockers	14	1	14	8
Digoxin				
With atrial fibrillation	25	2	29	2
Without atrial fibrillation	32	10	42	7
Nitrates	39	6	46	7

*All variables (other than hypertension status) for CHF cases and control subjects are defined at the time of the index examination at which the echocardiogram was obtained. Hypertension status was determined at the examination immediately preceding the onset of CHF. †Refers to smoking in the year before the index examination. ‡Refers to valve disease defined on the echocardiogram, i.e., moderate or greater degree of valve stenosis or regurgitation.

ACE = angiotensin-converting enzyme; BP = blood pressure; CHF = congestive heart failure; ECG = electrocardiogram; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy.

mortality risk (for normal systolic CHF, hazards ratio = 4.06, 95% CI 1.61 to 10.26; for systolic CHF, hazards ratio = 4.31, 95% CI 1.98 to 9.36).

To evaluate the impact of reduced left ventricular ejection fraction on the survival of CHF cases, several statistical models were explored. In proportional hazards models adjusted only for age, a 51% lower hazard for death was observed in normal-systolic CHF cases compared with systolic CHF cases (Table 3). In view of the striking gender differences in the composition of the two CHF groups and the reported favorable influence of female gender on survival of CHF cases (2,25,26), regression models incorporating gender were studied. In models adjusting for other covariates, female gender was associated with a 61% lower hazard for death; the association of normal-systolic CHF with a lower mortality was no longer statistically significant once gender was incorporated. These results were not affected when we stratified according to the presence or absence of valve disease, or when the variable left ventricular mass/height was forced into the multivariable models. When the effect of LVEF on the mortality risk of CHF cases was examined in multivariable models using LVEF as a continuous variable, a 5% increment in LVEF was associated with a 13% lower hazard of death (hazards ratio = 0.87, 95% CI 0.77 to 0.99; p = 0.039).

To obtain insights into the bias inherent in selecting subjects with adequate echocardiograms, we compared survival of the 73 CHF cases included in the study sample with that of the 33 CHF cases who were excluded because of unavailable or inadequate echocardiograms. Survival was significantly better for CHF cases included in the present investigation (hazard ratio for death = 0.54, p < 0.023) compared with the excluded CHF cases, reflecting the lower mortality risk of our study sample.

The cause of death could be ascertained in 75 of the 79 subjects who died on follow-up. Forty-seven percent of deaths among CHF patients with a normal LVEF, and 60% of deaths among CHF patients with a reduced LVEF were attributed to cardiovascular events. In comparison, cardiovascular diseases accounted for only 36% of deaths among the control subjects.

DISCUSSION

Although the epidemiology of CHF has been well characterized (1,2,27,28), the relative contributions of impaired versus intact LV systolic function to the prevalence of this
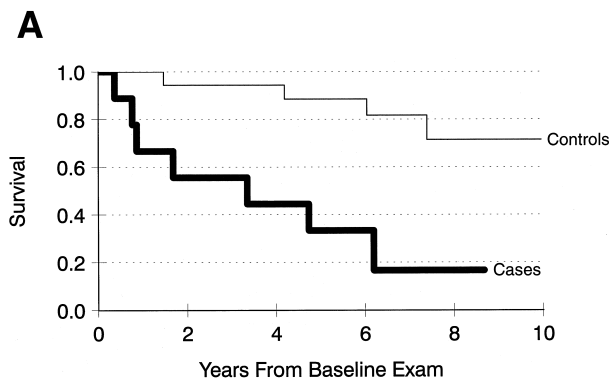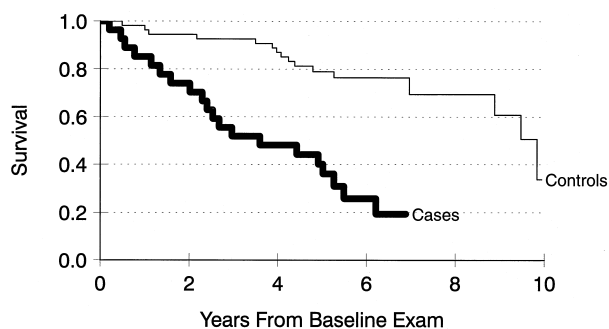
Figure 2. Kaplan-Meier survival plots of control and congestive heart failure (CHF) subjects with reduced left ventricular ejection fraction (LVEF) are displayed. Survival of men **(A)** and women **(B)** with CHF with reduced LVEF was lower than that of age-matched control subjects of the same gender. The overall 5-year survival for CHF cases with reduced LVEF was only 36%, compared with 78% for matched control subjects (log-rank p < 0.0001).

Figure 3. Kaplan-Meier survival plots of control and CHF subjects with normal LVEF are displayed. Survival of men **(A)** and women **(B)** with CHF with normal LVEF was lower than that of age-matched control subjects of the same gender. The overall 5-year survival was 68% for CHF cases with normal LVEF, compared with 82% for matched control subjects (log-rank p < 0.0001). Abbreviations as in Figure 2.

disease and their respective prognoses in the community are not known. Prior investigations of normal-systolic heart failure were hospital-based and suffered from several methodological limitations (10). We used echocardiography to evaluate left ventricular systolic performance in a prevalence cohort of CHF cases to assess the proportion with reduced and normal systolic function and to define their long-term prognoses.

Prevalence and predictors of normal left ventricular ejection fraction among CHF cases. We found that about half the CHF cases in our community-based sample had normal LVEF. Our results confirm and extend to the community prior findings from hospital-based series (3–10), which highlighted the frequent presence of normal left ventricular systolic function among CHF patients. Our findings also concur with estimates from the Helsinki Ageing Study (29) and with a preliminary report from the Cardiovascular Health Study (30).

In the present investigation, prior myocardial infarction was associated with systolic CHF. This observation is consistent with the well recognized adverse impact of myocardial damage on left ventricular contractility. Women with CHF were more likely than men to have a normal
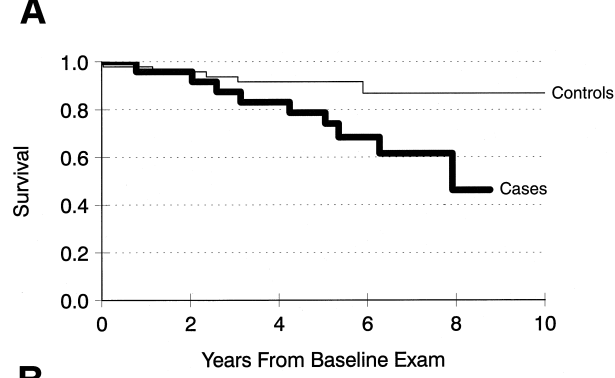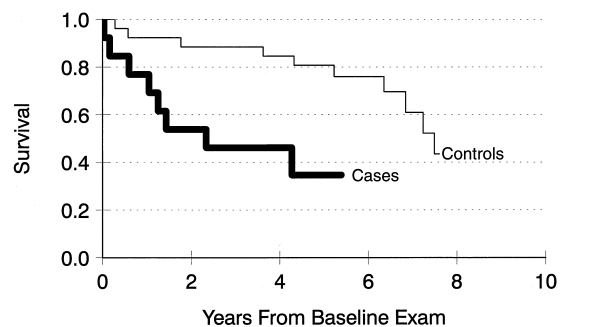
LVEF; among CHF cases, three quarters of the women had normal LVEF compared with one third of men. This finding is consistent with prior reports of a female preponderance among patients with CHF and normal left ventricular systolic function (3–5,31). Female gender has also been consistently associated with higher indexes of ventricular systolic performance in studies of experimental animals
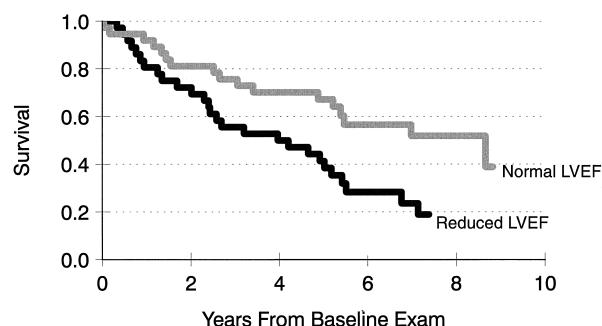

Figure 4. Kaplan-Meier survival plots of CHF patients with normal and reduced LVEF are displayed. The overall survival of CHF subjects with reduced LVEF is worse than that of CHF subjects who have a normal LVEF. This comparison does not account for gender differences in the composition of the two groups. Abbreviations as in Figure 2.

Table 2. Impact of Congestive Heart Failure on Mortality:
Results of Multivariable Cox Proportional Hazards
Regression Models

	Hazard Ratio for Death	95% CI Hazard Ratio	p Value
CHF with reduced LVEF vs. age- and gender-matched controls*	4.31	1.98–9.36	0.0002
CHF with normal LVEF vs. age- and gender-matched controls*	4.06	1.61–10.26	0.003

*Covariates included age, gender, history of coronary disease, diabetes, atrial fibrillation, valve disease, smoking status, systolic blood pressure and pulmonary disease. Variables not included (p ≥ 0.20 in stepwise models) were electrocardiographic left ventricular hypertrophy, stroke and diastolic blood pressure. When left ventricular mass was forced into the stepwise models, the hazard ratio for death was marginally reduced thus: CHF with reduced LVEF: 3.74 (95% CI 1.66 to 8.44); CHF with normal LVEF: 3.71 (95% CI 1.25 to 11.00).
CHF = congestive heart failure; CI = confidence interval; LVEF = left ventricular ejection fraction.

(32,33), healthy human subjects (34), patients with valvular aortic stenosis (35–37) and subjects with hypertension (38,39). Similarly, a preponderance of women has also been noted among elderly patients with hypertensive hypertropic cardiomyopathy (40).

Mortality of subjects with CHF and normal left ventricular ejection fraction. Despite the selection of a healthier sample of CHF cases in the present investigation, mortality of normal-systolic CHF cases was about four times that of age- and gender-matched control subjects without CHF (multivariable model results, Table 2). Nonetheless, mortality risk of this group was only about half that of systolic CHF cases. Due to a small sample size, we were unable to determine definitively whether the better prognosis of normal-systolic CHF cases (compared with systolic CHF cases) was due to a greater proportion of women in this group or if it was related to the preservation of left ventricular contractile function. Among

CHF patients, women, especially those with a nonischemic etiology of heart failure, have been noted to have a better prognosis than men (41).

The prognosis of our normal-systolic CHF cases resembles that reported for CHF patients with preserved left ventricular systolic function in the V-HEFT study (7) but is worse than that reported in another investigation (42). It must be pointed out that our CHF cases were considerably older than patients in the latter report (42). In other hospital-based investigations (43–45) the mortality of CHF cases with a normal LVEF was higher than in our study, in part because they included sicker individuals.

Strengths and limitations. Our study sample was a prevalence cohort of ambulatory subjects with chronic CHF. Such a community-based sample more closely represents the population of patients with chronic CHF who are followed by physicians on an outpatient basis (46). The use of well defined criteria for the diagnosis of CHF, the availability of matched control subjects from the same cohort, the routine nature of the echocardiogram and its blinded assessment, and the regular surveillance of the study sample for the development of morbid events are additional strengths of the present investigation.

Nevertheless, our study has several limitations. Our study sample consisted of prevalent cases who survived for a median of 2.8 years after onset of CHF before receiving an echocardiogram. Clinical correlates and mortality of such a prevalence cohort may differ from those of an incidence cohort of CHF cases (47). Due to the long interval between the onset of CHF and the echocardiographic assessment of left ventricular function, the left ventricular ejection fraction at the time of the index examinations may not represent that at onset of CHF; serial changes and spontaneous fluctuations in left ventricular ejection fraction among CHF subjects have been described (48,49). The exclusion of CHF cases due to nonavailability of an echocardiogram also

Table 3. Impact of Normal Versus Reduced Left Ventricular Ejection Fraction on the Mortality of Congestive Heart Failure Cases: Results of Cox Proportional Hazards Regression Models

Model	Hazard Ratio for Death	95% CI Hazard Ratio	p Value
I. Age-adjusted models			
Age	1.55	1.14–2.11	0.005
CHF with normal LVEF	0.49	0.27–0.91	0.023
II. Models with age and gender			
Age	1.55	1.14–2.11	0.006
Female gender	0.65	0.33–1.28	0.21
CHF with normal LVEF	0.59	0.30–1.16	0.13
III. Covariate*-adjusted models			
Age	1.57	1.10–2.25	0.013
Female gender	0.39	0.18–0.86	0.019
CHF with normal LVEF	0.65	0.31–1.35	0.25

*Covariates included diabetes, smoking status, systolic and diastolic blood pressure and duration of CHF. Hazard rates represent values for increments of 1 standard deviation for age (8 years), for female gender and for presence of CHF with normal LVEF. The hazard rate associated with CHF with normal LVEF changed minimally when left ventricular mass was forced into this model (hazards ratio = 0.66, 95% CI 0.26 to 1.69; p = 0.39). Abbreviations as in Table 2.

constitutes a drawback. The choice of ejection fraction (a load-dependent measure) as an index of left ventricular systolic performance also may be questioned. There is some evidence to suggest that patients with a normal ventricular ejection fraction but with high relative wall thickness may have depressed myocardial contractile function when more sensitive measures of left ventricular performance (such as midwall fractional shortening) are used (50,51). The selection of a partition value of 50% for separating normal from reduced LVEF may be criticized. It is uncertain, for instance, if an LVEF value of 45%, is depressed enough to initiate the maladaptive changes associated with the syndrome of CHF. We chose this partition value because it is the most frequently utilized cut point in published reports for separating normal left ventricular systolic function from systolic dysfunction (10).

Our data on the prognosis of CHF patients should also be interpreted with caution because a majority of patients in the study had CHF onset before 1990. Several reports have underscored the improvement in prognosis of CHF patients with impaired left ventricular systolic function in the period after 1990, in part related to major therapeutic advances (52–56). Last, our study population was elderly and most subjects were white; extrapolation of these findings to other populations or to different age groups may be inappropriate (57).

Clinical implications. The prevalence of CHF is estimated to be from 1% to 3% of the adult population worldwide, with a steep increase to approximately 10% in the elderly (1,2,25,28,58,59). Our study points out that a substantial proportion of ambulatory patients with CHF have normal left ventricular systolic function. The current treatment of patients with CHF who have normal left ventricular systolic function is empirical (10). The substantial burden of this condition and its unfavorable prognosis emphasize the need for controlled clinical trials to define the optimal treatment of these patients.

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