Relation of Disease Pathogenesis and Risk Factors to Heart Failure With Preserved or Reduced Ejection Fraction

Insights From the Framingham Heart Study of the National Heart, Lung, and Blood Institute

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Background—The contributions of risk factors and disease pathogenesis to heart failure with preserved ejection fraction (HFPEF) versus heart failure with reduced ejection fraction (HFREF) have not been fully explored.

Methods and Results—We examined clinical characteristics and risk factors at time of heart failure onset and long-term survival in Framingham Heart Study participants according to left ventricular ejection fraction ≤45% (n=314; 59%) versus >45% (n=220; 41%) and hierarchical causal classification. Heart failure was attributed to coronary heart disease in 278 participants (52%), valvular heart disease in 42 (8%), hypertension in 140 (26%), or other/unknown causes in 74 (14%). Multivariable predictors of HFPEF (versus HFREF) included elevated systolic blood pressure (odds ratio [OR]=1.13 per 10 mm Hg; 95% confidence interval [CI], 1.04 to 1.22), atrial fibrillation (OR=4.23; 95% CI, 2.38 to 7.52), and female sex (OR=2.29; 95% CI, 1.35 to 3.90). Conversely, prior myocardial infarction (OR=0.32; 95% CI, 0.19 to 0.53) and left bundle-branch block QRS morphology (OR=0.21; 95% CI, 0.10 to 0.46) reduced the odds of HFPEF. Long-term prognosis was grim, with a median survival of 2.1 years (5-year mortality rate, 74%), and was equally poor in men and women with HFREF or HFPEF.

Conclusions—Among community patients with new-onset heart failure, there are differences in causes and time-of-onset clinical characteristics between those with HFPEF versus HFREF. In people with HFREF, mortality is increased when coronary heart disease is the underlying cause. These findings suggest that heart failure with reduced left ventricular systolic function and heart failure with preserved left ventricular systolic function are partially distinct entities, with potentially different approaches to early detection and prevention. **(*Circulation*. 2009;119:3070-3077.)**

Key Words: coronary disease ■ epidemiology ■ heart diseases ■ heart failure ■ hypertension ■ mortality ■ ventricles

Individuals with heart failure (HF) are at increased risk for recurrent symptomatic exacerbations resulting in hospitalization or death.[1] The traditional categorization of HF has been according to underlying left ventricular (LV) systolic function based on LV ejection fraction (LVEF).[2,3] Although a substantial proportion of HF cases have preserved LV systolic function, few population-based studies have provided a clinical picture of patients before, during, and after the onset of symptomatic HF with preserved (HFPEF) versus reduced ejection fraction (HFREF).[4] Thus, the risk factors and underlying cardiac conditions antedating HF onset and their relations to LV systolic function have not been fully elucidated in the community.

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Characterization of HF by LVEF and underlying disease cause may enhance our knowledge of pathogenesis and prognosis and thereby promote earlier identification of individuals at increased risk for HF. Although potentially important, the implications of causal factors on disease presentation and outcomes have not been clearly delineated. Previous

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work from the Framingham Heart Study demonstrated that HF can be feasibly categorized by cause as due to (1) coronary heart disease (CHD), (2) valvular heart disease (VHD), (3) hypertensive heart disease, and (4) other/unknown causes with the use of a hierarchical approach.[5] However, the interrelations of preonset HF risk factors, causal factors, LV systolic function, and outcomes have not been explored in the community.

In this study, we examined risk factors, clinical onset characteristics, and outcomes of patients with HF. Our objectives were to examine clinical features before and at the time of HF onset and to determine their associations with LV systolic function at time of HF presentation. We also compared outcomes according to LV functional status and HF cause. We hypothesized that risk factor profiles and survival differ substantially in those with HFPEF versus HFREF, suggesting that these subtypes of HF have distinct pathophysiological mechanisms and outcomes.

Methods

Study Sample

The design and description of the Framingham Heart Study original cohort and offspring cohort have been reported previously.[6,7] All participants have been under continuous surveillance for HF since the inception of the original and offspring cohorts and have undergone periodic examinations. In the present study, we included participants with incident HF occurring between 1981 and 2004 with an evaluation of LV systolic function near the time of their initial HF episode. The study protocol was approved by the institutional review board of the Boston University Medical Center, and all participants provided written informed consent.

Identification of HF

Each original and offspring cohort participant underwent Framingham Heart Study clinic examinations approximately every 2 and 4 years, respectively, during which health history updates, physical examinations, and blood tests were performed routinely. Onset of HF was confirmed by a 3-physician panel using published criteria after examination of all outpatient and hospital records.[8] Preonset clinical data were obtained from the most recent Heart Study clinic visit before HF onset.

Myocardial infarction and acute coronary insufficiency (defined as prolonged ischemic symptoms with new ECG abnormalities in the absence of biomarker elevations indicative of infarction) were adjudicated by 3 physicians after examination of medical records. Occurrence of any atrial fibrillation was determined by examining all available ECGs from clinic, hospital, and outpatient physician visits before (preonset) or on the day of HF onset.

Antecedent Clinical Factors

Data on antecedent clinical variables were obtained from the most recent Framingham Heart Study clinic examination before HF onset. At each clinic visit, cardiovascular history, cigarette smoking, and medications were recorded. Blood pressure was measured by the physician in duplicate with a mercury column sphygmomanometer, and the values were averaged. Participants were examined by a physician for the presence of systolic and/or diastolic heart murmurs. Total and high-density lipoprotein cholesterol levels were determined at most visits, and diabetes was defined by a fasting glucose $\geq$126 mg/dL, nonfasting blood glucose $\geq$200 mg/dL, or use of insulin or oral hypoglycemic medications.

HF Onset Characteristics

The characteristics at HF onset were abstracted primarily from emergency department records at the time of hospitalization. The first-measured blood pressure, heart rate, respiratory rate, and blood tests were ascertained. All ECGs from the date of HF onset were examined. We determined LVEF from the echocardiogram or radionuclide ventriculogram performed at or near the HF onset date. Assessments of LVEF were eligible if performed after HF onset (eg, during hospital admission) or within 1 year before HF onset provided that no intervening myocardial infarction occurred. Intervening ST-elevation and non–ST-elevation myocardial infarctions were determined by detailed review of hospital, physician, and laboratory records. The presence of severe aortic or mitral valve disease (stenosis or regurgitation) at the time of HF onset was determined from the hospital echocardiogram.

Classification of HF

Each incident HF was classified sequentially by (1) LVEF and (2) hierarchical causal classification. HF was categorized as HFREF (LVEF $\leq$45%) or HFPEF (LVEF $>$45%) on the basis of an a priori cutoff value derived from a prior evaluation, which demonstrated a linear increase in mortality risk for ejection fractions (EFs) $\leq$45%.[9] HF cause was classified as CHD if prior myocardial infarction or coronary insufficiency were present. Those without CHD were classified as having VHD if there was severe aortic or mitral valve disease on echocardiography with the use of standard criteria.[10] The majority of participants with a systolic murmur grade $\geq$3/6 or any diastolic murmur by physician auscultation were also found to have significant valvular disease on echocardiography and were therefore also classified as having VHD. HF was attributed to hypertension if the participant did not have CHD or VHD but had Joint National Committee stage II hypertension (blood pressure $\geq$160/100 mm Hg) at a clinic visit or was taking antihypertensive therapy.[11] Those without CHD, VHD, or hypertension were classified as "other or unknown." Therefore, after the classification process described above, HF patients were categorized into 4 mutually exclusive causal groups.

Statistical Analysis

We performed descriptive analyses stratified by (1) LVEF and (2) HF causal classification. Age/sex-adjusted comparisons across causal strata were performed with the use of ANCOVA for continuous covariates and logistic regression for categorical variables. We examined preonset and time-of-onset characteristics after age and sex adjustment as predictors of HFPEF versus HFREF using logistic regression, and we examined multivariable associations using stepwise multiple logistic regression analysis with $P<0.10$ for selection and $P<0.05$ for covariate inclusion.[12] Model calibration was assessed with the use of the Hosmer-Lemeshow statistic ($P>0.05$) and discrimination with the use of the C statistic.

Survival after HF onset was assessed with the use of Cox proportional hazards regression with adjustment for age and sex, stratified by HFREF versus HFPEF. We further examined survival compared with control participants from the Framingham Heart Study, who were matched on age, sex, offspring versus original cohort, examination cycle, and year of study entry, using Kaplan–Meier analysis. Similarly, we compared the effect of cause on survival time with the CHD group as the referent category. The assumption of proportional hazards was confirmed. We examined survival of HF patients stratified by HFREF or HFPEF and the 4 hierarchical disease causes, using Kaplan–Meier analysis. Survival time was defined as the time of HF onset until the occurrence of death and censored on the last visit date for those still alive at the end of follow-up. In the analysis of matched controls, survival time began at the time that the participant attained the same age as the corresponding case with HF. $P<0.05$ was considered statistically significant. All analyses were performed with the use of SAS version 8.2 (Cary, NC).

Results

Among 655 participants with new-onset HF, those without LVEF (n=76) and laboratory test information (n=45) were excluded, leaving 534 participants for the analysis. Baseline

Table 1. Preonset Clinical Characteristics of HF Cohort

Variable	All HF (n=534)	LVEF ≤45% (n=314)	LVEF >45% (n=220)	Unadjusted *P*, LVEF ≤ vs >45%	Age/Sex-Adjusted *P*, LVEF ≤ vs >45%*
Median age (HF onset), y	78	78	80	0.02	0.25
Female, n (%)	269 (50%)	127 (40%)	142 (65%)	<0.001	<0.001
CHD pathogenesis, n (%)	278 (52%)	197 (63%)	81 (37%)	<0.001	<0.001
VHD pathogenesis, n (%)	42 (8%)	17 (5%)	25 (11%)	0.02	0.05
Hypertension pathogenesis, n (%)	140 (26%)	60 (19%)	80 (36%)	<0.001	<0.001
Systolic BP, mm Hg, mean (SD)	144 (24)	144 (24)	145 (24)	0.47	0.98
Diastolic BP, mm Hg, mean (SD)	76 (13)	76 (12)	76 (13)	0.97	0.42
Diabetes mellitus, n (%)	135 (25)	86 (27)	49 (22)	0.46	0.80
Smoking history, n (%)	356 (67)	192 (71)	99 (56)	<0.001	0.20
Prior atrial fibrillation, n (%)†	133 (25)	69 (22)	64 (29)	0.07	0.06
Hypertension treatment, n (%)	307 (57)	177 (56)	130 (59)	0.88	0.84
Total cholesterol, mg/dL, mean (SD)	215 (49)	214 (49)	218 (48)	0.21	0.57
Body mass index, kg/m^2, mean (SD)	27 (5)	27 (5)	27 (5)	0.84	0.62

BP indicates blood pressure.

*Age comparisons adjusted for sex; sex comparisons adjusted for age.

†Atrial fibrillation occurring before HF onset date.

characteristics between excluded individuals and the study cohort did not differ substantially. Participants were followed for 3.2±3.6 years, with a total of 1727 person-years of follow-up accrued. HFREF was present in 314 individuals (59%), and 220 had HFPEF (41%). Individuals with HFPEF were more likely to be women (65% versus 35%; $P<0.001$); those with HFREF were more likely to be men (60% versus 40%; $P<0.001$). The hierarchical approach classified 278 (52%) cases as due to CHD (215 with prior myocardial infarction), 42 (8%) as due to VHD, 140 (26%) as due to hypertension, and 74 (14%) as other or unknown causes.

Characteristics Stratified by LVEF

Pre-HF onset characteristics at the previous Heart Study clinic visit and clinical features at the time of acute HF onset, stratified by LVEF, are shown in Tables 1 and 2, respectively. Those with HFPEF had significantly higher systolic blood pressure ($P=0.04$), whereas resting heart rate and serum

Table 2. Time-of-Onset Clinical Characteristics*

Variable	All HF (n=448)*	LVEF ≤45% (n=270)	LVEF >45% (n=178)	Unadjusted *P*, LVEF ≤ vs >45%	Age/Sex-Adjusted *P*, LVEF ≤ vs >45%†
Median age (HF onset), y	78	77	79	0.02	0.25
Female, n (%)	222 (50)	108 (40)	114 (64)	<0.001	<0.001
Systolic BP, mm Hg, mean (SD)	146 (34)	143 (32)	150 (36)	0.01	0.04
Diastolic BP, mm Hg, mean (SD)	82 (20)	82 (19)	84 (21)	0.25	0.42
Heart rate, bpm, mean (SD)	91 (24)	94 (23)	88 (25)	0.04	0.01
Respiratory rate, /min, mean (SD)	25 (8)	26 (7)	24 (8)	0.19	0.11
Hemoglobin, g/dL, mean (SD)	12.7 (2.1)	12.9 (2.0)	12.4 (2.2)	0.02	0.16
Hematocrit, %, mean (SD)	38.0 (6.3)	38.6 (6.0)	37.1 (6.7)	0.02	0.16
Serum sodium, mEq/L, mean (SD)	138 (5)	138 (5)	139 (5)	0.58	0.50
Serum potassium, mEq/L, mean (SD)	4.3 (0.6)	4.4 (0.6)	4.2 (0.6)	<0.001	<0.001
Serum creatinine, mg/dL, mean (SD)	1.6 (1.2)	1.7 (1.3)	1.5 (0.9)	0.04	0.16
Serum BUN, mg/dL, mean (SD)	29 (17)	30 (18)	28 (15)	0.04	0.06
Rhythm sinus, n (%)‡	293 (66)	193 (73)	100 (56)	<0.001	<0.001
Atrial fibrillation at HF onset, n (%)‡	114 (25)	53 (20)	61 (34)	<0.001	<0.001
QRS duration, ms, mean (SD)‡	108 (29)	112 (31)	103 (27)	0.002	0.03
LBBB, n (%)	67 (15)	54 (20)	13 (7)	<0.001	<0.001
RBBB, n (%)	46 (10)	24 (9)	22 (12)	0.18	0.05

BP indicates blood pressure; BUN, blood urea nitrogen.

*Excludes those with missing covariate data.

†Age comparisons adjusted for sex; sex comparisons adjusted for age.

‡On day of HF onset only; total patients with ECGs available: 266 HFREF, 177 HFPEF.

Table 3. Preonset Clinical Characteristics According to Causal Classification

Variable	CHD (n=278)	VHD (n=42)	Hypertension (n=140)	Other (n=74)	P
Median age (HF onset), y	80	84	83	77	<0.001
Female, n (%)	118 (42)	29 (69)	87 (62)	35 (47)	<0.001
Systolic BP, mm Hg, mean (SD)	143 (25)	143 (25)	150 (24)	140 (21)	0.07
Diastolic BP, mm Hg, mean (SD)	76 (13)	74 (12)	76 (13)	76 (11)	0.91
Diabetes mellitus, n (%)	81 (34)	5 (15)	26 (22)	15 (25)	0.03
Smoking history, n (%)	161 (68)	17 (50)	71 (61)	42 (71)	0.11
Prior atrial fibrillation, n (%)*	61 (22)	14 (33)	41 (29)	17 (23)	0.21
Hypertension treatment, n (%)	165 (59)	17 (40)	90 (64)	27 (36)	<0.001
Total cholesterol, mg/dL, mean (SD)	218 (52)	203 (43)	213 (43)	215 (51)	0.44
Body mass index, kg/m^2, mean (SD)	27.0 (4.7)	27.3 (6.1)	26.5 (5.3)	27.9 (5.7)	0.18
Prior myocardial infarction, n (%)	215 (77)	0 (0)	0 (0)	0 (0)	...

BP indicates blood pressure.
*Atrial fibrillation occurring before HF onset date.

potassium concentration were higher among those with HFREF at HF onset. Sex and causal classification were the only preonset features that differed between HFPEF and HFREF (Table 1). Those with HFREF were more likely to have CHD ($P<0.001$), whereas patients with HFPEF were more likely to have VHD or hypertension ($P=0.05$ and $P<0.001$, respectively). Participants with sinus rhythm and left bundle-branch block (LBBB) QRS morphology at HF onset more frequently had HFREF, whereas atrial fibrillation was more often present with HFPEF (Table 2; all $P<0.001$).

Characteristics Stratified by HF Cause

Demographic features, preonset characteristics, and tests of homogeneity across causal classification strata are shown in Table 3. Those with hypertension were older than those with CHD (hypertension versus CHD, $P=0.03$). Patients with VHD or hypertension were more likely to be women than those with CHD (VHD versus CHD, $P=0.001$; hypertension versus CHD, $P<0.001$). HF cases with CHD were less likely to be women (CHD versus all others, $P<0.001$) but more likely to have diabetes mellitus (CHD versus all others, $P=0.003$) than other causal categories.

Characteristics at time of HF onset are shown by causal class in Table 4. Systolic blood pressure at HF onset was significantly increased in those with a pathogenesis of hypertension (hypertension versus others, $P<0.001$). ECG features were significantly different across causal groups, with sinus rhythm more frequent in those with CHD (CHD versus

Table 4. Time-of-Onset Clinical Characteristics According to Causal Classification

Variable	CHD (n=278)	VHD (n=42)	Hypertension (n=140)	Other (n=74)	P
Systolic BP, mm Hg, mean (SD)	142 (35)	140 (28)	158 (32)	143 (34)	<0.001
Diastolic BP, mm Hg, mean (SD)	81 (21)	82 (15)	86 (19)	81 (19)	0.07
Heart rate, bpm, mean (SD)	90 (23)	97 (25)	92 (27)	97 (26)	0.045
Respiratory rate /min, mean (SD)	26 (8)	24 (7)	25 (7)	25 (6)	0.57
Hemoglobin, g/dL, mean (SD)	12.9 (2.0)	12.4 (1.8)	12.5 (2.3)	12.8 (2.0)	0.24
Hematocrit, %, mean (SD)	38.4 (5.9)	37.0 (5.2)	37.7 (7.1)	38.5 (6.3)	0.49
Serum sodium, mEq/L, mean (SD)	138 (5)	139 (5)	139 (5)	138 (4)	0.05
Serum potassium, mEq/L, mean (SD)	4.3 (0.6)	4.2 (0.4)	4.3 (0.7)	4.4 (0.6)	0.76
Albumin, g/dL, mean (SD)	3.6 (0.6)	3.7 (0.5)	3.5 (0.6)	3.5 (0.7)	0.21
Serum creatinine, mg/dL, mean (SD)	1.6 (1.2)	1.2 (0.4)	1.6 (1.0)	1.6 (1.2)	0.17
Serum BUN, mg/dL, mean (SD)	29.1 (16.8)	27.9 (14.6)	29.9 (17.6)	29.5 (19.1)	0.92
Rhythm sinus, n (%)*	205 (74)	24 (57)	75 (54)	43 (58)	0.002
Rhythm atrial fibrillation, n (%)*	47 (17)	16 (39)	50 (36)	25 (34)	<0.001
QRS duration, ms, mean (SD)	109 (27)	111 (32)	109 (30)	102 (30)	0.41
LBBB, n (%)	31 (11)	9 (21)	33 (24)	10 (14)	0.04
RBBB, n (%)	31 (11)	3 (7)	14 (10)	6 (8)	0.94
LVEF ≤45%, n (%)	197 (71)	17 (40)	60 (43)	40 (54)	<0.001

BP indicates blood pressure; BUN, blood urea nitrogen.
*On day of HF onset only; total patients with ECGs available: 276 CHD, 41 VHD, 138 hypertension, 73 other.

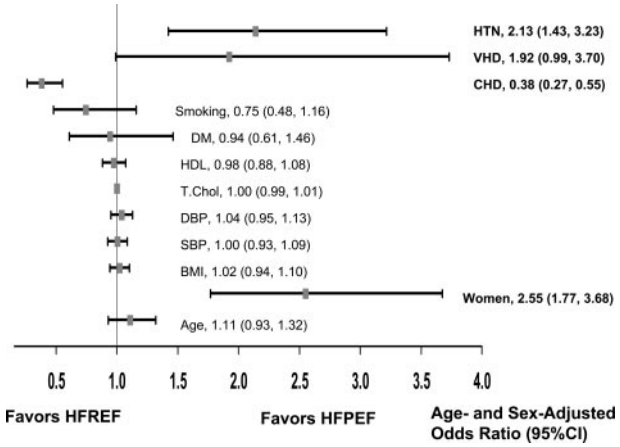

Figure 1. Age/sex-adjusted ORs of HFPEF using preonset factors (OR >1: greater odds of HFPEF). ORs for age are sex adjusted, and ORs for sex are age adjusted. ORs for continuous measures are as follows: age (per 10 years), body mass index (BMI) (per 2 kg/m^2), systolic blood pressure (SBP) (per 10 mm Hg), diastolic blood pressure (DBP) (per 5 mm Hg), total cholesterol (T.Chol) (per 10 mg/dL), and high-density lipoprotein (HDL) cholesterol (per 5 mg/dL). Reference groups for categorical variables are those without the characteristic. DM indicates diabetes mellitus; HTN, hypertension.

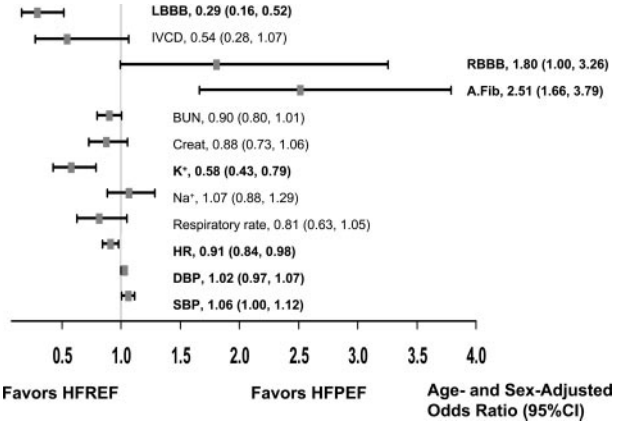

Figure 2. Age/sex-adjusted ORs of HFPEF using characteristics at time of HF onset (OR >1: greater odds of HFPEF). ORs for continuous measures are as follows: heart rate (HR) (per 10 bpm), respiratory rate (per 10 breaths/min), Na^+ (per 5 mEq/L), K^+ (per 1 mEq/L), creatinine (Creat) (per 1 mg/dL), and blood urea nitrogen (BUN) (per 10 mg/dL). Units for systolic (SBP) and diastolic blood pressure (DBP) are described in Figure 1. Reference groups for LBBB and RBBB were those without BBB. For all other categorical variables, reference groups were those without the characteristic. IVCD indicates intraventricular conduction delay; A.Fib, atrial fibrillation.

others, $P<0.001$) and atrial fibrillation present more commonly in those with non-CHD causes (CHD versus others, $P<0.001$). LBBB morphology was more frequent in those with hypertension or VHD causes (hypertension versus CHD, $P<0.001$; VHD versus CHD, $P=0.06$).

Clinical Factors Associated With HFREF or HFPEF

Women were more likely to present with HFPEF, with an age-adjusted odds ratio (OR) of 2.55 (95% confidence interval [CI], 1.77 to 3.68; $P<0.001$). Age at HF onset (sex adjusted) was not associated with HFREF. Other pre-HF onset characteristics at Heart Study clinic visits relating to HFPEF (versus HFREF) adjusted for age and sex are shown in Figure 1. The hierarchical causal classification was associated with HFPEF versus HFREF. Specifically, CHD was associated with reduced odds of HFPEF with an age/sex-adjusted OR of 0.38 (95% CI, 0.27 to 0.55; $P<0.001$). In contrast, those with hypertension were at substantially higher odds of HFPEF with OR of 2.13 (95% CI, 1.43 to 3.23; $P<0.001$). VHD conferred a trend to HFPEF with OR of 1.92 (95% CI, 0.99 to 3.70; $P=0.05$).

Characteristics at HF onset that were associated with HFPEF (versus HFREF) are presented in Figure 2. Atrial fibrillation on the day of HF onset was associated with HFPEF with OR of 2.51 (95% CI, 1.66 to 3.79; $P<0.001$). Wider QRS duration was associated with reduced odds of HFPEF with an OR of 0.92 per 10-ms increment (95% CI, 0.85 to 0.99; $P=0.025$). However, QRS complex morphology was also important; presence of LBBB conferred lower odds of HFPEF (OR=0.29; $P<0.001$), whereas increased odds of HFPEF was present with right bundle-branch block (RBBB) (OR=1.80; $P=0.05$). Higher blood pressure at HF onset was associated with greater odds of HFPEF ($P=0.04$), whereas higher heart rate ($P=0.01$), serum potassium ($P<0.001$), and blood urea nitrogen ($P=0.06$) were associated with HFREF (Figure 2).

Multivariable Analysis

Although female sex conferred a 2.3-fold increased odds of HFPEF, age was not associated with HFPEF (versus HFREF) after multivariable adjustment (Table 5). Higher systolic blood pressure and lower heart rates at HF onset were associated with HFPEF, and prior myocardial infarction predicted a lower probability of HFPEF. The presence of LBBB on the ECG strongly predicted reduced odds of HFPEF (OR=0.21; 95% CI, 0.10 to 0.46; $P<0.001$) after multivariable adjustment. The C statistic for the multivariable model was 0.80, suggesting good discrimination of HFPEF versus HFREF. There was no evidence of lack of model calibration (Hosmer-Lemeshow χ^2 statistic 4.37; $P=0.82$). A model adjusted only for age and sex had considerably lower discriminative ability (C statistic=0.64) than the multivariable model (Table 5).

Table 5. Clinical Characteristics at Time of HF Onset: Multivariable Predictors of HFPEF

Variable	OR (95% CI)	P
Age (per 10-y increment)	1.24 (0.96–1.62)	0.10
Female	2.29 (1.35–3.90)	0.002
Systolic BP (per 10-mm Hg increase)	1.13 (1.04–1.22)	0.004
Heart rate (per 10-bpm increase)	0.81 (0.73–0.90)	<0.001
Potassium concentration (per 1-mEq/L increase)	0.58 (0.38–0.89)	0.01
Atrial fibrillation present at HF onset	4.23 (2.38–7.52)	<0.001
LBBB	0.21 (0.10–0.46)	<0.001
Prior myocardial infarction	0.32 (0.19–0.53)	<0.001

BP indicates blood pressure.

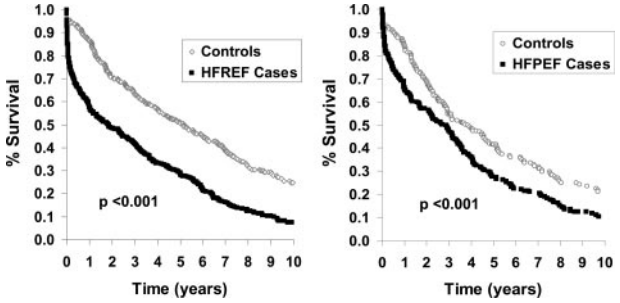

Figure 3. Survival in participants with HFPEF or HFREF compared with controls without HF.

Survival After HF Onset

Long-term prognosis after HF onset was grim, with a median survival of 2.1 years (interquartile range, 0.3 to 5.1 years) and mortality rates of 74% and 95% at 5 and 10 years, respectively. Survival after HF onset did not differ between HFREF and HFPEF, with age- and sex-adjusted HR of 1.14 (95% CI, 0.94 to 1.37; $P=0.18$). In sex-specific analysis, survival did not differ between HFREF and HFPEF in men ($P=0.14$) or women ($P=0.59$). However, participants with HFREF or HFPEF had significantly worsened survival compared with age-, sex-, and cohort-matched controls (both $P<0.001$; Figure 3).

Among those with HFPEF, cause did not differentiate age- and sex-adjusted survival (Figure 4). However, in those with HFREF, CHD pathogenesis conferred greater risk of death than a pathogenesis of VHD or hypertension (Figure 5), with an age- and sex-adjusted HR of 1.36 (95% CI, 1.02 to 1.80; $P=0.037$). When all 4 causes in those with HFREF were compared, there was a tendency for enhanced survival in those with hypertension (age- and sex-adjusted HR=0.74; 95% CI, 0.54 to 1.01; $P=0.06$) or VHD (adjusted HR=0.72; 95% CI, 0.41 to 1.28; $P=0.27$) but no differences for those with other/unknown causes (adjusted HR=1.03; 95% CI, 0.71 to 1.49; $P=0.88$) compared with the CHD group.

Discussion

We found that modifiable cardiovascular disease risk factors, including diabetes, smoking, and hypertension, commonly preceded the onset of both HFREF and HFPEF, but preonset risk factors did not distinguish between HF with preserved or

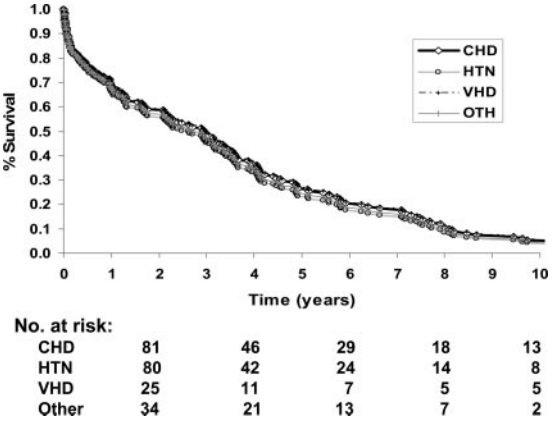

Figure 4. Survival of participants with HFPEF by cause. HTN indicates hypertension; OTH, other.

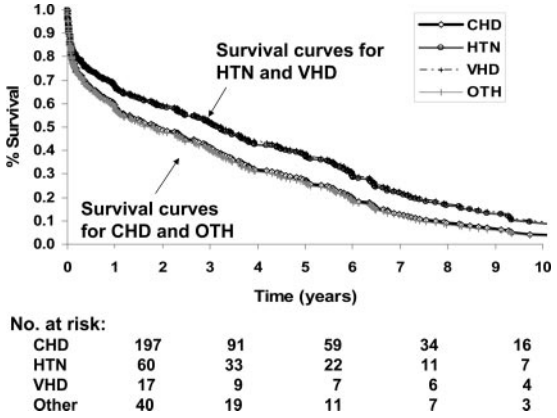

Figure 5. Survival for participants with HFREF by cause. HTN indicates hypertension; OTH, other.

reduced LV systolic function. By examining factors present before and at time of HF onset simultaneously, we found that the major factors conferring increased odds of HFREF were male sex, causal classification (ie, prior myocardial infarction), presence of LBBB, and higher potassium at HF onset. In contrast, HFPEF was more likely in those without a pathogenesis of CHD, women, those with higher time-of-onset systolic blood pressure, and those with atrial fibrillation. Thus, the differing features of HFREF and HFPEF were most apparent at the time of acute onset and were less discernible by risk factors antedating HF. This was exemplified by blood pressure, in which ambulatory pre–HF-onset blood pressure was not elevated among those with hypertension but was increased and perhaps "unmasked" at the onset of acute HF.

In addition, we found worsened survival in those with HF with LV systolic dysfunction or preserved EF compared with controls without HF. However, survival was comparable in those with HF and preserved or reduced EFs. Our findings seemingly contrast with an earlier smaller report from Framingham of worse prognosis with HFREF.[3] The different findings in our present report may be due to (1) the larger sample size in this study (eg, 534 versus 73 HF cases),[3] (2) recent improvement in relative survival of HFREF,[13] or (3) LV function assessment that occurred ≈2 years after HF onset in the prior study, which may have introduced conditional survival bias.[3] In contrast, in the present analysis LV function was assessed during the acute HF presentation. For HFREF, those with hypertension or VHD fared better than those with CHD or other/unknown causes. However, outcomes for HFPEF were uniform across causal categories.

In prior studies of HF prognosis, the presence of LV systolic dysfunction had no effect on survival[14] or conferred marginally worse prognosis[15] than preserved EFs. Some recommend that HF should be classified pathophysiologically or by the underlying disease cause rather than LVEF because the latter is continuously distributed with HF symptoms possible at any EF.[5,16] The effects of ischemic or nonischemic HF causes on outcome have not been well studied in the community. In tertiary care referral samples with cardiomyopathy, angiographically identified coronary disease was associated with higher mortality; however, such patients were

highly selected.[17,18] Randomized trial data have reported conflicting results. In Studies of Left Ventricular Dysfunction (SOLVD), an ischemic cause did not influence survival,[19] whereas other trials suggest worse outcome in those with ischemic pathogenesis.[20] A Swedish study of patients aged ≤65 years found higher mortality in those with ischemic heart disease,[21] but in a population-based study of HF patients of all ages, prior myocardial infarction was not a multivariate predictor of mortality.[1]

Our study suggests that both LV systolic function and disease pathogenesis are important given the heightened mortality risk in those with HFREF and CHD (Figure 5). This study extends the existing literature[22] by demonstrating that causal classification and onset-related clinical factors are predictors of HFPEF versus HFREF and by examining long-term survival according to a hierarchical HF classification. Among the predictors, atrial fibrillation at HF onset was associated with HFPEF. Atrial fibrillation may trigger diastolic HF via loss of the atrial contribution to LV filling and shortening of diastolic filling time.[23] In addition, we found that QRS duration[24,25] and the morphology of the QRS complex were of importance. In particular, the presence of LBBB was associated with HFREF, whereas RBBB was associated with HFPEF.

The interrelationship between disease pathogenesis and systolic versus diastolic HF and their joint effects on outcome demonstrated in our study suggest that disease pathogenesis is an important facet of HF, providing further understanding of risk factors and outcomes in HF. The association of pathogenesis with systolic or diastolic HF lends further support to the premise that HFREF and HFPEF are pathophysiologically disparate entities. Although we found factors strongly associated with HFREF or HFPEF, we do not propose that our statistical model should replace imaging to determine presence of preserved LV function or systolic dysfunction. However, many HF patients hospitalized in the community do not undergo LV function evaluation,[2,22] and the model may provide early clues to the diagnosis of HFPEF versus HFREF. The hierarchical classification of HF proposed in this study emulates the clinical practice of identifying the potential contributions of ischemic, valvular, and hypertensive heart disease in HF patients and is potentially useful because of its simplicity, clinical relevance, and applicability in other settings. Thus, classification of HF on the basis of EF and pathogenesis provides a foundation for future studies on risk and prevention of subtypes of HF.

A limitation of our study is that although we classified HF patients into common causal categories, we did not further stratify the "other/unknown" group, which may have been composed of rarer disease causes including familial and idiopathic cardiomyopathies. Alternatively, there may have been unrecognized coronary, valvular, or hypertensive disease in these individuals, which were not captured. Evaluation of LV function in some cases was not performed at the time of HF onset; therefore, we did not utilize LV function data if interim myocardial infarction occurred between HF hospitalization and performance of echocardiography. We excluded participants who did not have echocardiography performed; however, the rate of imaging was high compared with other community-based studies, and, additionally, patients excluded on this basis were comparable to the overall cohort. To enhance specificity, we defined valvular and hypertensive HF causes using stringent criteria (eg, VHD did not include moderate valve disease and hypertension did not include stage I hypertension). However, this would not have affected the finding of worsened survival in those with CHD compared with non-CHD causes in HFREF. Finally, our study was composed of participants who were primarily white with access to medical care; the generalizability of our findings to nonwhite patients and those with limited healthcare access could not be determined.

In conclusion, causal classification may help to reduce syndromic heterogeneity, providing a disease-oriented approach to patients with HF. Blood pressure, prior coronary disease, and clinical factors including ECG features may provide insights into pathogenesis and underlying cardiac function at time of HF onset. Furthermore, differences in prognosis emerge when HF is stratified by LVEF and HF cause. These findings advance understanding of HF with reduced versus preserved LV systolic function and may provide insight into approaches to earlier detection and prevention.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Few population-based studies have provided a detailed comparison of clinical characteristics and survival of participants with symptomatic heart failure with preserved (HFPEF) versus reduced ejection fraction (HFREF). In this study, we examined risk factors, clinical onset characteristics, and outcomes of patients with HFPEF and HFREF in the Framingham Heart Study. We found that preexisting cardiovascular disease risk factors, including diabetes mellitus, smoking, and hypertension, commonly preceded the onset of both HFREF and HFPEF and that these preonset risk factors alone did not distinguish between HFPEF and HFREF. In contrast, clinical features at the time of acute heart failure onset differentiated between a preserved and a reduced ejection fraction. The major factors conferring increased odds of HFREF versus HFPEF included male sex, prior myocardial infarction, or coronary heart disease and left bundle-branch block. Survival was reduced in those with HFPEF and HFREF compared with controls without heart failure, and mortality was increased when coronary heart disease was the underlying cause in those with HFREF. These findings suggest that HFPEF and HFREF are partially distinct entities, with potentially different approaches to early detection and prevention. Characterization of heart failure by left ventricular ejection fraction and underlying disease cause enhances our knowledge of heart failure pathogenesis and prognosis and may lead to earlier identification of individuals at increased risk for heart failure and its dire consequences.