Longitudinal Changes in Ejection Fraction in Heart Failure Patients With Preserved and Reduced Ejection Fraction

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Background—Heart failure (HF) can occur in patients with preserved (HFpEF, EF≥50%) or reduced (HFrEF, EF<50%) ejection fraction (EF), but changes in EF after HF diagnosis are not well described.

Methods and Results—Among a community cohort of incident HF patients diagnosed from 1984 to 2009 in Olmsted County, Minnesota, we obtained all EFs assessed by echocardiography from initial HF diagnosis until death or last follow-up through March 2010. Mixed effects models fit a unique linear regression line for each person using serial EF data. Compiled results allowed estimates of the change in EF over time in HFpEF and HFrEF. Among 1233 HF patients (48.3% male, mean age 75.0 years, mean follow-up 5.1 years), 559 (45.3%) had HFpEF at diagnosis. In HFpEF, on average, EF decreased by 5.8% over 5 years (*P*<0.001) with greater declines in older individuals and those with coronary disease. Conversely, EF increased in HFrEF (average increase 6.9% over 5 years, *P*<0.001). Greater increases were noted in women, younger patients, individuals without coronary disease, and those treated with evidence-based medications. Overall, 39% of HFpEF patients had an EF<50% and 39% of HFrEF patients had an EF≥50% at some point after diagnosis. Decreases in EF over time were associated with reduced survival whereas increases in EF were associated with improved survival.

Conclusions—These data suggest that progressive contractile dysfunction may contribute to the pathophysiology of HFpEF. Prospective longitudinal studies are needed to confirm these observations and establish the mechanism and clinical relevance of decline in EF over time in HFpEF.   (***Circ Heart Fail.*** 2012;5:720-726.)

Key Words: heart failure ■ echocardiography ■ ejection fraction ■ community ■ longitudinal

Heart failure (HF) is a major worldwide public health issue, and a substantial driver of hospital admissions and resource utilization in the United States. It is a clinically defined syndrome, and can occur in patients with preserved (HFpEF) or reduced (HFrEF) left ventricular ejection fraction (EF).

Clinical Perspective on p 726

Although patients with HFpEF and HFrEF can experience similar clinical signs and symptoms, there is an ongoing debate as to whether these are separate pathophysiological entities. There is mounting evidence to support the fact that they are distinct diseases. HFpEF and HFrEF tend to occur in different patient populations, as HFpEF patients are more likely to be women and older.[1,2] Furthermore, they respond differently to therapies such as angiotensin receptor blockers (ARB), which have been proven to improve outcomes in HFrEF but not HFpEF.[3,4] However, further information about the natural history and progression of these diseases, particularly HFpEF, is needed to better understand their pathophysiology and potential therapeutic approach.

Although patients are often classified as HFpEF or HFrEF on the basis of an EF assessment at HF diagnosis, little is known about changes in EF that occur over time in patients with HF. Clinical trials have demonstrated an improvement in EF in some patients with HFrEF in response to medical therapies such as β blockers.[5,6] However, follow-up in these patients is often limited, and there have been no data on the change in EF over time in patients with HFpEF.

To address these gaps in knowledge, we examined patterns of longitudinal change in EF among a cohort of incident, community HF patients from Olmsted County, MN. Further, we sought to determine whether changes in EF had prognostic implications in HFpEF and HFrEF.

Methods

Study Design

This is a cohort study conducted in Olmsted County, Minnesota. The population in the county was estimated at 145 769 (2011 US Census); 51% were female and 87% white. Population-based research is possible in Olmsted County as the county is relatively

isolated from other centers, and there are few providers, the largest of which is the Mayo Clinic. Medical records from all sources of care for Olmsted County residents are extensively indexed and linked via the Rochester Epidemiology Project.[7] This framework allows patients to be followed passively using their medical record, provided they have provided Minnesota Research Authorization (>97% of residents historically provide this).

Patient Identification

Olmsted County residents with a potential HF diagnosis from 1984 to 2009 were identified by International Classification of Diseases, ninth revision (ICD9) code 428 HF. Codes are assigned based on physician diagnoses during outpatient visits or at hospital discharge. The index date was defined as the first evidence of HF in the medical record. Patients with a diagnosis of HF before the study period were excluded. From all patients with ICD9 code 428, a random subset was selected to undergo validation and data abstraction. Experienced nurse abstractors reviewed records to ensure that each met Framingham criteria[8] and had a physician's diagnosis of HF. When this method was used previously, the interabstractor agreement was 100%.[9]

Echocardiography

All echocardiograms in Olmsted County through March 2010 were performed at the Mayo Clinic; no other providers offered these services. For each patient, all echocardiograms obtained from the time of HF diagnosis until death or last follow-up were obtained from the Mayo Clinic database. Patients were included in the analysis if they had an echocardiogram with EF measurement within 60 days pre- and 90 days postHF diagnosis. Left ventricular end diastolic dimension (LVEDD) was measured by 2-dimensional echocardiography or M-mode. The Mayo approach to EF assessment is based on the echocardiographer's collation of multiple methods of EF measurement (M-mode or 2-dimensional echocardiography using the Quinones formula from the parasternal views or by the quantitative 2-dimensional biplane volumetric Simpson method from 4- and 2-chamber views)[10–12] into an EF assessment quoted in the final impressions. The final EF assessment is rendered by the echocardiologist and may be based on any 1 of these methods or on a visual estimate that incorporates individual methods and any limitations which alters their validity. The mean EF in a population was similar, whether obtained by M-mode, biplane Simpsons, or visual-estimation methods.[13] Preserved systolic function was defined as an EF≥50%.[2]

Patient Baseline Characteristics

Baseline characteristics were abstracted from the medical record. Physician's diagnosis was used to define hyperlipidemia, chronic obstructive pulmonary disease, and cerebrovascular disease. Smoking status was classified as current or prior/never. Hypertension was defined by a physician diagnosis of hypertension or systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg. Diabetes mellitus was defined by fasting blood glucose levels or use of insulin or oral hypoglycemic medications.[14] Myocardial infarction (MI) before HF diagnosis was defined using standard epidemiological criteria.[15] MI occurring after HF diagnosis was identified using hospitalization ICD9 code 410. Coronary artery disease (CAD) was defined as a prior history of MI, percutaneous coronary intervention, or coronary artery bypass grafting. Body mass index was calculated using the first outpatient height recorded and weight at HF diagnosis. Laboratory values closest to the time of HF diagnosis (and within 1 year) including hemoglobin and creatinine were obtained. Anemia was defined as hemoglobin <12 mg/dL in women and <13 mg/dL in men. Glomerular filtration rate was estimated using the Modification of Diet in Renal Disease equation.[16] The degree of comorbidity was assessed using the Charlson Comorbidity Index.[17] Records were made on whether patients were prescribed β blockers, angiotensin-converting enzyme inhibitors (ACE-I), or ARB at the time of initial HF diagnosis.

Death

Mortality follow-up was via the medical record through March 2010. In addition to deaths noted in clinical care, the Mayo Clinic registration office records obituaries and local death notices. Death data are also obtained quarterly from the State of Minnesota Department of Vital and Health Statistics.

Statistical Analysis

Baseline clinical variables are presented as means with standard deviations, medians with 25th and 75th percentiles (if distribution skewed), or frequencies. Characteristics between groups were compared using t tests for continuous variables and χ^2 for categorical variables. Linear mixed effects regression models that fit a linear regression line for each person were used to assess the longitudinal change of EF. Results were compiled for the cohort to obtain estimates of the change in EF over time. (Please see online-only Data Supplement Methods for further details of the modeling approach used.) All results are presented categorically for ease of interpretation, though age and LVEDD were included as continuous variables in the model. To evaluate the prognostic significance of changes in EF over time, EF was evaluated as a time-dependent covariate using Cox proportional hazard regression models. Separate models were analyzed for patients with HFpEF and HFrEF. Missing data were minimal (≤3% per variable) with the exception of LVEDD (32% missing). Analysis was performed using SAS Version 9.2.1 (Cary, North Carolina). A P value <0.05 was used as the level of significance.

Results

In total, 1233 incident HF patients had EF measured at diagnosis and were included in the analysis. An additional 606 patients had incident HF but did not have an echocardiogram within the specified window surrounding HF diagnosis and thus were excluded. Patients without an echocardiogram were older (79.0 versus 75.0 years, P<0.001) and more frequently female (59.9% versus 51.7%, P=0.001), but had similar frequencies of hypertension, CAD, and diabetes mellitus. The EF quoted in the final impressions of the report was obtained by visual estimate (62%), parasternal 2-dimensional (21%), or M-mode (15%) measurements using Quiñones formula and Simpson's biplane (2%).

EF at initial diagnosis followed a bimodal distribution, with a predominance of preserved EF in women (Figure 1). In total, 559 patients (45.3%) had HFpEF at diagnosis (Table 1). Patients with HFpEF were older and more frequently anemic, but had a lower prevalence of prior smoking, MI, and diabetes mellitus compared with HFrEF patients. During a mean follow-up duration of 5.1 years, 935 (75.8%) patients died, and thus had their entire lifespan after diagnosis captured. During follow-up, <2% of the cohort emigrated away from the community.
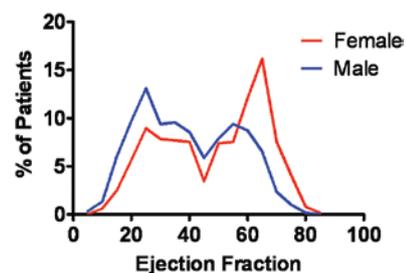

Figure 1. Distribution of ejection fraction (EF) at baseline. The distribution of EF (%) at incident heart failure (HF) diagnosis is shown for the 1233 HF patients.

Table 1.   Baseline Patient Characteristics

	N Missing	Overall (n=1233)	HFpEF (n=559)	HFrEF (n=674)
Age, y	—	75.0 (13.03)	77.2 (12.28)	73.2 (13.36)*
Men	—	596 (48.3)	209 (37.4)	387 (57.4)*
LVEDD, mm‡	398	53 (47–59)	48 (44–53)	57 (52–64)*
Risk factors and comorbidities				
Hypertension	—	910 (73.8)	426 (76.2)	484 (71.8)
Current smoker	7	189 (15.4)	57 (10.2)	132 (19.7)*
Hyperlipidemia	—	615 (49.9)	276 (49.4)	339 (50.3)
Diabetes mellitus	1	273 (22.2)	108 (19.4)	165 (24.5)†
Body mass index, kg/m²	—	27.7 (7.11)	27.8 (7.35)	27.5 (6.91)
Prior MI	1	251 (20.4)	78 (14.0)	173 (25.7)*
CAD	1	361 (29.3)	128 (22.9)	233 (34.6)*
COPD	—	274 (22.2)	133 (23.8)	141 (20.9)
Cerebrovascular disease	—	277 (22.5)	117 (20.9)	160 (23.7)
Anemia	38	530 (44.4)	261 (48.2)	269 (41.2)†
Estimated GFR, mL/min	17	54.2 (20.05)	54.2 (20.03)	54.2 (20.08)
Charlson Index ≥3	2	504 (40.9)	219 (39.3)	285 (42.3)
No. of echocardiograms	—	3.5 (3.3)	3.3 (3.0)	3.6 (3.6)

HFpEF indicates heart failure in patients with preserved ejection fraction; HFrEF, heart failure in patients with reduced ejection fraction; LVEDD, left ventricular end diastolic dimension; MI, myocardial infarction; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate.

*P<0.001 compared with HFpEF.

†P<0.05 compared with HFpEF.

‡LVEDD is listed as median (25th–75th percentile) while all others are listed as N(%) or mean (standard deviation).

The number of echocardiograms per person after HF diagnosis ranged from 1 to 30, with a median of 2 (Figure 2). As compared with patients with ≥3 echocardiograms, those with 1 or 2 echocardiograms were older (79.3 versus 70.4 years, P<0.001), more frequently female (56.8% versus 46.1%, P<0.001), equally likely to have hypertension and CAD but less likely to have diabetes mellitus (19.2% versus 25.3%, P=0.011). The number of subsequent echocardiograms was similar in patients with an initial diagnosis of HFpEF or HFrEF. The mean time from initial to final EF measurement
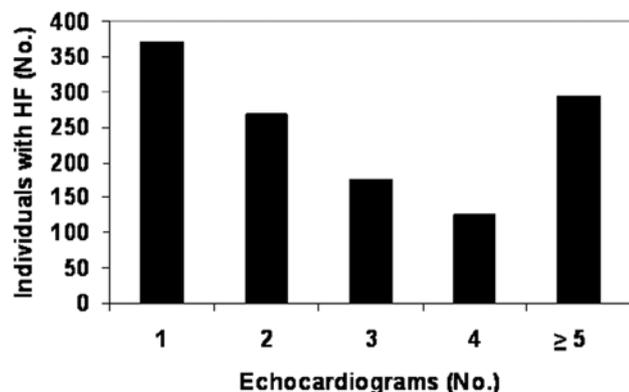

Figure 2. Number of echocardiograms per person after heart failure (HF) diagnosis. The number of echocardiograms per individual from HF diagnosis until death or last follow-up are shown.

was 3.1 years, and was similar in those with HFpEF (3.0 years) and HFrEF (3.2 years, P=0.39).

Temporal Change in EF: HFpEF

In HFpEF, EF averaged 59.4% at diagnosis and was higher in women, elderly patients, and those with small LVEDD (Table 2). EF decreased over time with greater decreases noted in those who were older at diagnosis and those who had CAD (Table 2 and Figure 3, Figure in the online-only Data Supplement). The pattern of change in EF over time was statistically different in HFpEF versus HFrEF (P value for interaction <0.001). In HFpEF, the change in EF over time did not differ by sex, according to baseline LVEDD, or use of medications at diagnosis. Only a small number of patients (n=36) had an MI after HF diagnosis. Excluding these patients from analysis, the decline in EF for the HFpEF population was similar (estimated 5.5% decline over 5 years). The decline in EF over time was statistically significant both in patients with an EF of 50% to 69% and ≥70% at diagnosis. To ensure that changes in the method used to measure EF over time did not impact results, a sensitivity analysis was performed restricting to patients who had EF assessments using methods other than visual estimation and the results were similar for both HFpEF and HFrEF (data not shown).

Table 2.   Change in Ejection Fraction Over Time: HFpEF

	Estimated Mean EF at HF Diagnosis (95% CI)	Estimated Change in EF Over 5 y (95% CI)
Overall (n=559)	59.4 (58.6, 60.2)	−5.8 (−7.3, −4.2) P<0.001
Sex		
Men (n=209)	56.7 (55.5, 57.9)	−6.0 (−8.2, −3.7)
Women (n=350)	61.1 (60.1, 62.0) *P<0.001	−5.6 (−7.7, −3.5) *P=0.79
Age		
<70 (n=131)	58.7 (57.2, 60.3)	−4.0 (−6.7, −1.4)
70–79 (n=141)	58.7 (57.2, 60.3)	−6.0 (−8.9, −3.1)
≥80 (n=287)	60.2 (59.1, 61.3) *P=0.04	−7.4 (−10.1, −4.7) *P=0.02
Coronary artery disease		
No (n=431)	59.7 (58.9, 60.6)	−4.6 (−6.4, −2.8)
Yes (n=128)	58.3 (56.7, 59.9) *P=0.11	−9.1 (−12.2, −6.0) *P<0.001
LVEDD		
<Median (48 mm) (n=172)	63.0 (61.7, 64.4)	−5.1 (−8.2, −1.9)
≥Median (n=223)	57.5 (56.4, 58.7) *P<0.001	−4.7 (−6.9, −2.5) *P=0.62
Medication use at baseline		
None (n=232)	59.1 (57.8, 60.3)	−6.5 (−8.9, −4.1)
β blocker, ACE-I, ARB (n=327)	59.6 (58.6, 60.6) *P=0.49	−5.3 (−7.3, −3.4) *P=0.44

HFpEF indicates heart failure in patients with preserved ejection fraction; HF indicates heart failure; EF, ejection fraction; LVEDD, left ventricular end diastolic dimension; ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers. *P indicates significance of difference in EF or change in EF according to indicated variables.
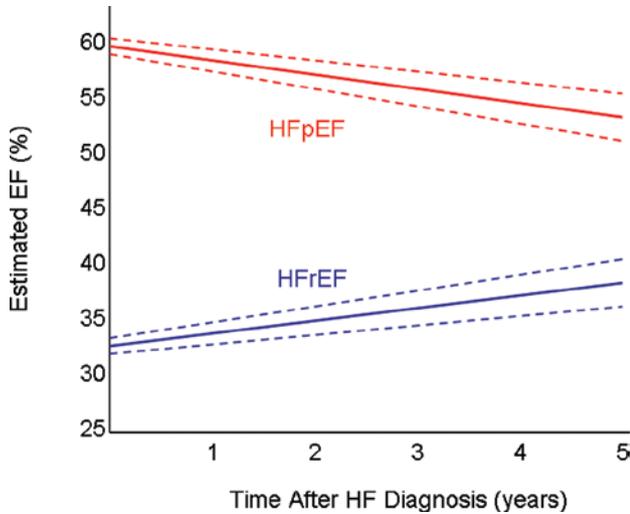
Figure 3. Change in ejection fraction (EF) for patients with preserved and reduced ejection fraction. The estimated EF (solid line) and 95% CI (dashed lines) for patients who initially had heart failure in patients with preserved ejection fraction (HFpEF) and heart failure in patients with reserved ejection fraction (HFrEF) are shown. HF indicates heart failure.

In total, 38.5% of HFpEF patients had a decline in EF to <50% (range of HFrEF) during follow-up and 25.1% had a decline in EF to <40%. Among HFpEF patients with an echo around 1 year after diagnosis (n=95), 21.1% had an EF<50%. For those with an echo performed from 4 to 6 years after diagnosis (n=117), 32.5% had an EF<50%.

Temporal Change in EF: HFrEF
In HFrEF, EF averaged 31.7% at diagnosis, and was lower in younger men, and those with larger LVEDD (Table 3). On average, EF increased in HFrEF (Figure 3), but this differed by sex, age, CAD status, and medication use (Table 3 and Figure in the online-only Data Supplement). EF increases were greater in those who were younger and in women, but there was a significant interaction between age and sex (interaction term age×sex×time *P*=0.003), and hence results were stratified by sex and age (Table 3). Those treated with evidence-based medications at diagnosis had a greater improvement in EF. Only a small number of patients had an MI after HF diagnosis (n=39), and excluding those patients from analysis, the increase in EF was similar (estimated 7.3% increase over 5 years). The estimated change in EF did not differ by baseline LVEDD. Sensitivity analyses performed using an EF<40% to define HFrEF yielded similar results.

In total, 38.8% of HFrEF patients had an increase in EF to ≥50% (normal) during follow-up. Among HFrEF patients with an echocardiogram around 1 year after diagnosis (n=105), 27.6% had an EF≥50%. For those with an echocardiogram from 4 to 6 years after diagnosis (n=158), 33.5% had an EF≥50%.

Prognostic Value of Change in EF
In HFpEF, survival was better in patients with less decline in EF over time while in HFrEF, survival was better in patients with greater improvements in EF (Table 4). Among patients with HFpEF, a decline in EF of 5% was associated with a 7%

Table 3. Change in Ejection Fraction Over Time: HFrEF

	Estimated Mean EF at HF Diagnosis (95% CI)	Estimated Change in EF Over 5 y (95% CI)
Overall (n=674)	31.7 (30.9, 32.5)	6.9 (5.4, 8.4) *P*<0.001
Men		
<70 (n=142)	29.0 (27.4, 30.6)	6.5 (4.2, 8.8)
70–79 (n=128)	30.9 (29.1, 32.6)	4.5 (1.8, 7.1)
≥80 (n=117)	32.2 (30.2, 34.1) *P*=0.002	1.8 (−2.3, 5.9) *P*=0.006
Women		
<70 (n=68)	34.1 (31.8, 36.4)	10.9 (8.2, 13.5)
70–79 (n=89)	33.1 (31.1, 35.2)	8.8 (6.1, 11.6)
≥80 (n=130)	33.2 (31.4, 35.0) *P*=0.002	6.2 (2.1, 10.3) *P*=0.006
Coronary artery disease		
No (n=441)	31.5 (30.5, 32.5)	9.4 (7.7, 11.1)
Yes (n=233)	32.2 (30.9, 33.0) *P*=0.42	0.3 (−2.5, 3.1) *P*=0.02
LVEDD		
<Median (57 mm) (n=210)	36.8 (35.5, 38.1)	7.6 (4.8, 10.4)
≥Median (n=230)	28.8 (27.5, 30.0) *P*<0.001	7.1 (4.6, 9.6) *P*= 0.93
Medication use at baseline		
None (n=197)	31.9 (30.4, 33.4)	4.0 (1.2, 6.9)
β blocker, ACE-I, ARB (n=477)	31.6 (30.7, 32.5) *P*=0.71	7.8 (6.1, 9.5) *P*=0.02

HFrEF indicates heart failure in patients with reduced ejection fraction; HF indicates heart failure; EF, ejection fraction; LVEDD, left ventricular end diastolic dimension; ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers.

*P indicates significance of difference in EF or change in EF according to indicated variables.

increase in mortality. In patients with HFrEF, a 5% increase in EF was associated with a 12% reduction in mortality.

Discussion
In this community population of incident HF patients, EF at HF diagnosis displayed a bimodal distribution in both sexes but with a higher prevalence of HFpEF in women. With passive longitudinal follow-up, changes in EF over time differed in patients with preserved and reduced EF. In those with HFpEF, EF declined with greater reductions noted in older patients and those with significant CAD. In patients with

Table 4. Prognostic Value of Change in Ejection Fraction Over Time

	Unadjusted	*Adjusted	
	HR (95% CI) for 5% Decrease EF	HR (95% CI) for 5% Decrease EF	P value
HFpEF	1.08 (1.04–1.12)	1.07 (1.03–1.12)	<0.001
HFrEF	1.12 (1.08–1.16)	1.12 (1.07–1.16)	<0.001

HR indicates hazard ratio; EF, ejection fraction; HFpEF, heart failure in patients with preserved ejection fraction.

*Adjusted for age, sex, and Charlson comorbidity index.

HFrEF, EF increased with greater improvements in women, younger patients, those without CAD, and those treated with evidence-based medications. At 1 and 5 years after diagnosis, significant proportions of patients with HFpEF had a decline in EF to <50% and a similar proportion of patients with HFrEF experienced an increase in EF to ≥50%. Greater decline or less improvement in EF was associated with worse prognosis in HFpEF and HFrEF patients, respectively. Although prospective longitudinal studies with serial measurement of EF are needed to confirm these observations, these data provide insight into the natural history of HF in the community. The finding that EF declines over time in HFpEF patients is particularly interesting and consistent with other studies suggesting that contractile dysfunction may contribute to the pathophysiology of HFpEF.

HFpEF Versus HFrEF

The clinical syndrome of HF occurs in patients with preserved EF in 50% of cases.[1,2] The prevalence of HFpEF is increasing,[2] either because of a change in the clinical recognition of the syndrome or evolving risk factors and population demographics. The bimodal distribution of EF among HF patients noted here and in previous studies,[18,19] suggests unique pathophysiology in the 2 forms of HF. Further, there are significant differences in the 2 populations with HFpEF patients tending to be older, more frequently female, and less likely to have CAD. Differential response to therapies has been demonstrated with clinical trials demonstrating that ACE-I or ARBs do not impact outcomes in HFpEF as they do in HFrEF[3,20] although the response to β-adrenergic receptor or aldosterone receptor antagonists in HFpEF have not been rigorously characterized. Herein, we found a differential response to ACE/ARBs and β blockers in patients with HFpEF versus HFrEF. Although HFrEF patients treated with these medications had a greater improvement in EF compared with those who were untreated, we found that treatment with ACE/ARBs and β blockers had no impact on the change in EF over time in patients with HFpEF. As we characterized patients by medication treatment at initial diagnosis and did not account for longitudinal treatment changes, we cannot fully evaluate the impact that medical therapy has had on the changes in EF observed. Furthermore, a greater proportion of patients with HFrEF versus HFpEF were treated with these medications, which may have influenced observed results.

Change in EF Over Time in HFpEF

On average, EF declined over time in patients with HFpEF with greater decreases noted in those who were older and had CAD. Interestingly, a large proportion (39%) of patients who were categorized as HFpEF at diagnosis, had an EF decline during follow-up that placed them in the range of HFrEF (EF<50%). HFpEF is commonly thought to represent maladaptive age- and hypertension-related remodeling which results in diastolic dysfunction, elevation of filling pressures and limitations in resting or exercise cardiac output.[18] However, recent studies have reported that subtle impairments in myocardial contractility and systolic reserve also exist in patients with HFpEF.[21,22] Some human and animal studies

suggest the potential for a transition from pressure overload induced concentric hypertrophy to systolic dysfunction.[23–25] Although interim MI has been invoked to explain the progression from HFpEF to HFrEF,[26] excluding patients with clinically apparent interim MI yielded similar results, suggesting other mechanisms. Neurohormonal activation has not been extensively characterized in HFpEF, but the limited studies available suggest that activation of the adrenergic and renin-angiotensin-aldosterone systems occur in HFpEF[27–29] and may contribute to progressive remodeling and contractile dysfunction. However, the lack of response to ACE/ARBs and β blockers observed would underscore that the mechanisms of progressive systolic dysfunction in HFpEF remain unclear.

Though progressive contractile dysfunction may represent a fundamental component of the pathogenesis of HFpEF, altered loading conditions, tachycardia, sepsis, development of valvular disease, infiltrative processes, or cardio-toxin ingestion may have contributed to systolic dysfunction in some patients. However, as patients with HFrEF were also elderly and burdened with comorbidities, the divergent trends in changes in EF in the 2 forms of HF may suggest unique mechanisms but underscore the need for further studies investigating the pathogenesis of these changes.

Change in EF Over Time in HFrEF

In contrast to HFpEF patients, on average, EF improved in patients with HFrEF although patients with CAD had no significant change in EF over time. Spontaneous improvement in EF in patients with profound systolic dysfunction has been reported.[30] In trial populations with HFrEF, adding β blockers and renin-angiotensin-aldosterone system antagonists resulted in between 4% and 8% improvements in EF within the first year after treatment.[5,6] Some,[30–32] but not all,[33] studies have suggested greater improvements in EF in nonischemic dilated cardiomyopathy, presumably reflecting a greater extent of viable, nonfibrotic myocardium and a greater degree of adrenergic activation[34] compared with those with an ischemic cause. Herein, women, particularly younger women, had a greater improvement in EF compared with men. As women and the elderly have historically been severely underrepresented in HF clinical trials,[35] few data exist to inform us on differential changes in EF by age or sex in HFrEF. Though women with HF have been demonstrated in some settings to have lower risk for cardiovascular hospitalization and death, the mechanisms for these differential outcomes are unexplained. Sex-related differences in cardiac remodeling and the protective effects of estrogen on apoptosis may be among the explanations for differential improvement in EF and clinical outcomes.[36]

Change in EF and Prognosis

In patients with HFrEF, lower EF may be associated with worse prognosis.[37] However, in most community cohorts, overall survival is similar in patients with HFpEF and HFrEF[1,38] despite the normal EF in HFpEF patients. Little is known about how changes in EF over time correspond to prognosis, particularly in HFpEF patients.

Our findings indicate that a decline in EF is associated with an increase in mortality in HFpEF, a finding consistent with

the observation that subtle impairment in resting myocardial contractility (assessed with stress corrected midwall fiber shortening) was associated with increased mortality in a separate HFpEF cohort.[21] Given the reliance on clinically obtained echocardiograms, confirmation in prospective longitudinal studies is needed.

Although the current study design precludes the ability to relate changes in EF to therapy, we speculate that much of the improvement or lack of progressive impairment in EF over time in patients with HFrEF may reflect appropriate HF therapy. In HFrEF, short-term improvements in EF in response to therapy have been associated with improved survival.[31,32] However, as clinical trial patients are frequently highly selected[35] and therefore differ from patients in the community, it is difficult to extrapolate results from clinical trials to community patients. Thus, the current observations provide unique insight into the natural history of HFrEF in the community, albeit during a period where therapies and clinical practice were evolving.

Limitations and Strengths

All echocardiograms were obtained at the discretion of the patient's providers rather than at prespecified intervals. This is a source of potential bias with EF assessment being influenced by clinical status, age, provider, and therapeutic era. Patients excluded from the study due to a lack of an echocardiogram at HF diagnosis were older and more often female, a population who would be more likely to have HFpEF. We must consider whether our findings regarding the change in EF over time represent regression to the mean, as EF improved for those with HFrEF and declined for those with HFpEF. However, divergent patterns of change according to age, sex, CAD, and medication use make regression to the mean a less plausible explanation. Furthermore, the average EF in the general adult (>45 years) population is 64%,[39] which is already higher than the observed EF at diagnosis in HFpEF (59%), such that further declines over time would be moving further from the mean. The prevalence of significant CAD or frequency of interim MI may be underestimated by the diagnostic criteria utilized. These data do not provide information on the mechanism(s) responsible for the decline in EF in patients with HFpEF, which are likely diverse and potentially different from the mechanisms for systolic dysfunction in HFrEF. Though it would be interesting to understand whether differences in cardiovascular, rather than all-cause, mortality exist according to change in EF over time, we do not have access to data on cause of death. Olmsted County remains a largely white community; findings may differ in populations of varying racial and ethnic composition. Several strengths should also be acknowledged. This is a large community population of patients who have been followed longitudinally from the time of incident, validated, HF diagnosis, often until death. Further, all echocardiograms have been performed at a single echocardiography laboratory which has followed strict standards of practice such that EF assessment likely has high internal validity.

Conclusions

EF changes differentially for HF patients with preserved and reduced EF at diagnosis. The observation that EF declines over time in HFpEF may suggest that progressive contractile dysfunction or unique remodeling contribute to the pathophysiology of HFpEF and thus, may represent therapeutic targets. However, prospective longitudinal studies are needed to confirm these observations and if confirmed, establish the mechanism and clinical relevance of decline in EF over time in HFpEF patients.

Disclosures

None.

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CLINICAL PERSPECTIVE

Heart failure (HF) can occur in patients with preserved (HFpEF) and reduced (HFrEF) ejection fraction (EF). These may represent distinct diseases, as they occur in different patient populations, and respond differently to therapies. Among 1233 community heart failure patients followed longitudinally, we found that changes in EF over time also differed in patients with HFpEF versus HFrEF. In those with HFpEF, EF declined with greater reductions noted in older patients and those with significant coronary artery disease. In patients with HFrEF, EF increased with greater improvements in women, younger patients, those without coronary artery disease, and those treated with evidence-based medications. Greater decline or less improvement in EF was associated with worse prognosis in HFpEF and HFrEF patients, respectively. These findings suggest that progressive contractile dysfunction may contribute to the pathophysiology of HFpEF. The clinical implications of these findings are 2-fold. First, when evaluating patients with HFpEF, it is important to recognize that progressive decline in EF can occur, and may be associated with worse prognosis. Second, HFpEF and HFrEF, while sharing similar clinical manifestations, represent distinct pathophysiological entities and require differential approaches to care.

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Longitudinal Changes in Ejection Fraction in Heart Failure Patients With Preserved and Reduced Ejection Fraction

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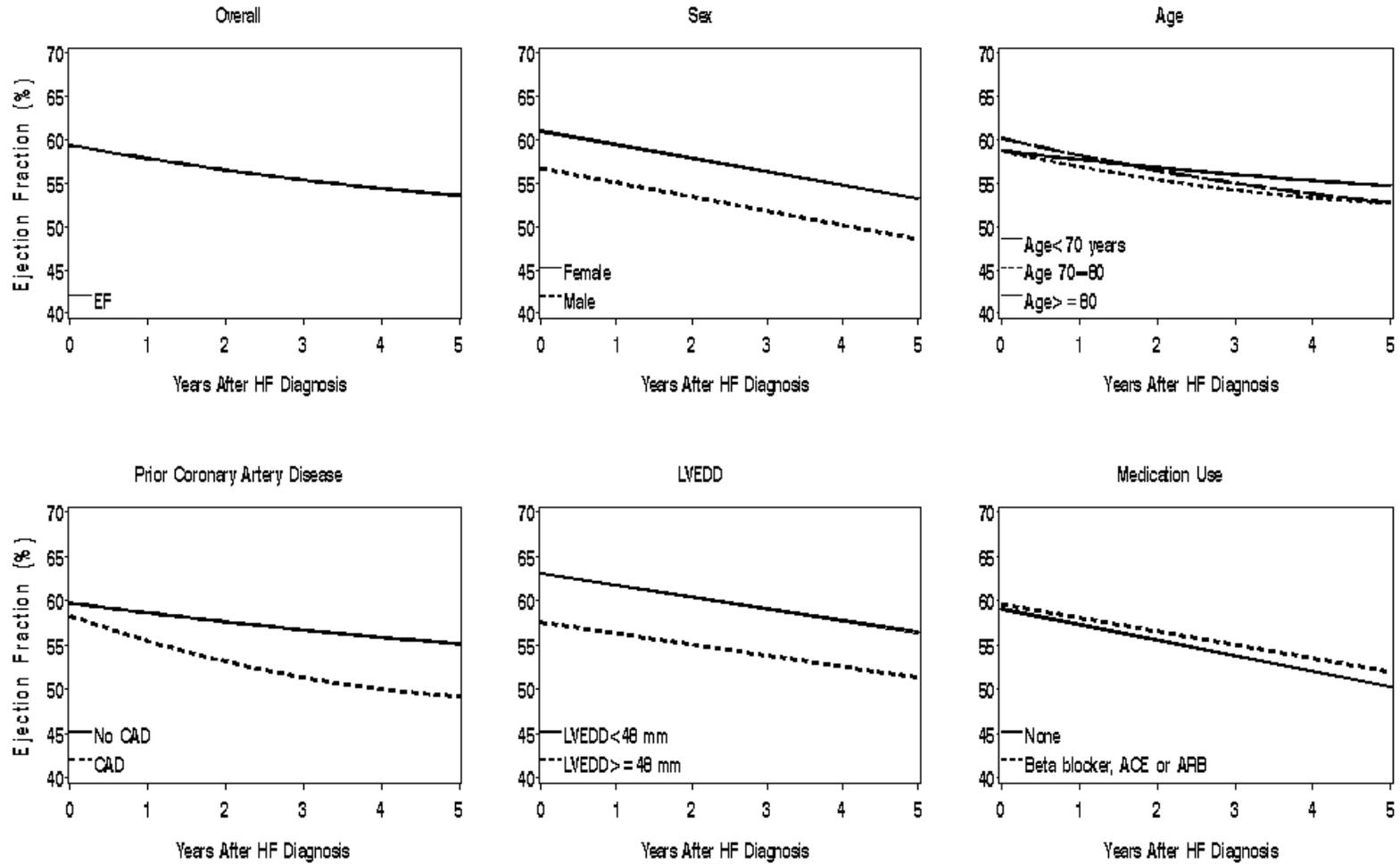
SUPPLEMENTARY MATERIAL

SUPPLEMENTARY METHODS

Linear mixed effects regression modeling. The basic formula for the model was

EF=time where the parameter estimate of time is the slope of the line and the y intercept

is the estimated mean EF at a time point after HF diagnosis. The model uses random

intercepts and slopes. The initial EF measurement was included in the model. Including

variables (such as sex) allows for different Y intercepts but assumes the slopes of the line

are the same by sex. Including an interaction term in the model (such as time*sex) allows

for different slopes and intercepts for different patient groups. In addition to overall

estimates, the change in EF over time according to age, sex, LVEDD, CAD, and

medication use was estimated.   Interactions between the variables were examined, and

results were further stratified if the interaction term p level was <0.05.   To account for

non-linear changes in EF over time, a quadratic term was included in the models if

statistically significant (p<0.05). Based on this criteria, the quadratic term was included

in the overall, age, and CAD models for HFrEF and overall and CAD for HFrEF. A

completely general (unstructured) covariance matrix was assumed where the covariances

are unconstrained.

SUPPLEMENTARY RESULTS

Figure. Change in Ejection Fraction According to Baseline Characteristics in Patients with Preserved and Reduced Ejection Fraction.

The estimated EF for patients who initially had HFpEF (A) and HFrEF (B) are shown according to baseline characteristics. HF=heart failure, CAD= coronary artery disease, LVEDD= left ventricular end-diastolic dimension, ARB= angiotensin receptor blocker, ACE= angiotensin converting enzyme inhibitor

A.

B.