

Systolic and Diastolic Heart Failure in the Community

Francesca Bursi, MD, MSc

Susan A. Weston, MS

Margaret M. Redfield, MD

Steven J. Jacobsen, MD, PhD

Serguei Pakhomov, PhD

Vuyisile T. Nkomo, MD

Ryan A. Meverden, BS

Véronique L. Roger, MD, MPH

HEART FAILURE (HF) IS A highly prevalent syndrome with diverse etiologies that may be associated with reduced or preserved ejection fraction (EF). The pathophysiology of HF with reduced EF has been extensively studied and management strategies are well defined.¹ Conversely, while clinical series, epidemiological surveys, and clinical trials have improved our understanding of HF and preserved EF,^{2,3} controversy remains on many key elements of this entity, including its prevalence, clinical characteristics, and outcome.⁴ To this end, the prevalence and distribution of diastolic dysfunction among patients with HF and reduced or preserved EF has not, to the best of our knowledge, been reported. Further, previous studies share key limitations, including retrospective design, inclusion of prevalent cases, inconsistent assessment of EF, infrequent assessment of diastolic function, and most being hospital based.²⁻⁴

We addressed these knowledge gaps by prospectively studying all Olmsted County residents presenting with HF at Mayo Clinic inpatient and outpatient facilities. Our objective was to determine

See also pp 2217 and 2259.

Context The heart failure (HF) syndrome is heterogeneous. While it can be defined by ejection fraction (EF) and diastolic function, data on the characteristics of HF in the community are scarce, as most studies are retrospective, hospital-based, and rely on clinically indicated tests. Further, diastolic function is seldom systematically assessed based on standardized techniques.

Objective To prospectively measure EF, diastolic function, and brain natriuretic peptide (BNP) in community residents with HF.

Main Outcome Measures Echocardiographic measures of EF and diastolic function, measurement of blood levels of BNP, and 6-month mortality.

Design, Setting, and Participants Olmsted County residents with incident or prevalent HF (inpatients or outpatients) between September 10, 2003, and October 27, 2005, were prospectively recruited to undergo assessment of EF and diastolic function by echocardiography and measurement of BNP.

Results A total of 556 study participants underwent echocardiography at HF diagnosis. Preserved EF ($\geq 50\%$) was present in 308 (55%) and was associated with older age, female sex, and no history of myocardial infarction (all $P < .001$). Isolated diastolic dysfunction (diastolic dysfunction with preserved EF) was present in 242 (44%) patients. For patients with reduced EF, moderate or severe diastolic dysfunction was more common than when EF was preserved (odds ratio, 1.67; 95% confidence interval [CI], 1.11-2.51; $P = .01$). Both low EF and diastolic dysfunction were independently related to higher levels of BNP. At 6 months, mortality was 16% for both preserved and reduced EF (age- and sex-adjusted hazard ratio, 0.85; 95% CI, 0.61-1.19; $P = .33$ for preserved vs reduced EF).

Conclusions In the community, more than half of patients with HF have preserved EF, and isolated diastolic dysfunction is present in more than 40% of cases. Ejection fraction and diastolic dysfunction are independently related to higher levels of BNP. Heart failure with preserved EF is associated with a high mortality rate, comparable to that of patients with reduced EF.

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the prevalence of preserved and reduced EF and that of diastolic dysfunction among all patients with HF in a contemporary community cohort. Further, we sought to define key clinical characteristics of patients with HF, including the burden of comorbidity, the severity of neurohumoral activation, and survival according to EF and diastolic dysfunction. The central hypothesis was that the community prevalence of HF with preserved EF is high, and that among patients with preserved EF, most have diastolic dysfunction of moderate to se-

vere degree. The prevalence of diastolic dysfunction in the general population of Olmsted County (assessed with a method similar to the one we used) has previously been reported,⁵ thereby provid-

Author Affiliations: Division of Cardiovascular Diseases, Department of Internal Medicine (Drs Bursi, Redfield, Nkomo, and Roger); Department of Health Sciences Research (Drs Jacobsen and Roger, Ms Weston, and Mr Meverden), Division of Biomedical Informatics (Dr Pakhomov), Mayo Clinic and Foundation, Rochester, Minn.

Corresponding Author: Véronique L. Roger, MD, MPH, Division of Cardiovascular Diseases, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (roger.veronique@mayo.edu).

ing the necessary framework to interpret the results.

METHODS

The Rochester Epidemiology Project

This study was conducted in Olmsted County, Minnesota. Population-based epidemiological research is feasible in Olmsted County because it is relatively isolated from other urban centers and only a few providers (Mayo Clinic, Olmsted Medical Center, and a few private practitioners) deliver all health care to residents. Most care is provided through the Mayo Clinic, which has maintained a unified medical record for the past 80 years. The Mayo Clinic unit record includes all outpatient office visits, clinic consultations, emergency department visits, nursing home care, hospital admission, autopsy examination, and death certification, which is indexed. The epidemiological potential of this index system is further enhanced because each provider uses an integrated medical record system, whereby all data collected for an individual patient are assembled in 1 file.

Identification of Patients

Our approach to case finding and data collection combined a 2-step prospective approach for patient recruitment with the use of the medical record for data collection.

First, for case finding, we used natural language processing of the unstructured text of the electronic medical record to prospectively identify patients presenting with clinical findings compatible with HF.⁶ As most clinical evaluations are electronically transcribed within 24 hours, this method, which was applied to all care settings including outpatient visits, allows rapid identification by electronic search of the transcribed notes for a wide range of terms indicative of HF. The search was restricted to patients at least 20 years old residing in Olmsted County. This approach yielded 100% sensitivity compared with billing data, which is the desired methodology for case finding.⁶

Second, the complete records (including inpatient and outpatient records) of potential cases were manually reviewed

to validate the diagnosis of HF using Framingham criteria⁷ and to collect clinical data. Patients were contacted directly and asked to consent to participate in the prospective study that included Doppler echocardiography and venous blood draw for the brain natriuretic peptide (BNP). Thus, the identification of study participants did not rely on a preexisting database, but rather on a prospective study design. The feasibility and reliability of the Framingham criteria for the ascertainment of HF in Olmsted County have been previously published.⁸

Study participants provided written consent to participate in the study, which was approved by the Mayo Clinic Institutional Review Board.

Echocardiography-Doppler

In Olmsted County, all echocardiograms are performed and interpreted in the Mayo Clinic Echocardiographic Laboratory. M-mode, 2-dimensional, Doppler, and Doppler tissue imaging (DTI) were performed according to guidelines of the American Society of Echocardiography.⁹ Digital echocardiographic data containing a minimum of 3 consecutive beats (5 in atrial fibrillation) were acquired and transferred to a server for storage and archiving (ProSolv Echo Management System, Problem Solving Concepts, Carmel, Ind). Left ventricular EF was measured by M-mode or 2-dimensional echocardiography using the Quinones formula from the parasternal views,¹⁰ by the quantitative 2-dimensional biplane volumetric Simpson method from 4- and 2-chamber views,⁹ and by the semiquantitative 2-dimensional visual estimate method from multiple echocardiographic views, all methods previously validated.^{10,11} The correlation between the methods of assessment of EF was excellent. Ejection fraction values were averaged when multiple measurements were performed. As recommended,¹² preserved systolic function was defined as an EF greater than or equal to 50%. Left ventricular end-diastolic diameter, interventricular septal, and posterior wall thickness were measured by M-mode or 2-dimensional echo from the parasternal views

at end-diastole as recommended by the American Society of Echocardiography, and they were used to calculate left ventricular mass, which was indexed to body surface area.⁹

Diastolic function was assessed by an approach similar to that used in the general population in Olmsted County.⁵ It integrates Doppler measurements of the mitral inflow and DTI of the mitral annulus using the medial annulus velocity, which is standard practice in our laboratory, as correlations of filling pressures with the medial annulus measurement were consistently equivalent to or better than the lateral annulus measurement or the combination of both measurements.¹³ Doppler tissue imaging is a sensitive and relatively load-independent measure of left ventricular relaxation (e' velocity). E/e' is a sensitive measure of filling pressures that offers greater reproducibility and feasibility than previously used measures.^{5,13-15} The algorithm thus relies on mitral inflow and DTI, both methods that can be applied to large numbers of patients with high reproducibility.^{13,16,17} While other indices (left atrial volume, use of Valsalva maneuvers, and color M-mode) have been proposed to evaluate diastolic function, they present notable methodological challenges without adding incremental value over those selected for the current study.^{13,17-19} Doppler tissue imaging indices have been validated in patients with reduced and preserved EF¹⁵ and provide reliable estimates of left ventricular filling pressures both in systolic and diastolic HF compared with invasive pressure recordings.¹⁴

This approach enabled classifying diastolic function in 4 categories: normal diastolic function, mild diastolic dysfunction (impaired relaxation without evidence of increased filling pressures), moderate diastolic dysfunction (impaired relaxation or pseudo-normal with moderate elevation of filling pressures), and severe diastolic dysfunction (advanced reduction in compliance)^{5,13} (FIGURE 1). Diastolic function was categorized as indeterminate in the presence of mitral valve prosthesis, severe mitral stenosis or regurgitation, or missing data. Isolated

diastolic dysfunction was defined as diastolic dysfunction with EF greater than or equal to 50%.

Patient Characteristics

The characteristics of patients at the time of HF diagnosis were determined from the medical records. Patients were classified as outpatient cases if not hospitalized within 7 days of the outpatient diagnosis. Clinicians' diagnoses were used to identify hypertension, hyperlipidemia, and former or current smoking. Diabetes mellitus was defined according to the American Diabetes Association criteria.²⁰ The hemoglobin value at the date of HF diagnosis was used to define anemia (hemoglobin concentration <13.0 g/dL in men and <12.0 g/dL in women).²¹ Height (first available outpatient value) and weight (last outpatient value prior to HF diagnosis) were used to calculate body mass index and body surface area.

Myocardial infarction (MI) was defined by published criteria.²² Chronic obstructive pulmonary diseases and other comorbid conditions were defined by clinicians' diagnoses and summarized using the Charlson index.²³ Atrial fibrillation and flutter were ascertained on the electrocardiogram that

was closest to the Doppler-echocardiography study. Valvular heart disease was considered present if any prosthesis or more than moderate aortic or organic mitral valve disease were noted.²⁴

Creatinine clearance was calculated using the last outpatient serum creatinine value prior to the diagnosis of HF with the Modification of Diet in Renal Disease Study (MDRD) equation (estimated glomerular filtration rate = $186.3 \times [\text{serum creatinine}]^{-1.154} \times \text{age}^{-0.203} \times [0.742 \text{ for women}] \times [1.21 \text{ if African American}]$). Renal function was deemed severely reduced when the creatinine clearance was less than or equal to 29 mL/min.²⁵

BNP Assays

All blood samples were collected by venipuncture in EDTA tubes. After centrifugation, plasma was stored at -70°C until BNP measurement by immunoradiometric assay (nonextracted) with antibody to human BNP using the Shionoria assay (Shionogi, Osaka, Japan). The mean (SD) interassay and intra-assay variability was 7.2 (1.7) pg/mL and 8.0 (1.4) pg/mL, respectively, with normal range in plasma of 12 (4) pg/mL. Brain natriuretic peptide was measured in the Immunochemical Core Laboratory of Mayo Clinic, Rochester, Minn.

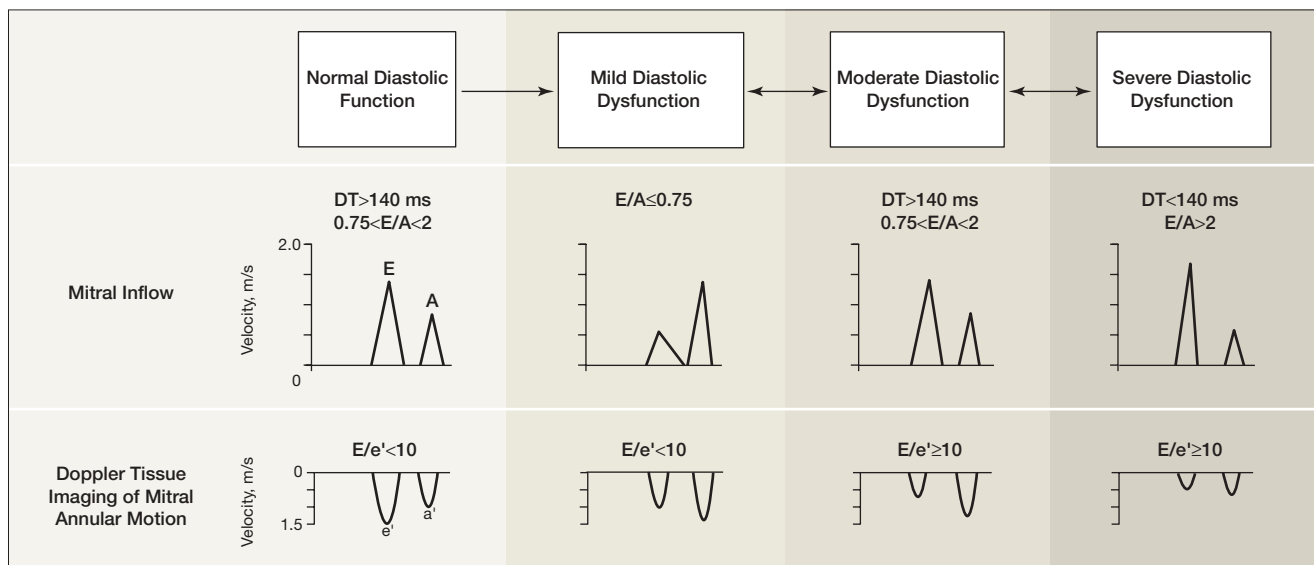
Statistical Analysis

Data are presented as frequencies or mean (SD). Characteristics were compared across groups using χ^2 tests for categorical variables and *t* test or analysis of variance (ANOVA) for continuous variables. As the distribution of BNP was skewed, natural log-transformed values were used. For display purposes, BNP data are shown as median (25th-75th percentile). All stratified analyses were performed on the basis of the prespecified aim to describe the distribution of EF and diastolic function among patients with HF.

Logistic regression was used to test the hypothesis that patients with reduced EF had more severe diastolic dysfunction than patients with preserved EF while adjusting for age and sex.

Survival was analyzed with the Kaplan-Meier method. The observed survival was compared with that expected for the general population with a similar age and sex distribution. Proportional hazards regression was used to examine the association between death and EF while controlling for age and sex. The proportional hazard assumption was tested using the Schoenfeld residuals and there was no evidence to suggest the assumption was invalid.

Figure 1. Echocardiography-Doppler Criteria for Assessment of Diastolic Function



E indicates early peak mitral inflow velocity; A, late peak mitral inflow velocity, DT, deceleration time of the E-wave; e', velocity of annulus early diastolic motion.

All statistical tests were 2-sided and a P value of .05 was selected for the threshold of statistical significance. Analyses were performed using SAS statistical software, version 8 (SAS Institute Inc, Cary, NC) and Splus statistical software, version 6.4 (Insightful Corp, Seattle, Wash).

RESULTS

Patient Identification and Characteristics

Between September 10, 2003, and October 27, 2005, 3562 Olmsted County residents were identified from the Mayo

Clinic electronic medical record as potential candidates for inclusion. After manual record review, 886 individuals with active HF (both incident and prevalent) were approached for participation in the study. Among these, 607 consented (participation rate of 69%) and 556 underwent echocardiography at a median (25th-75th percentile) of 1 (1-4) day within the diagnosis of HF and comprise the study population. A total of 501 patients underwent measurement of BNP at a median (25th-75th percentile) of 4 (2-8) days after diagnosis. The median (25th-75th percentile) time between ech-

ocardiography and BNP measurement was 1 (0-4) day.

The mean (SD) age of study participants was 76 (13) years, 517 (93%) met Framingham criteria for HF, and 50% were men; the burden of comorbidity was high in this population, as 384 (69%) of the patients presented with a Charlson index of 3 or greater (TABLE 1). Among the 556 study participants, 122 (22%) were diagnosed in the outpatient setting and 295 (53%) were incident cases. Outpatient cases were similar to their inpatient counterparts for all the clinical characteristics, with the exception of valvular disease, which was more frequent among patients diagnosed as outpatient (31 [25%] and 66 [15%] for outpatients and inpatients, respectively; *P* = .009) and anemia, which was less frequent among participants diagnosed as outpatient (45 [37%] and 240 [55%] for outpatients and inpatients, respectively; *P* < .001).

Left Ventricular Systolic and Diastolic Function

Of the 556 patients with HF, 308 (55%) had preserved EF. Compared with their counterparts with reduced EF, patients with preserved EF were older, more likely to be women, less likely to be smokers or have a history of MI, and had a lower New York Heart Association class, but they did not differ for other comorbidities. Patients with preserved EF also had smaller left ventricular size and mass (Table 1). In patients with reduced EF, the degree of left ventricular dilatation increased with the severity of systolic dysfunction, and in those with preserved EF, only 11 (4%) had a left ventricular end diastolic diameter that exceeded the upper limits of normal as defined by the American Society of Echocardiography.⁹

Among patients with preserved EF, diastolic dysfunction was mild in 22 (7%), moderate in 194 (63%), and severe in 26 (8%). Diastolic function was normal in 31 patients (10%) and indeterminate in 35 patients (11%). Patients who presented with isolated diastolic dysfunction (TABLE 2) made up 44% of the total number of patients presenting with HF in the community.

Table 1. Characteristics of Patients With Heart Failure*

Characteristic	Overall (n = 556)	Ejection Fraction ≥50% (n = 308)	Ejection Fraction <50% (n = 248)	P Value
Age, mean (SD), y	75.6 (13.3)	77.4 (12.5)	73.4 (14.0)	<.001
Men	276 (50)	132 (43)	144 (58)	<.001
Cardiovascular risk factors				
Hypertension	467 (84)	266 (86)	201 (81)	.09
Smoking (current or former)	342 (62)	177 (58)	165 (67)	.03
Diabetes mellitus	206 (37)	111 (36)	95 (38)	.56
Hyperlipidemia	437 (79)	238 (77)	199 (80)	.40
BMI, mean (SD)	29.4 (7.6)	29.6 (7.5)	29.1 (7.8)	.32
Comorbidity				
Prior MI	237 (43)	112 (36)	125 (50)	<.001
COPD	192 (35)	117 (38)	75 (30)	.06
Creatinine clearance, mean (SD), mL/min	54.4 (20.1)	54.2 (19.7)	54.7 (20.5)	.99
Severely reduced renal function	57 (10)	35 (11)	22 (9)	.34
Anemia	285 (51)	163 (53)	122 (49)	.38
Atrial fibrillation/flutter	173 (31)	95 (31)	78 (32)	.85
Valvular disease	97 (17)	53 (17)	44 (18)	.87
Charlson index ≥3	384 (69)	216 (70)	168 (68)	.59
NYHA class				.006
I	52 (9)	36 (12)	16 (6)	
II or III	246 (44)	143 (46)	103 (42)	
IV	258 (46)	129 (42)	129 (52)	
Echocardiographic variables				
Left ventricular mass index, mean (SD), g/m ²	117.8 (36.7)	106.9 (32.1)	131.1 (37.5)	<.001
Left ventricular end-diastolic diameter, mean (SD), mm	52.1 (9.2)	47.9 (6.3)	57.3 (9.5)	<.001
Medications before the echocardiographic study				
ACE inhibitors or angiotensin II receptor blockers	102 (18)	52 (17)	50 (20)	.32
β-Blockers	109 (20)	65 (21)	44 (18)	.32
Diuretics	126 (23)	73 (24)	53 (21)	.51
Medications after the echocardiographic study				
ACE inhibitors or angiotensin II receptor blockers	348 (63)	157 (51)	191 (77)	<.001
β-Blockers	387 (70)	193 (63)	194 (78)	<.001
Diuretics	406 (73)	218 (71)	188 (76)	.18

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; NYHA, New York Heart Association.

SI conversion factor: to convert mL/min to mL/s for creatinine clearance, multiply by 0.0167.

*Data are presented as No. (%) unless otherwise specified.

Of the 248 HF patients with reduced EF, diastolic dysfunction was mild in 10 (4%), moderate in 138 (56%), and severe in 56 (23%). Diastolic function was normal in 13 patients (5%) and indeterminate in 31 patients (13%). Patients with reduced EF were more likely to have moderate or severe diastolic dysfunction (odds ratio, 1.67; 95% confidence interval [CI], 1.11-2.51; $P=.01$) than their counterparts with preserved EF (Table 2).

The distribution of systolic and diastolic function abnormalities was similar when the analyses were restricted to cases of incident HF or to patients presenting in the outpatient setting (Table 2). Similar distributions were also observed while restricting analyses to patients meeting Framingham criteria, to patients not in atrial fibrillation, and in the absence of valvular disease.

All analyses were repeated using a value of 55% or greater to define preserved EF. Using this value, the prevalence of HF with preserved EF was 46%. The frequencies of diastolic function grades were similar to that observed in the main analysis.

At the time of the echocardiogram, the use of medications did not differ by EF ($P \geq .05$ for all comparisons) and there was no association between the use of any of these medications and the diastolic function grade. After the echocardiogram, patients with preserved EF were less likely to receive angiotensin-converting enzyme inhibitors (157 [51%] vs 191 [77%]) and β -blockers (193 [63%] vs 194 [78%]) ($P < .001$ for both comparison).

Among nonparticipants who underwent a clinically indicated echocardiogram and had authorized the use of their medical records for research under Minnesota law ($n=145$), the prevalence of HF with preserved EF was similar to that observed among participants (59% vs 55%; $P=.49$). After adjustment for age, sex, and EF, there was no association between diastolic function and participation. This supports the generalizability of our results.

Table 2. Distribution of Ejection Fraction and Diastolic Dysfunction Among Patients With Heart Failure*

	No. (%)				
	Normal Diastolic Function	Indeterminate Diastolic Function	Mild Diastolic Dysfunction	Moderate Diastolic Dysfunction	Severe Diastolic Dysfunction
All cases (N = 556)					
Ejection fraction $\geq 50\%$	31 (10)	35 (11)	22 (7)†	194 (63)†	26 (8)†
Ejection fraction $< 50\%$	13 (5)	31 (13)	10 (4)	138 (56)	56 (23)
Total	44 (8)	66 (12)	32 (6)	332 (60)	82 (15)
Incident cases (n = 295)					
Ejection fraction $\geq 50\%$	18 (11)	10 (6)	16 (9)†	114 (67)†	12 (7)†
Ejection fraction $< 50\%$	3 (2)	16 (13)	4 (3)	72 (58)	30 (24)
Total	21 (7)	26 (9)	20 (7)	186 (63)	42 (14)
Outpatient cases (n = 122)					
Ejection fraction $\geq 50\%$	7 (10)	4 (5)	6 (8)†	50 (68)†	6 (8)†
Ejection fraction $< 50\%$	3 (6)	4 (8)	3 (6)	25 (51)	14 (29)
Total	10 (8)	8 (7)	9 (7)	75 (61)	20 (16)

*Mild diastolic dysfunction represents impaired relaxation mitral inflow patterns with normal filling pressures; moderate diastolic dysfunction represents impaired relaxation mitral inflow patterns with elevated filling pressures or a pseudo-normal mitral inflow pattern with elevation of filling pressures; and severe diastolic dysfunction represents restrictive mitral inflow patterns.

†Patients with isolated diastolic dysfunction.

BNP Measurements

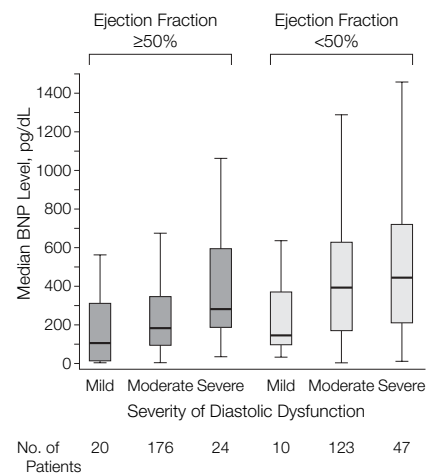
Median (25th-75th percentile) BNP level was 257.0 pg/dL (115.0-511.0 pg/dL) and was higher among patients with reduced EF than among those with preserved EF (median, 388 pg/dL [164.8-651.3 pg/dL] and 183.0 pg/dL [87.6-350.5 pg/dL], respectively; $P < .001$). Within EF categories, BNP levels were higher when diastolic dysfunction was more severe (P for trend, $< .001$ for preserved EF and $.045$ for reduced EF) (FIGURE 2).

Brain natriuretic peptide levels were independently associated with age, EF, and degree of diastolic dysfunction. There was no clinically significant correlation between BNP and time to presentation since the R^2 value was 0.01, indicating that time explained only 1% of the variance in BNP.

Mortality

After a mean (SD) follow-up of 292 (208) days, 147 patients died. Follow-up for vital status was 100% complete. A total of 444 (80%) patients died or had at least 6 months of follow-up. There was no difference in the mortality rates between patients with reduced and preserved EF (6-month Kaplan-Meier mortality rates 16% vs 16%; hazard ratio for reduced vs preserved EF, 1.06 [95% CI, 0.77-1.48]; $P=.72$). At 6 months, the mortality rate for pa-

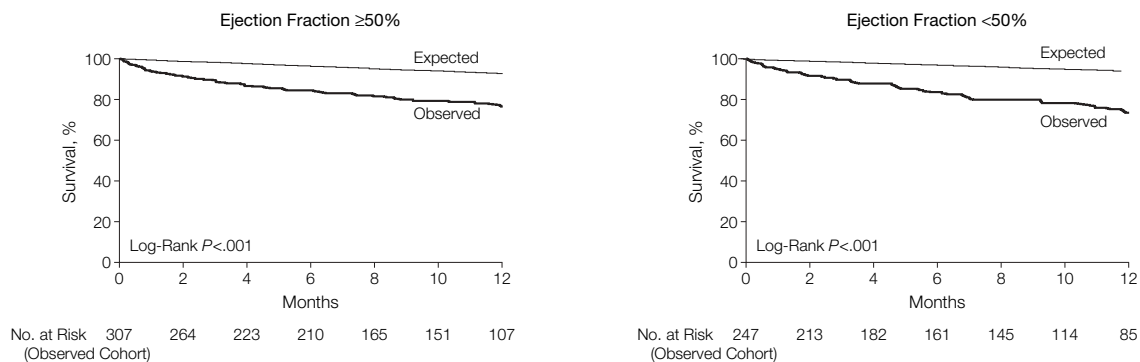
Figure 2. Median Brain Natriuretic Peptide (BNP) Levels by Ejection Fraction Categories



Each box displays the median, 75th percentile, and 25th percentile values; horizontal bars represent 1.5 times the interquartile range.

tients with reduced EF was 16% (95% CI, 11%-21%) compared with an expected mortality of 3% ($P < .001$). For patients with preserved EF, the mortality rate at 6 months was 16% (95% CI, 11%-20%) compared with an expected mortality of 4% ($P < .001$) (FIGURE 3). Compared with those with reduced EF and after adjusting for age and sex, patients with preserved EF had a similar risk of death (adjusted haz-

Figure 3. Expected and Observed Survival by Ejection Fraction Category



ard ratio, 0.85; 95% CI, 0.61-1.19; $P = .33$). After further adjustment for hypertension, comorbidity, and reduced renal function, the results were similar (adjusted hazard ratio, 0.91; 95% CI, 0.65-1.28; $P = .59$). Adjusting for duration of HF did not change the results.

COMMENT

In this large contemporary community-based prospective cohort of patients with HF, more than half (55%) of the individuals had preserved left ventricular EF. Diastolic dysfunction was present in 80% of patients, combined systolic and diastolic dysfunction was present in 37%, and isolated diastolic dysfunction was present in 44%. These distributions were robust irrespective of whether HF was identified in the inpatient or outpatient setting or whether prevalent or incident HF was examined. The severity of systolic and diastolic dysfunction was independently related to higher levels of BNP. Outcomes for HF are poor as mortality with preserved EF is similar to that with reduced EF.

Systolic Function

Previous studies reported wide variations in the proportion of patients with preserved EF among those with HF. On average, population-based studies and cross-sectional echocardiographic series report higher frequencies than earlier hospital cohort studies.^{2,3,26,27} These discrepancies in part reflect differences in the methods of measurement and cut-points for systolic dysfunction, but more importantly are related to the participant selection.

tion, but more importantly are related to the participant selection.

Previous reports included chiefly hospitalized patients and relied on clinically indicated tests to assess EF. The reliance on clinically indicated tests could result in biased findings.² To this end, several studies, including earlier data from Olmsted County, reported a noticeably lower proportion of HF with preserved EF than in the current one. This may reflect reliance on clinical echocardiography data that were not uniformly obtained in those studies. Alternatively, the greater frequency of HF with preserved EF reported in this and other more contemporary cohorts may reflect the emerging evidence of a temporal increase in the prevalence of HF with preserved EF.²⁷ Finally, the majority of published data may be affected by incidence-prevalence bias.

Thus, the current data more conclusively establish that the majority of patients with HF in the community present with preserved EF. The robustness of these findings is further supported by the fact that the distribution of preserved and reduced EF is similar among prevalent and incident cases of HF, and among inpatient and outpatient cases.

Diastolic Function

The pathophysiology of HF with normal EF is not fully defined,²⁸ although a previous study established that HF with preserved EF satisfied the key pathophysiological derangements characteristic of HF.²⁹ It has been assumed

that patients with HF and preserved EF either have impaired relaxation or impaired relaxation with reduced left ventricular compliance as the key perturbation mediating elevated filling pressures and symptoms of HF.³⁰ In small highly selected series of patients with HF and preserved EF studied at referral centers, there is evidence to support³¹ and refute³² this hypothesis.

Herein, in a consecutive series including all patients with incident or prevalent HF in the community, we provide evidence to support the importance of diastolic dysfunction in patients with HF and preserved EF. Doppler evidence of isolated impairment in left ventricular relaxation is common in elderly patients with cardiovascular disease.⁵ However, the prevalence of Doppler evidence of reduced left ventricular compliance (moderate or severe diastolic dysfunction) observed here in patients with HF and preserved EF (71%) is strikingly higher than that observed in elderly patients with cardiovascular disease but no history of HF (17%) in the general Olmsted County population in a study that used similar methods to assess diastolic function. These data, together with the absence of left ventricular dilatation in patients with HF and preserved EF, provide strong evidence that diastolic dysfunction is a key factor in the pathophysiology of HF with preserved EF.

Patient Characteristics

Patients with preserved EF were more likely to be elderly and were more fre-

quently women; those with reduced EF were more likely to have had a previous MI. These findings are consistent with previous reports.²⁹ Few studies compared the prevalence of comorbidities in patients with HF and preserved or reduced EF.^{33,34} Because HF is a disease of the elderly, it coexists with a high frequency of risk factors and comorbidities.^{3,26} As these may mimic HF symptoms, this generated concern of possible misdiagnosis of HF when the EF was preserved.³⁵ However, in the current study, the frequency of comorbid conditions was similar in patients with HF and preserved or reduced EF. Therefore, it is unlikely that HF-like symptoms were caused by other conditions (such as chronic pulmonary disease or renal failure) more often among patients with preserved compared with those patients who had reduced EF. Importantly, the potential for underestimating the burden of HF among patients with comorbid illness has recently been underscored.³⁶

Brain natriuretic peptide plasma levels were elevated compared with the values reported for asymptomatic individuals from the same population (range, 17-58 pg/dL),³⁷ supporting the fact that BNP levels help identify patients with HF.^{38,39} Further, we found that individuals with HF and reduced EF had higher BNP levels than patients with preserved EF, extending post-hoc analyses from previous studies in the community.^{29,40} Among individuals with HF, both EF and diastolic dysfunction are important determinants of BNP elevation, which is also independently associated with age and comorbidity.

Mortality

The current study clarifies previous inconsistent results on survival in patients with HF and preserved EF^{33,34,41,42} by indicating that, at 6 months, mortality is high irrespective of EF. These results underscore the importance of determining the prevalence and characteristics of HF with preserved EF in current populations. How the severity of diastolic dysfunction modulates survival should be the objective of future studies.

Limitations and Strengths

Potential limitations should be acknowledged to facilitate the interpretation of the results. We identified Olmsted County residents through the Mayo Clinic electronic medical record. The participation rate was high but cannot preclude some degree of participation bias. However, we did not detect an association between participation and EF or diastolic function distribution. The sample size allows detection of an absolute survival difference between preserved and reduced EF at 6 months of 6% based on a 2-sided test assuming $\alpha = .05$ and 80% power. This is of clinical and public health significance.

As no study will be generalizable to the entire US population, potential limitations related to the racial and ethnic composition of the population may impact the extrapolation of the data to underrepresented populations. Year 2000 US Census data indicate that Olmsted County is becoming more diverse (<http://www.census.gov/>), with nearly 10% of the population being nonwhite. The value of Olmsted County studies, however, lies in the ability to measure in one population the occurrence of disease and subsequent outcomes. Indeed, our data resources allow complete enumeration of a geographically defined population and provide the ability through the innovative ascertainment approaches outlined herein to actively ascertain newly diagnosed cases of HF in the population. Our data provide benchmarks for needed comparisons to other populations.

Strengths of this study include the community-based approach, which enhances its external validity, and the novel case-finding method, which enables rapid identification of all cases of HF and enhances the timeliness and completeness of the ascertainment by allowing the identification of cases as soon as they are diagnosed.⁶ Outpatient cases, which comprise a quarter of patients presenting with HF in the community, were included and incident as well as prevalent cases were identified. Further, we relied on rigor-

ously validated Doppler echocardiography techniques and measured BNP promptly after HF diagnosis.

While direct measurements of active relaxation and passive stiffness by catheterization are considered by some to be the criterion standard to measure diastolic function,³¹ they are not applicable clinically to large numbers of patients. The algorithm used to grade diastolic function is based on extensive evidence, experience, and state-of-the-art techniques including DTI.^{5,13,15} While the presence of moderate and severe diastolic dysfunction as classified assumes that elevated filling pressures are mediated by reductions in left ventricular compliance, the normal left ventricular dimensions observed in patients with HF and normal EF strongly supports these assumptions. Our algorithm allowed classification of diastolic function in the vast majority of patients.

CONCLUSIONS

In a large community-based prospective cohort of patients presenting with HF, the majority of the individuals had preserved left ventricular EF and most had Doppler evidence of diastolic dysfunction. The presence of comorbid conditions in this elderly HF cohort was high, but independent of EF. The prevalence of moderate and severe diastolic dysfunction among patients with HF and preserved EF was strikingly higher than that observed in elderly patients with cardiovascular disease but without HF in the same community, supporting the hypothesis that diastolic dysfunction is present in a large segment of patients presenting with HF and preserved EF. Similarly, the high prevalence of moderate and severe diastolic dysfunction in patients with HF and reduced EF supports the importance of diastolic dysfunction in both forms of HF. The importance of characterizing the pathophysiology of HF with preserved EF is underscored by the high mortality rate of these patients, which is comparable to that of patients with reduced EF.

Author Contributions: Dr Roger had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Bursi, Jacobsen, Roger.
Acquisition of data: Bursi, Weston, Jacobsen, Pakhomov, Nkomo, Roger.

Analysis and interpretation of data: Bursi, Weston, Redfield, Jacobsen, Pakhomov, Nkomo, Meverden, Roger.

Drafting of the manuscript: Bursi, Roger.

Critical revision of the manuscript for important intellectual content: Weston, Redfield, Jacobsen, Pakhomov, Nkomo, Meverden.

Statistical analysis: Weston, Meverden.

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Study supervision: Bursi, Roger.

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