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Clinical Epidemiology of Heart Failure with Preserved Ejection Fraction (HFpEF) in Comparatively Young Hospitalized Patients

Michael Zacharias, D.O.[1], **Samuel Joffe, M.D.**[2], **Elizabeth Konadu, M.D.**[3], **Theo Meyer, M.D.**[4], **Michael Kiernan, M.D.**[4], **Darleen Lessard, M.S.**[5], and **Robert J. Goldberg, Ph.D.**[5]

[1]University Hospitals, Case Medical Center, Section of Heart Failure and Transplantation, Cleveland, OH. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

[2]Catholic Medical Center, Department of Medicine, Manchester, NH. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

[3]Meritus Health, Hagerstown, MD. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

[4]Department of Medicine, Division of Cardiovascular Medicine, University of Massachusetts Medical School, Worcester, MA. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

[5]Department of Quantitative Health Sciences, University of Massachusetts Medical School, Worcester, MA. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

Abstract

Background—While heart failure with preserved ejection fraction (HFpEF) is primarily a disease of old age, risk factors that contribute to HFpEF are not limited to older patients. The objectives of this population-based observational study were to describe the clinical epidemiology of HFpEF in younger (<65 years) as compared with older (≥65 years) patients hospitalized with acute decompensated heart failure.

Methods and Results—We reviewed the medical records of residents of central Massachusetts hospitalized with HFpEF at all 11 greater Worcester (MA) medical centers during the 5 study years of 1995, 2000, 2002, 2004, and 2006. Among the 2,398 patients hospitalized with confirmed HFpEF, 357 (14.9%) were <65 years old. Younger patients were more likely to be male, non-Caucasian, obese, and to have a history of diabetes and chronic kidney disease than older patients with HFpEF. Younger patients hospitalized with HFpEF were less likely to have received

Address for reprints: Robert J. Goldberg, Ph.D., Department of Quantitative Health Sciences, University of Massachusetts Medical School, 368 Plantation Street, Worcester, MA 01605, Robert.Goldberg@umassmed.edu, Tel: (508) 856-3991, Fax: (508) 856-8993.

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commonly prescribed cardiac medications, had a longer hospital stay, and experienced significantly lower post discharge death rates than older hospitalized patients.

Conclusion—While HFpEF is predominantly a disease of old age, data from longitudinal studies remains needed to identify risk factors in younger individuals that may predispose them to the development of HFpEF.

Keywords

acute heart failure; young vs. older patients; population-based study

Introduction

Heart failure with preserved ejection fraction (HFpEF) has become an increasingly recognized phenotype among patients with heart failure and accounts for approximately one half of all cases of heart failure (1). While HFpEF is primarily considered to be a disease of old age (2), there are a paucity of data characterizing the descriptive epidemiology of comparatively young patients with HFpEF (3). Clinical risk factors that have been shown to contribute to the development of HFpEF, including hypertension, diabetes mellitus, and obesity, are not restricted to older individuals and the frequency of these risk factors has increased in younger persons in the general population during recent years (4–6).

Few studies have examined the characteristics of relatively young patients diagnosed with HFpEF, including differences in their clinical and demographic profile, management, and hospital and long-term outcomes compared with older patients with HFpEF. We hypothesized that different risk factors and pathophysiological mechanisms might be associated with the occurrence of HFpEF in comparatively young as compared with older hospitalized patients.

The objectives of this observational study, using data from the population-based Worcester Heart Failure Study (7–9), were to characterize HFpEF in comparatively young patients hospitalized at all 11 medical centers in central Massachusetts and compare their clinical/epidemiologic profile and hospital and post-discharge death rates to older patients with HFpEF.

Methods

The Worcester Heart Failure Study is a population-based observational study of residents of the Worcester, MA, metropolitan area (2000 census = 478,000) hospitalized with acute decompensated heart failure (ADHF) at all 11 medical centers in central Massachusetts (7–9). These medical centers include 2 large tertiary care academic centers and 9 small to mid-size community hospitals (7–9). This study was approved by the Institutional Review Board at the University of Massachusetts Medical School.

The overall study sample consisted of adult residents of central Massachusetts hospitalized for possible ADHF at all metropolitan Worcester hospitals during the 5 study years of 1995, 2000, 2002, 2004, and 2006. These study years were selected to coincide with population census estimates and due to the availability of federal grant support. Trained physicians and

nurses performed a standardized review of the medical records of metropolitan Worcester residents hospitalized at all 11 medical centers in central Massachusetts with primary or secondary International Classification of Disease (ICD)-9 codes consistent with the presence of possible heart failure. A discharge diagnosis of heart failure (ICD-9 code 428) was the principal diagnostic category reviewed. In addition, the medical records of patients with discharge diagnoses of hypertension, renal disease, acute cor pulmonale, cardiomyopathy, pulmonary congestion, acute pulmonary edema, and respiratory abnormalities were reviewed to identify patients who may also have had new onset heart failure (7–9).

The diagnosis of ADHF was confirmed based on use of the Framingham criteria, requiring the presence of 2 major criteria (e.g., rales, distended neck veins) or 1 major and 2 minor criteria (e.g., cough at night, dyspnea on ordinary exertion) (10). Patients who developed ADHF during admission for another acute illness (e.g., acute myocardial infarction) or following an interventional procedure were excluded. For purposes of the present investigation, we restricted our study sample to patients who had their ejection fraction assessed during their index hospitalization for ADHF. Only patients who met the Framingham criteria for ADHF, and had an ejection fraction of ≥50%, were included in the present population. Echocardiographic parameters, other than ejection fraction, such as diastolic function, were not included as part of this determination.

Data on patient demographics, medical history, clinical characteristics, presenting symptoms, physical examination findings, test results, medications, and other therapies were collected through the review of hospital medical records by trained study physicians and nurses. All previously diagnosed medical conditions, including prior hospitalizations for heart failure, were defined as either present or absent on the basis of information documented in the respective hospital's medical records and reviewed by our trained team of physician and nurse abstractors; our abstractors went as far back in the review of hospital medical records as this information was available to identify those with a previously diagnosed condition. A statewide review of death certificates and the Social Security Death Index, and review of hospital medical records at participating medical centers for subsequent medical care contacts, was conducted to ascertain the post-hospital discharge survival status of study patients through 2013.

Data Analysis

Differences in the distribution of selected demographic and clinical characteristics between the younger (<65 years) and older (≥65 years) greater Worcester residents hospitalized with HFpEF were examined using chi square and t-tests where appropriate. Multivariable adjusted logistic regression models were constructed to examine the association between age at the time of hospitalization for HFpEF and hospital death rates, as well as mortality at 1 and 2 years post discharge, with accompanying odds ratios (ORs) and 95% confidence intervals (CI). We also carried out a series of multivariable adjusted regression analyses to examine differences in factors associated with post discharge mortality in younger as compared with older hospitalized patients. All analyses were performed using SAS version 9.3 (SAS Institute Inc, Cary, NC).

Results

A total of 2,398 patients were hospitalized at all central Massachusetts medical centers with independently confirmed HFpEF in 1995, 2000, 2002, 2004, and 2006. The average age of this patient population was 77 years, 94% were Caucasian, and 66% were women (Table 1). Overall, patients hospitalized with HFpEF had a high burden of comorbid diseases including hypertension (74%), coronary artery disease (46%), diabetes (35%), COPD (35%), anemia (27%), and chronic kidney disease (23%) based on the review of information contained in hospital medical records (Table 1).

Characteristics of Young versus Older Patients with HFpEF

Compared to older patients with HFpEF, younger patients were significantly more likely to be male, non-Caucasian, and to be overweight or obese (average BMI 34 vs. 28) (Table 1); younger patients were also much more likely to be morbidly obese (BMIg35) (41% vs. 15%). Younger patients were more likely to have a longer hospital stay, and to have a history of diabetes, chronic kidney disease, and heart failure, but were less likely to have a history of coronary heart disease, hypertension, peripheral vascular disease, or stroke than older hospitalized patients (Table 1). Comparatively younger patients were more likely to have presented with symptoms of angina, dyspnea, and recent weight gain than older patients. These patients had better renal function, as reflected by eGFR lab values at the time of their acute hospitalization for HFpEF, but higher presenting diastolic blood pressures.

Hospital Treatment Practices

During their index hospitalization for HFpEF, comparatively younger patients were significantly less likely to have been treated with common cardiac medications including aspirin, beta blockers, diuretics, or digoxin than older patients (Table 2). The overall pattern of prescribing of cardiac medications was relatively similar at the time of hospital discharge, although younger patients were less likely to have received nitrates, but were more likely to have received statins, at the time of hospital discharge.

In-Hospital and Post Discharge Death Rates

Younger patients experienced relatively similar in-hospital death rates as older patients (6.7% vs 6.5%) (Table 3). On the other hand, post discharge death rates at 1 (32% vs 17%) and 2 years (46% vs 29%) after hospital discharge were significantly higher in older than in younger patients with HFpEF in both crude and multivariable adjusted analyses (Table 3).

In examining possible differences in these death rates in incident (first episode) cases only, relatively similar results were observed with slightly higher in-hospital death rates (7.1% vs 6.3%), but considerably lower 1 (28% vs 17%) and 2 year all-cause mortality rates (40% vs 25%), in younger vs older patients with HFpEF in both crude and multivariable adjusted analyses (Table 4).

Factors Associated With Post Discharge Mortality

Given the high death rates experienced by younger and older patients during the first year after hospital discharge for ADHF, we examined whether the factors that were associated

with 1-year post discharge death rates may have differed in younger as compared with older patients discharged from all central Massachusetts medical centers after HFpEF (Table 5).

Among older patients, those who had a lower eGFR during their index hospitalization and a longer hospital stay were more likely to have died during this high-risk period than respective comparison groups. On the other hand, patients with a first episode of ADHF, who had a history of hypertension, an admission diastolic blood pressure between 60 and 89 mm Hg, and those who presented with chest pain were less likely to have died during the first year post hospital discharge than respective comparison groups. Comparatively younger patients who presented with chest pain and with an admission diastolic blood pressure between 60 and 89 mmHg were less likely to have died during the first year post discharge than respective comparison groups.

Discussion

The results of this community-wide study of patients hospitalized with HFpEF suggest that comparatively younger patients were more likely to be male, non-Caucasian, obese, and have a history of diabetes and chronic kidney disease in comparison with older patients. In addition, younger patients were less likely to have a history of coronary artery disease, COPD, hypertension, or peripheral vascular disease than older patients hospitalized with HFpEF. Inhospital case-fatality rates were relatively similar in younger as compared with older patients while the long-term post discharge prognosis for older patients was significantly worse.

Comparatively younger patients with HFpEF were more likely to be male than older patients with HFpEF. One may speculate that these differences may be, in part, related to a greater frequency of coronary artery disease and hypertension, since a larger percentage of older women compared with men have these conditions (11).

In our primarily Caucasian study population, we found a small but significant difference in the percentage of patients with HFpEF based on race; 20% of relatively young patients diagnosed with HFpEF were non-Caucasian, while only 4% of older individuals were non-Caucasian. In examining racial differences and the incidence of heart failure among young adults in the Coronary Artery Risk Development in Young Adults (CARDIA) study, persons who developed heart failure before age 50 were more likely to have been black than white (12). Similar findings were observed in the Candesartan in Heart Failure Assessment in Reduction in Mortality and Morbidity programme (CHARM) where the youngest patients with heart failure were more likely to have been black (18% vs 2%) (3). One possible reason for these observed racial differences may be due to genetic polymorphisms, in particular, in blacks with known hypertension (12).

Potentially modifiable risk factors including obesity, diabetes mellitus, chronic kidney disease, and hypertension were significantly different between our two primary comparison groups. Younger patients with HFpEF were more likely to have been overweight or obese and have a history of diabetes mellitus and chronic kidney disease, while older individuals were more likely to have a history of previously diagnosed hypertension.

These data suggest that there may be different mechanisms underlying the development of HFpEF among individuals in these two age groups, although we can only speculate on these baseline differences since we were unable to follow apparently healthy young and older persons for the development of HFpEF over an extended period of time. In older patients, prolonged hypertension, leading to hypertrophy and fibrosis, may be sufficient to cause HFpEF. In contrast, in younger patients, multiple medical comorbidities, including obesity, diabetes mellitus, and chronic kidney disease are often present (14). These risk factors have been associated with a pro-inflammatory state resulting in myocyte damage at the cellular level and reduced levels of nitric oxide and protein kinase G which have been shown to cause myocyte hypertrophy and concentric left ventricular remodeling, which may lead to the development of HFpEF (14).

Using data from the Irbesartan in Heart Failure With Preserved Ejection Fraction (I-PRESERVE) study, patients with diabetes mellitus and chronic kidney disease were strong independent factors for all-cause mortality (15). In addition, diabetes mellitus, obesity, and chronic kidney disease have been shown to be associated with cardiac structural changes in patients with HFpEF (16). The present study adds to growing clinical and experimental evidence about the importance of focusing on these modifiable risk factors, especially elevated blood sugar levels and increased body weight, for preventing, or reducing the risk of dying from, HFpEF.

Somewhat surprisingly, younger patients with HFpEF had a longer hospital stay and relatively similar in-hospital death rates in comparison with older individuals. However, in the post-discharge period, older patients experienced considerably higher death rates than younger patients with HFpEF. These findings suggest that younger patients hospitalized with HFpEF may present with a “sicker, more decompensated” acute profile, while the higher long-term death rates among older individuals is likely related to their advanced age and frailty. Recent published data from the CHARM study showed that, when compared with older patients, younger patients with heart failure exhibited quite different clinical presentations and outcomes (3). This study also demonstrated an increased rate of obesity, reduced quality of life, and longer hospital stay in younger as compared with older patients with heart failure (3).

Study Strengths and Limitations

The primary strengths of this study were the large, population-based sample with independently validated ADHF, detailed information on patient’s demographic and clinical characteristics, and the comprehensive follow-up of discharged study patients. Limitations of this study included a predominantly Caucasian population from a single region in central New England, lack of information on post-discharge events other than death, and lack of data on cause-specific mortality. We also defined HFpEF as the presence of heart failure symptoms and a preserved ejection fraction ≥50% by echocardiography. Echocardiographic diastolic parameters were not included in the definition of HFpEF for this study. It also needs to be noted that patients included in the present study may differ from those enrolled in clinical trials where pre-specified inclusion/exclusion criteria are applied and more detailed diagnostic testing is available to more definitively rule in the presence of ADHF

(17,18). We did not take into account the potentially beneficial effects of the hospital therapies examined in this study given the nonrandomized nature of this investigation and the potential for confounding by drug indication. We also did not collect data on the use of, and adherence to, various cardiac medications by patients on a long-term basis after hospital discharge for ADHF nor were we able to assess the severity and duration of previously diagnosed comorbidities in this patient population.

Conclusions

While HFpEF is predominantly a disease of old age, the development of HFpEF in individuals less than 65 years of age is likely associated with the presence of multiple medical comorbidities and other predisposing factors. These findings reinforce the importance of carrying out longitudinal studies to follow healthy individuals of varying ages for the development of HFpEF so that risk factors for this condition can be identified, preventive strategies directed, and careful monitoring of these individuals take place as they age to reduce the long-term likelihood of developing HFpEF.

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Table 1

Characteristics of Patients Hospitalized with HFpEF According to Age

	Age (years)		
Characteristic	**<65 (n=357)**	**≥ 65 (n=2,041)**	**p-value**
Age (mean, years)	55.0	80.7	<0.001
Male (%)	42.6	32.0	<0.001
Caucasian (%)	80.2	96.1	<0.001
Body mass index (mean)	33.5	27.9	<0.001
Length of hospital stay (mean, days)	8.5	7.1	<.01
Medical history (%)			
Chronic kidney disease	29.1	23.9	<0.05
Chronic obstructive pulmonary disease	33.1	35.2	0.43
Coronary heart disease	39.5	45.6	<0.05
Diabetes	46.2	32.9	<0.001
Heart failure	47.6	41.2	<.05
Hypertension	63.9	75.3	<0.001
Peripheral vascular disease	13.5	21.8	<0.01
Stroke	8.1	13.4	<0.01
Presenting symptoms (%)			
Angina	39.2	27.6	<0.001
Dyspnea	95.0	90.2	<0.05
Edema	73.1	74.5	0.57
Generalized weakness	23.0	27.0	0.11
Nausea/Vomiting	19.3	16.5	0.20
Orthopnea	37.8	34.4	0.21
Weight Gain	13.7	8.3	<0.01
Laboratory Findings (mean, ±SD)			
Cholesterol (mg/dl)	162.4 (± 43.9)	154.8 (± 43.0)	0.12
Systolic blood pressure (mmHg)	147.0 (± 35.5)	146.5 (± 31.5)	0.79
Diastolic blood pressure (mmHg)	78.8 (± 21.1)	72.2(± 19.0)	<0.001
Estimated GFR (ml/min/1.73m^2)	58.7 (± 29.6)	51.7 (± 22.3)	<0.001
Glucose (mg/dL)	156.4 (± 75.1)	155 (± 62.7)	1.0

GFR - glomerular filtration rate; HFpEF - Heart failure with preserved ejection fraction

Table 2

Hospital Medical Treatment of Patients with HFpEF According to Age

	Age (years)		
	<65	65	
Hospital Medications (%)	**(n=357)**	**(n=2041)**	**p-value**
ACE-I/ARBs	50.4	51.7	0.65
Aspirin	48.5	60.2	<0.001
Beta blockers	55.5	64.7	<0.01
Digoxin	19.3	29.0	<0.001
Diuretics	93.8	97.7	<0.001
Statins	36.4	32.4	0.14
Nitrates	43.1	46.5	0.24
Discharge Medications (%)*			
ACE-I/ARBs	44.1	44.7	0.84
Aspirin	38.4	49.0	<0.001
Beta blockers	50.2	56.8	<0.05
Digoxin	13.2	22.4	<0.001
Diuretics	67.9	76.7	<.005
Statins	36.3	31.0	0.05
Nitrates	15.0	22.3	<0.01

ACE-I/ARBs – angiotensin converting enzyme inhibitor/angiotensin receptor blockers; HFpEF - Heart failure with preserved ejection fraction

*Among Hospital Survivors

Table 3

Hospital and Post Discharge Case-Fatality Rates (CFR) According to Age

	Age (years)			
Time Point	<65 (n=357) Crude CFR (%)	65 (n=2,041) Crude CFR (%)	Odds Ratio (95% CI)*	Odds Ratio (95% CI)**
In-hospital	6.7	6.5	1.06 (0.67,1.69)	1.12 (0.69,1.81)
1 year	17.1	31.7	0.48 (0.35,0.65)	0.50 (0.36,0.68)
2 years	28.5	45.6	0.53 (0.41,0.69)	0.53 (0.40,0.69)

*Controlling for age, sex, race, and history of heart failure

**Controlling for above variables plus history of coronary heart disease, hypertension, diabetes, peripheral vascular disease, renal disease, stroke, and presenting symptoms of chest pain, dyspnea, and weight gain.

Table 4

Hospital and Post Discharge Case-Fatality Rates (CFR) According to Age in Patients with a First Episode of Acute Heart Failure

	Age (years)			
Time Point	<65 (n=170)	≥ 65 (n = 841)		
	Crude CFR (%)	Crude CFR (%)	Odds Ratio (95% CI)*	Odds Ratio (95% CI)**
In-hospital	7.1	6.3	1.16 (0.59,2.26)	1.15 (0.56,2.34)
1 year	16.5	28.1	0.55 (0.35,0.87)	0.62 (0.38,1.00)
2 years	25.3	39.9	0.58 (0.39,0.87)	0.59 (0.39,0.89)

* Controlling for age, sex, and race

** Controlling for above variables plus history of coronary heart disease, hypertension, diabetes, peripheral vascular disease, renal disease, stroke, and presenting symptoms of chest pain, dyspnea, and weight gain.

Table 5

Factors Associated with 1 Year Post Discharge Mortality in Patients with HFpEF According to Age

Characteristic	Age (years)			
	<65		≥ 65	
	OR	95% CI	OR	95% CI
Age	1.03	0.98,1.08	**1.04**	**1.02,1.05**
Incident episode	1.03	0.50,2.10	**0.78**	**0.62,0.96**
Chest pain	**0.39**	**0.18,0.81**	**0.56**	**0.44,0.72**
Prior hypertension	0.58	0.27,1.23	**0.74**	**0.59,0.94**
Diastolic BP (mmHg)	1.0		1.0	
<60				
60–89	**0.42**	**0.20,0.89**	**0.77**	**0.61,0.97**
≥90	0.45	0.18,1.14	0.75	0.56,1.02
Estimated GFR (ml/min/1.73m^2)				
<30	1.57	0.59,4.13	**2.05**	**1.50,2.80**
30–59	1.12	0.51,2.47	1.12	0.88,1.44
≥60	1.0	--	1.0	-
Length of Stay	**1.05**	**1.02,1.09**	**1.05**	**1.04,1.07**

** Controlling for age, sex, race, history of coronary heart disease, heart failure, hypertension, diabetes, peripheral vascular disease, renal disease, and stroke, presenting symptoms of chest pain, dyspnea, and weight gain, admission diastolic blood pressure (BP), estimated glomerular filtration rate (GFR) findings, and hospital length of stay

GFR - glomerular filtration rate; HFpEF - Heart failure with preserved ejection fraction