

Comorbidity and Ventricular and Vascular Structure and Function in Heart Failure With Preserved Ejection Fraction A Community-Based Study

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Background—Patients with heart failure and preserved ejection fraction (HFpEF) display increased adiposity and multiple comorbidities, factors that in themselves may influence cardiovascular structure and function. This has sparked debate as to whether HFpEF represents a distinct disease or an amalgamation of comorbidities. We hypothesized that fundamental cardiovascular structural and functional alterations are characteristic of HFpEF, even after accounting for body size and comorbidities.

Methods and Results—Comorbidity-adjusted cardiovascular structural and functional parameters scaled to independently generated and age-appropriate allometric powers were compared in community-based cohorts of HFpEF patients (n=386) and age/sex-matched healthy n=193 and hypertensive, n=386 controls. Within HFpEF patients, body size and concomitant comorbidity-adjusted cardiovascular structural and functional parameters and survival were compared in those with and without individual comorbidities. Among HFpEF patients, comorbidities (obesity, anemia, diabetes mellitus, and renal dysfunction) were each associated with unique clinical, structural, functional, and prognostic profiles. However, after accounting for age, sex, body size, and comorbidities, greater concentric hypertrophy, atrial enlargement and systolic, diastolic, and vascular dysfunction were consistently observed in HFpEF compared with age/sex-matched normotensive and hypertensive.

Conclusions—Comorbidities influence ventricular-vascular properties and outcomes in HFpEF, yet fundamental disease-specific changes in cardiovascular structure and function underlie this disorder. These data support the search for mechanistically targeted therapies in this disease. (*Circ Heart Fail.* 2012;5:710–719.)

Key Words: anemia ■ heart failure with preserved ejection fraction ■ hypertension ■ diabetes mellitus
■ renal dysfunction ■ obesity

Patients with heart failure and preserved ejection fraction (HFpEF) are more frequently women, usually elderly with a history of hypertension and commonly have multiple comorbidities including obesity, anemia, diabetes mellitus, and renal dysfunction. Each of these comorbidities may influence ventricular and vascular structure and function, provoking debate as to whether HFpEF is a distinct disease requiring specific therapy or simply an amalgamation of age-related comorbidities.^{1–3} We hypothesized that HFpEF, as it presents in the community, is associated with unique alterations in ventricular-vascular properties after accounting for the confounding influences of age, sex, body size, and comorbidities.

Accordingly, we compared ventricular-vascular properties in a community-based cohort of HFpEF patients and control populations without heart failure (HF). To account for the effects of age, sex, and hypertension, we compared HFpEF patients with carefully age- and sex-matched normotensive (CON) and hypertensive (HTN) comparator populations from the same community. To account for body size differences, ventricular-vascular properties were scaled to allometric coefficients generated in an age-appropriate, disease-free, normal body size cohort. To account for the effects of comorbidities, comparison between HFpEF and control populations adjusted for comorbidities and the impact of comorbidities on ventricular-vascular properties and survival among HFpEF patients was defined.

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Methods

The study was approved by Mayo Clinic institutional review board and all subjects gave prospective consent or consent for use of medical records for research.

Study Subjects

Consecutive adult patients with HF (Framingham criteria) were prospectively enrolled between September 2003 and August 2009 by real-time interrogation of electronic medical records using natural language processing techniques as previously described.⁴ This cohort is derived from an ongoing prospective study and includes subjects included in earlier analyses of smaller subsets addressing other hypotheses. Subjects with significant left-sided valve disease, infiltrative, inflammatory or hypertrophic cardiomyopathy, congenital heart disease, pericardial disease, ejection fraction (EF) $<$ 50% or without assessment of vascular structure (ascending aortic diameter) were excluded. Vital status was determined from Rochester Epidemiology Project procedures as previously described.⁵

To identify unique age- and sex-matched CON (no HTN, diabetes mellitus, vascular or valve disease or HF) and HTN (but no HF) comparator groups, we used stratified random sampling of Olmsted County residents in the Mayo Clinic Echocardiographic Laboratory database (February 1998–June 2010) and manual medical record review (Selma F. Mohammed, MBBS) with matching in a 1:2:2 ratio of CON: HTN: HFpEF.

Physician's diagnoses with documentation of clinical features, supportive laboratory or imaging data, and medication use were used to define clinical characteristics (see Methods in the online-only Data Supplement) including medication use at the time of the index echocardiogram. Body surface area was calculated by the Gehan method ($BSA=0.0235 \times \text{height (cm)}^{0.42246} \times \text{weight (kg)}^{0.51456}$) and body mass index as weight/height^2 (kg/m^2).

Doppler Echocardiography

Echocardiograms were performed by registered cardiac diagnostic sonographers and interpreted by echocardiologists.

Cardiac Structure and Function

Left ventricle (LV) and atrial geometry were measured with 2D or M-mode echocardiography and used to calculate EF, LV mass, relative wall thickness, left atrial volume (area-length method), stroke volume (SV), and pulmonary artery systolic pressure (PASP) according to American Society of Echocardiography conventions.^{5,6} LV end-diastolic volume (EDV) was calculated using SV and EF to avoid geometric assumptions ($EDV=SV/EF$).^{4,7} Cardiac power output (CPO) was computed ($\text{cardiac output [CO]} \times \text{mean arterial pressure [MAP]} \times 2.22 \times 10^{-3}$) in watts.⁸ The early diastolic septal annular tissue velocity (e'), transmitral flow velocity (E), and deceleration time were used to quantify relaxation, filling pressure (E/e'), and operant diastolic stiffness. To estimate LV operating compliance (EDV at a given end diastolic pressure), natural log of EDV was compared between groups adjusting for age, sex, body size (natural log of height and natural log of weight), comorbidities, and quartiles of E/e' (see Methods in the online-only Data Supplement).

Vascular Structure and Function

Aortic diameter (D) was used to calculate aortic area ($\pi D^2/4$). Brachial pulse pressure (PP; systolic-diastolic blood pressure), (MAP, diastolic blood pressure+0.4128 \times PP),⁸ end systolic pressure (ESP; 0.9 \times brachial systolic blood pressure),⁹ effective arterial elastance (E_a ; ESP/SV),⁹ total systemic arterial compliance (SAC; SV/PP), and systemic vascular resistance (SVR; [MAP/CO] \times 80) were calculated as previously described.⁴ All comparisons of E_a and SAC between groups were adjusted for heart rate and MAP, respectively.

Allometric Scaling

Because the relationship between body size and physiologic parameters is often complex and nonlinear, simple ratiometric scaling to

height or BSA may yield erroneous conclusions.^{8,10–12} We assembled a disease-free, community-based cohort with a normal body size ($<$ 25 kg/m^2 ; $n=345$; characteristics in the online-only Data Supplement Table I) to derive age and sex appropriate allometric scaling coefficients (see Methods in the online-only Data Supplement). Allometric coefficients were obtained by regressing the natural log of the ventricular-vascular properties on log of height or BSA after adjustment for age and sex. This log-log method effectively results in a multiplicative model¹³ that has the same functional form as the standard allometric equations and yields nearly identical results as nonlinear regression.¹² Whereas sex–body size interaction terms were not significant, the age–body size interaction terms were significant for most parameters. Thus, scaling coefficients were derived in a subset (age $>$ median) of the normal cohort with an age distribution similar to the HFpEF and comparator populations (see Methods and Tables I and II in the online-only Data Supplement). This age-appropriate, normal body size cohort was also used to derive upper normal values (mean+2SD) for allometrically scaled LV mass measurements.

Sensitivity Analyses

To further evaluate differences in ventricular-vascular properties adjusting for body size, a sensitivity analysis was performed using multivariable least squares linear regression to compare log-transformed ventricular-vascular properties between groups (dummy variables) adjusting for log-transformed height and weight as well as age, sex, and comorbidities rather than using the allometric scaling indices derived in the normal populations.

Laboratory Data

Glomerular filtration rate was estimated using the modification of diet in renal disease formula.

Missingness

The missingness rate for all variables with $<$ 100% availability is shown in the online-only Data Supplement Table III.

Statistical Analysis

Data are presented as mean \pm SD or % frequency. For continuous variables, comparisons across groups were performed by 1-way ANOVA followed by Dunnett's test for group comparisons to HFpEF. For categorical variables, comparisons across and between groups were performed by the χ^2 test. Multivariable least squares linear regression was used to test multiple covariates where groups were entered as dummy variables appropriately constructed for the comparison of interest.

Comparisons of ventricular-vascular properties between HFpEF patients with or without an individual comorbidity (anemia, diabetes mellitus, or renal dysfunction) was performed in log-log models where the log-transformed variables were compared between groups adjusting for natural log of height, natural log of weight, and other concomitant comorbidities. Comparisons of ventricular-vascular properties between HFpEF patients with or without obesity was similarly performed adjusting for natural log of height and other concomitant comorbidities. For parameters not related to body size, comparisons adjusted for other comorbidities. The adjusted geometric means within groups and the P value for the group effect are presented.

Survival up to 5 years after HF diagnosis was assessed. The Kaplan–Meier method tested for differences in survival between groups by the log-rank test. Cox proportional-hazards regression was used to adjust for the effect of differences in baseline characteristics on survival.

All analyses were 2 tailed, and a $P<$ 0.05 was considered statistically significant. Analysis was performed using the JMP[®] analysis software.

Results

Clinical Characteristics

HFpEF subjects were elderly and predominately women with a high prevalence of obesity, anemia, diabetes mellitus, renal dysfunction, cardiovascular conditions, and medication use

Table 1. Characteristics of Normal (CON) and Hypertensive (HTN) Controls and HFpEF Patients

	CON	HTN	HFpEF
N	193	386	386
Age	77.1±8.5	76.9±11	77.5±11.4
Male, %	44%	44%	44%
Weight, kg	72±18	78±19	83±24*†
Height, m	1.67±0.11	1.66±0.11	1.66±0.1
Body surface area, m ²	1.83±0.27	1.91±0.27	1.97±0.31*†
Systolic blood pressure, mm Hg	121±12	137±20	132±23*†
Pulse pressure, mm Hg	52±12	65±18*	64±19*
Heart rate, bpm	71±14	69±15	72±15
Comorbidities			
Hypertension	0%	100%	86%*†
% Obese (BMI≥30Kg/m ²)	14%	33%	42%
Anemia (<12g/dl female; <13g/dL male)	29%	25%	56%*†
Diabetes mellitus	0%	18%	35%*†
GFR, mL·min ⁻¹ ·1.73 m ⁻²	70±18	65±20	56±23*†
Atrial fibrillation	14%	18%	47%*†
Coronary artery disease	0%	24%	51%*†
Peripheral vascular disease	0%	10%	21%*†
Cerebrovascular disease	0%	19%	31%*†
Dyslipidemia	30%	51%	65%*†
Cigarette smoking (ever)	39%	42%	51%*†
Medications			
β-blockers	8%	44%	63%*†
ACE-Is/ARBs	0%	43%	52%*†
Calcium channel blockers	3%	22%	36%*†
Diuretics	3%	48%	63%*†
Statins	11%	35%	48%*†

HFpEF indicates heart failure and preserved ejection fraction; BMI, body mass index; GFR, glomerular filtration rate; ACE-Is, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers.

* $P<0.05$ vs CON.

† $P<0.05$ HFpEF vs HTN.

‡ANOVA for continuous variables, χ^2 for discrete variables.

(Table 1). Systolic and mean blood pressures were higher in HFpEF than CON but lower in HFpEF than HTN, whereas PP was higher in HFpEF than CON but similar to HTN.

Differences across groups were similar in men and women (in the online-only Data Supplement Table IV) although men with HFpEF were younger and had more vascular disease than women with HFpEF.

Cardiac Structure

HFpEF patients had higher height- or BSA-scaled LV mass than CON or HTN (Table 2). In the sensitivity analysis, natural log of LV mass was greater in HFpEF than CON or HTN (Table 3). HFpEF patients had more abnormal LV geometry (Figure 1) whether the presence of LV hypertrophy was ascertained using the allometrically scaled or published (sex-specific LV mass/BSA) hypertrophy criteria.

Height- or BSA-scaled EDV was not different in HFpEF than CON but tended to be (height-scaled) or was (BSA-scaled)

smaller in HFpEF than HTN (Table 2). In the sensitivity analysis, natural log of EDV was similar in HFpEF and CON but smaller in HFpEF than HTN (Table 3).

HFpEF patients had larger height- or BSA-scaled left atrial volume than CON or HTN (Table 2). The difference in left atrial volume between HFpEF and CON ($P<0.001$) or HTN ($P<0.001$) persisted after also adjusting for the presence of atrial fibrillation. Similarly, in the sensitivity analysis, natural log of left atrial volume was greater in HFpEF than CON or HTN (Table 3) and when also adjusting for atrial fibrillation ($P<0.001$).

LV Systolic Function

EF was slightly but significantly lower in HFpEF than CON or HTN (Table 2). The lower EF in HFpEF compared with CON ($P=0.002$) or HTN ($P<0.001$) persisted after also adjusting for the presence of coronary disease.

Height-scaled SV was similar in HFpEF and CON but BSA-scaled SV was lower in HFpEF than CON (Table 2). Height- or BSA-scaled SV was lower in HFpEF than HTN. In sensitivity analysis, natural log of SV was smaller in HFpEF than CON or HTN (Table 3). Differences in CO were similar to SV (and significant) across groups (data not shown).

Height- or BSA-scaled CPO in HFpEF was similar to CON but lower than HTN (Table 2). In sensitivity analysis, natural log of CPO in HFpEF was similar to CON but <HTN (Table 3).

LV Diastolic Function

E/e', PASP, and deceleration time were more abnormal in HFpEF than CON or HTN (Table 2). Adjusting for age, sex, natural log of height, natural log of weight, comorbidities, and E/e', natural log of EDV was smaller in HFpEF than HTN (Table 4) consistent with lower diastolic operating compliance. Given the limited range of E/e' in CON, this analysis was restricted to HFpEF and HTN subjects.

Vascular Structure and Function

Aortic area was larger in HFpEF than CON but similar to HTN (Table 5). In sensitivity analysis, natural log of aortic area was similar in HFpEF, CON, and HTN (Table 3).

Height- or BSA-scaled Ea was higher in HFpEF than CON and tended to be higher in HFpEF than HTN (Table 5). In sensitivity analysis, natural log of Ea was higher in HFpEF than CON and tended to be higher than HTN (Table 3).

Height- or BSA-scaled SVR was higher in HFpEF than CON but similar in HFpEF and HTN (Table 5). In sensitivity analysis, natural log of SVR was higher in HFpEF than CON but similar in HFpEF and HTN (Table 3).

Height- or BSA-scaled SAC was lower in HFpEF than CON and tended to be (Height-scaled) or was (BSA-scaled) lower in HFpEF than HTN (Table 5). In sensitivity analysis, natural log of SAC was lower in HFpEF than CON or HTN (Table 3).

Comorbidities and Ventricular and Vascular Structure and Function in HFpEF

Obesity

Obesity was present in 42% of HFpEF patients (Table 6). Obese HFpEF patients were younger, more likely diabetic

Table 2. Ventricular Structure and Function in Normal (CON) and Hypertensive (HTN) Controls and HFpEF Patients

	CON	HTN	HFpEF	HFpEF vs CON‡			HFpEF vs HTN‡	
				ANOVA (P)	PE (HFpEF)	P‡	PE (HFpEF)	P‡
Cardiac structure								
LV mass/height ^{1,6}	66± 17	77± 20	89±27*†	<0.001	9.9	<0.001	4.8	<0.001
LV mass/BSA ^{1,19}	74± 16	81± 19	91±25*†	<0.001	7.9	<0.001	4.1	<0.001
Relative wall thickness	0.42±0.07	0.44±0.07	0.46±0.10*†	<0.001	0.02	<0.001	0.01	<0.001
End diastolic volume/height ^{1,4}	62.9±13.4	67± 15.5	66.1±17.7	0.029	0.8	0.32	-1.0	0.12
End diastolic volume/BSA ^{0,98}	72.1±15.2	72.9±17.3	69.9±18.0	0.063	-1.1	0.22	-1.7	0.013
Left atrial volume/height ^{2,26}	18.9±7.2	21.8± 7.7	28.7±10.7*†	<0.001	4.7	<0.001	3.2	<0.001
Left atrial volume/BSA ^{1,48}	24.7±9.5	26.8±9.9	34.1±13.2*†	<0.001	4.6	<0.001	3.5	<0.001
Systolic performance								
Ejection fraction,%	64.1±5.9	64.3±5.7	61.8±6.9*†	<0.001	-1.4	<0.001	-1.5	<0.001
Stroke volume/Height ^{1,29}	42.7±8.4	45.6±10.2	42.9±10.9†	0.001	-0.5	0.301	-1.8	<0.001
Stroke volume/BSA ^{0,92}	48.0±9.5	48.7±11.3	44.6±10.8*†	<0.001	-1.8	0.001	-2.3	<0.001
Cardiac power output/Height ^{0,97}	0.70±0.16	0.79±0.21	0.74±0.24†	<0.001	0.01	0.23	-0.03	<0.001
Cardiac power output/BSA ^{0,88}	0.68± 0.15	0.74±0.19	0.67±0.21†	<0.001	0.00	0.73	-0.03	<0.001
Diastolic function								
Mitral E/e'	10.8±4.1	13.0±5.8	17.2±8.4*†	<0.001	2.7	<0.001	1.7	<0.001
e', m/sec	0.070±0.021	0.063±0.019	0.062±0.022*	<0.001	-0.004	<0.001	-0.001	0.44
Deceleration time, ms	230±46	227±55	200±52*†	<0.001	-15	<0.001	-12	<0.001
PASP, mm Hg	33±11	36±11	48±15*†	<0.001	6.2	<0.001	4.8	<0.001

HFpEF indicates heart failure and preserved ejection fraction; PE, parameter estimate; LV, left ventricular BSA, body surface area; E/e', filling pressure; PASP, pulmonary artery systolic pressure.

*P<0.05 HFpEF vs CON

†P<0.05 HFpEF vs HTN.

‡Parameter estimate (PE) is increment in variable associated with the HFpEF state as compared to CON or HTN when adjusted for age, sex, hemoglobin, glomerular filtration rate, and diabetes.

and had higher hemoglobin and PP than nonobese HFpEF patients. Obese patients had higher LV mass, EDV, and atrial volume with higher relative wall thickness suggesting concentric remodeling. Obese HFpEF patients tended to have higher EF and had higher SV, CO, and CPO than nonobese HFpEF patients but diastolic function indices were similar. Whereas LV operating compliance (Table 4) increased with increasing weight and height, there was no leftward shift of this relationship in obese patients to suggest worse diastolic function.

Aortic area and SAC were larger, Ea was and SVR tended to be lower in obese HFpEF patients suggesting that the higher PP in obese patients reflects the higher SV rather than greater arterial stiffness. Mean and median follow-up among HFpEF survivors was 4.2±1.1 and 4.9 years, respectively. Obesity was associated with better outcome adjusting for age, sex, and other concomitant comorbidities (Figure 2A and 2E). The relationship between obesity and outcomes did not appear U-shaped (in the online-only Data Supplement Figure).

Table 3. Comorbidity-Adjusted Analysis Showing Effect of Body Size and Group on Ventricular-Vascular Parameters From Log-Log Models

Log-Transformed Variable	Natural log of Height, m		Natural Log of Weight, kg		HFpEF vs CON‡		HFpEF vs HTN‡	
	PE	P	PE	P	PE(HfPEF)	P	PE (HFpEF)	P
LV mass, g	0.304	0.15	0.523	<0.001	0.096	<0.001	0.045	<0.001
End diastolic volume, mL	0.812	<0.001	0.238	<0.001	-0.009	0.49	-0.024	0.012
Left atrial volume, ml	0.276	0.40	0.558	<0.001	0.160	<0.001	0.116	<0.001
Stroke volume, mL	0.691	<0.001	0.229	<0.001	-0.035	0.004	-0.050	<0.001
Cardiac output, L/min	0.604	0.003	0.266	<0.001	-0.035	0.004	-0.034	<0.001
Cardiac power output, watts	0.366	0.13	0.319	<0.001	-0.012	0.39	-0.057	<0.001
Aortic area, mm ²	0.470	0.009	0.199	<0.001	0.017	0.11	0.002	0.78
Arterial elastance, mm Hg/mL	-0.906	<0.001	-0.179	<0.001	0.066	<0.001	0.019	0.064
Systemic vascular resistance, dyne·s ⁻¹ ·cm ⁻⁵	-0.749	0.002	-0.225	<0.001	0.058	<0.001	0.010	0.38
Arterial compliance, mL/mm Hg	0.887	0.003	0.176	0.004	-0.068	<0.001	-0.033	0.013

HFpEF indicates heart failure and preserved ejection fraction; CON, normal; HTN, hypertension; PE, parameter estimate.

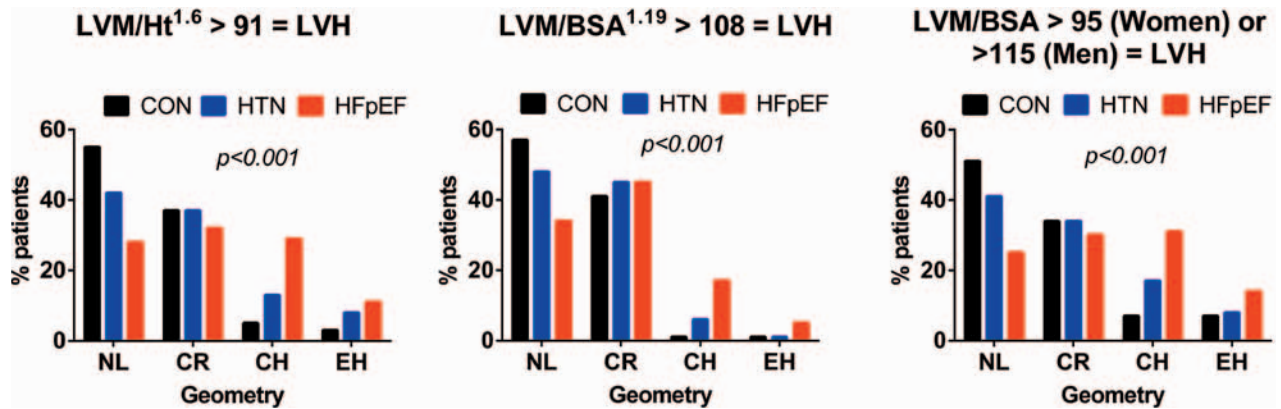


Figure 1. Left ventricular geometry in CON and HTN controls and HFpEF. The prevalence of NL, CR and CH or EH based on relative wall thickness (\leq or >0.42) and the presence or absence of LVH are shown using alternate methods of defining LVH. LVH indicates left ventricular hypertrophy; BSA, body surface area; LVM, left ventricular mass; CON, age/sex-matched normotensive controls; HTN, hypertensive; HFpEF, heart failure and preserved ejection fraction; NL, normal; CR, concentric remodeling; CH, concentric hypertrophy; EH, eccentric hypertrophy.

Anemia

Anemia was present in 56% of HFpEF patients (Table 6). Anemic HFpEF patients were older, had worse renal function and higher PP than nonanemic HFpEF patients. Adjusting for age, sex, height, weight, and other comorbidities, EDV and diastolic operating compliance (Table 4) were higher in anemic patients whereas other diastolic function parameters were similar to nonanemic HFpEF patients. SV, CO, and CPO were higher and SVR and E_a were lower with no difference in SAC suggesting that the increased PP in anemic patients reflects the higher SV. Anemia was associated with poorer

outcome adjusting for age and sex and other concomitant comorbidities (Figure 2B and 2E).

Diabetes Mellitus

Diabetes mellitus was present in 35% of HFpEF patients (Table 6). Diabetic HFpEF patients were younger, more obese and had worse renal function, and higher PP than nondiabetics. Adjusting for age, sex, height, weight, and other comorbidities, diabetic HFpEF patients tended to have higher LV mass but had similar EDV and systolic function to nondiabetics. Diabetics had higher E/e' but other diastolic

Table 4. Left Ventricular Operating Compliance

Term	Parameter Estimate	95% CI	P
Model for natural log of end diastolic volume ($R^2=0.29$) in HTN and HFpEF subjects			
Intercept	3.676	3.179; 4.173	<0.001
Sex(female)	-0.066	-0.094; -0.039	<0.001
Natural log weight, kg	0.241	0.146; 0.337	<0.001
Natural log height, m	0.833	0.375; 1.291	<0.001
Hemoglobin, g/dL	-0.017	-0.028; -0.006	0.002
E/e' quartile	0.031	0.011; 0.050	0.002
Age, y	-0.002	-0.004; 0.0002	0.079
Glomerular filtration rate, $\text{mL}\cdot\text{min}^{-1}\cdot 1.73\text{ m}^{-2}$	0.000	-0.0006; 0.0013	0.48
Diabetes mellitus	0.007	-0.017; 0.030	0.58
HFpEF vs HTN (HFpEF)	-0.033	-0.054; -0.012	0.002
Model for natural log of end diastolic volume (base model $R^2=0.27$) in HFpEF subjects			
Intercept	3.286	2.657; 3.915	<0.001
Age, y	-0.002	-0.004; 0.001	0.22
Female	-0.063	-0.100; -0.025	0.001
Natural log height	0.464	-0.169; 1.097	.0015
Natural log weight	0.321	0.199; 0.443	<0.001
E/e' quartile	0.032	0.006; 0.058	0.016
Addition of			
Obesity	0.014	-0.031; 0.059	0.55
Anemia	0.045	0.018; 0.072	0.001
Diabetes mellitus	0.012	-0.019; 0.043	0.45
Renal dysfunction, $\text{GFR}<60\text{ ml}/\text{min}/1.73\text{ m}^2$	0.002	-0.028; 0.032	0.91

HFpEF indicates heart failure and preserved ejection fraction; HTN, hypertension.

Table 5. Vascular Structure and Function in Normal (CON) and Hypertensive (HTN) Controls and HFpEF Patients

	CON	HTN	HFpEF	ANOVA P	HFpEF vs CON‡		HFpEF vs CON‡	
					PE (HFpEF)	P‡	PE (HFpEF)	P‡
Aortic area	955±193	991±257	986±262	0.23	32	0.004	6	0.50
Arterial elastance/height ^{-1.25}	2.58±0.53	2.79±0.79	2.89±0.88*	<0.001	0.19	<0.001	0.06	0.059
Arterial elastance/BSA ^{-0.77}	2.02±0.43	2.19±0.64	2.27±0.70*	<0.001	0.15	<0.001	0.05	0.066
Vascular resistance/height ^{-1.06}	2241±512	2398±645	2391±766*	0.038	137	<0.001	32	0.24
Vascular resistance/BSA ^{-0.62}	1879±431	2080±548	2106±671*	<0.001	151	<0.001	36	0.13
Arterial compliance/height ^{1.47}	0.78±0.27	0.69±0.25	0.65±0.25*	<0.001	-0.03	0.011	-0.02	0.092
Arterial compliance/BSA ^{0.79}	1.04±0.37	0.88±0.32	0.82±0.31*†	<0.001	-0.07	<0.001	-0.03	0.035

HFpEF indicates heart failure and preserved ejection fraction; BSA, body surface area.

*P<0.05 HFpEF vs CON

†P<0.05 HFpEF vs HTN.

‡Parameter estimate (PE) is increment in variable associated with the HFpEF stat as compared to CON or HTN when adjusted for age, sex, hemoglobin, glomerular filtration rate, and diabetes mellitus.

parameters, including operating compliance (Table 4) were similar. Diabetic patients had smaller aortas and lower SAC than nondiabetics. Whereas Ea and SVR were similar, PP was higher in diabetics before (P<0.001) and after adjustment for

age, sex and other comorbidities (Table 6). The higher PP was also apparent after also adjusting for MAP and MAP² (P<0.001) and given the similar SV, these parameters suggest stiffer vasculature in diabetic HFpEF patients.¹⁴ Diabetes

Table 6. Clinical Characteristics and Ventricular and Vascular Structure and Function in HFpEF Patients According to Comorbidities

	Nonobese	Obese	No Anemia	Anemia	No Diabetes Mellitus	Diabetes Mellitus	GFR≥56	GFR<56
n	222	164	165	206	251	135	183	188
Clinical characteristics	Unadjusted mean±SD							
Age, y	80±10	74±12*	76±12	78±11*	79±12	75±11*	74±12	80±11*
Male, %	43%	45%	41%	47%	42%	46%	52%	37%
Diabetic, %	22%	53%*	33%	36%	0%	100%	33%	38%
GFR, mL·min ⁻¹ ·1.73m ⁻²	56±24	57±21	59±17	54±26*	58±23	53±21*	73±18	40±13*
Hemoglobin, g/dL	11.9±2.0	12.4±2.2*	13.9±1.4	10.7±1.3*	12.1±2.0	12.1±2.3	12.6±2.0	11.6±2.1*
Body mass index, kg/m ²	25±3	37±7*	31±8	29±7	28±6	34±9*	31±8	30±8
Pulse pressure, mm Hg	63±19	67±19*	61±19	67±18*	62±19	69±18*	61±19	68±19*
Cardiac structure and function	Adjusted geometric means							
LV mass, g	182	218†	192	200	190	201‡	191	200
End diastolic volume, mL	103	111†	124	137†	128	132	131	130
Relative wall thickness	0.45	0.48†	0.46	0.46	0.47	0.46	0.45	0.46‡
Left atrial volume, mL	79	93†	83	85	85	83	82	86
Ejection fraction, %	61	62‡	62	61	62	61	61	62†
Stroke volume, mL	76	86†	76	83†	79	81	79	80
Cardiac output, L/min	5.36	5.86†	5.23	5.90†	5.58	5.53	5.65	5.46
Cardiac power output watts	1.1	1.24†	1.1	1.21†	1.16	1.15	1.16	1.14
Mitral E/e'	17.1	17.4	16.8	17.6	16	18.4†	16.6	17.8
e', m/s	0.061	0.061	0.06	0.062	0.063	0.059	0.063	0.06
Deceleration time, ms	199	207	207	199	200	206	203	203
PASP, mm Hg	48	46	49	45‡	47	47	45	49†
Vascular structure and function								
Aortic area, mm ²	908	1005†	943	952	988	908†	955	940
Arterial elastance, mm Hg/ml	1.53	1.41†	1.55	1.42	1.46	1.50	1.46	1.51
Vascular resistance, dyne·s ⁻¹ ·cm ⁻⁵	1378	1293†	1452†	1246†	1338	1351	1311	1379
Arterial compliance, mL/mm Hg	1.23	1.36†	1.30	1.26	1.35	1.22†	1.30	1.25

HFpEF indicates heart failure and preserved ejection fraction; GFR, glomerular filtration rate; LV, left ventricular; E/e', filling pressure; PASP, pulmonary artery systolic pressure.

* Unadjusted ANOVA P<0.05

† Adjusted P<0.05

‡ Adjusted P<0.10.

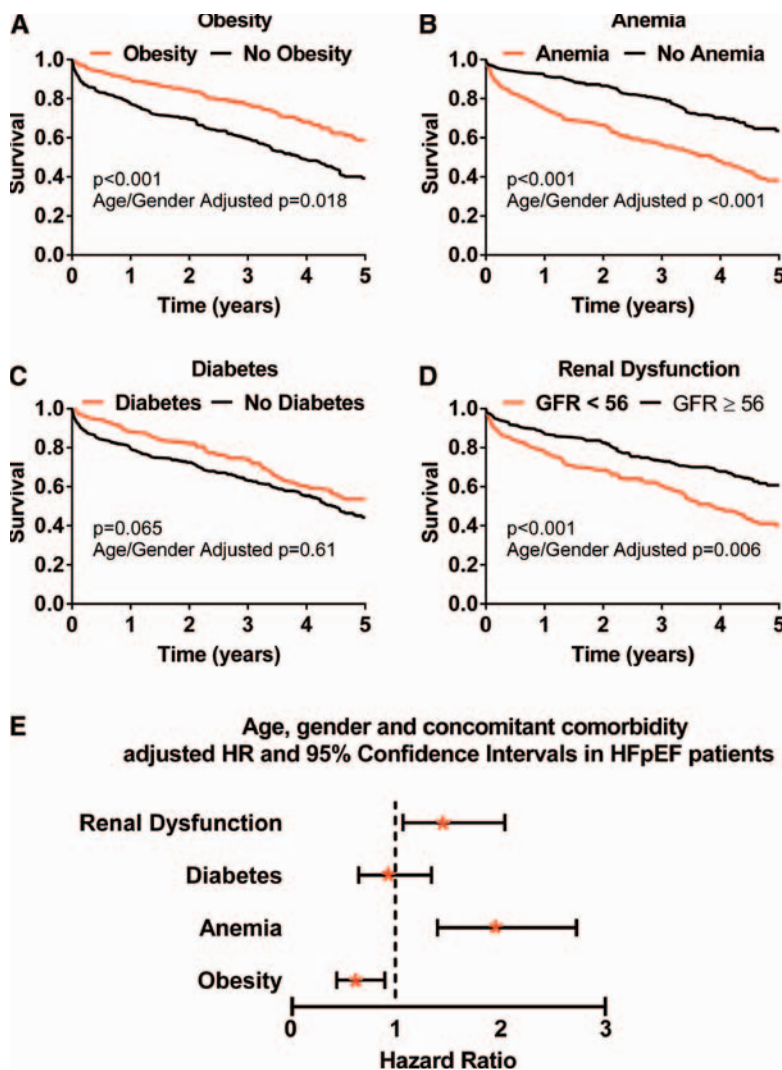


Figure 2. Kaplan–Meier survival curves in heart failure and preserved ejection fraction according to the presence of obesity (A), anemia (B), diabetes mellitus (C) or renal dysfunction (D) with age, sex, and concomitant comorbidity-adjusted hazard ratios and 95% CI for obesity, anemia, diabetes mellitus, or renal dysfunction (E). GFR indicates glomerular filtration rate.

mellitus was not associated with differences in outcome adjusting for age and sex and other concomitant comorbidities (Figure 2C and 2E). Compared with nondiabetics, diabetic HFpEF patients were more frequently treated with beta blockers (58% nondiabetic versus 72% diabetic), angiotensin antagonists (40% nondiabetic versus 73% diabetic) and statins (37% nondiabetic versus 67% diabetic) ($P < 0.01$ for all).

Renal Dysfunction

HFpEF patients with renal dysfunction were older, more often women, and had lower hemoglobin and pulse pressures than patients without renal dysfunction (Table 6). Adjusting for age, sex, height, weight, and other comorbidities, EF and PASP were higher in renal dysfunction patients but all other ventricular-vascular properties were similar to those with better renal function (Tables 5 and 6). Renal dysfunction was associated with poorer outcome adjusting for age and sex, and other concomitant comorbidities (Figure 2D and 2E).

Discussion

In this large, prospectively identified, rigorously characterized HFpEF cohort, we found that compared with age- and

sex-matched normotensive and hypertensive controls, HFpEF patients consistently displayed abnormalities in ventricular-vascular properties above and beyond that explainable by comorbidity burden and body size. Among HFpEF patients, comorbidities were associated with unique clinical, structural, functional, and prognostic profiles. Obese patients were younger, and whereas they displayed greater concentric remodeling, their LV systolic and vascular function and outcomes were better than nonobese HFpEF patients. Anemic patients were older, displayed ventricular and vascular characteristics consistent with a high(er) output state, and had worse outcomes than nonanemic HFpEF patients. Diabetic patients were younger and heavier and had higher filling pressures and stiffer vasculature, yet they were aggressively treated and their outcomes were similar to nondiabetics. Patients with renal dysfunction were older and despite a lack of unique structural or functional features, they had worse outcomes than patients with better renal function. Although these data confirm that comorbidities influence ventricular-vascular properties and outcomes among HFpEF patients, they underscore that fundamental disease-specific changes in cardiovascular function underlie this disorder and support the search for specific therapies.

Comorbidities and Ventricular and Vascular Structure and Function in HFpEF

We have previously characterized cardiovascular structure and function in a smaller cohort of HFpEF patients.^{4,7,15} The current analysis differs in several important ways. The prospectively enrolled HFpEF cohort is larger and the comparator groups are matched for age and sex, whereas comparator populations in the previous studies were on average 10 (HTN) to 20 (CON) years younger than the HFpEF population. The current data utilize more appropriate analyses to account for differences in body size, vascular structure is assessed, analyses are adjusted in the primary and sensitivity analyses for comorbidities, and potential differences among HFpEF patients according to the presence of key comorbidities are evaluated.

The current focus on the association between comorbidities and differences in ventricular-vascular properties between HFpEF and control populations or within HFpEF patients is important because comorbidities have significant effects on cardiovascular structure and function in non-HF populations and in animal models. Obesity has been linked to pathologic LVH, atrial enlargement, systolic and diastolic LV dysfunction, endothelial dysfunction, vasoconstriction and increased vascular stiffness.^{11,16} Chronic severe anemia decreases SVR and leads to volume expansion, eccentric remodeling, and LV systolic and diastolic dysfunction.^{17,18} Diabetes mellitus has been linked to LVH, systolic and diastolic LV dysfunction, endothelial dysfunction, and increased vascular stiffness.^{19,20} Intrinsic renal disease is associated with apoptosis, fibrosis, hypertrophy, and LV dysfunction.^{21,22} Thus, the potential for comorbidities to account for the alterations in LV structure and function observed in HFpEF patients is real.

Here, with strict attention to matching for age, sex, and hypertension, appropriate analyses for body size-related differences and adjustment for comorbidities, we demonstrate that HFpEF is independently associated with more severe alterations in ventricular-vascular properties than observed in healthy or hypertensive controls. Specifically, compared with healthy controls, HFpEF patients had more cardiac remodeling (concentric LVH and larger atria), systolic (lower EF) and diastolic (higher E/e' and PASP and lower e' and deceleration time) dysfunction, and more abnormal vascular function (higher Ea and SVR and lower SAC). Compared with hypertensive controls, HFpEF patients had more cardiac remodeling (concentric LVH and larger atria), systolic (lower EF, CO, and CPO) and diastolic (higher E/e' and PASP and lower e', deceleration time and operating compliance) dysfunction whereas vascular function was not consistently and only subtly more impaired in HFpEF than HTN.

Notably, adjusting for body size differences (Tables 3 and 5) aortic size was similar across the CON, HTN, and HFpEF groups. These data suggest that intrinsic stiffening of the aorta, rather than further degenerative expansion, contributes to vascular stiffening in HFpEF versus CON and HTN as previously suggested.²³

It may be that HFpEF represents a unique synergistic interaction between the effects of aging, hypertension, and comorbidities, particularly cardiovascular comorbidities, to promote ventricular and vascular remodeling and dysfunction but in the absence of a large myocardial infarction leading to

reduced EF.²⁴ If so, measures to ensure healthy aging, treatment of risk factors, and prevention of other comorbidities would likely prevent or delay the onset of HFpEF. The factors that mediate progression from HTN to HFpEF are not yet clear. Quantification of the severity, duration, and control of hypertension over time is difficult and thus we are unable to determine whether a greater lifetime burden of arterial HTN mediates the more severe remodeling, ventricular dysfunction and vascular dysfunction associated with HFpEF compared with age/sex-matched HTN controls. Because essential HTN is a polygenic disease, there may be greater susceptibility to HFpEF in certain genetic subtypes or unique interactions with behavioral modulators.

Impact of Comorbidities Among HFpEF Patients

It is notable that male, obese and diabetic HFpEF patients present at a younger age, underscoring the variability in the syndrome beyond the stereotypical profile of frail, elderly, hypertensive females. This may suggest that the interaction of aging and HTN is sufficient to cause HFpEF in some patients, but that comorbidities may play a role in accelerating progression to HFpEF in others.

Obese HFpEF patients had higher LV mass, EDV and atrial size, better preserved systolic performance and more preserved vascular function compared with nonobese HFpEF patients. Because most of these parameters are related to body size, and particularly weight, determining whether these changes represent a physiologic adaptation to higher metabolic demands or pathologic remodeling is difficult. It is important to note that in non-HF cohorts, body size-independent vascular parameters are more abnormal in obese subjects and increases in height-scaled LV mass are associated with poorer outcomes in general population-based studies.^{11,12} However, here, compared with nonobese HFpEF patients, obese HFpEF patients had better survival as has been noted in both HFpEF and HF reduced ejection fraction.²⁵⁻²⁸ This obesity paradox has been ascribed to diagnosis bias (misdiagnosis of HF in obese patients), lead time bias (earlier symptom onset attributable to additional metabolic demands of obesity), improved nutritional status or an anti-inflammatory effect of obesity in HF.²⁵⁻²⁸ The characterization of ventricular-vascular parameters in obese and nonobese HFpEF patients in the current study is unique and the better preserved systolic and vascular function may provide insight into the better outcomes observed in obese HFpEF patients. In this community study, the U-shaped relationship between obesity and mortality reported in a large clinical trial HFpEF cohort²⁸ after adjustment for a large number of covariates was not observed, but our data set and sample size may limit the power to detect such a relationship.

Consistent with studies of severe anemia in animal models and humans without HF,^{17,29,30} the relatively mild anemia in HFpEF patients was associated with increased LV size and operating compliance, a high(er) output state and lower SVR and Ea, suggesting that anemia uniquely influences ventricular-vascular properties in HFpEF. Whether the well described association between anemia and mortality in HFpEF and HF reduced ejection fraction³¹ reflects the additional load and reduced oxygen carrying capacity related to anemia or the effects of the factors causing anemia etiology (iron deficiency,

inflammation, hypervolemia) is not clear.³² Of note, a recent study demonstrated improved functional and structural indices in HFpEF with carefully titrated erythropoietin treatment.³³ It is of interest that LV dilatation; higher CO, and reduced arterial load E_a were seen in both anemic and obese compared with nonanemic/nonobese HFpEF patients but with divergent associations with outcome. This may suggest relatively more physiologic load in obesity versus pathophysiologic load in anemia in HFpEF but such interpretations are speculative.

Diabetic HFpEF patients had higher filling pressures and evidence of greater arterial stiffness, consistent with invasive studies suggesting increased chamber and myocyte stiffness in HFpEF with diabetes mellitus³⁴ and animal and human studies demonstrating vascular dysfunction in diabetic, non-HF subjects.¹⁹ The lack of association of diabetes mellitus with poorer outcomes is surprising given that diabetes mellitus was associated with worse outcomes in observational studies and clinical trials including HFpEF patients.^{35–40} However, variable strength of the association of diabetes mellitus with outcomes and variable associations of diabetes mellitus with outcomes according to HF age/etiology/comorbid conditions/treatment exist in the published studies. The older age of this HFpEF cohort, the more aggressive treatment of diabetic HFpEF patients, the unquantified duration/severity/type of diabetes mellitus in the current study, the community setting, and the high prevalence of obesity in diabetic subjects may have influenced our findings. Potentially, the lack of significant association of diabetes mellitus with worse outcomes relates to the presence of undiagnosed diabetes mellitus/glucose intolerance/metabolic syndrome in the (still overweight) nondiabetic HFpEF group.

HFpEF patients with renal dysfunction were older, had higher systolic, pulse and PASP, and higher EF but did not otherwise differ strikingly from those with better preserved renal function. The strong association of renal dysfunction, age, and diabetes mellitus may confound adjustment and obscure structural and functional changes specific to renal dysfunction. Renal function is dynamic in HF patients and a single point assessment may not reflect the chronic state. None the less, renal dysfunction was associated with worse outcomes in HFpEF as previously described.⁴¹

Limitations

Ventricular and vascular function indices were estimated from brachial blood pressure and echocardiographic measurements. All measurements were resting and this may limit the identification of important differences in ventricular or vascular reserve function among groups.⁴² Cause-specific mortality data were unavailable. Compared with clinical trial populations, all-cause mortality and rehospitalizations in observational studies such as this one are higher than that observed in clinical trial cohorts. However, the severity of HF relative to comorbidity severity may be less in observational studies. Some ventricular-vascular properties may be best scaled to lean body mass but neither lean body mass nor measures of body fat distribution were available.

Conclusion

Although HFpEF occurs in elderly patients with multiple comorbidities, perturbations in cardiovascular structure and function in HFpEF are greater than can be attributed to comorbidities alone, and the search for specific therapies for the more advanced ventricular and vascular dysfunction present in HFpEF should continue. However, among HFpEF patients, comorbidities are associated with important differences in the clinical profile and ventricular-vascular properties which provide insight into their impact on the natural history of HFpEF.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Heart failure and preserved ejection fraction (HFpEF) is common in the elderly and is usually associated with comorbidities. However, it is controversial whether HFpEF is a distinct entity, or merely a constellation of comorbidities that interact with and modify age-related ventricular and vascular dysfunction. Using a community-based cohort of HFpEF, age and sex matched to normotensive and hypertensive controls, this study defined cardiac structure and function in HFpEF independent of the confounding effects of age, sex, body size, and common comorbidities (anemia, diabetes mellitus, and renal dysfunction). Among HFpEF patients, obesity, anemia, diabetes mellitus, and renal dysfunction were each associated with unique clinical, structural, functional, and prognostic profiles. However, after accounting for body size and comorbidities, greater concentric left ventricular hypertrophy, atrial enlargement, systolic dysfunction, lower diastolic operating compliance, and more vascular stiffness were observed in subjects with HFpEF compared with normotensive and hypertensive age and sex-matched controls. Our study supports the notion that HFpEF is a distinct disease entity, wherein ventricular and vascular dysfunction occur independent of common comorbidities. This study also underscores the influence of each of the comorbidities on characteristics of patients with HFpEF and lends support for search for specific therapies for HFpEF.

Comorbidity and Ventricular and Vascular Structure and Function in Heart Failure With Preserved Ejection Fraction: A Community-Based Study

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Supplemental Material

Supplemental methods and data:

Comorbidity Definition: Hypertension was defined as systolic blood pressure (BP) > 140 or diastolic BP > 90 or a clinical diagnosis of hypertension with anti-hypertensive medication use regardless of BP. Dyslipidemia was defined as clinical diagnosis, elevated lipid values or use of lipid lowering agents. Coronary artery disease was defined as diagnosis of angina, coronary revascularization or $\geq 50\%$ stenosis of one or more coronary arteries. Cerebrovascular disease was defined as significant carotid artery stenosis on imaging, history of transient ischemic attack, or clinical or radiological evidence of stroke. Peripheral vascular disease was defined as diagnosis of claudication, revascularization or significant peripheral artery stenosis on imaging or functional tests. Diabetes mellitus was defined per the treating physician's clinical diagnosis. Anemia was defined as hemoglobin < 12 g/dl if female and < 13 g/dl if male. Overweight and obesity was defined as BMI ≥ 25 and 30 kg/m^2 respectively.

Allometric Scaling: Normal relationships between ventricular-vascular properties and body size were examined in a sample of disease-free individuals with normal body size (body mass index < 25 kg/m^2). This sample was drawn from: (1) subjects from the current study's normal comparator group with a BMI < 25 (n=96) and; (2) subjects without cardiovascular disease enrolled in a previous study in which echocardiography was performed in a randomly selected sample of the Olmsted County population over age 45 (Olmsted heart study, n=2042¹) in whom BMI was < 25 kg/m^2 (n=249). This yielded a disease-free, normal body size cohort (n=345) with a median (IQR) age of 61(52;74) years. Echocardiographic methods used for both studies were identical, with 2 exceptions: aortic cross-sectional diameter (AoD) was not measured in the

Olmsted heart study and LA volume was calculated by Dodge formula from two short-axis and one-long axis measurement. In contrast, AoD was measured and LA volume was calculated from the area-length method in the current study.

Allometric coefficients for ventricular-vascular properties were obtained by regressing the natural log of the ventricular or vascular parameters on the natural log of body surface area or height. Log-Log transformation linearizes exponential relationships between ventricular or vascular parameters and body size. Furthermore, this log-log model effectively results in a multiplicative model² with a similar functional form as the standard allometric equation and yields nearly identical results as non-linear regression^{3,4}. All allometric analyses were adjusted for age and gender. Tests for interactions of body size (height or BSA) with gender (gender*body size) and age (age*body size) were also performed in the log-log models.

Supplemental Table II shows the allometric powers with 95th percentile confidence intervals(CI) derived from this analysis, the p values for the age and gender adjusted allometric coefficients and the p values for gender-body size and age-body size interactions. The p values for the gender-body size interaction terms were all > 0.05 but the age-body size interaction p values were <0.10 for most variables. For variables with a significant (p<0.05) or near significant (p<0.10) age-body size interaction, the normal cohort was divided by the median age and the allometric powers derived in the older subset were used to scale for body size. The age distribution (median (IQR)) of subsets with age above (n=178) and below (n=167) the median age of 61 were 74 (66;79) and 52 (49;56). Thus, the older subset had an age distribution similar (albeit not identical) to the age distribution (median (IQR)) of the study population (79 (72;85)). The allometric constants, CI, p value for gender- and gender- adjusted non-linear associations in the older subset are also shown in Supplemental Table II. Derived allometric powers eliminated

the relationship between body size and cardiovascular parameters in the validation cohort (data not shown).

Of note, in the normal cohort used to validate allometric scaling coefficients, aortic area showed only a borderline non-linear association with height and no non-linear association with BSA in age and gender adjusted analysis (Supplemental Table II).

Assessment of LV diastolic function:

Determination of LV diastolic stiffness requires assessment of the (exponential) end diastolic pressure volume relationship (EDPVR) over a range of filling pressures with characterization of the stiffness constant which reflects the rate of pressure increase for any increase in volume. While single beat estimations of stiffness have been used^{5,6}, this method relies on a number of assumptions and the model is unstable at certain EDP. In grouped data, LV operating compliance can be measured which is the end diastolic volume at a given end diastolic pressure. Operating compliance is (inversely) related to diastolic stiffness but can also reflect parallel shifts in the EDPVR due to body size differences or other conditions. Thus, to compare diastolic operating compliance between groups, ln EDV was compared between groups adjusting for age, gender, body size (ln height and ln weight), comorbidities and quartiles of filling pressure (E/e').

Supplemental Table I. Normal population used for allometric scaling derivation

Entire cohort (n=345)	Median	25th %ile	75th %ile
Age (yrs)	61	52	74
Male (%)	28		
Height, m	1.65	1.60	1.70
Weight, kg	61	56	68
Body surface area, m ²	1.68	1.58	1.80
Body mass index, kg/m ²	22.7	21.3	24.0
Systolic BP mm Hg	116	107	126
Pulse pressure, mm Hg	47	40	57
Mean Arterial Pressure, mmHg	88	82	95
Heart rate, bpm	64	58	72
Elderly cohort (Age > 61; n=178)	Median	25th %ile	75th %ile
Age (yrs)	74	66	79
Male (%)	28		
Height, m	1.64	1.59	1.7
Weight, kg	59	54	67
Body surface area, m ²	1.66	1.56	1.78
Body mass index, kg/m ²	22.3	21.0	23.9
Systolic BP mm Hg	120	110	131
Pulse pressure, mm Hg	52	44	60
Mean Arterial Pressure, mmHg	88	83	96
Heart rate, bpm	65	59	73

Supplemental Table II. Allometric Scaling Constants											
Variable	n	Allometric Power	Lower 95%	Upper 95%	p value*	p value Gender interaction	p value Age interaction	Age ≥ 61 Allometric Power	Lower 95%	Upper 95%	p value*
Height-Scaled											
LV Mass	322	1.5	0.88	2.12	<0.001	0.18	0.065	1.60†	0.61	2.6	0.002
EDV Doppler, ml	329	1.49	0.99	1.99	<0.001	0.66	0.009	1.40†	0.57	2.22	0.001
Stroke Volume, ml	329	1.37	0.89	1.85	<0.001	0.91	0.004	1.29†	0.5	2.07	0.001
Cardiac Output, l/min	327	1.09	0.52	1.66	<0.001	1.00	0.019	1.01†	0.12	1.9	0.026
Cardiac Power Output, watts	326	0.99	0.33	1.66	0.003	0.96	0.014	0.97†	-0.02	1.95	0.054
Arterial Elastance, mmHg/ml	328	-1.45	-1.99	-0.91	<0.001	0.79	0.044	-1.25†	-2.12	-0.37	0.006
Vascular resistance, dyn•s•cm-5	326	-1.19	-1.81	-0.58	<0.001	0.98	0.096	-1.06†	-2.05	-0.06	0.037
Arterial compliance, ml/mmHg	328	1.47†	0.74	2.2	<0.001	0.25	0.11	1.04	-0.13	2.21	0.080
Aortic Area, mm2	96	0.87‡	-0.13	1.86	0.089	0.93	0.54	0.9	-0.11	1.91	0.081
LA Volume, Dodge (ml)	232	2.06	1.18	2.95	<0.001	0.38	0.033	2.26†	0.72	3.79	0.005
BSA-Scaled											
LV Mass	322	1.19†	0.87	1.51	<0.001	0.16	0.13	1.35	0.84	1.87	<0.001
EDV Doppler, ml	329	0.97	0.71	1.24	<0.001	0.35	0.007	0.98†	0.53	1.42	<0.001
Stroke Volume, ml	329	0.91	0.65	1.16	<0.001	0.49	0.002	0.92†	0.5	1.34	<0.001
Cardiac Output, l/min	327	0.71	0.4	1.02	<0.001	0.29	0.015	0.75†	0.27	1.23	0.003
Cardiac Power Output, watts	326	0.8	0.45	1.16	<0.001	0.74	0.018	0.88†	0.35	1.41	0.001
Arterial Elastance, mmHg/ml	328	-0.81	-1.1	-0.52	<0.001	0.36	0.035	-0.77†	-1.25	-0.3	0.002
Vascular resistance, dyn•s•cm-5	326	-0.62	-0.96	-0.29	<0.001	0.12	0.048	-0.62†	-1.17	-0.08	0.026
Arterial compliance, ml/mmHg	328	0.79†	0.39	1.18	<0.001	0.84	0.21	0.7	0.06	1.34	0.033
Aortic Area, mm2	96	0.11‡	-0.42	0.63	0.68	0.51	0.70	0.1	-0.43	0.63	0.72
LA Volume, Dodge (ml)	232	1.43	0.97	1.89	<0.001	0.30	0.037	1.48†	0.68	2.28	<0.001
*Age and gender adjusted non-linear association; † power used to scale in current study											
‡ unscaled data presented as relationship with body size not significant											

Supplemental Table III. Missing rate of variables; n (%)

	CON	HTN	HFpEF
hemoglobin	7 (4)	18 (5)	15 (4)
systolic blood pressure	0	4 (1)	3 (1)
pulse pressure	0	5 (1)	3 (1)
glomerular filtration rate	0	16 (4)	15 (4)
left ventricular mass	24 (12)	23 (6)	38 (10)
relative wall thickness	24 (12)	23 (6)	38 (10)
end diastolic volume	33 (17)	60 (16)	23 (6)
left atrial volume	85 (44)	119 (31)	78 (20)
stroke volume and cardiac output	33 (17)	60 (16)	23 (6)
cardiac power output	33 (17)	65 (17)	26 (7)
E/e'	37 (19)	48 (12)	37 (10)
e'	36 (19)	46 (12)	31 (8)
Deceleration time	31 (16)	60 (16)	55 (14)
Pulmonary artery systolic pressure	16 (8)	50 (13)	40 (10)
arterial elastance	33 (17)	64 (17)	26 (7)
systemic vascular resistance	33 (17)	64 (17)	26 (7)
systemic arterial compliance	33 (17)	64 (17)	26 (7)

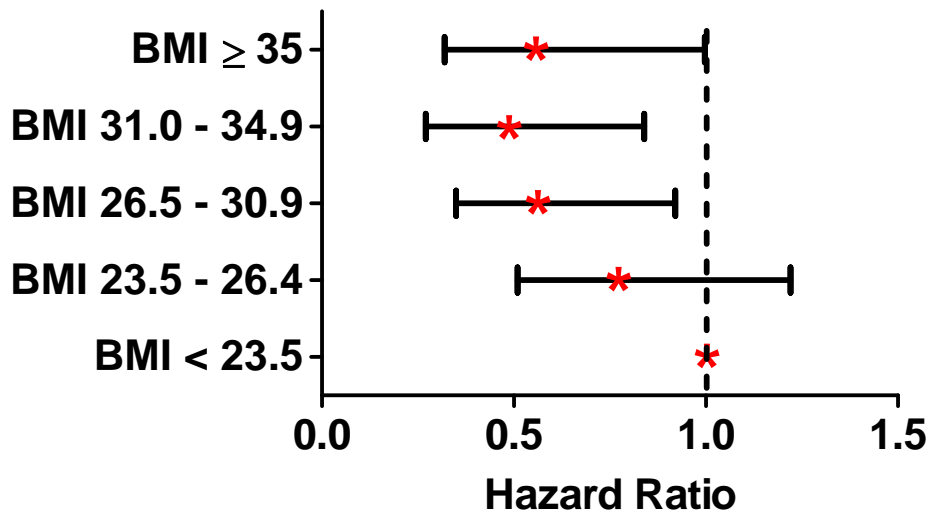
Supplemental Table IV. Group Characteristics by Gender

	FEMALE				MALE				HFpEF Male vs Female
	Control	HTN	HFpEF	p value [‡]	Control	HTN	HFpEF	p value [‡]	p value [‡]
N	109	218	218		84	168	168		
Age	78.8±7.5	77.9±10.8	78.9±11.2	na	74.9±9.3	75.5±11.1	75.8±11.6	na	0.009
Body surface area, m ²	1.67±0.2	1.75±0.23	1.83±0.29*†	<0.001	2.01±0.22	2.08±0.19	2.10±0.26*	0.009	<0.001
Body mass index, kg/m ²	25±5	28±6	30±8*†	<0.001	27±4	29±4	30±7*†	<0.001	0.65
Systolic BP mm Hg	121±12	138±20	132±22*†	<0.001	120±11	136±20	132±24*	<0.001	0.94
Pulse pressure, mm Hg	54±12	67±18	65±18*	<0.001	50±12	63±18	63±20*	<0.001	0.23
Comorbidities									
Hypertension	0%	100%	88%*†	<0.001	0%	100%	83%*†	<0.001	0.14
Atrial fibrillation	10%	14%	50%*†	<0.001	19%	22%	43%*†	<0.001	0.26
Diabetes mellitus	0%	15%	33%*†	<0.001	0%	21%	37%*†	<0.001	0.52
Coronary artery disease	0%	17%	44%*†	<0.001	0%	33%	59%*†	<0.001	0.006
Peripheral vascular disease	0%	8%	15%*†	<0.001	0%	13%	28%*†	<0.001	0.002
Cerebrovascular disease	0%	17%	26%*†	<0.001	0%	21%	38%*†	<0.001	0.015
Dyslipidemia	28%	50%	62%*†	<0.001	31%	54%	69%*†	<0.001	0.20
Cigarette smoking (ever)	32%	31%	38%	0.29	49%	56%	69%*†	0.004	<0.001
Hemoglobin, g/dl	12.6±1.4	12.7±1.4	11.8±1.8*†	<0.001	13.9±1.8	13.8±1.8	12.5±2.3*†	<0.001	0.003
Anemia (<12 female; <13 male)	31%	23%	53%*†	<0.001	26%	27%	59%*†	<0.001	0.29
GFR, mL/min/1.73m ²	68±18	64±22	54±21*†	<0.001	72±18	67±16	59±25*†	<0.001	0.037
Medications									
Betablockers	7%	43%	61%*†	<0.001	10%	45%	65%*†	<0.001	0.46
ACE-I/ARBs	0%	44%	55%*†	<0.001	0%	42%	48%	<0.001	0.18
Calcium channel blockers	4%	26%	38%*†	<0.001	2%	17%	34%*†	<0.001	0.45
Diuretics	2%	50%	67%*†	<0.001	4%	46%	57%*†	<0.001	0.056
Statins	6%	27%	44%*†	<0.001	18%	45%	53%*	<0.001	0.081

*p<0.05 HFpEF vs CON; †p<0.05 HFpEF vs HTN; ‡ ANOVA or Chi Square p value across groups

Supplemental Figure. Age, gender and comorbidity (diabetes, hemoglobin and glomerular filtration rate) adjusted hazard ratios for all cause mortality according to BMI. The strata for BMI are based on a recent clinical trial⁷ demonstrating a “U-shaped relationship” between BMI and mortality in HFpEF. The group with the lowest BMI had the worst outcomes and is used as the comparator. In this cohort and adjusting for a more limited number of comorbidities/covariates, no U shaped relationship between outcomes and BMI were demonstrated.

**Age, gender and concomitant comorbidity
adjusted HR and 95% Confidence Intervals in HFpEF patients**



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