

The Impact of Extra Cardiac Comorbidities on Pressure Volume Relations in Heart Failure and Preserved Ejection Fraction

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ABSTRACT

Background: Extracardiac comorbidities are common in patients with heart failure and a preserved ejection fraction (HFPEF). We sought to evaluate the relationship between comorbidities and ventricular structure and function in patients with HFPEF through evaluation of pressure-volume analysis.

Methods and Results: Two hundred twenty Chinese patients with a preserved ejection fraction who were either healthy (n = 75), hypertensive without heart failure (HTN; n = 89), or hypertensive with HFPEF (HFPEF; n = 56) were studied. Using echocardiographic measures, estimated end-systolic and end-diastolic pressure-volume relationships, and the area between them as a function of EDP, the isovolumic pressure-volume areas (PVA_{iso}), were calculated. Ventricular capacitance, as measured by V₃₀, was larger in patients with HFPEF compared with normal control subjects and tended to be larger compared with hypertensive control subjects. The presence of diabetes and renal insufficiency was independently associated with greater ventricular capacitance in patients with HFPEF. The PVA_{iso} was increased in patients with HFPEF compared with HTN and normal control subjects, and in particular, it was increased in HFPEF patients with multiple comorbidities.

Conclusions: The presence of comorbid conditions is associated with altered pressure-volume relations and enhanced pump function in subjects with HFPEF, supporting an important role for extracardiac comorbidities in the pathophysiology of patients with this condition. (*J Cardiac Fail* 2011;17:547–555)

Key Words: Heart failure, ejection fraction, comorbidities.

At least one-half of all patients with heart failure have preserved ejection fraction (HFPEF).¹ These patients are often older adults with hypertension and several extra

cardiac comorbidities including diabetes, obesity, anemia, and chronic kidney disease (CKD) among others.^{1–4} These comorbid conditions have been associated with adverse prognostic outcomes in patients with HFPEF.^{1,4,5} Concomitant medical conditions can impair exercise capacity and mimic symptoms of heart failure. Additionally, the presence of such comorbidities in patients with a phenotype compatible with HFPEF could confound the results of clinical trials which may be affected by competing risks from the comorbid conditions.⁶ Given the high prevalence of important comorbidities, and because these comorbidities strongly influence outcomes, it has been suggested that identification and aggressive treatment of these conditions should be instituted currently rather than waiting for new HFPEF-specific treatments to emerge.⁷

Although comorbidities could adversely affect the systolic and diastolic properties of the heart, their impact on ventricular structure and function in patients with hypertensive HFPEF has not been adequately addressed. The role of extracardiac comorbidities may be particularly important, because multiple mechanisms, both cardiac and noncardiac, have been proposed to explain the pathophysiology of this

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syndrome.^{8,9} Accordingly, we sought to characterize the impact of comorbid conditions on ventricular structure and function through the use of noninvasive pressure-volume indices. Specifically, we hypothesized that the presence of comorbidities would be associated with alterations in ventricular structure and function, and therefore in the HFPEF phenotype, as determined through evaluation of parameters that characterize systolic and diastolic ventricular properties.

Methods

Study Subjects

Two hundred twenty study subjects who were treated as inpatients or outpatients at the People's Liberation Army General Hospital (Beijing, China) from September 2005 to February 2008 were studied. These subjects included 56 patients with hypertensive HFPEF (EF > 50%) and 2 control groups of 75 healthy control subjects and 89 patients with hypertension but without heart failure (HTN).

Normal control subjects were identified after a detailed health investigation including history, physical examination, blood tests, chest x-ray, electrocardiogram, and echocardiogram did not demonstrate any abnormality. Specific exclusion criteria for the normal control group included hypertension, coronary heart disease, diabetes, renal insufficiency, cardiomyopathy, congenital heart disease, arrhythmias, and chronic obstructive pulmonary diseases. Subjects with hypertension (defined as a systolic blood pressure (SBP) > 140 or diastolic blood pressure (DBP) > 90 mm Hg or a clinical history of hypertension) but without concomitant heart failure constituted the HTN cohort. The presence of heart failure was based on the criteria developed by Rich et al¹⁰ and verified by 2 independent cardiologists. The protocol was reviewed and approved by the Institutional Review Board of the Chinese People's Liberation Army General Hospital, and each of the study subjects provided written informed consent.

Definition of Comorbid Conditions

Extracardiac comorbidities within the HTN and HFPEF populations were identified, including obesity, anemia, chronic renal insufficiency, and diabetes. Anemia was defined according to the World Health Organization criteria¹¹ as hemoglobin (Hb) < 13 mg/dL in men and < 12 mg/dL in women. Diabetes was defined based on a clinical history of diabetes, use of oral hypoglycemic or insulin or a fasting blood glucose of ≥ 126 mg/dL or random blood glucose of > 200 mg/dL.¹² Renal insufficiency was defined as glomerular filtration rate estimated by the Modification of Diet in Renal Disease formula of < 60 mL min⁻¹ 1.73 m⁻². Overweight patients were defined as having a body mass index (BMI) of > 25 kg/m².¹³ Coronary heart disease was defined by clinical history of myocardial infarction (as evidenced by Q waves on an electrocardiogram and/or segmental wall motion abnormality on echocardiography), previous percutaneous intervention or coronary artery bypass grafting, or a coronary stenosis > 70% on cardiac catheterization.

Diagnostic Evaluation

All patients underwent standardized clinical examination and research echocardiography, which were performed without

interruption of a subject's medical therapies. Blood pressure was measured by standard cuff sphygmomanometer in the supine position after a subject rested comfortably for 5 minutes immediately before the performance of echocardiography. Echocardiography was performed by a professional technician with the use of a Sequoia 512 ultrasound instrument with a 3.5–4.5-MHz sector scanner (Siemens, Munich, Germany). Two-dimensional guided M-mode measurements of chamber dimensions and wall thickness were obtained according to recommendations of the American Society of Echocardiography,¹⁴ and left ventricular mass (LVM) was derived from a formula described by Devereux and Reichek¹⁵ and indexed to body surface area (BSA). The presence of left ventricular hypertrophy (LVH) was defined, based on the recommendations of the American Society of Echocardiography, as posterior wall thickness > 1.0 cm for women and > 1.1 cm for men.¹⁶ Left ventricular end-diastolic (LVEDV) and end-systolic (LVESV) volumes and left ventricular ejection fraction were calculated with the Simpson biplane method. Transmitral and tissue Doppler were used to analyze diastolic filling indexes and myocardial velocities, as previously described.¹⁷ These included the measure of transmitral early-diastolic filling velocity (E) and average of the tissue Doppler measures of early-diastolic tissue velocity at the septal, lateral, and inferior walls (e'). Left ventricular end-diastolic pressure was estimated by the formula: end-diastolic pressure = $11.96 + 0.596 \times E/e'$.¹⁷ Blood samples for natriuretic peptide assay were obtained within 12 hours (after or before) of echocardiographic examination. B-Type natriuretic peptide (BNP) was measured by sandwich immunoassay using commercially available kits (Abbott Laboratories, Abbott Park, Illinois). The staff performing the measurements were blinded to the clinical data.

Noninvasive Pressure-Volume Indices

Parameters of end-systolic (ESPVR) and end-diastolic (EDPVR) pressure-volume relations were estimated by using validated single-beat techniques (Fig. 1). The ESPVR, a reflection of chamber stiffness at the point of maximal myofibrillar activation,¹⁸ indicative of chamber contractility, was quantified by measuring both the slope (E_{es}) and volume axis intercept (V_0) according to previously published methods.¹⁹ To account for changes in both E_{es} and V_0 of the ESPVR, which together represent chamber contractility, we calculated the volume of the left ventricle required to generate an end-systolic pressure of 120 mm Hg ($V_{120} = 120/E_{es}$ of ESPVR + V_0 of ESPVR). The EDPVR, a reflection of the passive mechanical properties of the myocardium during complete myofibrillar inactivation,¹⁸ is nonlinear and is represented by the formula $EDP = \alpha EDV^\beta$, where α and β are constants that specify the curvature of the line and are determined by the mechanical properties of the muscle as well as the structural features of the ventricle.^{20,21} Although it is usually measured invasively, a method developed by Klotz et al²⁰ allows noninvasive estimates of the EDPVR from the measured EDV and an estimate of left ventricular filling pressures derived from Doppler echocardiography. Because both α and β affect the shape and position of the EDPVR, we integrated these measures by calculating the EDV at a common end-diastolic pressure of 30 mm Hg ($V_{30} = [30/\alpha]^{1/\beta}$) which yields an index of ventricular capacitance.¹⁷ Accordingly, a larger V_{30} (increased capacitance) indicates a rightward/downward shift of the EDPVR (eg, remodeling) and a smaller V_{30} (decreased capacitance) indicates a leftward/upward shift of the EDPVR (eg, diastolic dysfunction; Fig. 1B).

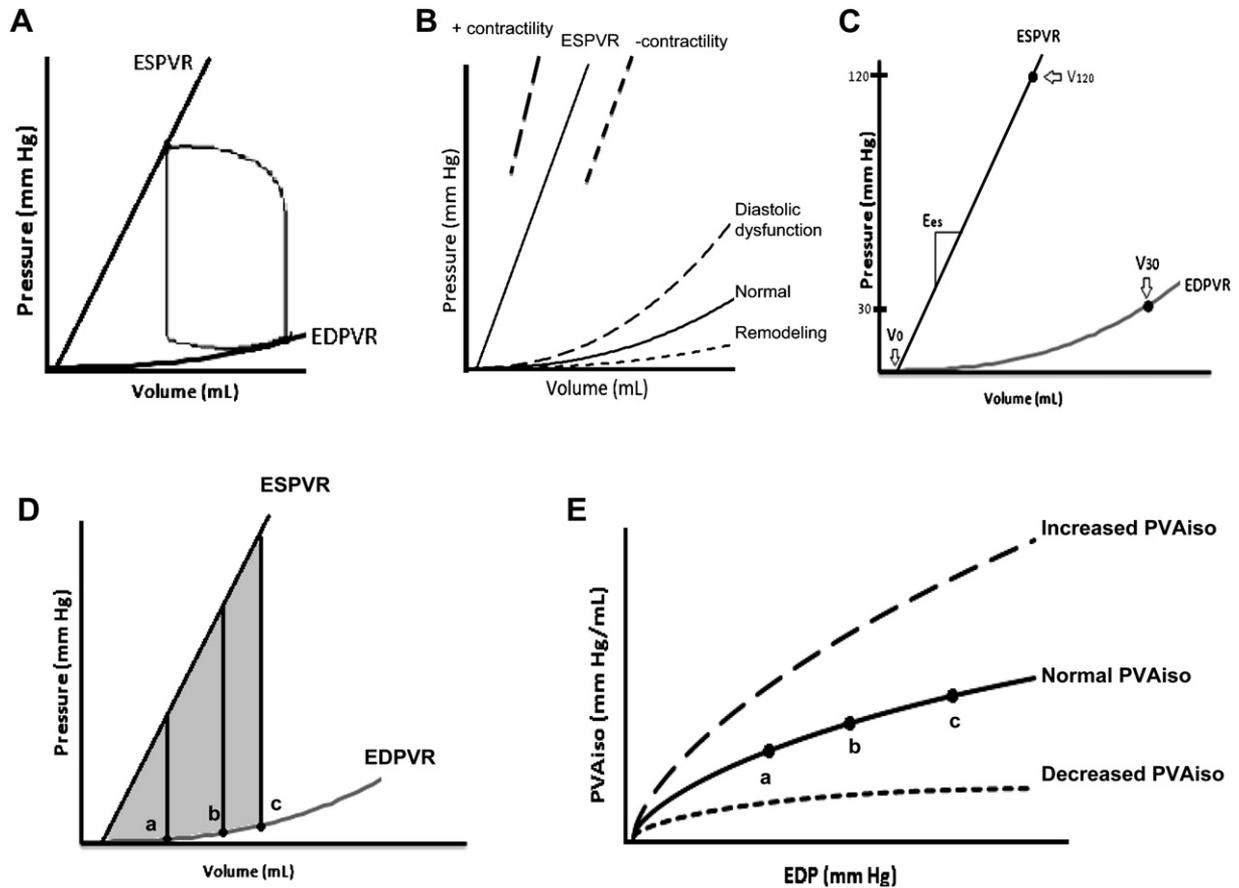


Fig. 1. (A–C) Pressure-volume (PV) analyses demonstrating the normal PV loop and the determinants of ventricular function, including the ESPVR and the EDPVR (A). Shifts in the ESPVR are often equated with changes in inotropic state (B), along with shifts in the EDPVR toward smaller volumes or reduced capacitance (diastolic dysfunction) or toward larger volumes or increased capacitance (remodeling). The ESPVR is characterized by the slope $[E_{es}]$ and the volume axis intercept $[V_0]$, which can be described collectively by the V_{120} , the volume of the left ventricle required to generate an end-systolic pressure of 120 mm Hg (C). Shifts in the EDPVR can be characterized by V_{30} , the ventricular volume at a pressure of 30 mm Hg (C). See Methods section for additional details. (D, E) Demonstration of how PVA_{iso} is calculated from the PV diagram. One value for PVA_{iso} (shaded area) can be obtained for each end-diastolic PV point shown by the black circles along the EDPVR. The points of a, b, and c in D correspond to the solid line PVA_{iso} curve in E. With shifts of the ESPVR and EDPVR (not shown), the PVA_{iso} curve can show increased or decreased cardiac function (dashed PVA_{iso} curves in E).

Because overall ventricular pump function is determined by both systolic and diastolic properties of the ventricle, the area between the EDPVR and the ESPVR measured as a function of EDP was calculated to index overall pump function.²² (Fig. 1D and E) This specific area, called the isovolumic pressure-volume area (PVA_{iso}), is independent of afterload and can be calculated analytically as a function of left ventricular end-diastolic pressure following curve fitting of the EDPVR and the ESPVR: $PVA_{iso}(V) = \int [P_{es}(V) - P_{ed}(V)]dV = 0.5E_{es}(sb)(VV_0)_2 - V_m(\beta/\alpha)e_{z(V/V_m)}$, where $P_{es}(V)$ and $P_{ed}(V)$ are the end-systolic and end-diastolic pressures, respectively, as a function of volume. Upward shifts of the PVA_{iso} -EDP relationship indicate enhanced overall pump function at that time point; specifically, this means that, at any given filling pressure, the heart is capable of generating more pressure and more work. In contrast, downward shifts of the PVA_{iso} -EDP relation indicate reduced overall pump function at that time point, indicating that at any given filling pressure, the heart generated less pressure and less work.

Effective arterial elastance (E_a), an index of vascular hemodynamic load, was estimated by $P_{es}/$ stroke volume, where P_{es} is

left ventricular end-systolic pressure estimated as $0.9 \times$ systolic blood pressure.¹⁷

Statistical Analyses

Data are expressed as mean \pm 1 SD. Ventricular volumes were indexed to BSA. Data were compared between normal control patients, hypertensive control patients without HF, and patients with HFPEF by analysis of variance with Bonferroni post hoc correction for continuous variables or chi-square for dichotomous variables. Patients with HFPEF were further characterized based on the presence of comorbidities, and analysis of variance was used to evaluate for trends associated with increasing comorbidity burden. Where values were not normally distributed, the nonparametric Kruskal-Wallis test was used. To evaluate the impact of comorbidities on the observed differences in pressure-volume relationships between the cohorts studied, we performed multivariate linear regression analysis with group (HFPEF, HTN, and control) and comorbidities (presence or absence) including diabetes, elevated BMI, renal insufficiency, anemia, coronary

heart disease, and left ventricular hypertrophy entered into a full model. Although coronary heart disease and left ventricular hypertrophy are not extracardiac comorbidities, they were included in the model because of their potential effects on ventricular remodeling. All statistical analyses were performed with SAS 9.1 (SAS Institute, Cary, North Carolina). A *P* value of $<.05$ was considered to be statistically significant.

Results

The baseline characteristics of the study population are presented in Table 1. Subjects with HFPEF were older and more often women than HTN control subjects and

Table 1. Demographic, Echocardiographic, and Pressure-Volume Measures Among Preserved Ejection Fraction (PEF) Control Subjects, Hypertensive Control Subjects (HTN), and Heart Failure Subjects (HFPEF)

| | HTN | | |
|---|-------------|--------------|-------------------------|
| | Control | Without HF | HFPEF |
| No. of subjects | 75 | 89 | 56 |
| Demographics | | | |
| Age (y) | 67 ± 7 | 65 ± 12 | 71 ± 9* |
| Gender (% women) | 45 | 18* | 30 |
| SBP (mm Hg) | 122 ± 10 | 141 ± 22* | 144 ± 26* |
| DBP (mm Hg) | 73 ± 8 | 81 ± 13* | 77 ± 16 |
| HR (beats/min) | 68 ± 9 | 68 ± 10 | 69 ± 10 |
| Comorbidities | | | |
| Hb (mg/dL) | 15.0 ± 1.3 | 14.5 ± 1.7 | 13.8 ± 2.3 [†] |
| Diabetes (%) | 0 | 21* | 30* |
| eGFR (mL/min) | 96 ± 21 | 94 ± 28 | 79 ± 26* [†] |
| CHD (%) | 0 | 40* | 64* |
| BMI (kg/m ²) | 24 ± 4 | 26 ± 3* | 26 ± 4* |
| BSA (m ²) | 1.71 ± 0.17 | 1.82 ± 0.15* | 1.82 ± 0.18* |
| Biomarker | | | |
| BNP (pg/mL) | 89 ± 98 | 80 ± 59 | 561 ± 701* [†] |
| Echocardiography parameters | | | |
| LVEDV/BSA (mL/m ²) | 48 ± 10 | 49 ± 14 | 55 ± 17* [†] |
| LVESV/BSA (mL/m ²) | 17 ± 4 | 18 ± 6 | 21 ± 9* [†] |
| SV (mL) | 52 ± 12 | 56 ± 17 | 61 ± 19* |
| EF (%) | 65 ± 3 | 64 ± 4 | 63 ± 6* |
| E/E' | 7.1 ± 1.6 | 7.8 ± 2.4 | 10.0 ± 2.8* |
| LVM/BSA (gm/m ²) | 86 ± 18 | 113 ± 25* | 125 ± 43* [†] |
| LVH (%) | 12 | 44* | 63* |
| PV indices | | | |
| E _a (mm Hg/mL) | 2.2 ± 0.5 | 2.4 ± 0.8 | 2.3 ± 0.8 |
| E _{es} (mm Hg/mL) | 2.1 ± 0.5 | 2.1 ± 0.7 | 1.9 ± 0.8 |
| E _a /E _{es} | 1.1 ± 0.2 | 1.3 ± 0.3* | 1.3 ± 0.3* |
| V ₀ (mL) | -27 ± 9 | -38 ± 22* | -42 ± 26* |
| V ₃₀ (mL) | 90 ± 21 | 98 ± 29 | 109 ± 37* |
| V ₃₀ /BSA (mL/m ²) | 53 ± 11 | 54 ± 15 | 60 ± 19* |
| V ₁₂₀ (mL) | 34 ± 12 | 30 ± 14 | 32 ± 19 |

Gender and percent with diabetes are analyzed via chi-square. SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; Hb, hemoglobin; eGFR, estimated glomerular filtration rate; CHD, coronary heart disease; BMI, body mass index; BNP, B-type natriuretic peptide; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; SV, stroke volume; EF, ejection fraction; LVM, left ventricular mass; LVH, left ventricular hypertrophy; BSA, body surface area; LVEDP, left ventricular end-diastolic pressure; PV, pressure-volume; E_a, arterial elastance; E_{es}, end-systolic elastance; V₀, estimated ventricular volume at an end-systolic pressure of 0; V₃₀, estimated ventricular volume at an end-systolic pressure of 30 mm Hg; V₁₂₀, estimated ventricular volume at an end-systolic pressure of 120 mm Hg.

**P* < .05 vs control by ANOVA with Bonferroni post hoc test.

[†]*P* < 0.05 between HTN with and without HF by ANOVA with Bonferroni post hoc test.

had higher blood pressures than normal control patients. Blood pressure did not differ between HFPEF and HTN control subjects. HFPEF patients had significantly elevated BNP and E/e' ratio compared with both HTN and normal control subjects, consistent with the diagnosis of heart failure. HTN control subjects and HFPEF patients had higher prevalence of elevated BMI, anemia, diabetes, renal insufficiency, and coronary heart disease than healthy control subjects (Table 1). Compared with HTN control subjects in an age-adjusted model, HFPEF patients had higher prevalence of renal insufficiency (21% vs 9%; *P* = .03) and tended to have higher prevalence of anemia (27% vs 10%; *P* = .07) but did not differ in the prevalence of diabetes (30% vs 21%; *P* = .24).

End-systolic elastance, arterial elastance, and ventricular vascular coupling (E_a/E_{es} ratio) did not differ between HFPEF patients and HTN control subjects, but both of these cohorts had a higher E_a/E_{es} ratio than control subjects. Among HFPEF patients, female gender, but not age, was associated with higher E_a (2.6 ± 0.7 vs 2.1 ± 0.7 mm Hg/mL; *P* = .02) and a trend toward higher E_{es} (2.3 ± 0.8 vs 1.8 ± 0.8 mm Hg/mL; *P* = .057). Among HFPEF patients, but not among the whole cohort or the whole hypertensive (HTN and HFPEF) cohort, the presence of diabetes was associated with lower E_a (1.9 ± 0.5 vs 2.5 ± 0.8 mm Hg/mL; *P* = .003) and a trend toward a lower E_{es} (1.6 ± 0.8 vs 2.1 ± 0.8 mm Hg/mL; *P* = .08). Among patients with HFPEF, differences in E_a remained significant, and differences in E_{es} became significant, when adjusted for age and gender and for age, gender, and the presence of other comorbidities. No other comorbidities in HFPEF patients were associated with significant changes in E_a, E_{es}, or the E_a/E_{es} ratio.

HFPEF patients had larger ventricular capacitance than healthy control subjects and trended toward having larger capacitance than HTN control subjects (*P* = .054) in unadjusted analyses (Fig. 2A). Capacitance was larger in HFPEF patients compared with HTN control subjects when adjusted for age, gender, and BMI (*P* = .003) and for age, gender, and the presence of anemia, diabetes, elevated BMI, and renal insufficiency (*P* = .038). The rightward-shifted EDPVR in the HFPEF cohort was most prominent in HFPEF patients with ≥2 comorbidities (Fig. 2B). Table 2 describes ventricular parameters in HFPEF patients stratified by the presence of 0, 1, and ≥2 comorbidities. Patients with no comorbidities had lower systolic and diastolic blood pressures compared with patients with ≥1 comorbidities (*P* values .036 and .009 for SBP and DBP, respectively, by *t* test).

Among HFPEF patients, both diabetes and renal insufficiency were associated with larger ventricular capacitance independent of age, gender, and other comorbidities (Table 3). The strength of the association of both comorbidities (diabetes and renal insufficiency) in HFPEF patients is similar based on the regression coefficient (Table 3).

The rightward shift in the EDPVR resulted in an increase in overall pump function, as measured by the PVA_{iso}-EDP

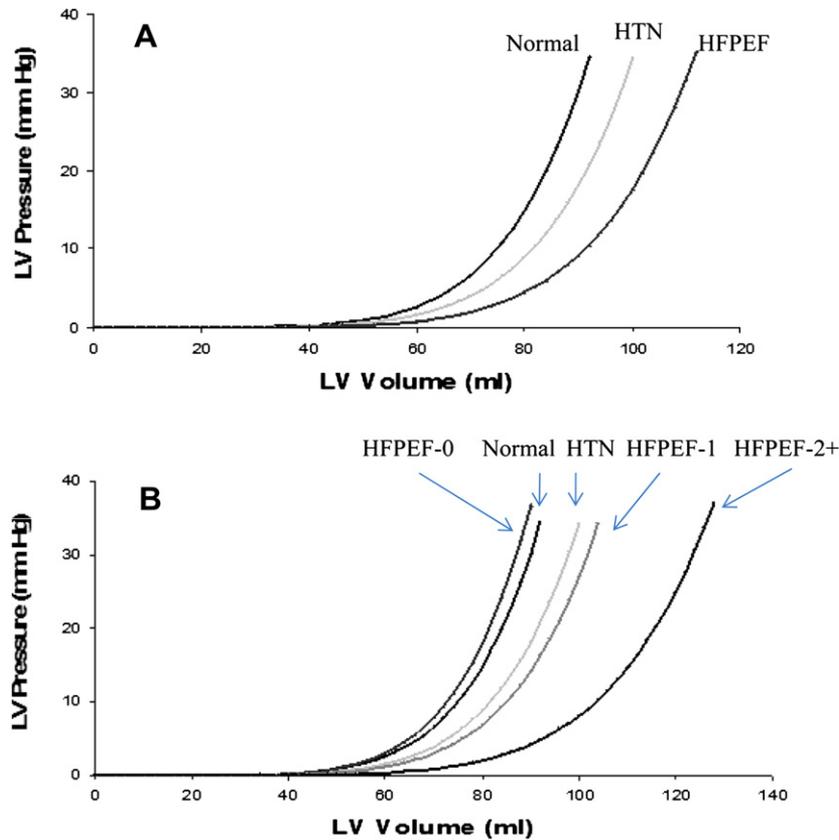


Fig. 2. (A, B) Estimated graphical representations of the end-diastolic pressure-volume relationships among the studied populations: Hypertensive without heart failure (HTN) and heart failure with preserved ejection fraction and 0, 1, and ≥ 2 comorbidities (HFPEF-0, HFPEF-1, HFPEF-2, respectively).

relationship among HTN and HFPEF subjects compared with normal control subjects (Fig. 3A). Additionally, as shown in Figure 3B, subjects with HFPEF without comorbidities had

overall pump function that was similar to healthy control subjects and below HTN control subjects, whereas those with ≥ 2 comorbidities demonstrated enhanced pump function.

Table 2. The Cohort of Patients with HFPEF Grouped by the Number of Extracardiac Comorbidities

| | Total | 0 | 1 | ≥ 2 | <i>P</i> Value |
|---|---------------|---------------|---------------|---------------|----------------|
| No. of subjects | 56 | 9 | 22 | 25 | |
| Demographics | | | | | |
| Age (y) | 71 \pm 9 | 74 \pm 5 | 71 \pm 8 | 70 \pm 11 | .47 |
| SBP (mm Hg) | 144 \pm 26 | 130 \pm 18 | 144 \pm 23 | 149 \pm 30 | .20 |
| DBP (mm Hg)* | 77 \pm 16 | 68 \pm 8 | 79 \pm 16 | 78 \pm 18 | .20 |
| Biomarker | | | | | |
| BNP (pg/mL)* | 561 \pm 701 | 246 \pm 111 | 721 \pm 924 | 570 \pm 577 | .84 |
| Echocardiography parameters | | | | | |
| LVEDV (mL) | 100 \pm 34 | 80 \pm 23 | 93 \pm 30 | 114 \pm 36 | .013 |
| LVESV (mL) | 38 \pm 17 | 29 \pm 12 | 34 \pm 14 | 45 \pm 18 | .016 |
| LVEDV/BSA (mL/m ²) | 55 \pm 17 | 47 \pm 12 | 53 \pm 18 | 60 \pm 17 | .14 |
| LVESV/BSA (mL/m ²) | 21 \pm 9 | 18 \pm 7 | 19 \pm 8 | 24 \pm 9 | .11 |
| SV (mL) | 61 \pm 19 | 50 \pm 14 | 58 \pm 17 | 69 \pm 20 | .022 |
| EF (%) | 63 \pm 6 | 63 \pm 6 | 64 \pm 5 | 61 \pm 5 | .31 |
| LVM/BSA (mL/m ²) | 12543 | 103 \pm 19 | 117 \pm 31 | 140 \pm 52 | .036 |
| Estimated PV indices | | | | | |
| E _a (mm Hg/mL) | 2.3 \pm 0.8 | 2.6 \pm 0.9 | 2.4 \pm 0.8 | 2.1 \pm 0.6 | .17 |
| E _{es} (mm Hg/mL)* | 1.9 \pm 0.8 | 2.1 \pm 0.7 | 2.0 \pm 0.9 | 1.8 \pm 0.8 | .13 |
| E _a /E _{es} * | 1.3 \pm 0.3 | 1.1 \pm 0.2 | 1.3 \pm 0.3 | 1.3 \pm 0.4 | .15 |
| V ₀ (mL)* | -42 \pm 26 | -30 \pm 18 | -45 \pm 31 | -43 \pm 25 | .34 |
| V ₃₀ (mL) | 109 \pm 37 | 87 \pm 26 | 102 \pm 33 | 124 \pm 38 | .0145 |
| V ₃₀ /BSA (mL/m ²) | 60 \pm 19 | 52 \pm 14 | 57 \pm 20 | 65 \pm 18 | .15 |
| V ₁₂₀ (mL) | 32 \pm 19 | 28 \pm 20 | 28 \pm 19 | 36 \pm 18 | .30 |

P values via analysis of variance (ANOVA) unless nonparametric test (*), Kruskal Wallis, was used. Abbreviations as in Table 1.

Table 3. Effects of Specific Comorbidities on Ventricular Capacitance V_{30} in Multivariate Analysis

| | C and HTN and HFPEF | | | HTN and HFPEF | | | HFPEF | | |
|-----------------|---------------------|------|---------|---------------|------|---------|-------------|------|---------|
| | Coefficient | SE | P Value | Coefficient | SE | P Value | Coefficient | SE | P Value |
| Age (per year) | -0.60 | 0.21 | .004 | -0.56 | 0.27 | .035 | — | — | .44 |
| Gender (female) | -11.6 | 4.3 | .007 | -14.9 | 5.7 | .017 | -21.0 | 8.8 | .021 |
| Comorbidities | | | | | | | | | |
| Anemia | — | — | .33 | — | — | .36 | — | — | .40 |
| Overweight | — | — | .57 | — | — | .33 | — | — | .78 |
| Diabetes | — | — | .22 | — | — | .13 | 18.4 | 9.1 | .049 |
| CKD | 13.0 | 6.9 | .059 | 14.4 | 3.5 | .063 | 24.7 | 10.2 | .019 |
| CHD | 8.6 | 4.5 | .057 | 11.9 | 5.4 | .03 | — | — | .29 |
| LVH | 7.6 | 4.3 | .08 | 9.1 | 5.4 | .09 | 28.8 | 8.8 | .002 |

C, normal control subjects; HTN, hypertensive control subjects without heart failure; HFPEF, heart failure subjects with a preserved ejection fraction; CKD, chronic kidney disease; CHD, coronary heart disease; LVH, left ventricular hypertrophy.

Discussion

The results of this investigation demonstrate that differences in ventricular structure and function as assessed by noninvasive pressure-volume analyses between subjects with HFPEF, HTN, and healthy control subjects are influenced by the presence of extracardiac comorbidities. Among patients with HFPEF, greater comorbidity burden, particularly of diabetes and CKD, is associated with greater ventricular capacitance, and diabetes is associated with lowered E_a and E_{es} . These changes in ESPVR and EDPVR in HFPEF patients resulted in enhanced pump function that was associated with the greater burden of comorbidities. These data provide insight into the pathophysiology of HFPEF in patients with and without multiple comorbidities by highlighting the association of comorbidities with cardiac structure and function in patients with HFPEF compared with normal control subjects and HTN subjects without HF.

Prevalence of Comorbidities and Impact on Prognosis

Comorbidities are known to play an important role in patients with HFPEF and are associated with significant

morbidity and mortality. Among extracardiac comorbidities, patients with HFPEF have high rates of obesity, anemia, diabetes, and renal insufficiency,² with the latter 3 serving as independent risk factors for mortality in multivariate analyses.⁴ Other studies further highlight the impact of comorbidities on outcomes in this population.^{5,6,23} Because data from large randomized clinical trials^{24–26} have not demonstrated significant benefits of cardiovascular therapies on outcomes in subjects with HFPEF, some researchers have suggested that the focus shift to treating comorbidities that are highly prevalent in this condition.^{7,27} In this regard, a further understanding of the impact of the most common comorbid conditions on the physiology of HFPEF is warranted.

Role of Comorbidities on Physiology of HFPEF

In addition to directly contributing to morbidity in HFPEF, current data suggest that comorbidities, particularly diabetes and renal insufficiency, are associated with changes in ventricular structure and function. Although the results of the current investigation do not establish a causal association between comorbidities and ventricular structure or function, it is possible to postulate that extracardiac comorbidities may

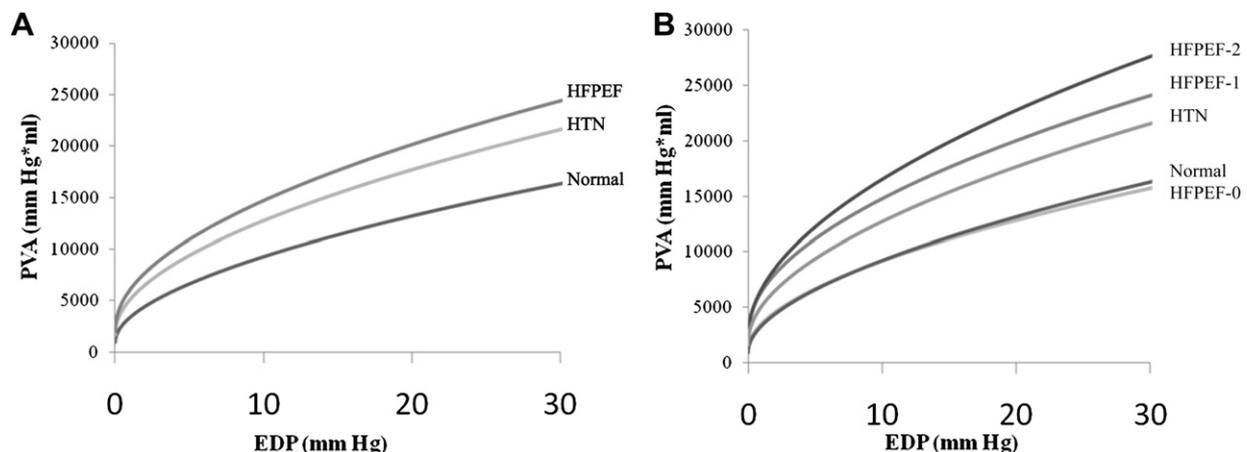


Fig. 3. PVA_{180} relationships, demonstrating cardiac function in patients with hypertension (HTN), normal control subjects, and heart failure patients (HFPEF) with preserved ejection fraction with 0, 1, or ≥ 2 comorbidities.

affect ventricular structure and function through various mechanisms. For example, diabetes leads to glycosylated end-product formation, impaired endothelial function, sympathetic nervous system activation, and derangements in myocardial metabolism, leading to so-called “diabetic cardiomyopathy.”^{28,29} Likewise, in obese individuals, accumulation of nonesterified fatty acids and metabolic dysregulation may result in the accumulation of toxic lipid byproducts and subsequent contractile dysfunction.³⁰ The systemic inflammation associated with obesity, diabetes, and other comorbidities may further contribute to cardiac dysfunction.³¹ Cardiorenal syndrome also plays a prominent role in cardiac structure and function, whether originating as HF leading to chronic kidney disease or chronic kidney disease leading to worsening of HF symptoms.³² Numerous pathophysiologic mechanisms are thought to underlie the cardiorenal syndrome, including ventricular hypertrophy, neurohormonal activation, cardiac remodeling, systemic inflammation, and venous congestion.^{32,33} The addition of anemia to this syndrome, termed cardiorenal-anemia syndrome, can further affect cardiac structure and function through inflammation, neurohormonal activation, and cardiac remodeling.³⁴ In addition to the direct effects of diabetes, anemia, and kidney disease on cardiac structure and function, these extracardiac comorbidities may alter such parameters through extracardiac effects, including expansion of plasma volume. Volume overload is an important mechanism in the pathophysiology of patients with HFPEF,³⁵ and anemia,^{36,37} diabetes,³⁸ obesity,³⁹ and renal insufficiency have all been associated with volume derangements. Because not all patients with HFPEF have significant extracardiac comorbidities, stratification based on the presence of comorbidities may be important in explaining disease occurrence and progression. Those without extracardiac comorbidities, who in our population had smaller ventricular capacitance and lower blood pressure than those with comorbid conditions, may have a pathophysiology similar to patients with diastolic heart failure, as described by others,⁴⁰ and may exhibit fundamentally different disease than those with multiple comorbidities, though both are currently labeled as having HFPEF.

Stratifying or subgrouping individuals with HFPEF by comorbidities may be important to consider in future studies of therapeutic interventions for patients with HFPEF. Additionally, specifically targeting comorbidities in this population may not only reduce the burden of the comorbidities themselves but may alter ventricular structure and function and thus affect the pathophysiology of HFPEF. Ventricular capacitance, as a marker of HFPEF pathophysiology through volume overload, may therefore be a potential target for treatment through management of extracardiac comorbidities. Additionally, trials to evaluate the benefits of more aggressively targeting volume status as a principal goal of therapy in this population should be explored.

Additional insight into cardiac function in patients with HFPEF can be gained through the evaluation of the heart not as a systolic or diastolic organ but by integrating

systolic and diastolic ventricular properties through the calculation of the PVA_{iso} -EDP relationship, an overall measure of pump function.²² The PVA_{iso} -EDP relation describes the total mechanical energy that can be generated at a given ventricular preload²² and therefore expresses cardiac function in a manner similar to the Frank-Starling curve, which typically demonstrates a measure of cardiac output at a given ventricular preload. The current cohort of patients with HFPEF exhibit increased cardiac function compared with HTN and healthy control subjects. Furthermore, HFPEF patients with no comorbidities exhibited pump function similar to normal control subjects and reduced compared with HTN subjects, whereas HFPEF patients with multiple comorbidities exhibited enhanced pump function. These findings are in accordance with animal data from salt-fed hypertensive Dahl rats, who exhibited increased overall pump function, as determined by PVA_{iso} , during the development of the heart failure state with a preserved ejection fraction.⁴¹

HFPEF has been associated with abnormalities in arterial-ventricular (AV) coupling, particularly with elevations in both E_a and E_{es} compared with healthy or HTN control subjects.⁴² Although AV mismatching explains some features of HFPEF, including altered blood pressure regulation and limited cardiovascular reserve,⁴² abnormal AV coupling has not been found in all patients with HFPEF.⁹ In the present cohort, there were no significant alterations in AV coupling at rest between HTN control subjects and HFPEF patients, indicating that other pathophysiologic mechanisms likely play a more prominent role in this population or that it is necessary to extend the evaluation to characterization of these properties during exertion. Among the present cohort of HFPEF patients, diabetes was an independent predictor of decreased E_a and E_{es} . Although impaired fasting glucose and diabetes have been associated with increased arterial stiffness through a variety of experimental techniques,^{43–45} animal models of diabetic heart disease using measures of stiffness used in the present study suggest that diabetic cardiomyopathy may be associated with decreases in both E_a and E_{es} ,^{46,47} which concurs with the present findings. Decreases in E_a in these animal models may be associated with vascular smooth muscle dysfunction or alterations in heart rate,⁴⁶ whereas decreases in E_{es} , a measure of contractility, may be associated with glycosylated end-product deposition or microvascular disease.

Limitations

There are several limitations of the present study. The study focused on a homogeneous Chinese population with lower rates of obesity than those found in the United States and other countries with subjects of European descent. The average BMI in the Chinese population has been reported to be 18.5–23.9 kg/m², with a BMI > 24 kg/m² therefore considered to be overweight.⁴⁸ The roles of ethnicity may additionally be an important factor in pathophysiology of

patients with HFPEF, which may affect the applicability of these findings to other populations. The analysis of ventricular-vascular coupling and pressure-volume relationships presented here is derived from noninvasive estimates using a single loading condition at rest. Although the criterion standard for such analysis is invasive determination of pressure-volume loops and end-systolic and end-diastolic pressure-volume relationships, invasive measures are impractical for large studies, and the noninvasive estimates applied here have been well validated for studying populations of subjects.²⁰ Arterial stiffness was not measured directly. Data about the duration of comorbidities, heart failure symptoms, and medication usage in this population were not available, and the absence of such data has the potential to confound study results. All comorbidities were treated as binary variables in regression analysis, even when continuous data were available, because effects on ventricular structure and function may only become evident when weight, fasting glucose, hemoglobin, and renal function sufficiently deteriorate. Indeed, it is quite likely that a certain threshold of abnormality in a given comorbidity is required to produce a change in ventricular pressure-volume relations. Future studies with longitudinal data will be required to address this. The study populations differed in age and gender, as can be expected based on demographics of patients with and without heart failure, and the regression models used attempted to correct for such differences.

Conclusions

Extracardiac comorbidities are prevalent in patients with HFPEF, and the comorbidities of diabetes and renal insufficiency are associated with greater ventricular capacitance in the HFPEF population. Among subjects with HFPEF and multiple comorbidities, overall pump function is enhanced compared with healthy control subjects and hypertensive control subjects without heart failure, but among HFPEF subjects without comorbidities, overall pump function is reduced compared with hypertensive control subjects. These data suggest that patients with HFPEF and extracardiac comorbidities may have different underlying pathophysiologies of their heart failure phenotype than patients with HFPEF without comorbidities and suggests that stratifying HFPEF patients based on comorbidities might provide insights into the pathophysiology and suggest pathways toward effective interventions for this growing population of older adults.

Disclosures

None.

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