Characterization of Static and Dynamic Left Ventricular Diastolic Function in Patients with Heart Failure and a Preserved Ejection Fraction

Running Title: Left Ventricular Diastolic Function in HFPEF

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Subject Codes: heart failure [110], Doppler echocardiography [31]
Abstract

Background: Congestive heart failure (CHF) in the setting of a preserved left ventricular (LV) ejection fraction (HFPEF) is increasing in prevalence among the senior population. The underlying pathophysiologic abnormalities in ventricular function and structure remain unclear for this disorder. We hypothesized that patients with HFPEF would have marked abnormalities in LV diastolic function with increased static diastolic stiffness and slowed myocardial relaxation as compared with age matched healthy controls.

Methods and Results: Eleven (73 ± 7 years of age; 4 men, 7 women) highly screened patients with a clear diagnosis of HFPEF were recruited to participate. Thirteen sedentary healthy (70 ± 4 years of age; 7 men, 6 women) seniors were included in the control group. All subjects underwent pulmonary artery catheterization with measurement of cardiac output, end-diastolic volumes and pulmonary capillary wedge pressures at baseline, cardiac unloading (lower body negative pressure/or upright tilt), and cardiac loading (rapid saline infusion). The data were used to define the Frank-Starling and left ventricular (LV) end-diastolic pressure volume relationships. Doppler echocardiographic data (tissue Doppler velocities, IVRT, propagation velocity of early mitral inflow [Vp], E/A ratio) were obtained at each level of cardiac preload. Compared with healthy senior controls, patients with HFPEF had similar LV contractile function and static LV compliance, but reduced LV chamber distensibility with elevated filling pressures and slower myocardial relaxation, as assessed by TDI.

Conclusions: In this highly screened, small patient population with hemodynamically confirmed diagnosis of HFPEF, increased end-diastolic static ventricular stiffness relative to aged matched controls was not a universal finding. Nevertheless, patients with HFPEF, even when well compensated, had elevated filling pressures, reduced distensibility and increased diastolic wall stress compared with controls. In contrast, left ventricular relaxation as assessed by tissue Doppler variables appeared consistently impaired in patients with HFPEF.

Key Words: heart failure, diastolic function, aging, Doppler echocardiography, hemodynamics
Introduction

Congestive heart failure (CHF) in the setting of a preserved ejection fraction (HFPEF) has been described as an epidemic in the senior population, accounting for up to half of all CHF admissions\(^1, 2\). Despite these statistics, limited progress has been made in elucidating the pathophysiology of HFPEF, particularly when compared to the study of CHF due to left ventricular (LV) systolic dysfunction. Investigation in this field has been hampered by inconsistent diagnostic criteria and challenges with the quantification of “diastolic function”\(^3\). To date, no single unifying theory has emerged to fully explain the etiology of HFPEF.

The term “diastolic heart failure” has often been used interchangeably in the literature with HFPEF and data from relatively younger, predominantly male subjects have implicated increased static LV stiffness and impaired lusitropic function as the primary source of symptoms in these patients\(^4\). However, our laboratory has demonstrated that static LV stiffness and dynamic myocardial relaxation are markedly “abnormal” even in otherwise healthy sedentary seniors compared with young controls\(^5, 6\). These data suggest that the presence of abnormal (i.e., not youthful) diastolic function is not pathognomonic for HFPEF, but instead these findings may represent an aging related substrate which when coupled with additional co-morbid conditions such as hypertension, ischemic heart disease or diabetes leads to CHF. Furthermore, numerous studies have suggested alternative or additive contributing mechanisms including elevation of LV end-diastolic volume, subtle impairments in LV systolic function, and increased ventricular-arterial stiffening\(^7, 9\). The lack of a comprehensive paradigm applicable to all patients, suggests
that the hemodynamic derangements responsible for this disorder may be quite heterogeneous.

The purpose of the present study was to perform a comprehensive, detailed characterization of hemodynamics and LV structure and function in a group of senior, mostly female patients with a clear diagnosis of HFPEF using normal age matched individuals as controls. We hypothesized that these HFPEF patients would have increased static left ventricular stiffness and slower myocardial relaxation in comparison with healthy sedentary senior controls leading to severely impaired ventricular filling and elevated diastolic filling pressures.

Methods

Subjects

2,054 patients over the age of 65 years with a discharge diagnosis of CHF were screened for inclusion in this study. Patients with HFPEF were defined as having a clear history of CHF by Framingham criteria with an ejection fraction (EF) > 50% documented by transthoracic echocardiography at the time of their index hospitalization. Exclusion criteria included the presence of atrial fibrillation at the time of the study, prior coronary artery bypass grafting (CABG), active myocardial ischemia, unrevascularized obstructive coronary disease (>50% lesions by prior angiography), stable angina, recent (< 1 year) myocardial infarction, renal failure (creatinine > 2.5 g/dl) or dialysis dependence, severe
COPD/or pulmonary disease, active malignancy, moderate or severe valvular heart
disease, and warfarin use. 1,119 patients had an EF of > 50%, and of these patients 23
met criteria for enrollment in the study, and 11 (73 ± 7 years of age; 4 men, 7 women)
agreed to participate (Figure 1). Thirteen sedentary healthy (70 ± 4 years of age; 7 men, 6
women) seniors used previously in our studies were included in the control group. The
baseline data for all these subjects are presented in Table 1. All patients at the time of
their index diagnosis met Framingham criteria of CHF11 and all had either an elevated
brain natriuretic peptide level (BNP) (median value 459 pg/ml) or documented
pulmonary congestion by chest X-ray or right heart catheterization. The healthy senior
subjects are the same patients (by design) who had their hemodynamic parameters, static
left ventricular compliance, and Doppler echocardiographic data reported previously5, 6.
The healthy senior subjects were carefully screened for hypertension and cardiac disease,
including structural heart and hemodynamically significant obstructive coronary disease,
using a history, physical examination, and resting and post-exercise transthoracic
echocardiograms. Additional exclusion criteria for this group included valvular heart
disease, atrial flutter/fibrillation, renal insufficiency, chronic lung disease, regular
cigarette smoking within the past 10 years, and cardiovascular medication. Both groups
of subjects underwent measurement of maximal oxygen uptake (VO2 max) using
previously described methods5. All subjects signed an informed consent approved by the
institutional review boards of the University of Texas Southwestern Medical Center at
Dallas, Medical City Hospital, Dallas, Texas, Doctors Hospital Dallas, Texas or
Presbyterian Hospital of Dallas.
Experimental protocol

Subjects were studied in the resting, supine, or left lateral position. A 6 Fr balloon-tipped fluid-filled catheter (Edwards Lifesciences, Irvine, California) was placed using fluoroscopic guidance through an antecubital vein into the pulmonary artery. The catheter was connected to a physiologic pressure transducer with the zero reference point set at 5.0 cm below the sternal angle. The wedge position of the catheter tip was confirmed using fluoroscopy, as well as by the presence of an appropriate pulmonary capillary wedge pressure (PCWP) waveform.

After at least 30 minutes of quiet supine rest, baseline data were collected. Subsequently, cardiac filling was first decreased using lower body negative pressure (LBNP) as previously described. Two levels of LBNP used were -15 and -30 mm Hg. Due to large body habitus limiting use of the LBNP apparatus in 2 of the HFPEF subjects, head-up tilt at (20 and 40 or 60 degrees) was used instead of LBNP, with the pressure transducer zero position carefully adjusted to the level of the right atrium documented by fluoroscopy and echocardiography. Measurements of mean PCWP, immediately followed by Doppler echocardiographic measurements were made after 5 minutes at each level of cardiac unloading. After release of the negative pressure (or return to supine position) and confirmed return to hemodynamic baseline, cardiac filling was increased through a rapid infusion of warm (37°C) isotonic saline solution at 100-200 ml/min. Measurements were repeated after the infusion of 10 and 20 ml/kg. At each level of cardiac preload,
hemodynamic measurements including heart rate (HR), blood pressure, and cardiac output by the acetylene rebreathing method were made

**Echocardiography**

For all subjects, at each level of cardiac loading/unloading, a transthoracic echocardiogram was obtained using an ATL (Advanced Technology Laboratories, Bothell, Washington) HDI 5000CV (software version 10.1) or an iE33 (Philips Healthcare, Bothell, WA) echocardiograph. Apical 4-chamber views were used to make each measurement. Volumes (left ventricular end-diastolic [LVEDV] and end-systolic volume [LVESV]) were determined using a modified Simpson’s method that was used in our previous studies. All images were evaluated blindly offline by an experienced sonographer.

**Doppler measurements**

Pulse-waved Doppler, using a sample volume of 2.0 mm placed at the tips of the mitral valve leaflets, was used to determine peak velocities of mitral inflow (E and A velocities). Using a 5-chamber apical view, the interval between aortic outflow during systole and opening of the mitral valve (IVRT) was also determined after the sample volume was increased to 4.0 mm. In the apical 4-chamber view, the septal wall was first highlighted in the tissue Doppler mode. Using pulse-wave Doppler, a sample volume of 4.0 mm was placed at the septal side of the mitral annulus. The resulting early diastolic waveform
velocity was recorded and the process was repeated for the lateral wall. Values were averaged to obtain TDI $E_{\text{mean}}^{15}$. A color M-mode image of left ventricular inflow was obtained with the sampling area positioned to extend from midatrium to the apex, directly through the mitral valve orifice. The scale was reduced sufficiently to result in clear aliasing within the early portion of the mitral inflow. The resulting mitral inflow spatiotemporal velocity profile pattern was used to derive the early propagation velocity of mitral inflow. This technique has been described previously$^{16}$.

**Cardiac MRI Measurements**

MRI was performed on a 1.5-T Philips NT MRI scanner. Short-axis, gradient-echo, cine MRI sequences with a temporal resolution of 39 ms were obtained to calculate LV masses and volumes as previously described$^5$. LV mass was computed as the difference between epicardial and endocardial areas multiplied by the density of heart muscle, 1.05 g/mL. For LV volume determination, the endocardial border of each slice was identified manually at end diastole and end systole, and volumes were calculated by summation. LV volumes were calculated by use of the Simpson’s rule technique as previously described$^{17}$. LV ejection fraction (LVEF) was computed according to the formula $$(\text{LVEDV}-\text{LVESV})/\text{LVEDV}.$$
The following physiological definitions are employed in the present study: 1) static LV chamber stiffness (or its inverse: chamber compliance) refers to the overall relationship between LV filling pressure and LVEDV as described by the stiffness constant “a” in the exponential equation described further below. 2) Operating or dynamic stiffness (or its inverse: operating compliance) is defined as dP/dV, or the instantaneous change in LV filling pressure relative to change in LVEDV. 3) LV chamber distensibility refers to the LVEDV for any given LV filling pressure independent of static or operating compliance. Thus, using this terminology, an upward and leftward shift in an end-diastolic pressure/volume curve with the same slope, shape, and stiffness constant would have reduced distensibility, but similar static chamber stiffness.

Data analysis

The LVEDV (determined by echocardiography) and PCWP data were used to construct LV end-diastolic pressure-volume curves using the following exponential model, which has been described previously5: 

\[ P = P_\infty (\exp^{a(V-V_0)}-1) \]

where \( P \) is PCWP, \( P_\infty \) is pressure asymptote of the curve, \( V \) is LVEDV index, \( V_0 \) is equilibrium volume or the volume at which \( P = 0 \) mm Hg, and “a” is a constant that characterizes the chamber stiffness. LV end-diastolic transmural pressure-volume curves were also constructed using estimated transmural pressure (estimated as [PCWP – right atrial pressure])18. The PCWP and stroke volume (SV) data obtained by the acetelyene rebreathing method were used to construct Frank-Starling curves. The LVEDV, SV, and MAP data were used to construct preload recruitable stroke work (PRSW) relationships. Circumferential LV wall stress
(σc) and strain were determined as previously described by use of the modified Laplace relation: σc = Pb/h[1-(h/2b)][1-(hb/2a2)], where P is estimated transmural pressure, h is LV midwall thickness, a is major semiaxis, and b is minor semiaxis5. The LV midwall thickness and semiaxis measurements were calculated from the transthoracic echocardiographic images. Ventricular strain was calculated as: strain= (V-Vmin)/Vmin where the smallest end-diastolic volume measured during cardiac unloading (Vmin) was determined. This value was subtracted from the end-diastolic volume at each loading/unloading condition (V-Vmin). The resulting data were used to construct stress-strain plots, which were modeled by an exponential equation (y = ae^{bx}). Total arterial compliance (TAC) was estimated by the ratio between the acetylene rebreathing derived SV and pulse pressure19. Effective arterial elastance (Ea) was estimated as the end-systolic LV pressure divided by SV, where end-systolic LV pressure was estimated as 0.9 * systolic blood pressure20,21.

**Statistical Methods**

Numerical data are presented as mean ± SD except for graphics, in which the SEM is used. Results for individual characteristics between the healthy controls and HFPEF patients were compared by use of Student’s t-test. For data obtained over the course of cardiac unloading and loading, 2-way repeated measures ANOVA (group, loading condition) was applied to evaluate the differences between the two groups for normally distributed data. The Mann-Whitney rank sum test was used for non-normally distributed data. Linear regression analysis was performed to assess the relationship between stroke
work and LVEDV in both groups as well as the relationship between PCWP and Doppler data. All analyses were performed by use of commercial software (SigmaStat 3.5, Systat Software, Chicago, IL). Given the relatively small sample size, P-values are reported and interpreted according to the American Physiological Society guidelines.22

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Subject characteristics

The baseline characteristics of the study subjects are presented in Table 1. Detailed data for the healthy seniors have been previously published.5, 6 The subjects were similar in terms of age, though the HFPEF patients were more obese and had markedly lower maximal oxygen uptakes. The HFPEF subjects were all hypertensive by history and the majority (55%) had diabetes mellitus. During their index hospitalization they had clear evidence of CHF and the majority had markedly elevated BNP levels (mean BNP, 448 ± 374 pg/ml). Most patients were on evidence based medical therapies for CHF (Table 1). Beta blockers were held for at least 24-48 hours before all studies and diuretics were delayed to the end of the study on the morning of examination.

Ventricular/Vascular characteristics
The ventricular-vascular characteristics of the study subjects are summarized in Table 2. Both groups of subjects had similar resting indexed LVEDVs, however, indexed LVESV were significantly smaller in the HFPEF patients (14.3 ± 5.5 ml/m² versus 20.3 ± 3.1 ml/m² in the controls, P=0.004), resulting in a higher ejection fraction in the HFPEF group (74.1 ± 7.5 % versus 68.2 ± 2.7 % in the controls, P=0.021). Though comparable in indexed LV mass and indexed LVEDV, the mass-volume ratio was significantly higher in the HFPEF patients (1.23 ± 0.32 g/ml versus 0.96 ± 0.15 g/ml in the controls, P=0.017). Measures of vascular function including SVR, TAC, and Ea were similar in both groups. Pulse pressure was wider in the HFPEF group (74.4 ± 10.4 mmHg versus 59.3 ± 8.56 mmHg in the controls, P<0.001) owing to a lower diastolic blood pressure (70.2 ± 10.4 mmHg in the HFPEF patients versus 78.2 ± 7.8 mmHg in the controls, P=0.042, Table 3).

**Hemodynamics**

The baseline hemodynamics are detailed in Table 3. There were no significant differences in resting heart rate, cardiac index, or systolic blood pressure between the two groups. The baseline resting PCWPs were significantly higher in the HFPEF patients (15.2 ± 5.1 mmHg versus 11.4 ± 2.0 mmHg in the controls, P=0.021). Norepinephrine levels increased modestly in response to lower body negative pressure in both groups (413 ± 196 at baseline to 601 ± 330 pg/ml at the highest level of cardiac unloading in the HFPEF group, P=0.001) and (279 ± 127 at baseline to 418 ± 217 pg/ml at the highest level of cardiac unloading in the controls, P=0.016).
LV contractility and systolic function

Overall contractile function was similar between the two groups as there were no differences noted in the LV Frank-Starling relationship (Figure 2a, second order regression analysis: r=0.99 for the HFPEF patients and r=0.99 for the controls, P=0.664) or in the preload recruitable stroke work relationship (Figure 2b, linear regression analysis: r=0.97 for HFPEF patients and r=0.98 for controls, P=0.995).

LV EDP/EDV index relationship

The grouped mean data for the demonstrated an upward and leftward shift of the end-diastolic pressure-volume curve for the HFPEF patients as compared with the controls (Figure 3a) indicating decreased distensibility (higher pressure for the same volume). However, there was no difference in overall static chamber compliance; evaluation of the stiffness constant “a”, revealed no significant difference between the two groups (0.041 ± 0.038 in the HFPEF patients and 0.061 ± 0.030 in the controls, P=0.172). This relationship persisted when estimated transmural pressure was used in place of PCWP (Figure 3b). Equilibrium volumes were smaller in the HFPEF patients compared with controls (9.2 ± 10 ml in the HFPEF patients and 21.2 ± 8.9 ml in the control group, P=0.006).

End-diastolic stress-strain relationship
Baseline circumferential wall stress was higher in the HFPEF patients as compared with the controls (26.5 ± 14.4 kdynes/cm² in the HFPEF patients and 7.5 ± 5.2 kdynes/cm² in the controls, P<0.001) and this relationship was maintained across loading conditions (figure 4). Accordingly, at zero strain, end-diastolic wall stress was higher in the HFPEF patients as compared with the controls (10.9 ± 5.1 kdynes/cm² versus 2.9 ± 1.5 kdynes/cm², P=0.015). For any equivalent degree of ventricular deformation, the patients with HFPEF had a higher wall stress during cardiac unloading (P=0.024), but not during saline loading (P=0.339).

**Doppler measures of diastolic function**

**TDI velocities**

The resting baseline TDI E\textsubscript{mean} velocities were substantially slower for the HFPEF patients as compared with the healthy control subjects (7.62 ± 1.53 cm/sec in the HFPEF patients versus 9.49 ± 1.61 cm/sec in the healthy seniors, P=0.014). This significant difference was present across all loading conditions (P=0.013). The increased TDI E\textsubscript{mean} velocities in the healthy seniors were driven by faster TDI E\textsubscript{septal} velocities. At baseline TDI E\textsubscript{septal} velocity was 6.42 ± 1.31 cm/sec in the HFPEF patients and 8.40 ± 1.68 cm/sec in the healthy seniors, P=0.008. The overall difference between the two groups for TDI E\textsubscript{septal} was highly significant at P=0.002. In contrast, the difference in TDI E\textsubscript{lateral} velocities between the two groups at baseline was less (8.82 ± 2.13 cm/sec in the HFPEF patients versus 10.6 ± 2.15 cm/sec in the healthy seniors, P=0.068) with a lower degree of statistical difference across all loading conditions (P=0.078). Data for TDI E\textsubscript{mean} are shown in Figure 5a.
Transmitral flow velocities: Peak E wave velocity, peak A-wave velocity, and E/A ratio

In the HFPEF patients, the resting baseline peak E wave velocities were elevated as compared with the controls (76.5 ± 25.8 cm/sec in the HFPEF patients and 56.8 ± 13.9 cm/sec in the controls, P=0.031). Similarly, the baseline resting A wave velocities were higher in the HFPEF patients (100.7 ± 28.9 cm/sec in the HFPEF patients and 70.7 ± 17.6 cm/sec in the controls, P=0.006). The concomitant increase in both peak E and peak A wave velocities in the HFPEF patients resulted in no difference in the resting E/A ratio between the two groups at baseline or across loading conditions, Figure 5b.

IVRT

Baseline IVRT was shorter in the HFPEF patients as compared with the control subjects (96.4 ± 35.4 msec in the HFPEF patients and 146.7 ± 18.8 msec in the controls, P<0.001). This difference was present across all preload conditions (P=0.002), Figure 5c.

Vp

Baseline Vp was faster in the HFPEF group as compared with the controls (42.9 ± 12.8 cm/s in the HFPEF patients versus 34.2 ± 7.2 cm/s in the control group, P=0.051). The Vp values were also significantly higher in the HFPEF patients as compared with the healthy controls at the lowest filling pressures (39.4 ± 12.6 cm/s in the HFPEF patients and 27.6 ± 8.6 cm/s in the healthy seniors, P=0.038) and at the highest filling pressures (50.8 ± 10.8 cm/s in the HFPEF patients and 40.8 ± 8.8 cm/s in the controls, P=0.043).
There was a significant difference in the overall relationship between preload and Vp between the two groups (P=0.023), Figure 5d.

**Gender differences in diastolic function**

*Doppler data*

Of the 11 patients with HFPEF, 4 were male and 7 female. The Doppler data were analyzed by group (HFPEF or control) and by gender. There were no gender based differences in the E/A ratio (P = 0.868) or Vp (P = 0.292). In contrast, IVRT was shortest in the females with HFPEF across loading conditions when compared to control females (P=0.008), control males (P<0.001), and males with HFPEF (P=0.030), Figure 6a. TDI E_mean velocities were slower in the HFPEF females versus control females, (P=0.017) and slower in the HFPEF males versus all other subjects, P<0.001, (Figure 6b).

**LV EDP/EDV index relationships**

Despite the small numbers of subjects, there were large differences noted in the static LV compliance curves between males and females with HFPEF (Figure 6c). Male patients with HFPEF had a prominent leftward and upward shift of their end-diastolic pressure volume relationship in comparison with male controls. In contrast control females and female patients with HFPEF had little difference in static LV compliance. Moreover the curves for male HFPEF patients and female controls appeared quite similar – both shifted similarly upward and to the left compared to male controls. The stiffness constants for
the male patients appeared higher versus the female patients (0.070 ± 0.053 and 0.025 ± 0.010 respectively), however statistical comparisons between the groups was limited by the small sample size of the gender subgroups.

Discussion

The primary purpose of the present study was to determine if patients with HFPEF do, or do not, have clinically meaningful abnormalities of diastolic function. Therefore, we were quite rigorous in excluding patients who might have alternative reasons for the development of heart failure. For example, we excluded patients with atrial fibrillation at the time of the study since afib may trigger and/or exacerbate HFPEF, especially if the heart rate is uncontrolled23-26. Secondly, we excluded patients with ischemic heart disease. Ischemia clearly elevates filling pressures and alters diastolic function24-26. Furthermore, we excluded patients with prior CABG as loss of the pericardium alters LV compliance and interventricular interactions and these patients may be prone to incomplete revascularization27. Finally, we excluded patients with renal insufficiency who may have elevated plasma volume and thereby elevated filling pressures. As a consequence of these strict criteria, we selected a cohort characterized by the clear presence of CHF, but without any alternative explanation for diastolic dysfunction. Furthermore, this is the only study which used a healthy age matched cohort, not being catheterized for the presence of angina, against which to compare invasive measurements of diastolic function.
Static left ventricular stiffness is not increased in all patients with HFPEF

There are few studies which have examined LV chamber compliance in patients with HFPEF using invasively derived data. Kawaguchi et al, studied mostly female and non-senior (9 females, 1 male, mean age 60.5yrs) patients. Using inferior vena cava (IVC) occlusion and a single beat method to extrapolate the LV diastolic pressure-volume relationship in 6 of the HFPEF patients, they demonstrated higher LVEDPs but similar stiffness constants in patients with HFPEF. In contrast, using multiple data points within a single beat and mathematically deriving diastolic pressures, Zile et al demonstrated a marked increase in static LV stiffness in younger patients (16 females, 31 males, mean age 59yrs) with HFPEF. Data from the a group of Belgian investigators also reported elevated stiffness constants (IVC occlusion, conductance catheter) in young (mean age under 60 yrs) mostly female patients with HFPEF versus mostly male, non-CHF controls with chest pain. Two additional, completely non-invasive, studies warrant mention. Lam et al, using Doppler to estimate end-diastolic pressure demonstrated that senior, mostly female patients with HFPEF (134 females, 110 males; age 76yrs) from a population-based study had increased passive LV diastolic stiffness compared to both hypertensive and non-hypertensive controls. Lastly, He et al compared non-invasively derived end-diastolic pressure-volume relationships in patients with HFPEF (n=128; 72yrs) with normal controls (n=93) without hypertension or CHF and noted a slight rightward shift of the end-diastolic pressure-volume curve in the HPPEF group but no difference in the static compliance relationship.

In some, but not all of the above studies, the increased passive elastance of the HFPEF group is striking with stiffness constants 2-3 times higher than controls. Our data
in an older population with confirmed HFPEF are notably different. In the present study, the HFPEF group did demonstrate modestly decreased LV distensibility but no significant difference in static LV compliance relative to the sedentary seniors. Our data extend these previous studies by providing an important signal that excessive static LV stiffness may not be a universal finding in all patients with HFPEF when compared to healthy, sedentary seniors.

**Doppler measures of diastolic function**

There has been considerable debate regarding Doppler measures of diastolic function in the diagnosis of HFPEF. For example, Oh et al have suggested that in the appropriate clinical setting, the diagnosis of HFPEF can be confirmed if Doppler transmitral velocity patterns and myocardial tissue velocities suggest impaired left ventricular relaxation and compliance\(^3\). In contrast, Maurer et al have argued that Doppler patterns do not adequately characterize the static LV end-diastolic pressure-volume relationship or the intrinsic relaxation properties of the myocardium\(^3\). Previous studies have been inconsistent with regards to both the magnitude and direction of change in specific Doppler variables \(^9, 28, 30, 34, 35\). This disparity is likely multifactorial and influenced by patient age, level of clinical compensation, heterogeneity in the diagnostic inclusion criteria, and inconsistent control groups.

The present study provides further evidence that the differences in conventional Doppler parameters of diastolic function such as E and A wave velocities, the E/A ratio and IVRT, between healthy sedentary seniors and patients with HFPEF are not sufficient to differentiate these two groups. For example, in this study, HFPEF patients had higher
transmitral E and A velocities (but similar E/A ratios) and shorter IVRT across loading conditions. These findings are likely explained by the higher LA pressure driving faster early and late filling velocities (higher atrio-ventricular gradients) and earlier opening of the mitral valve. The normal E/A ratio, shorter IVRT and slightly faster Vp in these HFPEF patients highlight the limitations of traditional Doppler variables to accurately quantify left ventricular relaxation.

Nevertheless, despite, higher LA pressures, patients with HFPEF had slower TDI velocities, suggesting an inherent abnormality in LV relaxation, independent of the influence of elevated filling pressure. We previously demonstrated that TDI velocities are markedly slowed with normal sedentary aging in comparison to young individuals. The present study suggests an additional slowing of myocardial relaxation in patients with HFPEF which is not explainable by aging alone. TDI therefore may be a more specific marker for the possible relaxation abnormalities in patients with HFPEF.

The Doppler and static LV compliance data from the present study, when examined by gender, further emphasize the heterogeneity in the pathophysiology underlying this disorder. Males with HFPEF, in comparison to females with HFPEF, appear to have more severe abnormalities in diastolic function including higher left atrial pressures, higher static LV stiffness, and slower myocardial relaxation. By contrast, senior women with and without HFPEF appear to be more similar in terms of static LV compliance and myocardial relaxation properties (and both similar to HFPEF men). The influence of gender on ventricular diastolic function in this context remains poorly understood and requires larger studies powered to specifically address this issue.
Systolic and ventricular-vascular function in HFPEF

Subtle impairments in systolic function have been postulated to play a role in the pathophysiology of HFPEF\(^\text{36}\). In this study, the Frank-Starling curves and preload recruitable stroke work slopes were similar between the two groups, suggesting no substantial differences in LV contractile function. Moreover, despite larger pulse pressures, there was little evidence of increased arterial stiffening in the HFPEF patients such as total arterial compliance or effective arterial elastance, perhaps because HFPEF patients were well treated with antihypertensive medications and compensated at the time of study.

Clinical Perspective and study limitations

There are several key differences in patient selection and methodology in this study compared with previous publications. First, we included HFPEF patients who are most representative of the population described in large epidemiological studies, clinical trials, and registry data. Specifically the patients were mostly female, older (all \(\geq 65\) years), hypertensive, with a well documented diagnosis of CHF. Second, the controls were healthy seniors of similar age, who were rigorously screened for cardiovascular disease, allowing a direct comparison with sedentary aging. The methods used to derive the end-diastolic pressure-volume curves were comprehensive including directly measured PCWP and near simultaneous LVEDV across multiple levels of cardiac preload. With this technique we could generate a complete representation of static LV chamber compliance across a wide spectrum of clinically relevant filling pressures, including the evaluation of operational compliance during elevated filling pressures which are
associated with symptomatic decompensation. Given, the strict selection criteria and invasive nature of the protocol, we evaluated a relatively small group of subjects. However we also avoided studying patients who had alternative non-CHF related etiologies for dyspnea, edema, and exercise tolerance which may be one of the reasons for the high prevalence of HFPEF cases. Lastly, while not powered for gender based analysis, the disparate findings in males and females with HFPEF are novel and hypothesis generating.

Conclusions

Patients with a clear diagnosis of HFPEF compared with healthy, sedentary seniors have:
1) an elevated left atrial pressure, even when clinically compensated, associated with reduced distensibility and increased diastolic wall stress; 2) similar static LV compliance, 3) no substantial differences in LV contractile function, 3) slower tissue Doppler velocities suggestive of impaired myocardial relaxation. These data highlight the need for additional study of this complex disease, particularly in a broader subset of patients to improve the external validity of these results.
Sources of Funding

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Disclosures

None.
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### Table 1. Baseline subject characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>HFPEF (n=11)</th>
<th>Healthy Seniors (n=13)</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>73.0 ± 6.8</td>
<td>70.2 ± 3.5</td>
<td>P=0.259</td>
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<td>6</td>
<td>P=0.414</td>
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<tr>
<td>BSA* (m²)</td>
<td>1.99 ± 0.27</td>
<td>1.85 ± 0.17</td>
<td>P=0.159</td>
</tr>
<tr>
<td>VO₂ Max† (ml/kg/min)</td>
<td>13.7 ± 3.4*</td>
<td>21.6 ± 3.6</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>VO₂ Max (L/min)</td>
<td>1.23 ± 0.51</td>
<td>1.56 ± 0.34</td>
<td>P=0.075</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Co-morbid conditions</th>
<th>HFPEF Patient Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>11 (100%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6 (55%)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Renal Insufficiency</td>
<td>1 (9%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>9 (82%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Index Hospitalization Evaluation</th>
<th>HFPEF Patient Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea on exertion</td>
<td>11 (100%)</td>
</tr>
<tr>
<td>Pulmonary edema or rales</td>
<td>9 (82%)</td>
</tr>
<tr>
<td>Lower extremity edema</td>
<td>8 (73%)</td>
</tr>
<tr>
<td>SerumCreatinine (mg/dl)</td>
<td>1.2 ± 0.23</td>
</tr>
<tr>
<td>BNP‡ (pg/ml)</td>
<td>448 ± 374</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medications</th>
<th>HFPEF Patient Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretic</td>
<td>10 (91%)</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>6 (55%)</td>
</tr>
<tr>
<td>Calcium Channel Blocker</td>
<td>5 (45%)</td>
</tr>
<tr>
<td>ACE-I/ARB</td>
<td>9 (82%)</td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitor</td>
<td>9 (82%)</td>
</tr>
</tbody>
</table>

* BSA (body surface area), †VO₂ Max (Maximal oxygen consumption), ‡ BNP (brain natriuretic peptide)
Table 2. Baseline ventricular-vascular function

<table>
<thead>
<tr>
<th>Left ventricular characteristics</th>
<th>HFPEF</th>
<th>Healthy Seniors</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDV* (ml)</td>
<td>111.5 ± 25.7</td>
<td>118.2 ± 22.7</td>
<td>P=0.526</td>
</tr>
<tr>
<td>EDV index (ml/m²)</td>
<td>56.3 ± 12.1</td>
<td>63.7 ± 8.4</td>
<td>P=0.109</td>
</tr>
<tr>
<td>ESV† (ml)</td>
<td>27.5 ± 9.3</td>
<td>37.5 ± 7.7</td>
<td>P=0.012</td>
</tr>
<tr>
<td>ESV index (ml/m²)</td>
<td>14.3 ± 5.5</td>
<td>20.3 ± 3.1</td>
<td>P=0.004</td>
</tr>
<tr>
<td>SV‡ (ml)</td>
<td>82.2 ± 23.3</td>
<td>80.7 ± 15.8</td>
<td>P=0.856</td>
</tr>
<tr>
<td>SV index (ml/m²)</td>
<td>41.3 ± 10.0</td>
<td>43.5 ± 5.9</td>
<td>P=0.525</td>
</tr>
<tr>
<td>EF (%)</td>
<td>74.1 ± 7.5</td>
<td>68.2 ± 2.7</td>
<td>P=0.021</td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>140.1 ± 58.9</td>
<td>114.0 ± 26.4</td>
<td>P=0.181</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>69.3 ± 21.8</td>
<td>61.0 ± 9.4</td>
<td>P=0.249</td>
</tr>
<tr>
<td>LV mass/EDV (g/ml)</td>
<td>1.23 ± 0.32</td>
<td>0.96 ± 0.15</td>
<td>P=0.017</td>
</tr>
<tr>
<td>LV stiffness constant</td>
<td>0.041 ± 0.038</td>
<td>0.061 ± 0.030</td>
<td>P=0.172</td>
</tr>
<tr>
<td>LV equilibrium volume (ml)</td>
<td>9.2 ± 10</td>
<td>21.2 ± 8.9</td>
<td>P=0.006</td>
</tr>
<tr>
<td>Pressure asymptote (mmHg)</td>
<td>9.4 ± 8.5</td>
<td>5.5 ± 4.3</td>
<td>P=0.124</td>
</tr>
<tr>
<td>Operating stiffness during cardiac unloading (mmHg * m²/ml)</td>
<td>0.60 ± 0.7</td>
<td>0.63 ± 1.3</td>
<td>P=0.258</td>
</tr>
<tr>
<td>Operating stiffness during cardiac loading (mmHg * m²/ml)</td>
<td>0.88 ± 1.1</td>
<td>1.1 ± 1.5</td>
<td>P=0.258</td>
</tr>
<tr>
<td>SVR§ (dyne<em>s</em>cm⁻²)</td>
<td>1375 ± 740</td>
<td>1583 ± 280</td>
<td>P=0.357</td>
</tr>
<tr>
<td>SVRi (dyne<em>s</em>cm⁻⁵*m²)</td>
<td>706 ± 390</td>
<td>872 ± 222</td>
<td>P=0.205</td>
</tr>
<tr>
<td>PPI (mmHg)</td>
<td>74.4 ± 10.4</td>
<td>59.3 ± 8.56</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>TAC# (ml/mmHg)</td>
<td>1.17 ± 0.27</td>
<td>1.31 ± 0.45</td>
<td>P=0.379</td>
</tr>
<tr>
<td>Ea** (ml/mmHg/ml)</td>
<td>1.60 ± 0.52</td>
<td>1.75 ± 0.50</td>
<td>P=0.490</td>
</tr>
</tbody>
</table>

* Left ventricular volumes and mass obtained by MRI. EDV (end-diastolic volume), † ESV (end-systolic volume), ‡ SV (stroke volume), § SVR (systemic vascular resistance), PP (pulse pressure), # TAC (total arterial compliance), ** Ea (effective arterial elastance)
Table 3. Baseline Resting Hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>HFPEF Patients</th>
<th>Healthy Seniors</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP*</td>
<td>144.6 ± 11.5</td>
<td>137.5 ± 14.2</td>
<td>P=0.198</td>
</tr>
<tr>
<td>DBP†</td>
<td>70.2 ± 10.4</td>
<td>78.2 ± 7.8</td>
<td>P=0.042</td>
</tr>
<tr>
<td>MAP‡</td>
<td>95.0 ± 9.6</td>
<td>98.0 ± 9.6</td>
<td>P=0.461</td>
</tr>
<tr>
<td>Qreb§</td>
<td>6.72 ± 2.90</td>
<td>5.03 ± 0.63</td>
<td>P=0.052</td>
</tr>
<tr>
<td>Qrebi (L<em>min⁻¹</em>m⁻²)</td>
<td>3.41 ± 1.54</td>
<td>2.73 ± 0.27</td>
<td>P=0.129</td>
</tr>
<tr>
<td>HR rebŒ</td>
<td>75.8 ± 21.5</td>
<td>68.9 ± 10.3</td>
<td>P=0.316</td>
</tr>
<tr>
<td>SV reb# (ml/min)</td>
<td>86.7 ± 21.1</td>
<td>75.5 ± 19.8</td>
<td>P=0.193</td>
</tr>
<tr>
<td>SVi reb (ml<em>min⁻¹</em>m⁻²)</td>
<td>44.4 ± 14.1</td>
<td>40.7 ± 8.9</td>
<td>P=0.440</td>
</tr>
<tr>
<td>PCWP**</td>
<td>15.2 ± 5.1</td>
<td>11.4 ± 2.0</td>
<td>P=0.021</td>
</tr>
<tr>
<td>RAP††</td>
<td>9.55 ± 3.3</td>
<td>7.98 ± 1.9</td>
<td>P=0.160</td>
</tr>
<tr>
<td>ETMP‡‡</td>
<td>5.66 ± 3.0</td>
<td>3.39 ± 1.4</td>
<td>P=0.023</td>
</tr>
</tbody>
</table>

* SBP (systolic blood pressure), † DBP (diastolic blood pressure), ‡ MAP (mean arterial pressure), § Qreb (cardiac output by acetylene rebreathing [reb] technique), Œ HR (heart rate), # SV (stroke volume) SVi (stroke volume index), **PCWP (pulmonary capillary wedge pressure), ††RAP (right atrial pressure), ‡‡ETMP (estimated transmural pressure, PCWP-RAP).
Figure Legends

Figure 1. Patient enrollment flowchart
CABG (coronary artery bypass grafting), COPD (chronic obstructive pulmonary disease)

Figure 2a. Frank Starling relationship
Overall contractile function was similar between the HFPEF and senior control subjects.
Second order regression analysis: $r=0.99$ for the HFPEF patients and $r=0.99$ for the
controls, ($P=0.664$).

Figure 2b. Preload recruitable stroke work
No differences were noted in preload recruitable stroke work. Linear regression analysis:
$r=0.97$ for HFPEF patients and $r=0.98$ for the senior controls, ($P=0.421$).

Figure 3a. End-diastolic pressure volume relationships
Decreased distensibility in the HFPEF patients versus senior controls with no significant
differences in overall chamber compliance.

Figure 3b. End-diastolic transmural pressure volume relationships
The end-diastolic pressure volume relationship is maintained even when PCWP is
substituted for by estimated transmural pressure (PCWP- right atrial pressure).

Figure 4. End-diastolic stress strain relationship
Baseline circumferential wall stress was higher in the HFPEF patients as compared with the senior controls (P<0.001). For any equivalent degree of ventricular deformation, the patients with HFPEF had a higher wall stress during cardiac unloading (P=0.024), but not during saline loading (P=0.339).

Figure 5a. Mean of lateral and septal tissue Doppler mitral annular velocities (TDI E$_{\text{mean}}$)
TDI E$_{\text{mean}}$ velocities were significantly slower in the HFPEF patients versus the senior controls across loading conditions, (P=0.013).

Figure 5b. Ratio of early and late mitral inflow velocities (E/A)
There was no difference in the E/A ratio across loading conditions between the HFPEF patients and senior control subjects, (P=0.431).

Figure 5c. Isovolumetric relaxation time (IVRT)
IVRT was prolonged in the senior controls versus the HFPEF patients across loading conditions, (P=0.002).

Figure 5d. Propagation velocity of early mitral inflow (Vp)
Vp was faster in the senior controls versus the HFPEF patients across loading conditions, (P=0.023).

Figure 6a. Gender based differences in IVRT
IVRT was shortest in the female HFPEF patients across loading conditions when compared to control females (P=0.008), control males (P<0.001), and males with HFPEF (P=0.030).

Figure 6b. Gender based differences in TDI $E_{\text{mean}}$ velocities

TDI $E_{\text{mean}}$ velocities were slower in the HFPEF females versus control females (P=0.017) and slower in the HFPEF males versus all other subjects (P<0.001).

Figure 6c. Gender differences in end-diastolic pressure volume relationships

Male patients with HFPEF had a leftward shift of their end-diastolic pressure volume relationship in comparison with females with HFPEF. In contrast control females and female patients with HFPEF had little difference in static LV compliance.
Screened 2,054 Patients (age > 65) with a discharge diagnosis of CHF

1,119 patients with a LVEF > 50 %

<table>
<thead>
<tr>
<th>Reason for exclusion</th>
<th># of patients excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation at the time of study</td>
<td>313</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>179</td>
</tr>
<tr>
<td>Incomplete records</td>
<td>111</td>
</tr>
<tr>
<td>Left bundle branch block or paced rhythm</td>
<td>90</td>
</tr>
<tr>
<td>No clear documentation of CHF</td>
<td>77</td>
</tr>
<tr>
<td>Active malignancy</td>
<td>55</td>
</tr>
<tr>
<td>Myocardial ischemia/infarction</td>
<td>53</td>
</tr>
<tr>
<td>Dementia/cognitive impairment</td>
<td>44</td>
</tr>
<tr>
<td>Deceased prior to enrollment evaluation</td>
<td>41</td>
</tr>
<tr>
<td>Dialysis dependant or creatinine (&gt; 2.5 g/dl)</td>
<td>40</td>
</tr>
<tr>
<td>Severe COPD/pulmonary disease</td>
<td>39</td>
</tr>
<tr>
<td>Warfarin use</td>
<td>30</td>
</tr>
<tr>
<td>Moderate to severe valvular heart disease</td>
<td>13</td>
</tr>
<tr>
<td>History of organ transplantation</td>
<td>6</td>
</tr>
<tr>
<td>Ejection fraction unclear</td>
<td>5</td>
</tr>
</tbody>
</table>

Total Patients Excluded 1096

935 patients with a LVEF ≤ 50 % (excluded)

23 patients met criteria for enrollment

11 patients agreed to participate
4 men and 7 women
Preload Recruitable Stroke Work

Left Ventricular End-Diastolic Volume (ml)

Estimated Stroke Work (ml*mmHg)

- Senior controls
- HFPEF patients

Downloaded from http://circheartfailure.ahajournals.org/ by guest on July 6, 2017
Estimated Transmural Pressure (mmHg) vs. LVEDV index (ml * m^{-2})

- **HFPEF**
- **Senior Controls**

**Graph Details:**
- The x-axis represents the LVEDV index in ml * m^{-2}.
- The y-axis represents the estimated transmural pressure in mmHg.
- The graph compares the HFPEF and senior control groups.
- Error bars indicate variability within each group.

**Legend:**
- Solid black circles for HFPEF patients.
- Open white circles for senior controls.
End Diastolic Stress Strain Relationship

Circumferential Left Ventricular End-Diastolic Wall Stress (kdynes/cm^2)

Natural Strain \((V-V_{min})/V_{min}\)

HFPEF patients
Senior Controls
E/A ratio

PCWP (mmHg)

Senior controls
HFPEF patients

Circulation
Heart Failure
JOURNAL OF THE AMERICAN HEART ASSOCIATION
Characterization of Static and Dynamic Left Ventricular Diastolic Function in Patients with Heart Failure and a Preserved Ejection Fraction
Anand Prasad, Jeffrey Hastings, Shigeki Shibata, Zoran B. Popovic, Armin Arbab-Zadeh, Paul S. Bhella, Kazunobu Okazaki, Qi Fu, Martin Berk, Dean Palmer, Neil L. Greenberg, Mario J. Garcia, James D. Thomas and Benjamin D. Levine

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