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Left Ventricular Volume-Time Relation in Patients with Heart Failure with Preserved Ejection Fraction

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Abstract

Elevated left ventricular (LV) filling pressures are commonly reported in patients with Heart Failure with Preserved Ejection Fraction (HFpEF) and are associated with impaired relaxation in diastole. Relaxation has been assessed by Doppler, but the methods for doing so are indirect and heavily influenced by loading conditions. The aim of this study is to assess LV volume-time relationship in patients with HFpEF, when correcting for left atrial driving pressure and chamber size, using cardiac-MRI (cMRI). Cine short-axis views by cMRI (1.5T-magnet) at 26 Hz were used for measurement of LV volume. We compared the following diastolic parameters: (PFR/end-diastolic-volume (PFR/EDV); PFR/EDV/pulmonary capillary wedge pressure (PFR/EDV/PCWP); time to PFR (TPFR); %TPFR for cardiac cycle) calculated by cMRI between HFpEF patients (N=10, 73±7 years) and age-matched controls (N=12, 70±3 years). PCWP was significantly greater in the HFpEF group than in controls (HFpEF vs. Controls: 15.6±5.2 vs. 11.2±1.3 mmHg, $P = 0.0092$). PFR/EDV was significantly slower in the HFpEF group than in controls (2.68±0.85 vs. 3.59±0.87 s⁻¹, $P = 0.03$), and was nearly 50% slower when corrected for left atrial driving pressure: PFR/EDV/PCWP (0.18±0.07 vs. 0.33±0.10 s⁻¹/mmHg, $P = 0.002$). In addition, TPFR (246±17.2 vs. 188±15.7 ms, $P=0.04$) and %TPFR of cardiac cycle (36.4±10.4 vs. 25.6±5.9 %, $P=0.012$) were significantly longer in the HFpEF group than in controls. HFpEF patients have an abnormal volume-time relationship, including lower PFR/EDV (PFR/EDV/PCWP) and prolonged time to PFR, due to the impairment of active relaxation during early diastole.

Keywords

HFpEF; Diastolic function; cMRI; Left Ventricular Volume-time Relationship

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Introduction

The most frequently used method to quantify diastolic function in the clinical setting is E/e' , which is central in the guidelines for diastolic evaluation.¹ However, echocardiographic Doppler measures are indirect and can be misleading, due to their dependence on loading conditions. Even an elevated pulmonary capillary wedge pressure (PCWP) obtained from cardiac catheterization reflects diastolic function only at end-diastole. Therefore, to most accurately assess diastolic “function” in HFpEF, both precise quantification of volumetric filling, as well as LA driving pressure are necessary; thus, we chose cardiac MRI combined with right heart catheterization for this study. Cardiac MRI is a high spatial resolution tool that allows for the precise measurement of LV volume without geometric assumptions,^{2,3} making it more accurate than echocardiographic methods in assessing LV morphology.^{4,5} Furthermore, using accurate LV volume measured by cMRI enables the calculation of LV filling rates and the LV volume-time relationship.^{3,6} In particular, peak filling rate (PFR), PFR divided by EDV (PFR/EDV), and time to PFR (TPFR) are derived from the time-volume curve.^{3,6-9} In the present study, we hypothesized that a highly screened population of HFpEF patients would demonstrate an abnormal LV volume-time relationship as well as a slower PFR/EDV or prolonged TPFR during the early diastolic phase even when normalized for LA driving pressure.

Methods

Ten highly screened patients (age ≥ 65 years) with the diagnosis of HFpEF and available data of cMRI were reviewed for this study; the screening process, documentation of HFpEF, and Doppler and pressure-volume curves for these highly screened patients have been reported previously.¹⁰⁻¹² Twelve healthy, similar aged, sedentary individuals with no major medical conditions and available data of cMRI served as controls.¹⁰⁻¹² One participant from each group (HFpEF group and controls) did not have cMRI data available. In brief, criteria for the diagnosis of HFpEF included: the presence of Framingham criteria for the diagnosis of heart failure; an index hospitalization with evidence of pulmonary congestion, an elevated PCWP, or an elevated brain-type natriuretic peptide within 6 months of enrollment; and LV ejection fraction $\leq 50\%$. With the exception of the LV ejection fraction, echocardiographic indices were specifically not used for the diagnosis of HFpEF since the overall goal of this project was to determine the nature and extent of abnormalities of ‘diastolic function’ in patients who clearly have this complicated syndrome; this approach is similar to other recent work regarding HFpEF.¹³ Nevertheless, the Doppler data for these patients were quite abnormal compared to healthy controls and well within guidelines for making the diagnosis of HFpEF.²⁰ Exclusion criteria included significant valvular heart disease defined as any regurgitation or stenotic lesion greater than ‘mild’ when assessed by transthoracic echocardiography; acute atrial fibrillation; congenital heart disease; coronary artery disease with provokable ischemia as assessed by exercise stress echocardiography, an acute coronary syndrome, or a history of surgical revascularization or multi-vessel percutaneous revascularization; New York Heart Association functional class IV heart failure; suspicion of a restrictive or infiltrative cardiomyopathy; or any additional medical condition that may have explained the subject’s heart failure symptom complex. HFpEF patient co-morbidities and cardiac medications have been published previously.¹⁰ All subjects signed an informed

consent approved by the institutional review boards of the University of Texas Southwestern Medical Center and Texas Health Presbyterian Hospital Dallas.

A 6-F balloon-tipped fluid-filled catheter (Edwards Lifesciences, Irvine, CA) was placed using fluoroscopic guidance through an antecubital vein and into the pulmonary artery. Three measures of the mean heart rate, blood pressure, PCWP, and right atrial pressure, were obtained at end-expiration using a previously described technique and reported in this population; cardiac output (Qc) was similarly obtained by the foreign gas rebreathing method.¹⁰ Stroke volume and effective arterial elastance were obtained by Qc divided by heart rate and 0.9 times systolic blood pressure divided by stroke volume. Qc, stroke volume, and effective arterial elastance were indexed to body surface area.

For all subjects, a transthoracic echocardiogram was obtained using an Advanced Technology Laboratories HDI 5000CV or an iE33 echocardiograph (Philips Medical Systems, Andover, MA, USA). Pulse-waved Doppler imaging, 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-wave velocities). Using a 5-chamber apical view, the interval between aortic outflow during systole and opening of the mitral valve (isovolumic relaxation time) was measured using a sample volume of 4.0 mm. Corrected isovolumic relaxation time was calculated by isovolumic relaxation time divided by the square root of R-R interval. Using pulse-wave Doppler imaging, a sample volume of 5.0 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 e' mean. All images were evaluated off line by a blinded well-experienced sonographer and have been previously reported.¹⁰

MRI measurements were performed on a 1.5-T Philips NT MRI scanner. Short-axis, gradient-echo, cine MRI sequences with a temporal resolution of 39 milliseconds were obtained to calculate LV mass and volume as previously described.¹⁴ 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 and epicardial border of each slice was identified manually between end diastole and end systole, and LV volumes were calculated by summation. All time-phases and slices have to be segmented and analyzed; therefore, a few hundred images were obtained for each individual, depending on LV chamber size and heart rate. LV volumes were calculated by use of the Simpson rule technique as previously described.¹⁵ Image analysis was performed by post-processing software (Qmass MR 7.1, Medis medical imaging systems, Netherlands). Peak filling rate (PFR) is the maximal LV filling rate defined by maximal change in LV volume between sequential temporal phases (volume/ time). This index was also adjusted for LVEDV to generate standardized peak filling rate (PFR/EDV). In addition, to normalize for left atrium pressure, PFR/EDV/PCWP was obtained by dividing PFR/EDV by PCWP. Time to peak filling rate (TPFR) is the time interval between end systole and peak filling rate. To standardize the HR, the corrected TPFR was calculated by TPFR divided by the square root of the R-R interval. The TPFR for a cardiac cycle (% PFR for cardiac cycle) was obtained by TPFR divided by the time interval of one cardiac cycle.

Numerical data are presented as mean $\pm$ SD. Nonparametric data were analyzed by Mann-Whitney U test. Correlations between PFR/EDV and E/e' was calculated using Pearson's correlation. P-value of < 0.05 was considered statistically significant. Statistical analysis was performed by computer software (JMP 11.0, SAS Institute Inc., Cary, NC, USA).

Results

The baseline characteristics, hemodynamic, and echocardiographic parameters of the participants are presented in Table 1.^{10–12} There were no significant between-group differences in age, gender rate, blood pressure, and body surface area, except for body weight. The patients with HFpEF were more obese and had markedly lower maximal oxygen uptakes (HFpEF vs. Controls: 14.4 ± 2.8 vs. 21.9 ± 3.6 ml/min/kg, $P = 0.0004$). The PCWP and right atrial pressure were significantly greater in the HFpEF group than in the controls (HFpEF vs. Controls: PCWP: 15.6 ± 5.2 vs. 11.2 ± 1.3 mmHg, $P = 0.0092$, and right atrial pressure: 9.5 ± 3.5 vs. 5.2 ± 1.9 mmHg, $P = 0.0033$) (Table 1). Cardiac index and stroke volume index were also significantly greater in the HFpEF group than controls (HFpEF vs. Controls: cardiac index: 3.5 ± 1.6 vs. 2.7 ± 0.2 L/min/m², $P = 0.04$, and stroke volume index: 45 ± 5.7 vs. 38 ± 5.5 ml/m², $P = 0.0084$). There were no significant differences in effective arterial elastance, and effective arterial elastance index between the 2 groups. The E/e' was significantly greater in the HFpEF group than in controls (HFpEF vs. Controls: 11.6 ± 4.0 vs. 6.2 ± 1.6 mmHg, $P = 0.001$).

The cMRI parameters are shown in Table 1, Figure 1 and Figure 2. The PFR/EDV was significantly slower in the HFpEF group than in controls (HFpEF vs. Controls: 2.68 ± 0.85 vs. 3.59 ± 0.87 s⁻¹, $P = 0.03$), as was PFR/EDV/PCWP (0.18 ± 0.07 vs. 0.33 ± 0.10 s⁻¹/mmHg, $P = 0.002$). In addition, Time to PFR (TPFR) (246 ± 17.2 vs. 188 ± 15.7 ms, $P = 0.04$), corrected TPFR (297 ± 78 vs. 219 ± 46 ms, $P = 0.0083$), and %TPFR of cardiac cycle (36.4 ± 10.4 vs. 25.6 ± 5.9 %, $P = 0.012$) were significantly greater in the HFpEF group than in controls.

There was a significant inverse-correlation between PFR/EDV and E/e' ($PFR/EDV = 4.18 - 0.117 * E/e'$, $R = -0.48$, $P = 0.023$) (Figure 3).

Discussion

This study demonstrates that HFpEF patients have an abnormal LV volume-time relationship characterized by: (a) slower PFR/EDV compared to controls even after normalization for higher preload (PFR/EDV/PCWP); and (b) the time to PFR from end-systole is longer in HFpEF patients than controls; similarly, HR corrected PFR and %TPFR are significantly longer in HFpEF patients. These findings suggest that active relaxation in HFpEF patients is impaired during the early diastolic filling phase. A theoretical summary of these findings are highlighted in Figure 4.

In clinical practice, trans-mitral flow velocities in pulsed-wave Doppler and/or E/e' in tissue Doppler imaging have been widely used as parameters for diastolic function.¹ One limitation of echocardiographic measurement is the dependence on imaging plane orientations, which may not be always be in the direction of flow and/or LV wall motion, resulting in systematic underestimation of inflow and/or tissue velocity.⁹ Furthermore, all echocardiographic

Doppler parameters are load dependent. In contrast to echocardiography, cMRI is generally regarded as the gold standard for assessing LV chamber volume (which is also load dependent of course) and, as such, is well suited to assess LV volume changes over time.¹⁶ cMRI, but not echocardiography, quantitatively and objectively can assess the PFR and time to PFR from the end of systole. As noted by others,¹⁷ a slower PFR in HFpEF provides further direct evidence of the impact of “diastolic function” on HFpEF pathophysiology.¹⁹ In addition to PFR, TPFR is a complementary cMRI parameter for diastolic function; in situations where the relaxation of the heart is impaired, TPFR increases as PFR decreases. The prolonged TPFR in patients with HFpEF supports the hypothesis that the extent of relaxation during early diastole may be insufficient and may compromise diastolic relaxation as heart rate increases, such as during exercise.¹⁸ By linking these cMRI findings in patients whom have already been demonstrated to have impaired static stiffness, and slow longitudinal mitral annular velocities,¹⁰ together these findings demonstrate the interaction between early diastole (slowed filling rates) and late diastole (increased stiffness) in patients with non-ischemic causes of HFpEF.

This study further adds to the current knowledge regarding diastolic function in HFpEF by carefully adjusting for many factors which may influence the measurement of LV lusitropy. For example, adjustment for LV chamber size, preload and heart rate is necessary to normalize the influences of higher preload on peak filling rate, scale chamber size to adjust for volumetric differences, and R-R interval to control for diastolic filling time between subjects. These corrections enhance the reliability of the assessment of diastolic filling in the present study. Mendoza et al. demonstrated that PFR by cMRI increased with the grade of the diastolic dysfunction and that impaired relaxation was associated with prolonged filling intervals, whereas restrictive filling was characterized by increased filling rate.⁵ The finding that PFR increased with worsening grade of diastolic dysfunction parallels our results, demonstrating a relationship between PFR and E/e' . However, the Mendoza participants were all post myocardial infarction with diastolic dysfunction defined by echocardiography, and were not strictly HFpEF patients. Moreover, PCWP representing LA driving pressure was not normalized. Mao-Yuan M. Su et al. demonstrated that PFR by cMRI was significantly lower in the patients with HFpEF than that in controls or HFpEF, but unlike the present study, there was no significant difference in PFR between controls and the HFpEF patients.¹⁷ Eighty-four % of their HFpEF patients had ischemic heart disease, and as such were not pure HFpEF patients like the participants in this study; moreover their PCWP pressures were not assessed.

To our knowledge, the present results are the first to directly assess the LV volume-time relationship by cMRI after normalization for higher PCWP in patients with HFpEF, and showing prolonged TPFR during early diastole in HFpEF patients compared to age-matched controls. Moreover, the patients reported here were highly screened and documented NOT to have other cardiovascular diseases that can impair LV filling rates and stiffness, specifically coronary artery disease. PFR with high temporal resolution is convenient though time consuming and offers excellent repeatability and accuracy, indicating suitability for clinical use, particularly when echo/Doppler and PCWP results are either not available or not dispositive.¹⁹ Thus, the PFR and/or the TPFR from cMRI can accurately characterize LV

volume-time relationships reflecting LV relaxation and diastolic function during early diastole.

This report has several study limitations. First, the number of participants was small; however, statistically significant differences in diastolic parameters including the PFR/EDV, PFR/EDV/PCWP, corrected TPFR, and %TPFR for cardiac cycle between the patients with HFpEF and controls were evident despite small numbers. Second, the cMRI measurements and PCWP were not obtained at the same time; however, it is very difficult to measure them simultaneously because electronic devices that measure PCWP cannot be in the same room as cMRI. Third, each time-phase and slice must be segmented and analyzed; therefore, a few hundred images were obtained, depending on LV chamber size and heart rate, which is quite time-consuming for clinical practice, even with use of improvements in post-processing tools.⁶ Fifth, limited temporal resolution for cMRI, may affect the ability to interpret diastolic function, especially at the very onset of diastole when relatively few frames were available.

In conclusion, the results from this study highlight that HFpEF patients have an abnormal volume-time relationship including a decreased PFR/EDV, even after normalization for higher preload (PFR/EDV/PCWP), and prolonged time to PFR due to the impairment of active relaxation during the early diastolic phase. These data provide further evidence of the impact of “diastolic function” on HFpEF pathophysiology.

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Figure 1. Peak Filling Rate / End-Diastolic Volume (PFR/EDV) (Figure 1A.), and Peak Filling Rate / End-Diastolic Volume / Pulmonary Capillary Wedge Pressure (PFR/EDV/PCWP) (Figure 1B.) in controls and HFpEF patients.

PFR, peak filling rate; EDV, end-diastolic volume; PCWP, pulmonary capillary wedge pressure; HFpEF, heart failure with preserved ejection fraction.

Figure 2. Time to Peak Filling Rate (TPFR) (Figure 2A.), corrected TPFR (Figure 2B.), and %TPFR for cardiac cycle (Figure 2C.) in controls and HFpEF patients.

TPFR, time to peak filling rate from end-systolic point; HFpEF, heart failure with preserved ejection fraction. The corrected TPFR was calculated by TPFR divided by square root of R-R interval. The %TPFR for cardiac cycle was obtained by TPFR divided by time of one cardiac cycle.

Figure 3. Relationship between PFR/EDV and E/e'.

PFR, peak filling rate; EDV, end-diastolic volume; E/e', a ratio between early mitral inflow velocity and mitral annular early diastolic velocity.

Impairment of active relaxation at early diastolic phase in HFpEF

Figure 4. Examples of a LV volume-time relationship in HFpEF and age-matched controls. Graph shows LV volume-time relationship in HFpEF (red-line) and age-matched controls (blue-line). IVCT, iso-volemic contraction time; ESV, end-systolic volume; TPFR, time to peak filling rate from end-systolic point; PFR, peak filling rate during early diastole, EDV, end-diastolic volume; IVRT, iso-volemic relaxation time.

Table. 1.

Baseline Characteristics, Hemodynamic, Echocardiographic, and Cardiac MRI Parameters

	Controls												HFpEF											
	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10		
Baseline Characteristics																								
Gender	F	F	F	M	M	F	M	M	F	F	M	M	F	F	M	F	F	M	F	F	M	F		
Age (year)	65.0	66.0	66.0	69.0	69.0	70.0	70.0	71.0	71.0	71.0	72.0	77.0	62.0	66.0	66.0	68.0	73.0	76.0	76.0	77.0	79.0	85.0		
Height (cm)	165.5	167.6	167.5	167.6	177.0	153.0	178.5	182.9	166.5	147.3	173.5	173.0	165.8	151.5	180.0	168.5	154.3	159.3	155.0	153.8	170.0	155.0		
Weight (kg)	79.0	58.8	67.0	77.0	78.6	61.5	83.9	80.0	65.5	57.4	87.6	83.0	105.3	98.2	137.0	79.2	65.8	79.7	87.3	95.7	85.0	56.1		
BMI (kg/m ²)	28.8	20.9	23.9	27.4	25.1	26.3	26.3	23.9	23.6	26.5	29.1	27.7	38.3	42.8	42.3	27.9	27.6	31.4	36.3	40.5	29.4	23.4		
BSA (m ²)	1.91	1.65	1.77	1.89	1.97	1.62	2.04	2.02	1.74	1.53	2.05	2.00	2.20	2.03	2.62	1.93	1.68	1.88	1.94	2.02	2.00	1.55		
Hemodynamic Parameters																								
HR (beats/min)	71	71	66	72	67	78	59	68	79	69	61	45	80	87	88	54	65	56	68	129	56	78		
sBP (mmHg)	108	108	150	138	142	132	122	128	130	148	137	123	133.5	147	137.3	138	131.5	140.5	139	141	145	154		
dBp (mmHg)	78	60	69	76	80	101	83	70	68	73	64	54	65	66	66	88	70	69	75	49	76	66		
PCWP (mmHg)	10.8	11.7	12.8	11.2	10.2	8.0	11.2	11.7	12.5	11.5	12.2	11.0	15.7	11.2	25.6	22.5	12.5	18.9	9.0	14.5	14.2	12.3		
RAP (mmHg)	3.7	8.0	2.1	6.3	5.0	4.5	3.8	8.2	5.2	4.1	7.3	4.3	13.0	9.0	14.0	15.0	7.7	11.0	7.0	6.3	5.7	6.3		
Qc index (L/min/m ²)	2.29	2.77	3.21	2.43	2.65	2.64	2.42	2.91	2.60	2.57	2.68	2.80	2.91	3.40	3.86	1.51	2.95	2.98	2.80	6.17	2.24	6.31		
Ea index (mmHg/ml/m ²)	0.86	0.93	0.86	1.10	0.87	1.34	0.64	0.72	1.17	1.57	0.67	0.79	0.68	0.82	0.41	0.73	0.92	0.67	0.81	0.65	0.81	1.08		
Echocardiographic Parameters																								
E' (cm)	76	61	68	55	43	70	52	61	63	60	43	46	59	78	111	102	44	92	74	115	62	115		
A (cm)	108	49	78	57	76	100	68	73	65	103	70	46	71	114	131	73	66	87	103	158	88	143		
E/A	0.71	1.26	0.88	0.95	0.57	0.70	0.77	0.84	0.97	0.58	0.61	1.01	0.83	0.68	0.84	1.38	0.67	1.06	0.72	0.73	0.70	0.80		
E' mean (cm)	8.6	9.6	12.4	8.1	10.3	7.5	8.2	9.9	12.5	8.7	9.5	9.8	9.2	6.3	5.4	7.9	6.7	7.4	8.3	9.1	6.3	8.6		
E/e'	8.9	6.4	5.5	6.8	4.2	9.3	6.4	6.2	5.0	6.9	4.5	4.7	6.4	12.3	20.4	12.8	6.6	12.4	9.0	12.7	9.8	13.4		
Cardiac MRI Parameters																								
LVESV (ml)	36.0	24.9	49.2	33.7	40.0	34.2	41.5	39.8	30.0	42.5	52.8	45.0	29.2	40.7	41.5	46.4	21.0	56.4	39.3	40.1	32.0	27.4		
LVEDV (ml)	121.0	91.2	106.9	103.2	96.7	105.7	104.7	113.3	152.4	95.9	166.4	140.2	108.6	146.7	185.4	134.8	66.9	171.4	103.9	84.0	127.0	97.5		
SV (ml)	85.0	66.3	79.1	69.5	72.0	69.6	143.8	74.2	84.9	53.7	102.3	80.8	79.5	105.9	143.8	88.4	46.0	114.9	68.8	65.2	96.0	70.1		

	Controls												HFpEF									
	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10
LVEF (%)	66.0	68.0	61.6	67.4	64.3	67.7	77.6	65.1	54.6	55.8	68.3	67.9	73.2	72.2	77.6	65.6	68.7	67.1	67.4	61.9	65.0	71.9
LV Mass (g)	102.0	75.3	62.7	90.4	69.3	89.9	205.9	84.1	105.7	59.2	135.9	147.3	96.8	113.0	205.9	81.4	51.2	142.5	67.1	69.1	153.0	77.1

Controls: age-matched control subjects; HFpEF, heart failure with preserved ejection fraction; F, female; M, male; BMI, body mass index; BSA, body surface area; HR, heart rate; sBP, systolic blood pressure; dBP, diastolic blood pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; Qc, cardiac output; Ea, Effective arterial elastance; E, early mitral diastolic inflow velocity; A, late mitral diastolic inflow velocity; e', early diastolic mitral annular velocity; LVESV, left ventricular end-systolic volume; LVEDV, left ventricular end-diastolic volume; SV, stroke volume; LVEF, left ventricular ejection fraction; LV mass, left ventricular mass.