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SHORT COMMUNICATION

Left atrial conduit flow rate at baseline and during exercise: an index of impaired relaxation in HFpEF patients

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Abstract

Aims In healthy subjects, adrenergic stimulation augments left ventricular (LV) long-axis shortening and lengthening, and increases left atrial (LA) to LV intracavitary pressure gradients in early diastole. Lower increments are observed in patients with heart failure with preserved ejection fraction (HFpEF). We hypothesized that exercise in HFpEF would further impair passive LV filling in early-mid diastole, during conduit flow from pulmonary veins.

Methods and results Twenty HFpEF patients (67.8 ± 9.8 years; 11 women), diagnosed using 2007 ESC recommendations, underwent ramped semi-supine bicycle exercise to submaximal target heart rate (∼100 bpm) or symptoms. Seventeen asymptomatic subjects (64.3 ± 8.9 years; 7 women) were controls. Simultaneous LA and LV volumes were measured from pyramidal 3D-echocardiographic full-volume datasets acquired from an apical window at baseline and during stress, together with brachial arterial pressure. LA conduit flow was computed from the increase in LV volume from its minimum at end-systole to the last frame before atrial contraction (onset of the P wave), minus the reduction in LA volume during the same time interval; the difference was integrated and expressed as average flow rate, according to a published formula. The slope of single-beat preload recruitable stroke work (PRSW) quantified LV inotropic state. 3D LV torsion (rotation of the apex minus rotation of the base divided by LV length) was also measurable, both at rest and during stress, in 10 HFpEF patients and 4 controls. There were divergent responses in conduit flow rate, which increased by 40% during exercise in controls (+17.8 ± 37.3 mL/s) but decreased by 18% in patients with HFpEF (−9.6 ± 42.3 mL/s) (P = 0.046), along with congruent changes (+1.77 ± 1.13°/cm vs. −1.94 ± 2.73°/cm) in apical torsion (P = 0.032). Increments of conduit flow rate and apical torsion during stress correlated with changes in PRSW slope (P = 0.003 and P = 0.006, respectively).

Conclusions In HFpEF, conduit flow rate decreases when diastolic dysfunction develops during exercise, in parallel with changes in LV inotropic state and torsion, contributing to impaired stroke volume reserve. Conduit flow is measurable using 3D-echocardiographic full-volume atrio-ventricular datasets, and as a marker of LV relaxation can contribute to the diagnosis of HFpEF.

Keywords Heart failure with preserved ejection fraction; Exercise; 3D echocardiography; Diastolic function

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Background

Exercise capacity is an important prognostic marker in most cardiovascular diseases, but there is little consensus about what limits it in patients with heart failure and preserved ejection fraction (HFpEF).[1] The culprit mechanism has usually been regarded as a stiff left ventricle (LV) with little reserve, such that the chamber is unable to fill adequately in diastole without excessive increases in pressure,[2] but another hypothesis links limited performance during exercise to the impairment of long-axis function that characterizes a hypertrophied LV.[3]

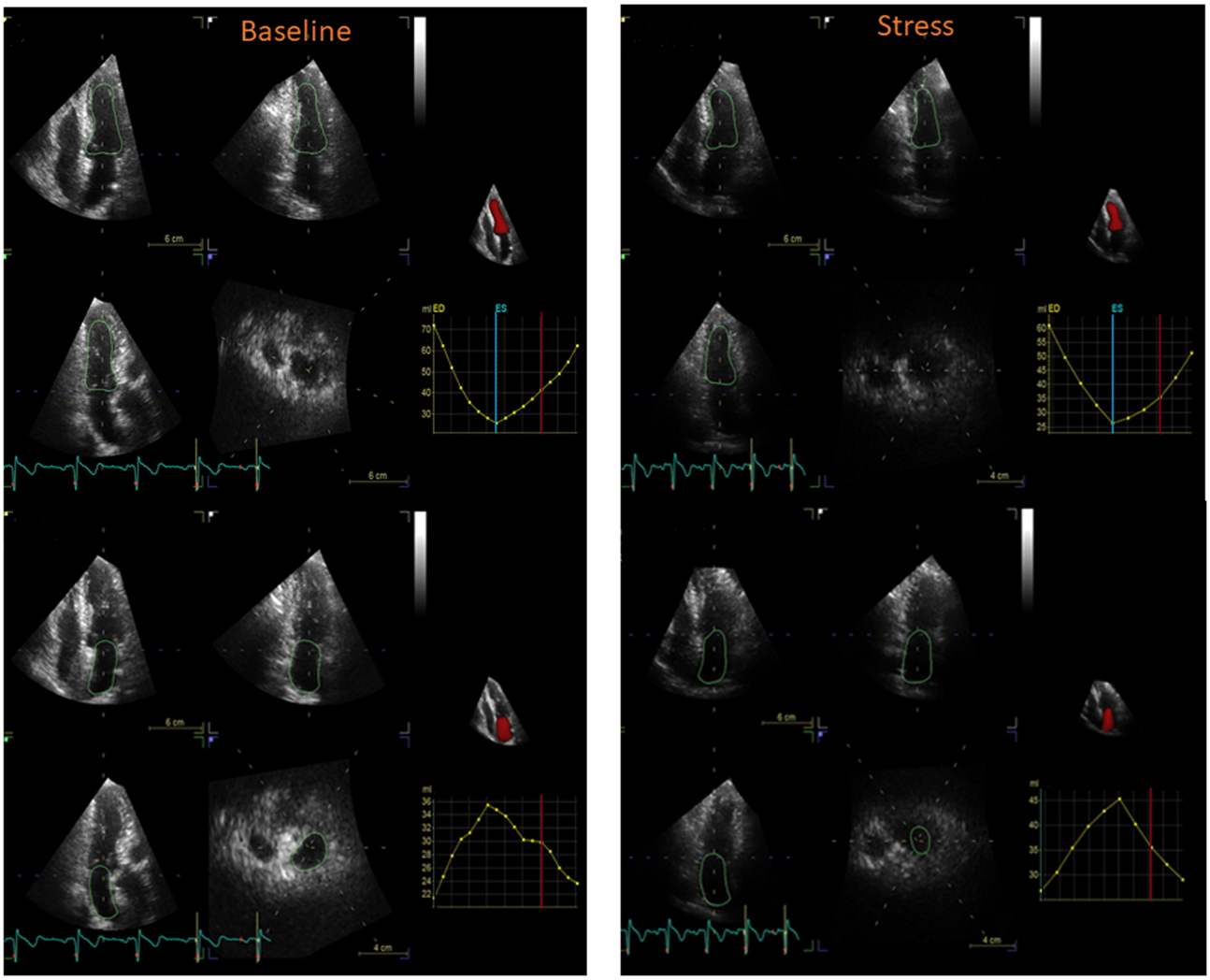
The normal LV response to the elevated oxygen requirements of dynamic exercise is an increase in cardiac output obtained through increments in heart rate and stroke volume. Augmentation of LV longitudinal contraction and subsequent lengthening, both in response to adrenergic stimulation, mediates an increment in passive flow during early diastole when the ventricle is filling from conduit flow (from the atrial reservoir and from blood drawn into the LV from the pulmonary veins).[4] This phenomenon is modulated by faster LV untwisting secondary to increased elastic recoil and by enhanced active relaxation.[4,5]

Patients with diastolic dysfunction and a normal EF exhibit reduced LV longitudinal systolic strain as well as attenuated and delayed early diastolic untwisting, particularly during exercise.[6] During inotropic stress, they have reduced adrenergic augmentation of the LV intraventricular pressure gradient compared with normal subjects, which is consistent with impaired apical suction.[7] Thus, on exercise in HFpEF, the stiff LV loses some of its ability to enhance diastolic suction and augment stroke volume.[8]

Methods

In order to test the hypothesis that HFpEF impairs reserve of early diastolic LV suction and filling, we studied the effects of submaximal exercise on LV and left atrial (LA) volumes and function, and their interaction, in 20 patients (mean age 67.8 ± 9.8 years, nine male patients) with HFpEF previously

Figure 1 pyramidal 3D-echocardiographic full-volume dataset acquired from the apex in a patient, using a 3 V transducer. Volume data can be displayed in real-time: three orthogonal apical views and one cross-sectional slice, with optional volume rendering. The vertical red line corresponds to the P wave on the electrocardiographic trace. The light blue line identifies minimum ventricular systolic volume (ES). The light blue and red lines identify timing of conduit flow.



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diagnosed according to the 2007 recommendations from the European Society of Cardiology.[9] All were in sinus rhythm with no more that mild mitral or aortic regurgitation, and 12 out of 20 (60%) had been enrolled in the MEDIA study (Metabolic Road to Diastolic Heart Failure) at the Novara site. The subjects underwent low-level exercise according to a ramped exercise protocol on a semi-supine bicycle, starting at 15 W and with increments of 5 W/min to a submaximal target (heart rate ~ 100 bpm, or symptoms).[10] The characteristics of the population enrolled in the MEDIA study have been published.[10,11] The local ethics committee approved the protocol, the study complied with the Declaration of Helsinki, and the subjects gave informed consent. Seventeen subjects of comparable age (64.3 ± 8.9 years, 10 male patients) who were free from symptoms of heart failure and of risk factors except for hypertension (*n* = 13), dyslipidaemia (*n* = 7), type 2 diabetes (*n* = 1), and revascularized coronary or peripheral artery disease (*n* = 1, each), served as controls.

Pyramidal 3D full-volume datasets were obtained from apical windows with a dedicated 4V-D cardiology probe. Simultaneous acquisitions of the LV and the LA were recorded at baseline and during exercise while a heart rate of 100–110 bpm was maintained by keeping the workload constant for ~3 min.[11] With optimal alignment, 3D images, presently considered as the most accurate echocardiographic method for measuring volumes,[12] were acquired after sample volume optimization with an average frame rate > 16 Hz (mean temporal resolution 54 ± 7 ms) and in multislice (12 slice) and multibeat (6 cardiac cycles) mode. Indirect echocardiographic indices of LV diastolic pressure and function were also recorded, and arterial pressure was measured by brachial plethysmography.

Figure 2 Left ventricular and simultaneous atrial data at baseline and during stress in two patients enrolled in the study. Light blue and red vertical lines identify minimum cavity volume and timing of the P wave on the ECG, respectively. PRSW, slope of single-beat preload recruitable stroke work.

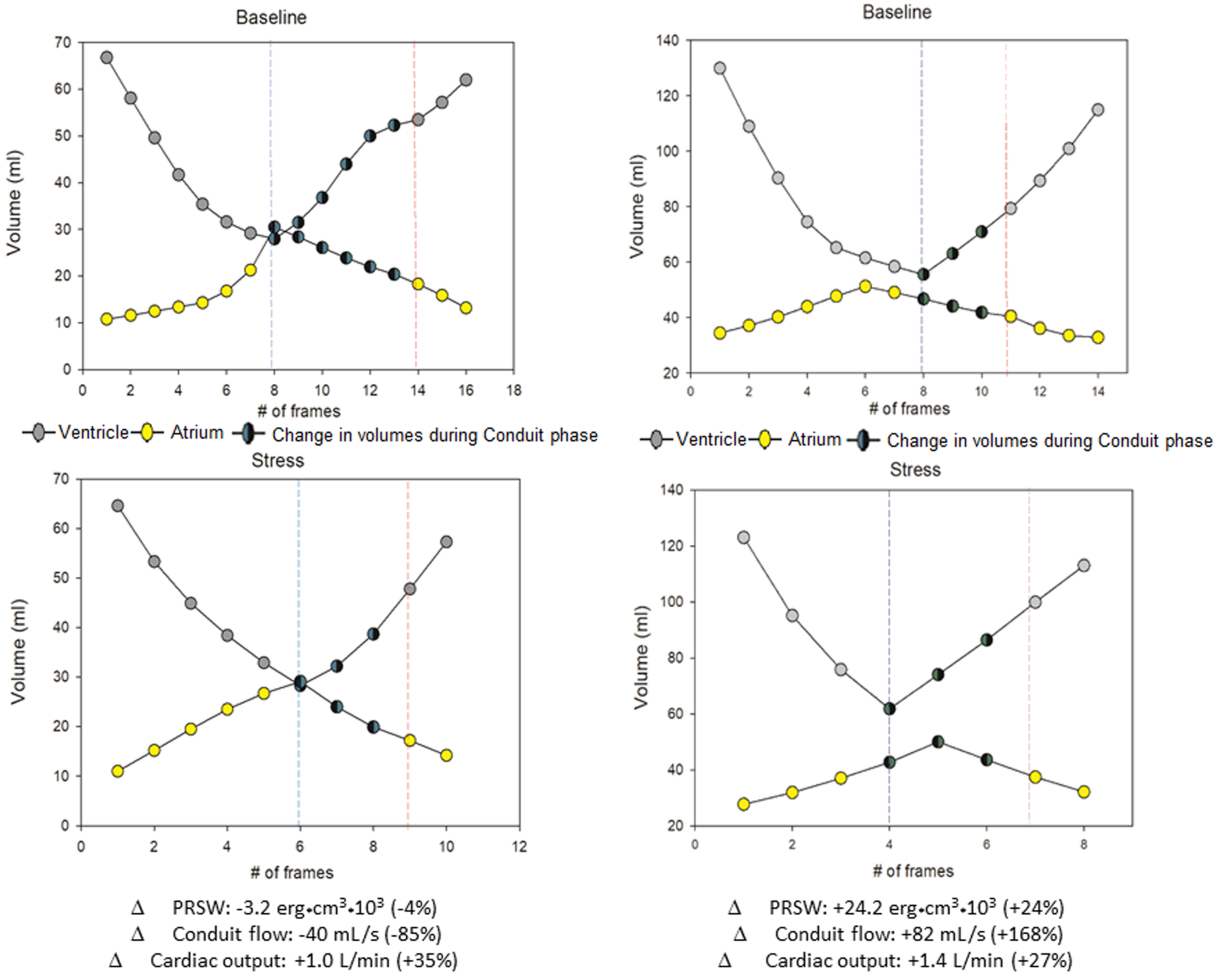

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Image analysis

Images were analysed off-line with a dedicated software package (EchoPAC PC v. 201, GE Healthcare). The endocardial borders of the LV and LA were delineated manually at end-diastole, corresponding to maximum ventricular and minimum atrial volumes, and at end-systole, corresponding to minimum ventricular and maximum atrial volumes. The integrated 4D Auto LVQ quantification instrument produced LV and LA volume curves along an entire cardiac cycle (*Figure 1*) that were imported into a Microsoft Excel worksheet for further analysis.[13] The epicardial borders of the LV were traced, and the LV mass was computed from the difference between the epicardial and the endocardial 3D meshes.

Left ventricular function

Left ventricular ejection fraction (LVEF) was calculated as LV stroke volume/maximum volume. The LV inotropic condition at baseline and during stress was assessed according to the slope (Mw) of the single-beat preload recruitable stroke work (PRSW) relationship, which is recognized as a load-insensitive index of contractile function, with constant k estimated by the equation: k = 0.0004 × LV mass + 0.6408.[14] Stroke work was estimated as LV (maximum minus minimum) volume × mean aortic pressure computed as diastolic pressure + [(systolic pressure minus diastolic pressure)/3]. The ratio between mean ejection pressure, approximated as mean aortic pressure, and slope of PRSW was used as a measure of ventricular-arterial coupling.[15,16]

Left atrial function

Left atrial emptying fraction was computed as LA maximum minus LA minimum volume, divided by LA maximum volume. The reservoir LA volume was expressed as the difference between maximum minus minimum cavity volume. The volume of conduit flow was calculated using a published formula,[5,13] with time t considered as the last frame of the conduit phase, immediately before the P wave on the simultaneous ECG in late diastole, as follows:

Table 1 Comparison of patients and control subjects enrolled in the study

Variable	Controls (n = 17)		HFpEF (n = 20)		P
Gender M (n, %)	10	59	9	45	0.402
Age (years)		64.3 ± 8.9		67.8 ± 9.8	0.289
NYHA class				2.2 ± 0.4	
Body surface area (m^2)		1.80 ± 0.18		1.76 ± 0.22	0.542
Body mass index (kg/m^2)		26.2 ± 3.8		28.1 ± 5.1	0.220
Left ventricular mass (g)		108.2 ± 7.5		111.2 ± 15.1	0.476
BNP (n, pg/mL)			15	214 ± 531	
Smoking habit (n, %)	6	35.3	8	40.0	0.769
Hypertension (n, %)	13	76.5	20	100.0	0.022
Diabetes mellitus (n, %)	1	5.9	11	55.0	0.001
Dyslipidaemia (n, %)	7	41.2	12	60.0	0.254
Coronary artery disease (n, %)	1	5.9	3	15.0	0.373
History of stroke/TIA (n, %)	0	0.0	2	10.0	0.180
Peripheral artery disease (n, %)	1	5.9	2	10.0	0.647
COPD (n, %)	0	0.0	1	5.0	0.350
Sleep apnoea syndrome (n, %)	0	0.0	1	5.0	0.350
ACE-I (n, %)	2	11.8	7	35.0	0.101
ARB (n, %)	6	35.3	8	40.0	0.769
Beta-blockers	7	41.2	13	65.0	0.147
CCB (n, %)	5	29.4	11	55.0	0.117
MRA (n, %)	0	0.0	2	10.0	0.180
Furosemide (n, %)	0	0.0	3	15.0	0.096
Indapamide (n, %)	1	5.9	0	0.0	0.272
Hydrochlorothiazide	4	23.5	11	55.0	0.052
Torasemide (n, %)	1	5.9	0	0.0	0.272
Doxazosin (n, %)	2	11.8	1	5.0	0.452
Nitrates (n, %)	1	5.9	2	10.0	0.647
Ranolazine (n, %)	0	0.0	1	5.0	0.350
Antiplatelets (n, %)	9	52.9	8	40.0	0.431
Statin (n, %)	6	35.3	6	30.0	0.732
Hypoglycaemic drugs (n, %)	1	5.9	3	15.0	0.373
Insulin (n, %)	1	5.9	2	10.0	0.647

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; MRA, mineralcorticoid receptor antagonist; NYHA, New York Heart Association; TIA, transient ischemic attack.

$$[\text{LV volume}\ (t)\text{–LV minimumvolume}]\text{–}[\text{LA maximumvolume–LA volume}\ (t)]$$

and then integrated over time to give the average conduit flow rate between minimum LV volume and the onset of the P wave (*Figure 2*). Booster pump function was computed as LV stroke volume minus (reservoir plus conduit). Atrial phasic function was expressed in mls, and also normalized to the LV stroke volume. We have previously reported the interobserver reproducibility of conduit flow, which was 4.5 mL ± 1.3% and 15.0 mL/s/m^2 ± 0.9% (absolute mean difference ± the percentage coefficient of variation).[13]

Left ventricular diastolic function was assessed at baseline and during stress from apical pulsed Doppler recordings of the mitral valve and mitral annulus, to obtain the mitral peak E velocity and E deceleration time and the annular e' velocities, and to calculate the E/e' ratio. Atrial stiffness (K_{la}) was assessed relying on a non-invasive estimate of pulmonary arterial wedge pressure (PAWP) according to an invasively validated formula[17]: PAWP = 1.91 + [1.24 × (E/e')]. Then, K_{la} was computed as PAWP/LA reservoir volume and expressed in mmHg/mL, acknowledging the limitations inherent in such non-invasive K_{la} estimation. LV 2D longitudinal strain (not obtainable, for technical reasons, in two control subjects and six HFpEF patients) was also computed, using the same four-chamber view utilized for mitral flow and annular e' velocity assessment.

Using the same epicardial and endocardial 3D meshes, it was possible in 14 subjects (4 control and 10 HFpEF) to compute 3D LV torsion (rotation of the apex minus rotation of the base, divided by LV length) both at rest and during stress using a published method.[18] Regional torsion, from the apex to the base of the heart, was computed as the absolute difference between the most apical and most basal rings of the corresponding segment, indexed for the length of that segment.[18]

Statistical analysis

Data are reported as mean ± 1SD or as numbers and percentages for categorical variables. Differences between means were assessed using unpaired *t*-tests. Differences in percentages were evaluated using χ^2 tests. Two-way repeated measures ANOVA [one factor (rest vs. stress) repeated] was

Table 2 Baseline and stress echo data

Baseline Mean + SD	Controls (n = 17)			HFpEFs (n = 20)			
	Baseline	Stress	*P*	Baseline	Stress	*P*	Interaction
Heart rate (beat/min)	73.8 ± 10.2	108.2 ± 11.7	<0.001	69.9 ± 11.4	99.2 ± 16.1	<0.001	0.233
Systolic aortic pressure (mmHg)	141.2 ± 19.6	178.8 ± 25.2	<0.001	149.8 ± 18.0	177.8 ± 23.0	<0.001	0.283
Diastolic aortic pressure (mmHg)	85.6 ± 10.0	92.6 ± 9.4	0.003	86.0 ± 11.7	92.8 ± 10.4	0.002	0.920
Mean aortic pressure (mmHg)	104.1 ± 12.0	121.4 ± 14,1	<0.001	107.3 ± 11.8	121.1 ± 12.5	<0.001	0.455
E mitral peak (cm/s)	61.0 ± 20.8	90.9 ± 21.2	<0.001	63.7 ± 16.6	101.1 ± 34.3	<0.001	0.135
e' peak (cm/s)	8.12 ± 2.51	12.15 ± 3.11	<0.001	6.58 ± 1.68	8.68 ± 2.77	<0.001	**0.045**
E/e'	8.17 ± 3.23	7.78 ± 1.99	0.253	10.09 ± 2.91	12.04 ± 7.10	0.035	0.091
Mitral deceleration time (ms)	208 ± 81	148 ± 75	0.035	228 ± 43	133 ± 91	<0.001	0.321
LV diastolic volume (mL)	94.5 ± 26.1	93.1 ± 19.0	0.690	92.4 ± 20.0	85.9 ± 19.8	0.059	0.312
LV systolic volume (mL)	43.2 ± 14.6	38.7 ± 10.2	0.074	40.8 ± 11.1	39.0 ± 12.6	0.427	0.423
LV stroke volume (mL)	51.3 ± 13.0	54.3 ± 11.3	0.144	51.5 ± 10.2	46.9 ± 9.1	0.021	**0.01**
LV ejection fraction (LVEF)	0.55 ± 0.04	0.59 ± 0.05	0.012	0.56 ± 0.05	0.55 ± 0.06	0.560	**0.031**
Cardiac output (L/min)	3.76 ± 0.98	5.88 ± 1.35	<0.001	3.61 ± 0.90	4.67 ± 1.25	0.611	**0.005**
LA maximum volume (mL)	39.6 ± 11.6	39.4 ± 12.9	0.971	53.6 ± 16.7	51.7 ± 22.8	0.611	0.750
LA minimum volume (mL)	20.4 ± 8.2	20.8 ± 7.3	0.899	33.6 ± 14.1	32.4 ± 18.2	0.648	0.687
LA emptying fraction (LAEF)	0.49 ± 0.10	0.47 ± 0.09	0.646	0.38 ± 0.09	0.38 ± 0.10	0.979	0.701
Reservoir (mL)	19.1 ± 6.3	18.7 ± 7.3	0.826	20.1 ± 6.1	17.2 ± 6.2	0.156	0.417
Reservoir (%)	39.6 ± 16.5	35.8 ± 14.5	0.380	40.0 ± 12.2	37.8 ± 14.4	0.582	0.783
Pump (mL)	20.2 ± 14.7	27.8 ± 12.5	0.057	16.9 ± 11.0	21.8 ± 10.0	0.174	0.618
Pump (%)	36.8 ± 23.6	50.0 ± 16.4	0.045	32.1 ± 17.0	45.5 ± 16.6	0.029	0.989
Conduit (mL)	11.9 ± 8.1	7.6 ± 4.9	0.074	14.4 ± 10.1	8.0 ± 6.0	0.005	0.501
Conduit (%)	23.7 ± 14.9	14.2 ± 9.5	0.033	27.9 ± 18.7	16.7 ± 12.8	0.008	0.776
Conduit duration (s)	0.26 ± 0.11	0.11 ± 0.05	<0.001	0.25 ± 0.10	0.15 ± 0.06	<0.001	0.198
Conduit flow rate (mL/s)	44.2 ± 22.1	62.0 ± 30.0	0.076	54.6 ± 37.7	44.9 ± 30.6	0.291	**0.046**
LA stiffness (mmHg/mL)	0.47 ± 0.21	0.45 ± 0.15	0.881	0.52 ± 0.23	0.76 ± 0.48	0.008	**0.046**
LV strain (%)	−16.6 ± 5.3	−19.4 ± 5.4	0.025	−17.8 ± 3.7	−18.4 ± 4.5	0.715	0.195
Slope of the preload recruitable stroke work (PRSW) relation (erg*cm^3*10^3)	84.2 ± 13.9	105.5 ± 17.4	<0.001	88.1 ± 13.7	94.6 ± 19.3	0.055	**0.004**
Mean aortic pressure/PRSW	1.26 ± 0.19	1.17 ± 0.16	0.012	1.24 ± 0.16	1.32 ± 0.19	0.016	<**0.001**
LV torsion[a] (°/cm)	0.52 ± 0.42	1.30 ± 0.60	0.128	0.69 ± 0.60	0.59 ± 0.71	0.748	0.146
Basal LV[a] torsion (°/cm)	0.41 ± 0.61	1.69 ± 0.94	0.424	−0.39 ± 2.49	0.29 ± 1.91	0.503	0.747
Apical LV[a] torsion (°/cm)	−0.10 ± 1.17	1.67 ± 1.65	0.196	1.04 ± 1.90	−0.90 ± 1.80	0.035	**0.032**

HFpEF, heart failure with preserved ejection fraction; LA, left atrial; LV, left ventricular.
[a]Available for 4 control subjects and 10 HFpEF patients.

used for comparisons between the two groups at baseline and during stress, with the Student–Newman–Keuls test used for pairwise multiple comparisons. Multivariate linear regression analysis was adopted to evaluate the relationship between changes in conduit flow rate (stress minus baseline) and changes in other measurements that demonstrated a

Figure 3 Behaviour of the single-beat preload recruitable stroke work (PRSW) relation at baseline and during stress in the two populations considered. LV inotropic state, as reflected by the slope of the relation, increases with stress only in controls ($P < 0.001$, interaction $P = 0.004$). Refer also to text and Table 2 for details. HFpEF, heart failure with preserved ejection fraction.

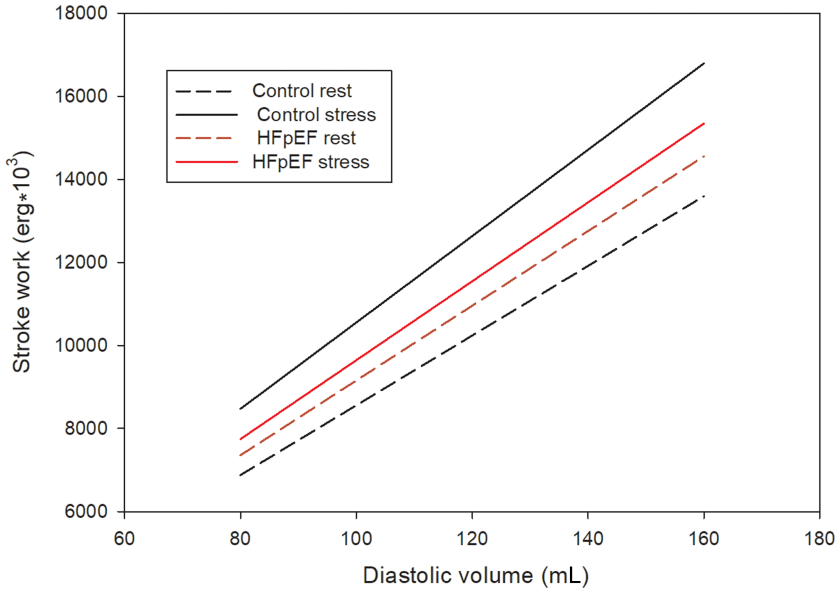
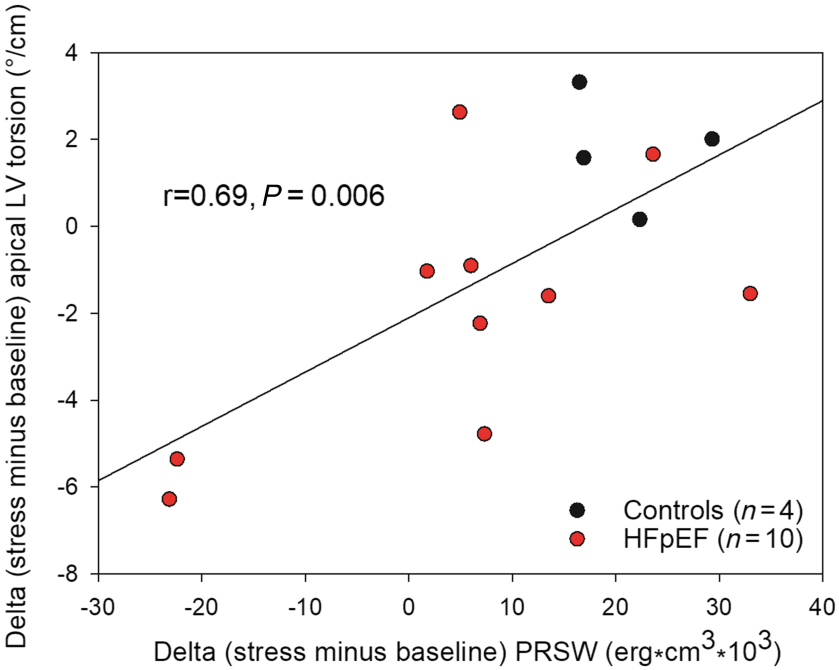


Figure 4 Dispersion plot and regression line of the difference (stress minus baseline) of apical LV torsion (*y*-axis) vs. slope of single-beat preload recruitable stroke work (PRSW, *x*-axis) in 10 HFpEF patients and 4 controls. There is a significant relation between the two variables. HFpEF, heart failure with preserved ejection fraction.



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significant interaction across the test between the two groups, apart from LV torsion given the limited number of subjects in whom it could be assessed. Software used for statistical analysis was *SigmaStat* Version 4.0 for Windows (Jandel; San Rafael, CA, USA).

Results

There were no significant differences in demographic characteristics between the two cohorts, except that HFpEF patients more often had hypertension (100% vs. 77%, $P = 0.022$) and diabetes (55% vs. 6%, $P = 0.001$) (*Table 1*). There were few differences at baseline in heart rate or systolic and diastolic LV function (*Table 2*); baseline e' was 19% lower in the HFpEF patients ($P = 0.003$), and thus, E/e' was higher.

No patient developed signs of ischemia during the test, while heart rate, cardiac output, and blood pressure increased ($P < 0.001$) in both groups (*Table 2*). LV strain improved (became more negative) with stress, particularly in controls (absolute increment −2.8 ± 4.9%, vs. −0.5 ± 3.8% in HFpEF; *Table 2*), but the difference was not significant (interaction $P = 0.195$). LV inotropic state, as reflected by LVEF ($P = 0.012$, interaction $P = 0.031$) and the slope of PRSW ($P < 0.001$, interaction $P = 0.004$) increased with stress only in controls (*Figure 3*), in whom it was associated with an improvement in ventricular-arterial coupling ($P = 0.012$). In HFpEF patients, instead, ventricular-arterial coupling worsened ($P = 0.016$, interaction $P < 0.001$) and LVEF did not change (*Table 2*), while LV stroke volume decreased ($P = 0.021$, interaction $P = 0.01$) impacting negatively on cardiac output (interaction $P = 0.005$). With stress, apical LV torsion increased in controls (+1.77 ± 1.13°/cm) but fell in HFpEF (−1.94 ± 2.73°/cm, interaction $P = 0.032$, *Table 2*), with changes correlating with changes in the slope of PRSW (*Figure 4*, $P < 0.007$). No significant interactions could be detected for basal ring or 'global' LV torsion (*Table 2*).

During submaximal exercise, early diastolic dysfunction became overt in HFpEF, with e' increasing less than in controls

Figure 5 Dispersion plot of the difference (stress minus baseline) of conduit flow rate (*y*-axis) vs. slope of single-beat preload recruitable stroke work (PRSW, *x*-axis) in 20 HFpEF patients and 17 controls. The two patients depicted in Figure 2 are identified by arrows. HFpEF, heart failure with preserved ejection fraction.

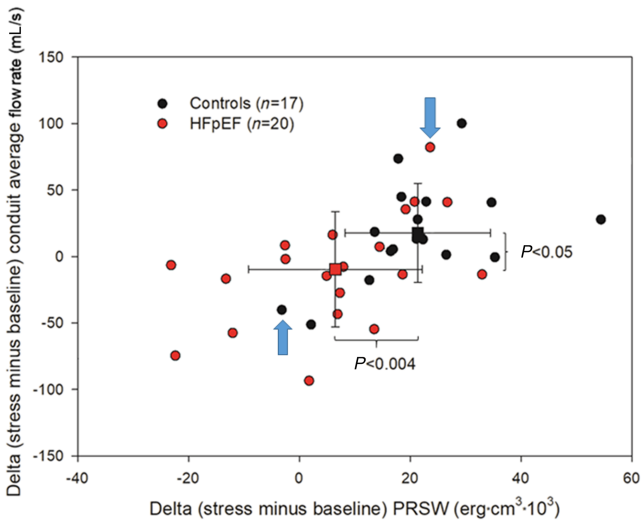

Table 3 Multivariate analysis ($r^2 = 0.37$) for prediction of changes (stress minus baseline) in conduit flow rate in the two cohorts (dependent variable) vs. those parameters that showed a significant interaction at two ANOVA in Table 2 (independent variables)

Variable	Coefficient	β	*P*
Constant	−5.259		0.696
Slope of the preload recruitable stroke work (PRSW) relation ($erg_{*}cm^{3}_{*}10^{3}$)	1.712	0.665	0.004
e' peak (cm/s)	−3.291	−0.174	0.274
Cardiac output (L/min)	−2.598	−0.073	0.694
Ejection fraction	25.482	−0.039	0.827
K_{la} (mmHg/mL)	2.926	0.028	0.862

Two variables (stroke volume and mean aortic pressure/PRSW) have been excluded in order to minimize multicollinearity.
K_{la}, left atrial stiffness.

(+44.7 ± 38.5% vs. +59.1 ± 44.4%, interaction P = 0.045). Estimated atrial stiffness (K_{Ia}) increased during exercise by 45% in HFpEF patients (P = 0.008) and was higher than in controls (interaction P = 0.046) (*Table 2*).

There were no significant differences between groups in LA reservoir or pump function, but there were differences in conduit flow rate which increased in controls by 40% (+17.8 ± 37.3 mL/s) but decreased in HFpEF by 18% (−9.6 ± 42.3 mL/s) (interaction P = 0.046), nothwithstanding a comparable shortening in its duration (−0.14 ± 0.11 s vs. −0.10 ± 0.10 s, interaction P = 0.198) (*Table 2*). Increments in conduit flow rate from baseline to submaximal exercise correlated with changes in the slope of PRSW (*Figure 5*), with diastolic conduit flow being greater in subjects with higher LV systolic contractile function.

The slope of PRSW (β = 0.75, P = 0.003) was the only independent variable that was significant in predicting changes in conduit flow rate with exercise, in the multivariate analysis (r^2 = 0.39). No significant contribution came from the other variables tested, even if potential multicollinearity was avoided by eliminating stroke volume and the estimate of ventricular-arterial coupling (slope of PRSW β = 0.67, P = 0.004, r^2 = 0.37, *Table 3*). Changes in heart rate or conduit duration during stress, if forced into the model, did not exert any effects on the results of the multivariate regression (slope of PRSW β = 0.64, P = 0.007 and β = 0.67, P = 0.004, respectively), as did changes in LV strain (slope of PRSW β = 0.60, P = 0.036).

Discussion

In this study, we calculated LV filling during the conduit phase of atrial function, from the difference in volumes between LA emptying and LV filling. We report that variations in conduit flow rate between baseline and submaximal exercise correlate with changes in LV inotropic status.

It is known that augmented conduit flow contributes to the increasingly rapid filling of the LV during exercise, following the decrement in early diastolic LV pressure related to faster LV relaxation and greater restoring forces induced by the preceding ventricular ejection below the equilibrium cavity volume.[5,19] Given that LV longitudinal lengthening and shortening are coupled and that in HFpEF patients both myocardial contractility and longitudinal strain are likely impaired,[20,21] all contributing to poor LV functional reserve, it is not surprising that conduit flow rate worsened during exercise in the patients compared with the controls. Our results reinforce the concepts that there is a significant interaction between LV systolic function and diastolic filling and that with adrenergic stimulation during exercise, the interaction persists from early into mid-diastole. The attenuated response that we observed on exercise in HFpEF patients suggests that their ability to generate an early diastolic pressure gradient between the LV apex and LA is impaired. Reduced LV torsion,[22] as shown in *Figure 4*, suction[23] and rapid early diastolic filling[7] all contribute.

Limitations and conclusion

The small sample size in this detailed pathophysiological study implies that the multivariate analysis should be interpreted with caution, due to the possibility of overfitting of the model. Secondly, the control subjects had some risk factors, but none was symptomatic. Thirdly, changes in conduit flow during exercise can be related to the shortening of diastasis, but the exercise protocol that we used meant that there were no significant differences in heart rate between patients and controls during steady-state submaximal exercise when the echocardiographic images were obtained (+49 ± 22% in controls vs. +43 ± 22% in HFpEF; P = 0.451).

Our results are concordant with those of other investigators who reported equivalent findings during stress in patients with HFpEF, by measuring changes in chamber volumes obtained by real-time magnetic resonance imaging.[24] Thus, we have demonstrated that conduit filling of the LV can be quantified relatively easily using 3D echocardiography. It can be used to study the complex interaction between the LA and LV at rest and particularly during exercise when in HFpEF LV apical torsion fails to increase normally, causing reduced LV suction and an impaired increase in stroke volume.[6]

The consistency of stress-induced changes measured using a truly integrated diagnostic approach, such as a 3D echocardiographic atrio-ventricular full-volume acquisition, provides a powerful tool to address the complex pathophysiology that characterizes the HFpEF syndrome, in the everyday diagnostic routine.

Conflict of interest

No conflict of interest disclosures reported for the authors.

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