Influence of Left Atrial Function on Exercise Capacity and Left Ventricular Function in Patients With Heart Failure and Preserved Ejection Fraction

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Background—Although left atrial (LA) dysfunction is common in heart failure with preserved ejection fraction (HFpEF), its functional implications beyond the reflection of left ventricular (LV) pathology are not well understood. The aim of this study was to further characterize LA function in HFpEF patients.

Methods and Results—We performed cardiac magnetic resonance myocardial feature tracking in 22 patients with HFpEF and 12 patients without HFpEF. LA reservoir strain, LA conduit strain, and LA booster pump strain were quantified. Peak oxygen uptake (VO2max) was determined. Invasive pressure–volume loops were obtained to evaluate LV diastolic properties. LV early filling was determined from LV volume–time curves as derived from cardiac magnetic resonance. LA reservoir and conduit strain were significantly lower in HFpEF (LA reservoir strain, 22±7% versus 29±6%, P=0.04; LA conduit strain, −9±5% versus −15±4%, P<0.01). Patients with HFpEF showed lower oxygen uptake (17±6 versus 29±8 mL/(kg min); P<0.01). Strain measurement for LA conduit function was strongly associated with VO2max (r=0.80; P<0.01). On multivariable regression analysis, LA conduit strain emerged as strongest predictor for VO2max even after inclusion of LV stiffness and relaxation time (β=0.80; P<0.01). LA conduit strain correlated with the volume of early ventricular filling (r=0.67; P<0.01), but not LV stiffness constant β (−0.34; P=0.051) or relaxation constant τ (r=−0.33; P=0.06).

Conclusions—Cardiac magnetic resonance myocardial feature tracking–derived conduit strain is significantly impaired in HFpEF and associated with exercise intolerance. Impaired conduit function is associated with impaired early ventricular filling, as potential mechanism leading to impaired oxygen uptake. Our results propose that impaired LA conduit function represents a distinct feature of HFpEF, independent of LV stiffness and relaxation.

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Heart failure with preserved ejection fraction (HFpEF) is a syndrome with increasing significance because it accounts for morbidity, mortality, and impaired exercise capacity in a growing number of patients.[1,2] Different pathophysiological mechanisms are found to contribute to HFpEF, including left ventricular (LV) diastolic dysfunction, exercise-induced pulmonary hypertension, marked arterial hypertension on exertion, chronotropic incompetence, or right ventricular pathologies.[3–6]

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Left atrial (LA) remodeling and dysfunction are common in this population. In addition, LA dilatation and LA dysfunction were found to be independent risk factors for development and progression of HFpEF.[7–9] To date, the majority of studies on LA function in HFpEF have used echo-derived parameters, including deformation techniques such as tissue Doppler and speckle tracking for LA imaging.[10–12]

Magnetic resonance imaging is regarded as the most accurate technique for LA volume assessment, with its high spatial resolution and excellent myocardial border detection throughout the cardiac cycle. Cardiac magnetic resonance feature tracking (CMR-FT) is a novel tool to assess myocardial deformation directly from standard steady-state–free precession cine CMR images.[13] This allows for quantifying myocardial deformation without the need for complex tagging sequences.[14,15]

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LV diastolic function in HFpEF and LA dysfunction have been shown to be linked with each other.[16] However, it remains unclear whether the assessment of LA dysfunction can provide additional information, independent of active and passive LV diastolic function. Accordingly, the mechanisms involved and the impact of LA function on exercise capacity, independent of LV stiffness, are still poorly understood.

This study therefore aimed, first, to assess LA morphological and functional properties in HFpEF patients using CMR-FT–derived strain analysis; second, to assess the role of LA performance as a predictor for functional capacity when compared with other parameters of HFpEF pathology; and, third, to link LA performance to load-dependent and load-independent parameters of LV diastology and LV filling properties using CMR and invasive conductance catheters measurements.

Methods

Study Protocol

This study is a substudy of the STIFFMAP trial (Left Ventricular Stiffness vs. Fibrosis Quantification by T1 Mapping in Heart Failure With Preserved Ejection Fraction).[17] Patients with indication for coronary angiogram were prospectively recruited between July 2014 and January 2016 if they met the following criteria: HFpEF patients had to fulfill the following criteria (1) signs and symptoms of heart failure (New York Heart Association class ≥II) and (2) echocardiographic signs of diastolic dysfunction according to the consensus article of the European Society of Cardiology[18] (LV ejection fraction [LVEF] ≥50%, and E/E′ >15 or E/E′ 8–15 and an elevation in NT-proBNP [N-Terminal Pro-B-Type Natriuretic Peptide, Cobas; Elecsys NT-proBNP II, Roche, Basel, Switzerland; assay-specific elevations over 220 pg/mL]). Control patients had to be (1) free of heart failure symptoms (2) have an LVEF ≥50% and be free of echocardiographic signs of severe diastolic dysfunction (E/E′ <8). Patients with relevant coronary artery disease, contraindication to CMR imaging, acute coronary syndrome, more than mild valvular disease, or atrial fibrillation (AF) during CMR/cardiac catheterization were excluded from the study.

As part of the initial screening, echocardiographic studies were performed. Subsequently, eligible patients underwent cardiopulmonary exercise testing and magnetic resonance imaging and cardiac catheterization. To assure comparable levels of intravascular volumes, echocardiography, CMR, and invasive catheterization were performed consecutively and within a 5-hour time window.

The study was approved by the local ethics committee, and all patients gave written informed consent.

Exercise Testing

Cardiopulmonary exercise testing was performed on a supine bicycle ergometer (Ergoline, Germany). Work rate was started with 20 to 40 W. The patients were instructed to maintain a pedaling rate of 60 rotations per minute with stepwise workload increments of 10 to 20 W/min. Patients were encouraged to exercise until exhaustion. VO_2, CO2 production, and ventilation were measured on a breath-to-breath basis and calculated using established methodology (ZAN 600; ZAN, Steyr-Dietach, Austria). Peak VO_2 and respiratory exchange ratio were measured in the last 20 s at maximal exercise. A test with an respiratory exchange ratio ≥1.0 was considered sufficient. We defined peak VO_2 as the highest VO_2 obtained during an adequately performed test.[19]

Echocardiography

Transthoracic echocardiography was performed on Vivid E9 (GE Healthcare, Chalfont St. Giles, Great Britain). Analysis was performed offline using commercially available software (Echopac PC 6.1.0, GE Healthcare). LV size and LVEF were quantified according to current guidelines.[20] Diastolic properties were assessed by determining maximum early (E wave) and late (A wave) diastolic velocities on pulsed wave Doppler and by tissue Doppler peak diastolic velocities of the septal and lateral mitral annulus (E′). The E/E′ ratio was calculated.

CMR Protocol

CMR scans were performed on a 1.5-T scanner (Phillips Intera 1.5T, Best, The Netherlands). Electrocardiographic tracing and triggering were performed with the system's built-in patient monitoring unit. Initially, steady-state–free precession sequences were obtained in 2- and 4-chamber views and a short-axes cine stack covering the entirety of the heart (repetition time, 3.8 ms; echo time, 1.6 ms; flip angle, 60°; voxel size, 1.25×1.25×8 mm^2; 8–10 mm slice thickness).

Evaluation of volumes was performed offline on a remote workstation using commercially available software (cmr42, Circle Cardiovascular Imaging Inc, Calgary, Alberta, Canada). LVEF, LV end-diastolic volume, and LV end-systolic volume were assessed from the short-axis stack. Calculated volumes were normalized to body surface area. Semiautomated tracings of the LA area and length were performed in the 2- and 4-chamber views. LA volumes were calculated using the previously validated biplane area-length method.[21]

For assessment of LV filling properties, LV volumes throughout the cardiac cycle were calculated. Early LV filling, defined as the increase in LV volume during the first one third of diastole, was calculated. All volumes were indexed to body surface area.[22] T1-based extracellular volume fraction was assessed as previously described.[17] For further details see the Methods in the Data Supplement.

Feature Tracking

LA myocardial feature tracking was performed using dedicated software (2-dimensional cardiac performance analysis magnetic resonance, Version 1.1.2.36; TomTec Imaging Systems, Unterschleissheim, Germany) as previously described.[23] Temporal solution was 25 to 30 frames per cardiac cycle.

In brief, LA endocardial borders were manually traced in the 2- and 4-chamber views, and an automated tracking algorithm was applied (Figure 1A and 1B). In case of insufficient automated border tracking, manual adjustments were made to the initial contour, and the algorithm was reapplied. If the tracking quality was not sufficient, for example, because of the presence of pulmonary veins or LA appendage, the corresponding segment was excluded from the analysis. Tracking was repeated for 3× in both the 2- and 4- chamber views, and the respective averages of these repetitions were used for further analyses.

LA longitudinal strain (ε) and strain rate (SR) curves were generated from the averages of all 3 repetitions in both views. Three aspects of atrial strain were analyzed (Figure 1C): passive strain (εe, corresponding to atrial conduit function), active strain (εa, corresponding to atrial contractile booster pump function), and total strain (εs, corresponding to atrial reservoir function), the sum of passive and active strain. Accordingly, 3 SR parameters were evaluated (Figure 1D): peak positive strain rate (corresponding to atrial reservoir function), peak early negative strain rate (corresponding to atrial conduit function), and peak late negative strain rate (corresponding to atrial contractile booster pump function).[24] Negative values mean shortening. For description and statistical analysis, only the absolute values were used, and figures were edited accordingly. Thus, for example, better LA conduit strain means higher negative values.

Cardiac Catheterization Protocol

Standard invasive coronary angiography was performed via right femoral artery access to exclude significant coronary artery disease. Subsequently, a conductance catheter was introduced into the LV to simultaneously record pressures and volumes as previously described.[17] Briefly, using a 7F conductance catheter (CD Leycom, Zoetermeer, The Netherlands), continuous real-time LV pressure and volume signals were recorded for 10 s at baseline, with volume calibration performed using LV volumetric data from the preceding CMR scan. For reduction of preload, transient occlusion of the

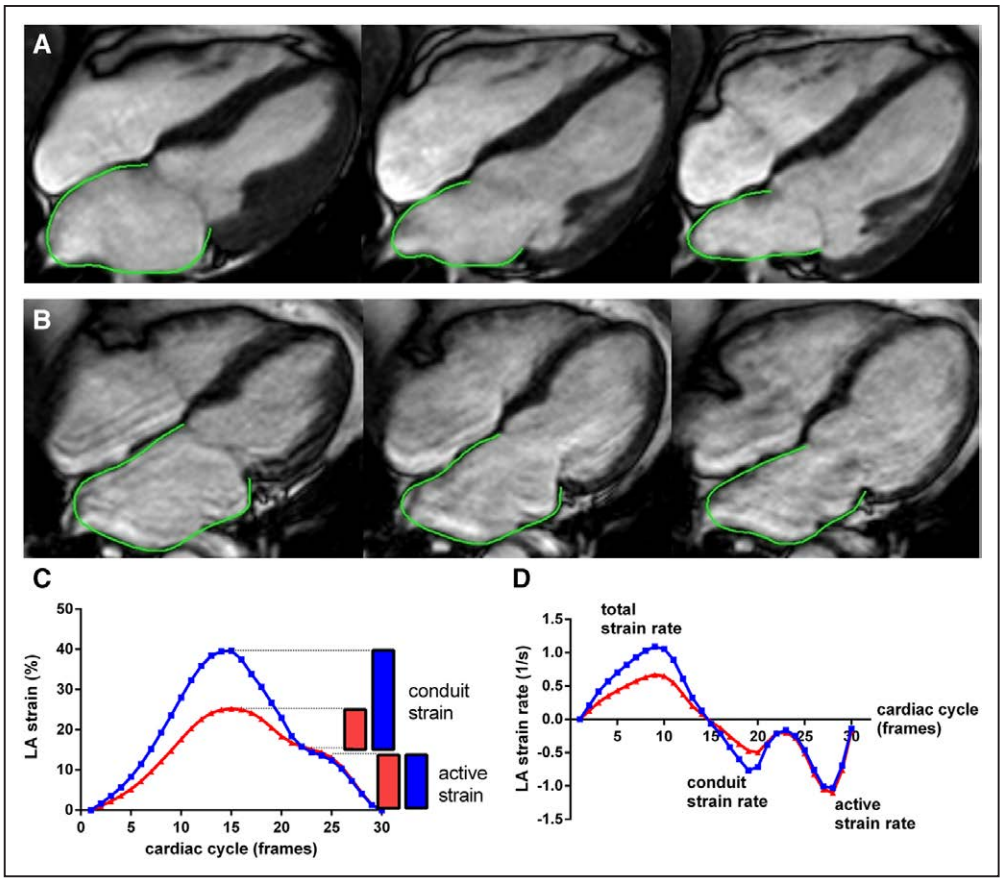

Figure 1. A and **B**, Left atrial (LA) tracking at maximal LA volume (**left**), atrial volume pre atrial contraction (**middle**), and minimal LA volume (**right**) with A showing better and B showing worse conduit function. **Bottom**, Corresponding strain curves. **C**, **bottom left**, LA strain showing better (blue) and worse (red) LA conduit strain and total strain with similar active strain; LA total strain=LA conduit strain+LA active strain. **D**, **bottom right**, corresponding LA strain rate.

inferior vena cava (VCO) was achieved by inflation of an Amplatzer sizing balloon (St. Jude Medical, Saint Paul, MN). On average, 12 pressure–volume loops were acquired during inflation and deflation of the balloon. The load-independent LV stiffness constant (ß) was extrapolated from the end-diastolic pressure–volume relations from the equation $EDP=C\times e^{ß\times EDV}$, where EDP is LV end-diastolic pressure (LVEDP), C is a fitting constant, and EDV is LV end-diastolic volume. Loops were analyzed from the last heartbeat before the onset of volume/pressure decline for a minimum of 5 beats without increase in heart rate. Curve fitting was realized through Microsoft Excel (Version 14.0).

To increase afterload, patients were asked to perform handgrip exercise for 1 minute, and pressure–volume loops were acquired at baseline and throughout peak exercise.

The time constant of active relaxation (τ) was calculated after the method of Mirsky,[25] which evaluates the time needed for LV pressure to fall to one half of its value from peak rate of LV pressure fall (dP/dtmin).

Statistics

Data for continuous variables are presented as mean±SD, if normally distributed, or as median and interquartile range if non-normally distributed. Distribution was tested using Shapiro–Wilk test. Categorical variables are presented as frequencies and percentages. Comparisons between groups were made using Fisher exact test for categorical variables. Continuous variables were compared with unpaired t tests or nonparametric Mann–Whitney U test where appropriate. HFpEF and controls were compared, and male controls were compared with age-matched female subjects from a previous study with regard to LA and LV function.[23,26]

Pearson (r) and Spearman (ρ) tests were used to find factors associated with VO2max. Univariate linear regression analysis and stepwise forward multivariable linear regression analysis were performed to search and control for influencing factors of VO2max in the whole cohort and partial correlation was analyzed. Different models were calculated, including the factors strongest correlated (with $P\leq0.005$) with VO2max. Standardized β coefficients are reported for multivariable regression analysis. To avoid possible multicollinearity between factors of LA dynamics, only 1 aspect of LA function at a time was included into analysis. Features of impaired LA function were searched using Pearson test, Spearman test, and univariate linear regression, including diastolic ventricular properties.

Results

Clinical and Demographic Data

A total of 44 patients were recruited, out of whom 10 patients were excluded in the course of the study: 2 because of incomplete CMR studies, 5 because of significant coronary artery disease, 2 because of AF, and 1 control subject with markedly younger age (34 years) when compared with the remaining population to reduce potential age-dependent confounding. For the final analyses, 34 patients were available, 22 patients with HFpEF and 12 control subjects. Baseline characteristics are displayed in Table 1.

All patients were stable patients without signs of decompensation. Referral for coronary angiogram was part of the diagnostic workup for HFpEF (mostly because of unexplained exertional dyspnea) and control patients (mostly because of

Table 1. Baseline Characteristics

	HFpEF (n=22)	Control (n=12)	*P* Value
Age, y	65±9	58±9	0.03*
Female, sex	19/22 (86%)	3/12 (25%)	0.001*
BMI, kg/m^2	30.3±4.1	26.8±2.6	0.004*
NT-proBNP, ng/L	331 (IQR 205–456)	51 (IQR 28–78)	<0.0001*
NT-proBNP elevation	15/22 (68%)	0/12 (0%)	0.0001*
NYHA I	0/22 (0%)	12/12 (100%)	<0.0001*
NYHA II	19/22 (86%)	0/12 (0%)	
NYHA III	3/22 (14%)	0/12 (0%)	
Smoking	2/22 (9%)	7/12 (58%)	0.004*
Hypertension	21/22 (96%)	8/12 (67%)	0.04*
Hypercholesterolemia	18/22 (82%)	11/12 (92%)	0.63
Diabetes mellitus	3/22 (14%)	4/12 (3%)	0.21
COPD	2/22 (9%)	0/12 (0%)	0.53
Paroxysmal AF	5/22 (23%)	0/12 (0%)	0.14
OSA	3/22 (14%)	0/12 (0%)	0.54
β-blockers	10/22 (45%)	2/12 (17%)	0.14
ACE inhibitors/ARB	16/22 (73%)	5/12 (42%)	0.14
Ca^2+ antagonist	7/22 (32%)	3/12 (25%)	1.0
Aldosterone antagonists	0/22 (0%)	0/12 (0%)	n.a.
Statins	8/22 (36%)	4/12 (34%)	1.00
Diuretics	8/22 (36%)	1/12 (8%)	0.11

Values are presented as means±SD, medians+IQR or frequencies (percentages). ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive lung disease; HFpEF, heart failure with preserved ejection fraction; IQR, interquartile range; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; n.a., not applicable; NYHA, New York Heart Association; and OSA, obstructive sleep apnea.

**P* values below the significance level of 0.05.

atypical retrosternal pain without exertional symptoms) with onset of symptoms within 6 to 12 month before study inclusion.

HFpEF patients were older, more frequently female, had a higher body mass index, and more frequently arterial hypertension. Elevation of NT-proBNP was present in two thirds of HFpEF patients, who all reported exertional dyspnea, predominantly in New York Heart Association class II. Patients without heart failure symptoms presented with indication for coronary angiography because of chest pain and had a marked cardiovascular risk profile.

HFpEF patients showed significantly reduced functional capacity (97±33 versus 154±43 W; $P<0.001$) and maximal oxygen uptake (VO2max 17±6 versus 28±7 mL/(kg min); $P<0.001$) when compared with controls.

Echocardiography, CMR, and Invasive Parameters

No statistically significant differences on LVEF, LV dimensions, and LV stroke volume were found, whereas HFpEF patients had higher E-wave velocities and lower E′ velocities with resulting higher E/E′ ratios. HFpEF patients had higher LVEDPs at baseline and during exercise as shown in Table 2. Patients in the heart failure group showed a significantly higher intrinsic LV stiffness constant β and T1-based extracellular volume fraction.

LA Function

Results are shown in Figure 2. HFpEF patients had higher maximal LA volume (52±18 versus 34±8 mL/m^2; $P=0.001$),

Table 2. CMR, TTE, and Invasive Measures Results

	HFpEF (n=22)	Control (n=12)	*P* Value
Echocardiography			
E–Vmax, m/s	0.9±0.2	0.7±0.1	0.001*
A–Vmax, m/s	0.8±0.3	0.7±0.1	0.21
E/A, ratio	1.0 (IQR 0.8–1.4)	0.9 (IQR 0.8–1.20)	0.58
E′ septal, m/s	0.06±0.02	0.08±0.01	0.006*
E′ lateral, m/s	0.07±0.02	0.12±0.03	0.0004*
E/E′ avg	14.6±4	7.2±1	<0.0001*
Mitral deceleration time, ms	197±43	213±281	0.23
CMR imaging			
LV EDV, mL/m^2	69±12	70±13	0.66
LV ESV, mL/m^2	23±8	27±9	0.25
LV EF, (%)	67±8	63±10	0.16
LV stroke volume, mL/m^2	46±7	44±9	0.54
LV mass, g	131±40	125±30	0.62
LV mass index, g/m^2	67±19	62±12	0.45
Extracellular volume fraction (%)	33±3.0	29±3	0.003*
Invasive measures			
Heart rate baseline, bpm	68±10	73±7	0.09
LV ESP baseline, mm Hg	156±22	147±20	0.23
LV EDP baseline, mm Hg	18±4	13±4	0.004*
PC wedge, mm Hg	12±5	8±3	0.03*
τ baseline, ms	37±9	31±4	0.04*
Heart rate exercise, bpm	89±12	100±7	0.005*
LV ESP exercise, mm Hg	181±29	186±27	0.65
LV EDP exercise, mm Hg	27±8	21±4	0.004*
τ exercise, ms	38±5	34±6	0.04*
LV stiffness (ß)	0.036±0.006	0.022±0.008	<0.0001*

Values are presented as means±SD or medians+interquartile range. E′avg is calculated as (E′septal+E′lateral)/2. CMR indicates cardiac magnetic resonance; EDP, end-diastolic pressure; EDV, end-diastolic volume; EF, ejection fraction; ESP, end-systolic pressure; ESV, end-systolic volume; HFpEF, heart failure with preserved ejection fraction; LV, left ventricular; τ, time constant of relaxation; and TTE, transthoracic echocardiography.

**P* values below the significance level of 0.05.

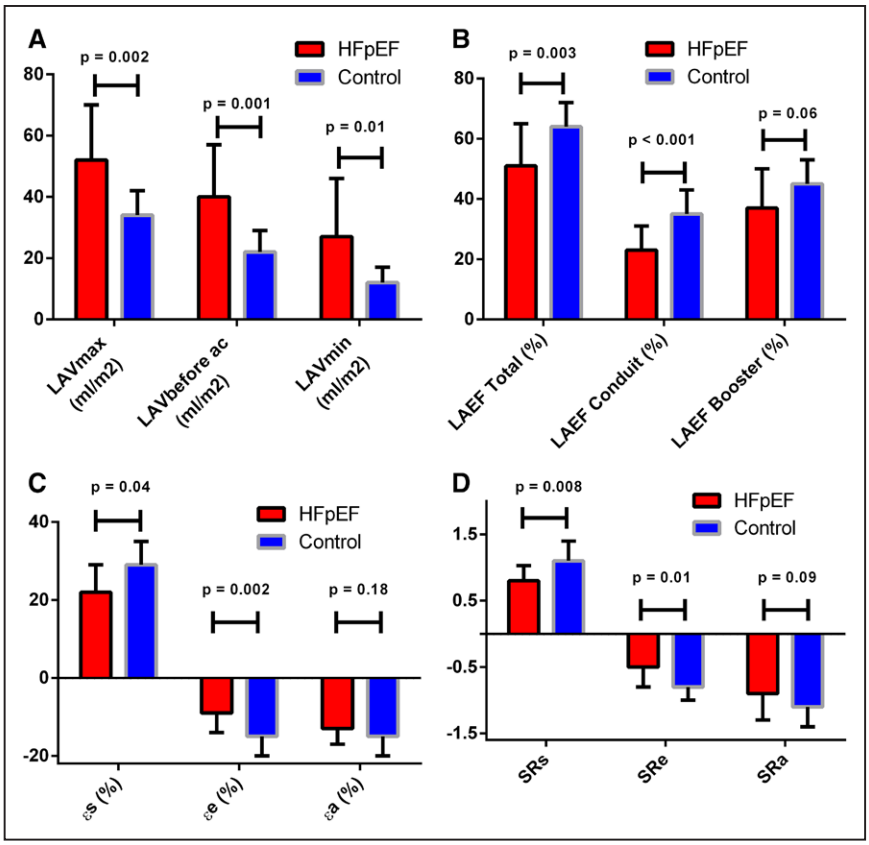

Figure 2. A, Left atrial volumes (LAV): maximal LA volume (LAVmax), LA volume before atrial contraction (LAVbefore ac), and minimal LA volume (LAVmin). **B**, LA function according to volumetric measurements: LA ejection fraction (LAEF). **C**, LA strain measurements: LA total strain (εs), LA conduit strain (εe), and LA active strain (εa). **D**, LA strain rate measurements: LA total strain rate (SRs), LA conduit strain rate (SRe), and LA active strain rate (SRa). HFpEF indicates heart failure with preserved ejection fraction.

higher LA volume before atrial contraction (40±17 versus 22±7 mL/m^2; P=0.001), and higher minimal LA volume (27±19 versus 12±5 mL/m^2; P=0.01). LA total EF and conduit EF were lower in HFpEF patients (LAEF total, 51±14% versus 64±8%, P=0.003; LAEF conduit, 23±8% versus 36±8%, P<0.001), whereas active LA contraction was not significantly different between both groups (LAEF booster, 37±13 versus 45±8%; P=0.06). Despite impaired volumetric LA reservoir and conduit function, similar LA stroke volumes (25±6 versus 21±5 mL/m^2; P=0.13) were observed in both groups, resulting from LA dilatation and higher LA active stroke volume in the HFpEF group (13±5 versus 10±3 mL/m^2; P=0.03). HFpEF patients had impaired LA total strain (εs, 22±7% versus 29±6%; P=0.04) and LA conduit strain (εe, 9±5% versus 15±4%; P=0.002) and a decreased peak positive strain rate (0.79±0.25 versus 1.1±0.3; P=0.008) and peak early negative strain rate (0.54±0.27 versus 0.77±0.20; P=0.014). No significant differences were found comparing markers of LA booster pump function (P=0.18 for strain and P=0.09 for strain rate). No significant difference on LA conduit function was found when comparing HFpEF patients with and without elevated NT-proBNP (εe, 8±4% versus 11±6%; P=0.08).

Factors Associated With Functional Capacity

Factors associated with maximal oxygen uptake are listed in Table 3. The strongest correlations with VO2max were present for LA conduit function (strain εe, r=0.8, P<0.001; conduit peak early negative strain rate, r=0.61, P<0.001; and LAEF conduit, r=0.58, P<0.001), E/E′ (r=−0.56; P=0.001), LA total strain (r=0.56; P=0.001), and age (r=−0.54; P=0.001). The univariate linear regression of εe with VO2max is shown in Figure 3.

Various multivariable linear models were tested: in a model including LA conduit strain and invasive markers of LV diastolic properties (stiffness constant ß and isovolumetric relaxation time τ), LA conduit strain remained the only independent predictor of VO2max (β=0.8; P<0.001). Another model, including conduit strain and the baseline characteristics, sex and age, showed a preserved strong influence of conduit strain (β=0.73; P<0.001) with a comparably weak influence of female sex (β=−0.27; P=0.01) on VO2max. When including E/E′ and εe, LA conduit strain remained the only independent predictor (P<0.001). Details of the multivariable models are shown in Table I in the Data Supplement.

Features of Impaired Conduit Function

To assess a potential link of LA conduit function and load-dependent and load-independent parameters of LV diastology, Pearson correlation was performed, including LV stiffness constant ß, E/E′, LVEDP, age, sex, and BMI. The factor strongest associated with LA conduit function was age (r=−0.59; P≤0.001). No relevant correlation with LV stiffness constant ß (r=−0.34; P=0.05), extracellular volume fraction (r=−0.34; P=0.05), relaxation constant τ (r=−0.3; P=0.09), or LVEDP (r=−0.3; P=0.08) at rest were present. Correlations with τ under maximal exercise (r=−0.46; P=0.007), NT-proBNP (r=−0.49; P=0.004), and E/E′ (r=−0.53; P=0.001) were observed.

Table 3. Univariate Correlation With Maximal Oxygen Uptake (mL/[kg min])

	Correlation Coefficient	*P* Value
Age, y	*r*=–0.54	0.001*
BMI, kg/m²	*r*=–0.40	0.02*
NT-proBNP, ng/L	ρ=–0.66	<0.0001*
E/E′ mean	*r*=–0.56	0.001*
εs (%)	*r*=0.56	0.001*
εe (–%)	*r*=0.80	<0.0001*
εa (–%)	*r*=0.03	0.87
SRs (%/s)	*r*=0.42	0.01*
SRe (–%/s)	*r*=0.61	0.0001*
SRa (–%/s)	*r*=0.11	0.52
LAVmax, mL/m²	*r*=–0.27	0.12
LAVmin, mL/m²	*r*=–0.32	0.065
LAVp-ac, mL/m²	*r*=–0.36	0.04*
LAEF total (%)	*r*=0.46	0.006*
LAEF conduit (%)	*r*=0.58	0.0003*
LAEF booster (%)	*r*=0.30	0.09
LV EDP baseline, mm Hg	*r*=–0.29	0.11
τ baseline, ms	*r*=–0.23	0.20
Heart rate exercise, bpm	*r*=0.31	0.08
LV ESP exercise, mm Hg	*r*=–0.02	0.92
LV EDP exercise, mm Hg	*r*=–0.16	0.40
τ exercise, ms	*r*=–0.25	0.16
LV stiffness (ß)	*r*=–0.41	0.02*
Extracellular volume fraction (%)	*r*=–0.35	0.049*

BMI indicates body mass index; EDP, end-diastolic pressure; ESP, end-systolic pressure; LAEF, left atrial ejection fraction; LAV, LA volume; LAVbefore ac, LA volume before atrial contraction; LAVmax, maximal LA volume; LAVmin, minimal LA volume; LAVp-ac, LA volume before atrial contraction; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; *r*, Pearson correlation; ρ, Spearman correlation; SRa, LA active strain rate; SRe, LA conduit strain rate; SRs, LA total strain rate; LV, left ventricular; τ, time constant of relaxation; εa, LA active strain; εe, LA conduit strain; and εs, LA total strain.

**P* values below the significance level of 0.05.

Potential Mechanisms and Functional Implications of LA Conduit Function

The potential impact of LA conduit function on LV filling properties was assessed by analyzing time–volume curves of the LV (Figure 4A). On echocardiography, no patient had more than trace aortic regurgitation (as possible confounder for ventricular filling). Despite having similar stroke volumes, early ventricular filling was significantly lower in HFpEF (35±15 versus 53±11 as % of LV filling volume; *P*=0.001; Figure 4B). Early LV filling correlated significantly with LV conduit function (*r*=0.67; *P*<0.001) and age (*r*=–0.53; *P*=0.001), but not with LV stiffness (*r*=–0.32; *P*=0.07) or τ (*r*=–0.33; *P*=0.06). On bivariate linear regression analysis, including LA conduit function and age, conduit strain remained the only independent predictor of early LV filling (β=0.67; *P*<0.001). Figure 5 depicts the correlations of early LV filling with maximal oxygen uptake and LA conduit function, respectively.

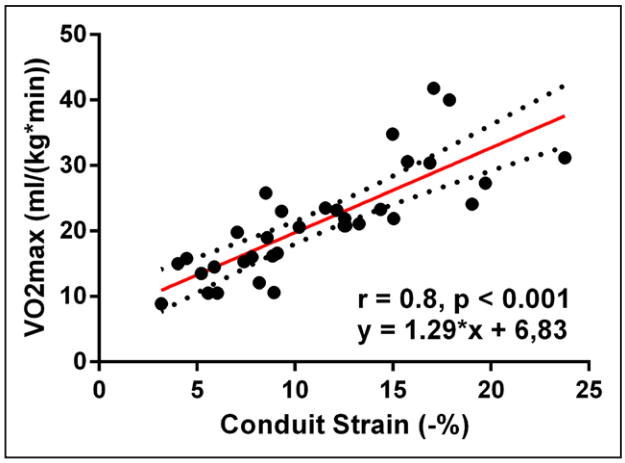

Figure 3. Univariate linear regression of conduit strain and VO2max.

Characteristics of the Control Group

Patients in the control group were more often male. When male control patients were compared with an age-matched female control group, no significant differences on LV and LA size and function were found. Table II in the Data Supplement shows the results.

Potential Influence of AF on LA Conduit Function

Within the HFpEF group, 5 patients had paroxysmal AF (PAF) with potential influence on LA function. During the time course of the study, all of them remained in sinus rhythm.

To detect potential confounders on AF and LA function, baseline, imaging, and invasive data from HFpEF patients with and without PAF were compared. The results are shown in Tables III through V in the Data Supplement. No differences with regard to baseline and invasive data were found. After excluding patients with PAF, correlation of LA conduit strain and VO2max remained highly significant (*r*=0.77; *P*<0.0001).

Discussion

This study comprehensively assessed LA and LV diastolic function using CMR-FT and LV pressure volume curves in HFpEF patients. The main findings are that (1) CMR-FT–derived LA conduit function is significantly impaired in HFpEF and a strong predictor of exercise intolerance; (2) impaired LA conduit function is associated with impaired early diastolic LV filling; (3) as such, LA conduit function seems as a distinct pathophysiological entity in HFpEF independent of load-independent LV stiffness or instantaneous LV relaxation.

Role of LA Dilatation and Dysfunction in HFpEF

For a longer period, HFpEF was thought to be primarily a diastolic LV filling problem with an increase in LVEDP and elevated LA pressure and dilatation. The dilated LA was primarily seen as a prognostic marker for disease progression, and indeed the prognostic relevance of LA dilatation is well established.[8,10] Recently, LA functional remodeling has been proposed as an independent prognostic marker in HFpEF patients.[12] Although

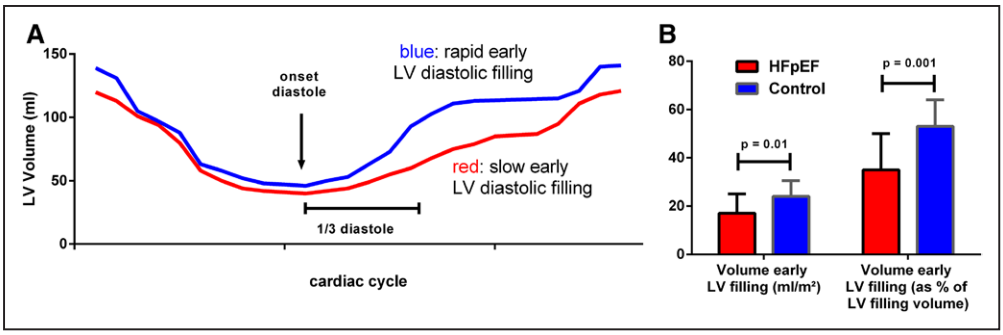

Figure 4. A, Left ventricular (LV) volume curves showing better (blue) and worse (red) early diastolic LV filling. **B**, LV filling volumes in heart failure with preserved ejection fraction (HFpEF) and controls.

LA remodeling is thought to be the consequence of LV diastolic dysfunction, little is known about the relations between LA functional parameters and individual aspects of LV diastolic function in HFpEF patients. Our study, therefore, sought to give insight into the pathophysiological role of LA function as measured by CMR-FT, given the advantages in myocardial border delineation and spatial resolution,[13,23] in relation to exercise capacity, invasively determined diastolic LV function and CMR-derived LV volume–time curves.

Time Course of LA Dysfunction

Consistent with previous reports, we demonstrated functional LA remodeling in HFpEF patients, who presented with higher filing pressures and increased LV stiffness. LA volumes were significantly increased at each point of the atrial cycle. LA reservoir and conduit function were decreased, whereas active LA function was comparable between HFpEF patients and controls. Importantly, active LA stroke volume was increased in HFpEF patients, allowing for compensation of impaired early LV filling as demonstrated in this population of HFpEF patients. This increase in active stroke volume at comparable booster pump function between groups can only be achieved with LA dilatation. Although cause and consequence remain speculative, LA dilatation might also be seen as a phenomenon known from the LV, which dilates with impaired systolic function and EF to maintain adequate stroke volumes. A biphasic time course of LA remodeling in response to LV remodeling has been described: although initially adaptive changes lead to an increased atrial contribution to LV filling, further LV stiffening is associated with a progressive decline in LA global and in particular booster function.[16] These variations in different aspects of LA function over time could explain the conflicting data on the role of different aspects of LA function in HFpEF, where many studies showed a predominant decline in LA total strain and LA active strain.[16,23] A recent echocardiographic speckle-tracking study found LA total strain (reservoir function) to be the most accurate predictor of VO2max. Whereas the influence of LA conduit function on oxygen uptake was not reported,[12] these differing results compared with our study might be explained by the course of LA remodeling over time and disease severity of the studied patient population. Our study included stable ambulatory patients only, without previous hospitalization for heart failure, exhibiting a higher maximal oxygen uptake when compared with the study population of Freed et al.[12] This suggests a less advanced stage of the disease. Nevertheless, most studies showed that LA conduit function is affected early and consistently in the course of LA remodeling and has therefore been proposed as an early marker of LA functional decline.[16] The fact that strain parameters were superior to volumetric assessment of LA function as a predictor for exercise capacity mirrors the results of previous studies.[12,27]

Influence of LA Function on Exercise Capacity

Parameters of LA function, especially LA conduit function, correlated closely with patients' exercise capacity. When adjusting for clinical, echocardiographic, and invasively measured clinical parameters, LA conduit strain emerged as best predictor of peak oxygen uptake. This suggests that LA dysfunction should not be considered as an innocent bystander of global cardiac pathology but is associated with functional limitations. In contrast to LA active (booster) function, which is thought to be mainly influenced by worsening of LV stiffness,[16] conduit function is predominantly modulated by passive LA parameters (elastance and stiffness)[9] and in our study to lesser degree by LV diastolic properties.[16] This suggests that conduit function might be a better reflect of early LA remodeling causing increased

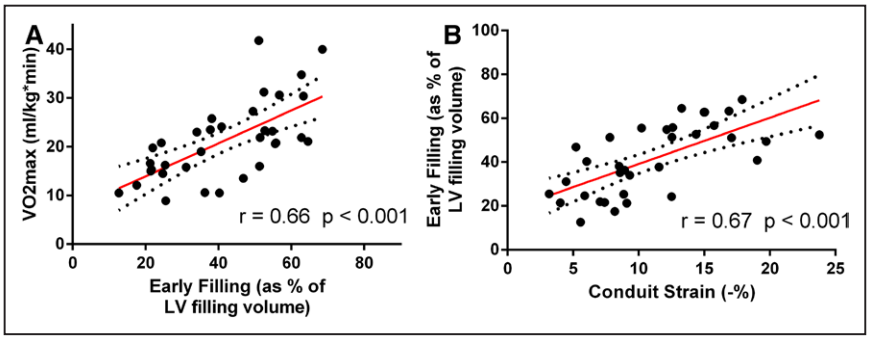

Figure 5. A, Correlation of early left ventricular (LV) filling with maximal oxygen uptake. **B**, Correlation of left atrial (LA) conduit strain and early LV filling.

stiffness and decreased elastance, whereas LA booster pump function reflects LV remodeling, causing stiffness and exacerbation of ventricular filling pressures. Another important finding of this study is the association of LA conduit function and early LV filling, which was not the case for LV stiffness or relaxation. This again points toward an important role of intrinsic LA function, which, if not independent, is at least only marginally explained by parameters of LV diastolic properties. Given the multifactorial modifiers of patients exercise capacity, the reproducible impact of LA function on peak oxygen uptake among different studies is intriguing.[12,28] Early diastolic filling has been shown to be a key determent of LV filling and thereby stroke volume during exercise. With shortening of diastole and partial fusion of passive and active filling phases,[29] alterations in LA conduit function governing early diastolic filling are likely to become even more relevant under exercise than at rest. In healthy subject, rise in stroke volume during exertion requires increased LA conduit emptying with consequent higher LV filling volumes. This emphasizes the physiological need for an increased early LV filling as an adaptation to exercise.[30] In HFpEF, limited conduit function at rest is likely to exaggerate during exercise and might no longer be compensated for by active LA contraction, impacting on LV early filling, LV stroke volume, cardiac output, and ultimately exercise capacity.

Determinants of LA Function

One of the strengths of our study is the ability to relate LA function to load-independent markers of LV stiffness and load-dependent markers of LV relaxation, both derived from pressure–volume loop analysis. This analysis showed that conduit function was not significantly associated with LV stiffness or relaxation, further supporting our discussion above that LA conduit function reflects intrinsic LA pathology, which cannot be sufficiently explained by ventricular pathology. The structural changes of the LA are also known to occur with aging. In our patients, LA conduit function showed a significant correlation to age. However, current data support the theory that LA dilation and impaired LA function reflect rather the clinical conditions that frequently accompany aging than the effects of physiological aging alone.[16] Data on the influence of known factors contributing to the HFpEF syndrome (eg, obesity, hypertension, diabetes mellitus, and age) and their specific influence on LA conduit function are currently lacking and might be of potential interest for analysis in future studies. Although the observed changes in LA function are closely related to disturbances in LV filling, the relative independence of other established markers of LV diastolic function and the strong relation between LA function and exercise capacity imply the ability to gain additional information on hemodynamic alterations in HFpEF patients by assessing LA function. Especially strain analyses seem to be of diagnostic value because they inform early and more specific on functional LA remodeling when compared with volumetric assessment only. Although LA dilatation could also be a physiological response to compensate for decreased LA function, LA strain analysis reveals intrinsic LA dysfunction and LA stiffness at an early stage. Our study confirms the hypothesis of the presence of an independent contribution of LA disease in HFpEF patients, although especially LA conduit function might be a promising diagnostic and therapeutic goal in future studies.

Limitations

Given the complexity and invasiveness, the acquisition of pressure–volume loops resulted in a limited sample size. To justify invasive catheterization in the control group, control subject had to have risk for coronary artery disease. This led to a wide variety of cardiovascular risk factors in these control subjects and to some differences in baseline characteristics between the control and the HFpEF group which could have introduced some confounding.

Importantly, recent data imply that many of the mechanistic abnormalities involved in HFpEF are noted with normal aging and are more pronounced in HFpEF.[31] Thus, progressive acquisition of cardiovascular risk factors and cardiovascular function abnormalities underlie the development of more symptomatic stages in patients at risk for HFpEF. We are therefore confident that our results and conclusions represent pathophysiological mechanisms contributing to the HFpEF syndrome, rather than resembling baseline group differences alone. We did not include imaging exercise testing using either stress echo or stress CMR imaging. This would have further clarified the influence of LA mechanics under exercise conditions. Five patients with PAF were included in the analysis. Because of the study protocol we did not acquire information on previous AF episodes. Although the inclusion of patients with PAF did not alter the results about the main results of this study, future research should clarify the impact of AF on atrial function in HFpEF.

Conclusions

CMR-FT–derived conduit strain is significantly impaired in HFpEF and associated with exercise intolerance. Impaired conduit function could lead to impaired early ventricular filling as a potential mechanism for decreased exercise capacity in HFpEF. LA conduit function emerges as a distinct feature of HFpEF, with functional implications independent of LV stiffness and relaxation.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Accumulating evidence shows that heart failure with preserved ejection fraction is not an isolated diastolic heart disease but rather a syndrome of different intra- and extracardiac pathologies. This includes increased ventricular stiffness, increased systemic and pulmonary arterial stiffness, chronotropic incompetence, right ventricular disease, and left atrial disease. Quantifying the extend of each contributing factor permits a complete diagnostic workup. Measuring atrial function and especially left atrial conduit function allows explaining patients' decreased functional capacity. Especially in patients with poor echocardiographic image quality, cardiac magnetic resonance is an alternative with excellent image quality. Feature tracking is done from standard cine sequences without the need for gadolinium application and can also be done in patients with contraindication to contrast agents. Although cardiac magnetic resonance contrast is safe in most patients, this allows expanding the pool of new contrast-free imaging modalities.