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Titel: Exercise-Stress Real-time Cardiac Magnetic Resonance Imaging for Non-Invasive Characterisation of Heart Failure with Preserved Ejection Fraction: The HFpEF Stress Trial

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Zusammenfassung des wissenschaftlichen Inhalts
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Die Herzinsuffizienz mit erhaltener Ejektionsfraktion (HFpEF) macht die Hälfte aller Herzinsuffizienzpatienten aus. Referenzstandard für eine sichere und frühe Diagnosestellung ist die Rechtsherzkatheteruntersuchung (RHK) unter physiologischer Belastung mit einem Fahrrad Ergometer zur Messung des pulmonal-arteriellen Verschlussdrucks (PCWP). Auf Grund der Invasivität der Untersuchung und der Herausforderung der körperlichen Belastung mit dem Ergometer im Katheterlabor wird der RHK nur zurückhaltend eingesetzt. Die in Göttingen entwickelte Echtzeit-Magnetresonanztomographie (MRT) in Kombination mit einem nicht-magnetischen MRT kompatiblen Fahrrad Ergometer erlaubt erstmals eine physiologische Belastungsuntersuchung mit sofortiger Visualisierung der Wandbewegung ohne Zeitverzögerung in der kardialen MRT. Die Investigator initiierte und durch das deutsche Zentrum für Herz Kreislauf Forschung geförderte HFpEF-Stress Studie (DZHK-17, NCT03260621) hat prospektiv 75 Patienten mit echokardiographischen Zeichen der diastolischen Dysfunktion und Belastungsatemnot eingeschlossen. Diese wurden in Ruhe und unter physiologischer Belastung mittels RHK, MRT und Echokardiographie untersucht. Anhand des PCWP (≥15mmHg in Ruhe oder ≥25mmHg unter Belastung als beweisend für die HFpEF) wurden 2 Gruppen aus HFpEF bzw. nicht-kardialer Luftnot klassifiziert.
Die Echtzeit MRT quantitative Funktion des linken Vorhofs LA LAS war nach Adjustierung für klinische und Bildgebungsparameter ein unabhängiger (Odds Ratio 0.657, 95% Konfidenzintervall [0.516; 0.838], p=0.001) und der beste (Fläche unter der Kurve Ruhe 0.82 vs. Belastung 0.93, p=0.029) Prädiktor für das Vorliegen einer HFpEF.
Die Belastungs-Echtzeit MRT ist ein neu entwickelter diagnostischer Test bei der HFpEF, den wir erstmals in einer Originalarbeit in Circulation beschreiben und in der Late Breaking Clinical Trial Session der diesjährigen Jahrestagung der deutschen Gesellschaft für Kardiologie in Mannheim vorstellen werden. Sie erlaubt zusammenfassend eine akkurate Identifikation von HFpEF Patienten während physiologischer Belastungsuntersuchungen und stellt somit eine nicht-invasive alternative Untersuchungsstrategie dar. Ergänzende Multi-Center-Studien werden für die Bestätigung dieser Ergebnisse vor einer weitläufigen klinischen Etablierung gebraucht. Sollten sich die Ergebnisse der vorliegenden Arbeit bestätigen könnte die in Göttingen entwickelte MRT Untersuchung die belastende Herzkatheteruntersuchung bei der diastolischen Herzinsuffizienz ersetzen.

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Exercise-Stress Real-time Cardiac Magnetic Resonance Imaging for Non-Invasive Characterisation of Heart Failure with Preserved Ejection Fraction: The HFpEF Stress Trial

Running Title: *Backhaus et al.; Exercise-Stress RT-CMR in HFpEF*

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Abstract

Background: Right heart catheterisation (RHC) using exercise-stress is the reference standard for the diagnosis of heart failure with preserved ejection fraction (HFpEF) but carries the risk of the invasive procedure. We hypothesized that real-time cardiovascular magnetic resonance (RT-CMR) exercise imaging with pathophysiologic data at excellent temporal and spatial resolution may represent a contemporary non-invasive alternative for diagnosing HFpEF.
Methods: The HFpEF stress trial (DZHK-17, NCT03260621) prospectively recruited 75 patients with echocardiographic signs of diastolic dysfunction and dyspnea on exertion (E/e'>8, New York Heart Association (NYHA) class ≥II) to undergo echocardiography, RHC and RT-CMR at rest and during exercise-stress. HFpEF was defined according to pulmonary capillary wedge pressure (PCWP ≥15mmHg at rest or ≥25mmHg during exercise stress). RT-CMR functional assessments included time-volume curves for total and early (1/3) diastolic left ventricular (LV) filling, left atrial (LA) emptying and LV/LA long axis strain (LAS).
Results: HFpEF patients (n=34, median PCWP rest 13mmHg, stress 27mmHg) had higher E/e' (12.5 vs. 9.15), NT-proBNP (255 vs. 75ng/l) and LA volume index (43.8 vs. 36.2ml/m²) compared to non-cardiac dyspnea patients (n=34, rest 8mmHg, stress 18mmHg, p≤0.001 for all). Seven patients were excluded due to the presence of non HFpEF cardiac disease causing dyspnea on imaging. There were no differences in RT-CMR LV total and early diastolic filling at rest and during exercise-stress (p≥0.164) between HFpEF and non-cardiac dyspnea. RT-CMR revealed significantly impaired LA total and early (p<0.001) diastolic emptying in HFpEF during exercise-stress. RT-CMR exercise-stress LA LAS was independently associated with HFpEF (adjusted odds ratio 0.657, 95% confidence interval [0.516; 0.838], p=0.001) after adjustment for clinical and imaging parameters and emerged as the best predictor for HFpEF (area under the curve rest 0.82 vs. exercise-stress 0.93, p=0.029).
Conclusions: RT-CMR allows highly accurate identification of HFpEF during physiological exercise and qualifies as a suitable non-invasive diagnostic alternative. These results will need to be confirmed in multi-centre prospective research studies to establish widespread routine clinical use.
Clinical Trial Registration: URL: https://www.clinicaltrials.gov Unique Identifier: NCT03260621

Key Words: HFpEF; real-time cardiovascular magnetic resonance; exercise stress; atrial function; deformation, strain

Non-standard Abbreviations and Acronyms

AF	atrial fibrillation
CMR	cardiovascular magnetic resonance
FT	feature tracking
GLS	global longitudinal strain
HFpEF	heart failure with preserved ejection fraction
LA	left atrium
LGE	late gadolinium enhancement
LV	left ventricle
PCWP	pulmonary capillary wedge pressure
RHC	right heart catheterisation
RT	real time
STE	speckle-tracking echocardiography

TAPSE tricuspid annular plane systolic excursion

Clinical Perspective

What is new?

- Real-time cardiovascular magnetic resonance (CMR) imaging allows highly-accurate non-invasive assessment of cardiac mechanics during exercise-stress for early identification of heart failure with preserved ejection fraction.

What are the clinical implications?

- Clinical work up of HFpEF should include exercise-stress testing.
- Real-time CMR offers highly accurate information to establish the diagnosis especially if clinical and echocardiographic assessments remain inconclusive, and without the need for further invasive examinations.

Introduction

Heart failure remains a major disease burden with approximately 1-2% of the adult population affected in the western world [1]. Heart failure with preserved ejection fraction (HFpEF) accounts for almost half of all heart failure patients [2]. The complex pathophysiology that involves heterogenous causes leading to diastolic dysfunction, [3,4] and onset of symptoms only by advanced stages of disease [5] result in delayed diagnosis of HFpEF. Current guidelines recommend consideration of invasive right heart catheterisation (RHC) including exercise-stress testing [5,6] as the reference test for diagnosing HFpEF [1,7–9]. However, due to the invasive nature of the test and the difficulty for patients to exercise during catheterization, [10] RHC, the reference standard for the diagnosis of HFpEF remains underused. Non-invasive rest echocardiography on the other hand cannot identify HFpEF patients reliably, while physiological exercise-stress echocardiography is often limited by reduced image quality [5,6].

Recent advances in cardiovascular magnetic resonance (CMR) enable novel real-time (RT) imaging at high temporal resolutions (about 20 ms) while maintaining the advantages of conventional cine sequences [11] including image quality, spatial resolution and the absence of plane restrictions [12]. In this study we combine free-breathing RT-CMR during physiological exercise using a MR-compatible ergometer. Because motion artefacts prevent the use of conventional CMR sequences during pedalling, previous studies often combined CMR with exercise stress by performing the MR scans immediately after exercise cessation when the heart rate is already declining. In contrast, the RT-CMR method used here allows CMR stress testing during actual exercise with live image reconstruction, good image quality, and good temporal and spatial resolution which makes this test a potentially valid non-invasive alternative to RHC. Consequently, we hypothesized that left atrial and left ventricular functional imaging parameters derived from CMR exercise stress testing may (a) allow an enhanced pathophysiological

understanding of HFpEF, and (b) advance non-invasive diagnostic pathways in HFpEF by identifying predictors of invasively proven disease.

Methods

The HFpEF stress (German Centre of Cardiovascular Research, DZHK-17) trial was a prospective single-centre clinical trial (NCT03260621) that included 75 patients referred to the Heart Centre Goettingen for echocardiography (**Figure 1**). Patients were eligible for study participation in the presence of echocardiographic signs of diastolic dysfunction (E/e' ≥8) and preserved LVEF ≥50% after presenting with exertional dyspnea (NYHA class ≥ II). Exclusion criteria comprised of typical contraindications for CMR imaging (non CMR-conditional devices, claustrophobia, allergy to gadolinium based contrast agents, active bronchospastic disease) [13], pulmonary (forced expiratory volume in 1 second or vital capacity <80% of the reference) and other cardiac causes of dyspnea (coronary artery disease - stenosis >50%, moderate to severe valvular heart disease and heart rhythm abnormalities). Patients had to be in stable sinus rhythm to be recruited and undergo CMR imaging and RHC. The clinical HFpEF likelihood was defined using the established H2FPEF [14] and HFA-PEFF [9] scores. The study was approved by the local ethics committee at the University of Goettingen. All patients gave written informed consent before participation. The study was conducted according to the principles of the Helsinki Declaration and funded by the German Centre for Cardiovascular Research (DZHK, HFpEF Stress trial DZHK-17). All patients were in sinus rhythm during medical examinations. The data underlying the findings is available at the imaging database of the German Centre for Cardiovascular Research (DZHK) and access will be granted to researchers that meet the criteria for access upon formal request.

Blood Sampling

Blood sampling was conducted on the day of admission. Assessments included a complete blood count, renal function as assessed by creatinine and calculated glomerular filtration rate as well as N-terminal prohormone of brain natriuretic peptide (NT-proBNP). Additional sampling for haematocrit assessments were conducted on the day of CMR if necessary.

Right Heart Catheterisation

Standard fluoroscopy assisted RHC was performed using a Swan-Ganz catheter introduced through a 7F-sheath via the right internal jugular vein using ultrasound guidance [15]. After careful positioning and zeroing of the pressure transducer, right atrial and ventricular pressures as well as pulmonary artery and pulmonary capillary wedge pressures (PCWP) were measured and averaged over several respiratory cycles to compensate for respiratory fluctuations. Oxygen saturations were measured in blood samples obtained from the pulmonary artery. Cardiac output was assessed using thermodilution, averaged from 3 or more valid measurements and indexed to body surface area (cardiac index). Data acquisition was performed at rest followed by a repetition of analyses during exercise-stress. Exercise-stress was conducted using supine bicycle ergometry. Data acquisition started 3 minutes after surpassing a heart rate of 100 beats/min using a 5 Watt increasing ramp protocol based on an electronic braking principle at a rotation speed between 50 to 60 rpm. The workload was then adjusted accordingly to maintain heart rates between 100 to 110 beats/min [16]. Heart rate at rest and during exercise stress as well as exercise-power are reported in **Tables I and II in the Supplement**. The presence of HFpEF was defined according to PCWP of ≥15 mmHg at rest or ≥25mmHg during exercise-stress respectively. Patients that did not meet the HFpEF definition on RHC were referred to as non-cardiac dyspnea. RHC and CMR imaging were performed one day apart, with the exception of 1 case with 2 day interval.

Echocardiography

Additional echocardiographic assessments at rest and during exercise-stress were performed simultaneously with RHC. The standardized protocol included apical 2, 3, and 4 chamber views as well as parasternal long (at rest only) and short axis (SA) views. Colour Doppler assessments were performed for the evaluation and grading of aortic, mitral and tricuspid valve regurgitation in appropriate views. Continuous wave Doppler was used to assess aortic outflow and mitral inflow for the evaluation of valve stenoses, and tricuspid regurgitation velocity for estimation of pulmonary artery pressure (PAPsys). Pulsed wave Doppler was performed in the apical 4 chamber view for the evaluation of passive (E) and active (A) mitral inflow velocity. Tissue Doppler was performed in apical views for the evaluation of septal and lateral mitral annular velocity (e') with subsequent calculation of the mean E/e'. The tricuspid annular plane systolic excursion (TAPSE) was measured using M-Mode from the 4 chamber view. Speckle-tracking Echocardiography (STE) was performed at rest and during exercise stress assessing LV global longitudinal strain (GLS) in 2,3 and 4 CV as well as LA reservoir strain (Es) in 2 and 4 CV.

Cardiovascular magnetic resonance imaging

CMR imaging was performed on a clinical 3.0 Tesla Magnetom Skyra MRI scanner (Siemens Healthcare, Erlangen, Germany) using a 32-channel cardiac surface receiver coil (**Figure I in the Supplement**).

Conventional imaging at rest

Conventional imaging at rest included balanced steady state free precession (bSSFP) electrocardiogram-gated cine sequences at 2-, 3- and 4- chamber long axis orientations as well as a SA stack covering the entire heart including both ventricles and atria. Typical bSSFP imaging parameters were as follows: 30 frames/cardiac cycle and a spatial resolution of 1.8x1.8mm in

plane and 8mm through-plane. Post processing analyses comprised of first a volumetric and second a deformation-based approach.

1) LV mass as well as LV and RV end-diastolic and -systolic volumes for EF calculation were made from bSSFP SA images at rest.
2) Feature-tracking (FT) deformation imaging was performed in an experienced core-laboratory by an operator blinded to RHC results [17]. Analyses were based on the average of 3 independently repeated measurements [18]. The LV was tracked in the 2, 3 and 4 chamber views for GLS, as well as at basal, midventricular and apical SA locations for GCS and GRS assessment. Slice positions were defined as follows: In the apical slice, the blood pool remains visible in the end-systole while the basal slice does not show outflow tract in any timeframe throughout the cardiac cycle. The mid-ventricular slice was chosen centred between the selected apical and basal slices with presence of papillary muscles. LA borders were tracked in the 2 and 4 chamber views; RA borders in the 4 chamber view only. Atrial function was classified according to total, passive and active strain measurements characterizing atrial physiology into atrial reservoir function Es (collection of venous return during ventricular systole), conduit function Ee (passive early diastolic blood flow during ventricular filling) and booster pump function Ea (late diastolic augmentation of ventricular filling) [19]. FT was performed using TomTec (2D CPA MR, Cardiac Performance Analysis, TomTec Imaging Systems, Unterschleissheim, Germany). Borders were manually traced in end-systole and -diastole, followed by application of the tracking algorithm and automatic propagating the contour-line along the cardiac features throughout the cardiac cycle. Tracking accuracy was visually reviewed, and if needed adjustments were made to the initial contours prior to repeating the automated tracking.

Tissue characterisation was performed using different approaches. Modified Look-Locker Inversion recovery (MOLLI) sequences were performed pre- (5(3)3) and post-contrast (4(1)3(1)2) application for the evaluation of native and post-contrast T1 times as well as calculation of extracellular volume (ECV) [20]. T1 times were assessed in one midventricular SA slice for the entire myocardium as well as a septal region of interest separately. Late gadolinium enhancement (LGE) imaging was performed 10-20 minutes after the administration of gadolinium-based contrast agent (0.15 mmol/kg) using inversion-recovery gradient echo sequences. Volumetric and tissue characterisation post-processing analyses were performed using Medis (QMass®, Medical Imaging Systems, Leiden, Netherlands).

Real-Time imaging at rest and during exercise stress

RT-CMR data acquisition at rest and during stress was based on bSSFP sequence using a strongly undersampled radial encoding scheme as described previously [12]. Exercise-stress was performed using a CMR compatible ergometer in the supine position (Lode, Leiden, Netherlands). Parameters for functional imaging with the RT-CMR sequence were: 30 frames/ second temporal resolution,1.6 mm x 1.6 mm spatial resolution, and 6 mm slice thickness. The exercise-stress protocol was identical to RHC surveys. Imaging comprised of functional evaluations in 2-, and 4-chamber views as well as the SA stack. RT cardiac function was quantified using 2 different approaches.

1) Time-volume curves were generated from RT SA stacks at rest and stress over one cardiac cycle. LV and LA volumes were plotted over the course of one cardiac cycle. Assessments included total LV filling and its counterpart total LA emptying volumes during ventricular diastole, as well as early diastolic LV filling and LA emptying respectively during the first third of ventricular diastole. Furthermore, the slope of LV filling or LA emptying curves was averaged over the diastolic phase by superimposing a straight line connecting the beginning

and end of the diastolic phase [$mean\ slope = \frac{volume\ change}{time\ frames}$] **(Figure 2)**. LA ejection fraction was calculated as [$LA\ EF = \frac{end{-}diastolic\ atrial\ volume}{end{-}systolic\ atrial\ volume} * 100$].

2) Manual long axis strain (**Figure II in the Supplement**) was determined as previously described [21]. Briefly, for LV LAS assessment the distance between the middle of a line connecting the origins of the mitral leaflets and the epicardial apical border was measured in end-diastole and end-systole. LA LAS was assessed between the identical line connecting the mitral annulus and the most distal wall of the left atrium. These differences were divided by the end-diastolic length, thus representing a surrogate parameter for LA total strain assessments were performed in the 2 and 4 chamber view acquired during rest and exercise stress testing. Manual long axis strain was analysed using OsiriX MD (Pixmeo SARL, CH-1233 Bernex, Switzerland).

Statistical Analyses

Continuous variables are reported as median with associated interquartile ranges (IQR). Categorical variables are presented as frequencies and corresponding percentages. Comparisons were performed using the nonparametric Mann-Whitney U test for continuous variables and the chi-square test for categorical data. Baseline characteristics and functional CMR/RHC/echocardiogram findings are reported according to the predefined presence of HFpEF. Predictors for the presence of HFpEF were identified from multiple logistic regression analyses using 2 approaches. First including clinical (age, NYHA, AF), laboratory (NT-proBNP), echocardiographic (E/e', LAVI, mitral regurgitation) and CMR functional parameters (GLS, LA LAS rest and stress) as independent variables and second, including variables defined by the H2FPEF score [14]. The results are reported as odds ratios (OR) with 95% confidence intervals and p-values testing the null hypothesis of no association (i.e. OR=1). Furthermore, the areas under

the ROC curve (AUC) were computed for individual parameters and reported with 95% confidence intervals. AUCs were compared using the method proposed by DeLong et al [22]. The correlations between LA LAS and PCWP was assessed by means of the Spearman rank correlation coefficients in non-cardiac dyspnea and HFpEF at rest and during exercise stress. A 2-tailed p-value <0.05 was considered statistically significant. Analyses were performed with SPSS version 23.0 (IBM, Armonk, New York, USA) and MedCalc version 18.2.1 (MedCalc Software bvba, Ostend, Belgium).

Results

Study population

Baseline characteristics are reported in **Table 1**. From the initially recruited 75 patients with suspected diastolic dysfunction, 7 were excluded due to unexpected findings during CMR imaging: being coronary artery disease (n=4) as defined by stress-induced perfusion defects, amyloidosis (n=1) on late enhancement imaging and subsequent confirmation by biopsy, HCM (n=1) by septal wall thickness over 16mm with patchy LGE, and moderate aortic valve stenosis evident during exercise-stress using Doppler echocardiography (n=1). The remaining 68 patients were classified as HFpEF (n=34) and non-cardiac dyspnea (n=34) according to the prespecified cut-offs determined by RHC.

HFpEF patients defined by RHC were median 3 years older (p=0.034) and suffered more often from atrial fibrillation (AF) (n=16 vs n=5, p=0.004). Eight patients were treated with antiarrhythmic drugs because of AF in their medical history, including 5 HFpEF and 3 non-cardiac dyspnea patients; drugs included flecainide (n=1), dronedarone (n=2) and amiodarone (n=5). NT-proBNP was increased in HFpEF patients (255 vs. 75 ng/l, p<0.001). NYHA class (p=0.110), sex (p=0.128) and cardiovascular risk factors (active smoking, hypertension, diabetes,

hyperlipoproteinemia and body mass index, p≥0.339 for all) were distributed similarly in the groups. Mitral regurgitation was absent in 36 patients, 31 patients suffered from mild and 1 from mild to moderate regurgitation with no statistical differences between the HFpEF and non-cardiac dyspnea groups (p=0.246).

Right heart catheterisation

PCWP pressures at rest were 13 vs 8 mmHg (p<0.001) and during exercise stress 27 vs 18 mmHg (p<0.001) comparing HFpEF to non-cardiac dyspnea respectively. 44% (n=15/34) of patients were identified as HFpEF patients according to RHC at rest while 56% (n=19/34) patients were identified during exercise-stress only. PA pressures at rest were 22 vs 17 mmHg (p<0.001) and during exercise-stress 44 vs 34 mmHg (p<0.001) when comparing HFpEF to non-cardiac dyspnea. The cardiac index was similar when comparing HFpEF to non-cardiac dyspnea patients at rest (2.85 vs 2.90, p=0.663), but significantly lower in HFpEF patients during exercise (5.15 vs 5.84, p=0.022).

Echocardiography

Echocardiographic evaluations performed simultaneously to RHC were available with sufficient image quality for analyses in 59 patients at rest and in 50 patients during exercise stress. At rest, E/e' was significantly higher in HFpEF patients (12.5 to 9.15, p<0.001), but was not significantly altered during exercise stress (13.8 to 11.0, p=0.120). The left atrial volume index (LAVI) was significantly higher in HFpEF patients (43.8 vs 36.2 ml/m², p=0.001). Patient data from STE assessments was available for LV (n=53) and LA (n=54) at rest as well as LV (n=46) and LA (n=47) during exercise stress. LV GLS and LA Es were significantly impaired in HFpEF (p≤0.008, **Table 1)**. AUCs were larger for LA (rest: 0.79, stress: 0.82) compared to LV (rest: 0.71, stress: 0.75) function but not significantly different between rest and exercise stress (p≥0.833, **Table 2**).

H2FPEF and HFA-PEFF score

The H2FPEF score identified HFpEF patients with an AUC of 0.72. Based on the Youden index the highest sensitivity (41%) and specificity (94%) product was obtained at 6 points. The HFA-PEFF score provided an AUC of 0.77. The highest sensitivity (62%) and specificity (85%) determined by the Youden index was obtained at 5 points (**Table 2**).

Cardiovascular magnetic resonance imaging

Conventional CMR

Conventional CMR morphology and function at rest is reported in **Table 3**. LV morphological and functional parameters (both volumetric and deformation derived) showed no differences when comparing HFpEF to non-cardiac dyspnea. Similarly, LV tissue characterisation by native T1 and ECV mapping revealed no differences. There was no LGE present in both groups. In contrast, LA function as assessed by FT was significantly impaired in HFpEF patients. RV volumes and function as assessed by strain were similar comparing HFpEF to non-cardiac dyspnea only RVEF was in median 3.8% higher in HFpEF (p=0.034). RA function was similar comparing both groups.

RT-CMR: Rest and Exercise-Stress test

Left ventricular function

RT functional metrics at rest and during exercise stress are reported in **Table 4**. At rest, there were no significant differences in RT LV time volume metrics comparing HFpEF to non-cardiac dyspnea. Total LV diastolic filling volumes increased significantly with exercise-stress both in HFpEF and non-cardiac dyspnea and remained similar between the groups during exercise-stress. Early diastolic filling numerically decreased during exercise-stress, reaching statistical significance only in non-cardiac dyspnea. Notwithstanding, early diastolic filling remained statistically similar during exercise stress. LV filling slopes increased significantly during

exercise-stress, but to a lower extent in HFpEF patients revealing impaired filling slopes in HFpEF compared non-cardiac dyspnea during exercise-stress **Table 4**.

There were no significant differences in RT LV LAS comparing HFpEF to non-cardiac dyspnea at rest (13.5% vs 13.9%, p=0.524). LV LAS increased both in HFpEF and non-cardiac dyspnea with stress. However, the increase in LV LAS was distinctly lower with a significantly lower LV LAS in HFpEF compared to non-cardiac dyspnea during exercise-stress (14.9% vs 18.9%, p<0.001).

Left atrial function

LA total diastolic emptying was similar at rest between HFpEF and non-cardiac dyspnea. During exercise-stress, total LA emptying did not significantly change in HFpEF but increased in non-cardiac dyspnea resulting in a significantly lower total LA emptying in HFpEF compared to non-cardiac dyspnea during exercise. LA early diastolic emptying at rest was higher in HFpEF compared to non-cardiac dyspnea. However, during exercise-stress, LA early diastolic emptying decreased in HFpEF as opposed to an inverse increase in non-cardiac dyspnea. Subsequently, LA early diastolic emptying emerged significantly impaired in HFpEF compared to non-cardiac dyspnea during exercise-stress. The diastolic emptying slope was similar at rest and increased both in HFpEF and non-cardiac dyspnea. This exercise induced increase was distinctly smaller in HFpEF revealing significant differences in emptying slope comparing HFpEF to non-cardiac dyspnea during exercise-stress. LA EF was significantly impaired in HFpEF at rest and during exercise stress, with HFpEF patients failing to increase LA EF during exercise-stress as opposed to patients with non-cardiac dyspnea.

RT LA LAS was already impaired in HFpEF at rest compared with non-cardiac dyspnea (15.6% vs 22.7%, p<0.001). As opposed to non-cardiac dyspnea, HFpEF patients had no further

increase of RT LA LAS during exercise, resulting in larger differences of RT LA LAS during exercise stress (15.7% vs 28.1%, p<0.001).

RT-CMR to detect HFpEF

Left ventricular function

The AUC for identification of HFpEF are reported in **Table 2 and Figure 3**. At rest, AUC ranged from 0.51 for volumetric LV parameters to 0.60 (FT GLS) for deformation derived LV functional parameters. Exercise-stress numerically increased the diagnostic accuracy for all LV functional parameters, while achieving statistical significance only for LV LAS (AUC rest 0.55 vs. stress 0.76, p=0.002, **Table 2**).

Left atrial function

At rest, AUC ranged from 0.55 for volumetric to 0.84 (FT Es) for deformation derived LA functional parameters. Exercise-stress increased diagnostic accuracy numerically for LA total and early diastolic emptying, and statistically significant for LA emptying slope (AUC rest 0.56 vs. stress 0.76, p=0.008), LA EF (AUC rest 0.73 vs. stress 0.83, p=0.002) and LA LAS (AUC rest 0.82 vs. stress 0.93, p=0.029).

LA function identified HFpEF more accurately compared to their LV functional counterpart at rest and during exercise-stress. The LA early diastolic emptying vs. LV early diastolic filling was: rest AUC LA 0.67 vs LV 0.53, p=0.044; stress AUC LA 0.79 vs LV 0.60, p=0.036 and LA LAS vs. LV LAS (rest AUC LA 0.82 vs LV 0.55, p<0.001; stress AUC LA 0.93 vs LV 0.76, p=0.003).

There was no influence of mitral regurgitation (AUC of 0.93 for respective subgroup analyses) on the diagnostic accuracy of LA LAS. Furthermore, the diagnostic accuracy of LA LAS was similar in patients with [rest: 0.81 (0.61-1.00), stress: 0.93 (0.81-1.00) and without [rest 0.75 (0.60-0.89), stress 0.93 (0.86-1.00)] AF in their medical history. LA LAS correlated

significantly with PCWP at rest (r=-0.57, p<0.001) and during exercise-stress (r=-0.75, p<0.001) (**Figure 4**). In the first logistic regression model LA LAS during exercise-stress was the only parameter independently associated with HFpEF (adjusted OR=0.63, p=0.001, **Table III in the Supplement**), the highest sensitivity and specificity described by the Youden index was found at 18.92%. In the second model based of the H2FPEF score, PAPsys (adjusted OR=1.46, p=0.024) and LA LAS stress (adjusted OR=0.56, p=0.004) emerged as independent predictors of HFpEF (**Table IV in the Supplement)**. Similar diagnostic accuracy was seen for LA LAS during exercise-stress but not at rest in patients with intermediate risk according to the H2FPEF (2-5) and HFA-PEFF (2-4) scores (**Table V in the Supplement)**.

Discussion

Results of the HFpEF Stress trial demonstrate the feasibility and high accuracy of RT-CMR as a non-invasive method for clinical detection of HFpEF. Functional evaluations with exercise-stress outperform evaluations at rest and unmask heart failure during exercise, with atrial dysfunction representing the most sensitive indicator. Among the various CMR parameters, LA longitudinal shortening during exercise-stress was the most accurate parameter for detection of HFpEF in this early clinical feasibility trial and this can easily be implemented in clinical diagnostic algorithms.

Early diagnosis of HFpEF

CMR has an established role in the non-invasive diagnostic workup of HFpEF. CMR enables tissue characterisation by measuring native T1 and ECV for diffuse fibrosis, and LGE for focal fibrosis [20]. Rommel et al. have demonstrated changes in tissue composition in HFpEF using ECV, as it independently predicted invasively assessed LV stiffness from pressure-volume loops in the STIFFMAP trial [23]. The present study showed no differences in tissue characterisation using native T1 and ECV mapping between HFpEF and non-cardiac dyspnea. An underlying reason

may be the early identification of patients using exercise-stress. Fibrotic changes are likely to occur primarily during later stages of diastolic dysfunction and LV stiffness [23]. Beyond observations from the STIFFMAP trial, which also demonstrated LV stiffness and relaxation independent association of atrial function and exercise intolerance in HFpEF [24], the present study identified atrial functional failure during exercise as a key feature in the early identification of HFpEF. These functional alterations occur primarily during exercise-stress [25] and may precede measurable changes in LV tissue composition. Ito et al. [26] have reported impaired GLS at later stages of diastolic dysfunction and its association with altered LV relaxation in HFpEF patients with increased ECV. The published literature lacks information on changes in cardiac mechanics and haemodynamics during exercise-stress [26]. Based on our results, we propose exercise-stress CMR as a test that may be applicable for earlier stages of the disease to examine subtle changes in atrial mechanics during exercise. LA LAS emerged as the strongest predictor for the presence of HFpEF as defined by PCWP. Furthermore, it was the only parameter independently associated with the presence of HFpEF in a multivariate analysis that also included clinical, laboratory, echocardiography and other functional CMR parameters. In a second model, considering the parameters defined by the H2FPEF score, [14] PAPsys and LA LAS stress emerged as independent predictors. However, considering that the median PAPsys at rest in the HFpEF population was 28 mmHg, its clinical relevance and the cut-off of 35 mmHg should be considered critically. Especially in patients at intermediate risk for HFpEF according to the H2FPEF (2-5) and HFA-PEFF (2-4) scores, LA LAS during exercise-stress testing showed high diagnostic accuracy (**Table V in the Supplement)**.

Left atrial and ventricular function are inevitably connected with one another with both left atrial compliance and contractility linked to LV stroke volumes [27,28]. However, volumetric analyses may not entirely reflect cardiac mechanics, and preserved EF does not reflect preserved

systolic function [29]. Longitudinal shortening has previously shown greater association with cardiovascular mortality compared to volumetry derived functional analyses [21,30–32]. Impaired LA longitudinal shortening leads to disturbed LA emptying with increased PCWP and pulmonary venous congestion. Moreover, failure to increase LA longitudinal shortening during exercise aggravates this disease mechanism. The rapid increase in PCWP during exercise in HFpEF patients is closely related to the onset and severity of symptoms [33–36]. Although initially thought to be a late effect of LV dysfunction [3,37], current diagnostic strategies in HFpEF increasingly incorporate LAVI as a surrogate for LV remodelling beyond LV mass [1]. The significance of left atrial physiology on its own has been recognized [38] apart from its relation to LV physiology [24,31]. Novel concepts in HFpEF pathophysiology include the role of atrial function in the early part of the disease process [39]. It is known that alterations in atrial mechanics and function precede volumetric changes during the cascade of atrial remodelling [37,40]. In addition, atrial dysfunction may reflect deteriorating LV function as a surrogate marker of LV failure, and also the inability of the atrium to compensate. Consequently, atrial functional decompensation might represent a composite of innate atrial as well as LV functional failure. We speculate this may be the reason why the diagnostic accuracy of atrial emptying and LA LAS exceeded that of their counterparts LV filling and LV LAS.

RT-CMR as a novel non-invasive exercise-stress test

The addition of physiological exercise RT-CMR in the diagnostic work-up of HFpEF patients offers several advantages. These include the ability of live real time physiology assessment during actual exercise with temporal resolution comparable to echocardiography in modern scanners. Additionally, there are benefits from the standpoint of conventional CMR imaging such as high spatial resolution and absence of imaging plane restrictions [12]. Moreover, RT-CMR renders the need for breath-holding during imaging obsolete and enables the implementation of

exercise-stress during imaging, the importance of which has been well established for RHC within major guideline recommendations [1,8,9]. Our results demonstrate feasibility of exercise RT-CMR in the clinical setting. Notably, all enrolled patients were able to complete the exercise protocol, including the obese (maximum body mass index of 41.7 kg/m²), the dyspnoeic with distinct increases in PCWP (maximum of 49 mmHg during exercise) and the elderly (up to 85 years). An underlying reason for the feasibility of exercise-stress assessments in heart failure patients may be the individually adapted workload adjusted for heart rate (aimed between 100-110/min [16]) rather than a predefined and fixed power output. In the present cohort, 56% of HFpEF patients were identified on RHC according to stress-thresholds only and had normal PCWP at rest. Similarly, CMR exercise-stress analyses were superior for the identification of invasively proven HFpEF compared to evaluations at rest, which can easily be appreciated from the improved correlation coefficients of LA LAS and PCWP during exercise (Figure 4). The high spatial resolution enabled detailed and reliable analyses of changes in cardiac volumes and longitudinal shortening during the cardiac cycle. Importantly, exercise-stress does not negatively impact image quality in RT-CMR. This represents a significant advantage over echocardiography, which suffers from impaired data reliability during physiological exercise [6]. Consequently, reduced diagnostic value was observed for E/e' at stress compared to evaluation at rest, and the increase in AUC for exercise-stress STE was lower compared to LAS. However, the supine position catheterization laboratory setting in the present study is suboptimal for echocardiographic assessments and has impacted imaging quality, which can be generally challenging in obese patients. Echocardiography, especially functional evaluations using LA EF or STE derived deformation have previously shown value in the identification of HFpEF patients [41]. The diagnostic performance of STE in the present study is in line with previously reported

data [42]. Considering the wide availability of echocardiography, exercise examinations [6], potentially also including STE are recommended by relevant guidelines [9].

Notwithstanding, in comparison to other diagnostic tests including echocardiography CMR offers comprehensive non-invasive cardiac evaluations comprised in one methodology. Assessments include morphological [11], functional and ischaemia testing as well as myocardial tissue characterisation. Beside the highly accurate identification of early disease stage alterations in diastolic dysfunction [25] the addition of tissue characterisation allows the visualisation of the morphologic consequences of these alterations at later disease stages [23]. It is interesting to speculate whether preventative and therapeutic interventions at such early disease stages may in fact allow a favourable prognostic interference, which has not yet been demonstrated in randomized clinical trials in HFpEF [43]. Furthermore in the present population, 4 patients were identified to have perfusion defects during exercise-stress before the advent of wall motion abnormalities and were referred to invasive catheterisation and diagnosed as well as treated for coronary artery disease which underpins the comprehensive nature of the test.

However, CMR including exercise-stress is limited to tertiary care centers. Notwithstanding, this novel approach allows an in-depth noninvasive assessment of diastolic dysfunction and provides higher diagnostic accuracy compared to established clinical markers, algorithms, and echocardiography. It may be particularly suited for patients with insufficient ultrasound image quality during exercise stress or those with inconclusive findings.

The currently proposed strategies for the detection of HFpEF including the H_2FPEF score [14] and the HFA-PEFF algorithm [9] are targeted to combine enhanced diagnostic accuracy with clinical feasibility. However, they may fail in the early detection of diastolic dysfunction. The ideal parameter for routine clinical implementation would have the combined strengths of feasibility, exercise-stress, non-invasiveness, and high accuracy for the detection of heart failure.

LAS is a fast and reproducible measure for the assessment of longitudinal shortening [44] that has been well validated in cardiovascular disease [21,45,46] similar to LV longitudinal strain [21,30]. In the present study, assessment of LAS was feasible in all RT-CMR data sets and allowed functional assessment of LV and LA function; the latter is increasingly recognized to be important in HFpEF pathophysiology [47]. It is known that increased preload from diastolic dysfunction and/or mitral regurgitation leads to atrial remodelling, dilation and fibrillation [48]. Moreover, the term atrial cardiomyopathy has been introduced to define intrinsic atrial dysfunction [38]. It has been shown that AF burden progressively deteriorates atrial mechanics in HFpEF, worsening disease severity [47]. The presence of AF in the medical history was significantly more in HFpEF patients compared to non-cardiac dyspnea. Although a prerequisite for study inclusion was stable sinus rhythm during CMR and RHC, AF burden in the past medical history may have influenced atrial and cardiac mechanics to different degrees. Notwithstanding, LA LAS classified HFpEF and non-cardiac dyspnoea with the same accuracy in AF and non-AF. Furthermore, LA LAS was significantly associated with HFpEF which was independent of AF and mitral regurgitation in multivariate regression models.

Study limitations

This was a feasibility study performed in an experienced CMR core-laboratory for a newly developed diagnostic test. Conclusions derived therefore represent single center experience derived from a highly selected HFpEF population. There was a difference in absolute numbers for atrial emptying and ventricular filling. Because of the closed mitral valve, subtracting end-systolic from end-diastolic volume represents accurate ventricular stroke volume. In contrast, atrial volume changes are more complex including diastolic atrial inflow and flow reversal through the pulmonary veins [49]. Therefore, subtracting atrial end-systolic from end-diastolic volume does not represent the real atrial emptying but rather a surrogate. However,

underestimated atrial volumes in this study were only compared with each other, so within their own reference. More detailed evaluation of early diastolic filling/emptying during exercise-stress using mathematical approaches is limited by the temporal resolution of RT-CMR especially at relatively high heart rates of 100-110/min. Notwithstanding this limitation, LA LAS was easily applicable, software independent and not influenced by technical limitations.

Conclusion

The HFpEF stress trial demonstrates high accuracy of RT-CMR bicycle exercise stress testing for the diagnosis of HFpEF. Among the various functional parameters in this early clinical trial, left atrial longitudinal shortening during exercise stress emerged as the best independent predictor of invasively proven HFpEF and should be considered for improved clinical detection and management of patients with HFpEF once these results are confirmed in multi-centre prospective research studies.

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Disclosures

None declared.

Supplemental Materials

Supplemental Figures I - II

Supplemental Tables I - V

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Table 1. Patients characteristics

Variable	HFpEF n=34	Non cardiac dyspnea n=34	significance p
Age (years)	69 (67, 77)	66 (52, 73)	**0.034**
Sex male/female	9/25	15/19	0.128
NYHA class	21 x II, 13 x III	27 x II, 7 x III	0.110
Atrial Fibrillation	16	5	**0.004**
H2FPEF Score	5.0 (3.0, 6.3)	3.0 (2.0, 5.0)	**0.003**
HFA-PEFF Score	5.5 (3.8, 6.0)	4.0 (2.0, 4.0)	**<0.001**
Cardiovascular Risk Factors			
Active smoking	4	5	0.720
Hypertension	27	27	1.000
Hyperlipoproteinemia	21	21	1.000
Diabetes	5	5	1.000
Body mass index (kg/m² BSA)	28.7 (26.8, 33.2)	27.6 (25.2, 32.3)	0.339
Laboratory Testing			
NT-proBNP (ng/l)	255 (102, 606)	75 (50, 134)	**<0.001**
Creatinine (mg/dl)	0.89 (0.74, 1.03)	0.83 (0.72, 1.04)	0.995
Echocardiography			
E/e' rest	12.5 (9.7, 13.3)	9.15 (7.5, 10.7)	**<0.001**
E/e' stress	13.8 (10.8, 15.9)	11.0 (10.0, 14.0)	0.120
LAVI (ml/m² BSA)	43.8 (36.6, 54.2)	36.2 (29.2, 41.1)	**0.001**
TAPSE (mm)	24 (21.2, 27.2)	22.5 (20.5, 25.7)	0.335
PAPsys (mmHg)	28 (23.5, 33.1)	22.8 (19.6, 24.7)	**0.001**
STE LV GLS rest (%)	-14.8 (-11.3, -16.9)	-17.9 (-14.2, -20.2)	**0.008**
STE LV GLS exercise (%)	-13.9 (-11.7, -16.1)	-18.6 (-14.5, -20.7)	**0.004**
STE LA Es rest (%)	22.8 (12.4, 30.1)	31.3 (26.4, 34.8)	**<0.001**
STE LA Es exercise (%)	21.4 (12.9, 25.7)	30.4 (27.5, 40.8)	**<0.001**
Right Heart Catheterisation			
PCWP rest (mmHg)	13 (11, 18)	8 (6, 10)	**<0.001**
PCWP stress (mmHg)	27 (26, 31)	18 (11, 22)	**<0.001**
PA rest (mmHg)	22 (20,28)	17 (14, 19)	**<0.001**
PA stress (mmHg)	44 (39, 52)	34 (25, 39)	**<0.001**
PA pO_2 rest (%)	73 (70, 76)	75 (72, 77)	0.225
PA pO_2 stress (%)	42 (36, 51)	48 (43, 52)	0.118
Cardiac Index rest (l/m² BSA)	2.9 (2.4, 3.2)	2.9 (2.6, 3.4)	0.663
Cardiac Index stress (l/m² BSA)	5.2 (3.7, 6.1)	5.8 (4.7, 6.7)	**0.022**

LAVI: left atrial volume index, TAPSE: tricuspid annular plane systolic excursion, PAPsys: systolic pulmonary artery pressure, STE: speckle-tracking echocardiography, LV GLS: left ventricular global longitudinal strain, LA Es: left atrial reservoir function, PCWP: pulmonary capillary wedge pressure, PA: pulmonary artery pressure, BSA: body surface area. Categorical parameters are reported in absolutes numbers and were compared using the Chi-squared test. Independent continuous parameters are presented as medians with interquartile ranges and were compared by using the Mann-Whitney U test. Bold p-values indicate statistical significance.

Table 2. Receiver Operating Curve Analyses.

Variable	AUC (95% CI) Rest	AUC (95% CI) Stress	Significance p rest vs stress
Conventional parameters			
NT-proBNP	0.83 (0.73-0.92)		
E/e‘	0.80 (0.68-0.91)	0.61 (0.45-0.76)	
H2FPEF Score	0.72 (0.61-0.84)		
HFA-PEFF Score	0.77 (0.66-0.88)	*0.78 (0.67-0.89)	0.705
Left Ventricular Function			
STE GLS (%)	0.71 (0.57-0.85)	0.75 (0.60-0.90)	1.000
FT GLS (%)	0.60 (0.46-0.73)		
FT GCS (%)	0.55 (0.41-0.68)		
LV total filling (ml/m² BSA)	0.51 (0.37-0.65)	0.59 (0.45-0.73)	0.193
LV early diastolic filling (ml/m² BSA)	0.53 (0.39-0.67)	0.60 (0.46-0.74)	0.366
LV diastolic filling slope (ml/m² BSA)	0.52 (0.37-0.66)	0.65 (0.52-0.78)	0.088
LV LAS (%)	0.55 (0.41-0.68)	0.76 (0.65-0.88)	**0.002**
Left Atrial Function			
LAVI (ml/m² BSA)	0.71 (0.59-0.83)		
STE Es (%)	0.79 (0.67-0.91)	0.82 (0.69-0.94)	0.833
FT Es (%)	0.84 (0.74-0.94)		
FT Ee (%)	0.77 (0.66-0.88)		
FT Ea (%)	0.80 (0.69-0.91)		
LA total emptying (ml/m² BSA)	0.55 (0.41-0.69)	0.65 (0.52-0.79)	0.441
LA early diastolic emptying (ml/m² BSA)	0.67 (0.53-0.80)	0.79 (0.68-0.90)	0.218
LA diastolic emptying slope (ml/m² BSA)	0.56 (0.42-0.70)	0.76 (0.64-0.88	**0.008**
LA ejection fraction (%)	0.73 (0.60-0.85)	0.83 (0.73-0.94)	**0.002**
LA LAS (%)	0.82 (0.72-0.91)	0.93 (0.87-0.99)	**0.029**

STE: Speckle-Tracking Echocardiography, FT: Feature-Tracking, GLS/GCS: global longitudinal/circumferential strain, LV/A: left ventricle/atrium, BSA: body surface area, LAS: long axis strain, Es/Ee/Ea: atrial reservoir/conduit/booster pump function. AUC analyses were compared using the nonparametric approach introduced by De Long et al. 22 *refers to the HFA-PEFF score including stress echocardiography. Bold p-values indicate statistical significance.

Table 3. Cardiovascular Magnetic Resonance Imaging at rest

Variable	HFpEF n=34	Non-cardiac dyspnea n=34	significance p
Left Ventricle			
LV Mass (g/m² BSA)	57.0 (51.0, 66.9)	55.6 (50.4, 72.0)	0.932
LV EDV (ml/m² BSA)	68.3 (60.7, 77.3)	68.5 (57.4, 76.8)	0.741
LV ESV (ml/m² BSA)	19.6 (14.8, 25.9)	20.4 (14.8, 24.3)	0.917
LV SV (ml/m² BSA)	49.6 (42.1, 54.5)	46.7 (40.1, 53.0)	0.447
LV EF (%)	69.0 (66.3, 76.1)	69.0 (65.0, 75.6)	0.731
FT LV GLS (%)	-19.9 (-18.8, -22.5)	-21.0 (-19.0, -23.2)	0.194
FT LV GCS (%)	-35.2 (-30.9, -39.0)	-34.9 (-30.7, -36.9)	0.516
FT LV GRS (%)	66.2 (57.7, 74.2)	63.4 (56.5, 70.1)	0.275
Native T1 myocardium (ms)	1216 (1189, 1248)	1202 (1173, 1233)	0.202
Native T1 septal ROI (ms)	1210 (1179, 1238)	1196 (1177, 1234)	0.249
ECV myocardium (%)	26.0 (24.2, 28.2)	25.5 (24.0, 27.4)	0.278
ECV septal ROI (%)	25.5 (23.3, 28.4)	25.0 (23.4, 26.9)	0.535
Left Atrium			
FT LA Es (%)	24.8 (16.7, 30.6)	35.9 (30.7, 42.3)	**<0.001**
FT LA Ee (%)	10.9 (8.56, 16.6)	16.5 (13.0, 22.1)	**<0.001**
FT LA Ea (%)	12.1 (7.82, 16.4)	18.2 (15.1, 22.4)	**<0.001**
Right Ventricle			
RV EDV (ml/m² BSA)	67.7 (54.1, 72.1)	65.4 (57.9, 76.1)	0.825
RV ESV (ml/m² BSA)	20.1 (16.9, 25.3)	23.9 (18.8, 28.4)	0.109
RV SV (ml/m² BSA)	44.7 (37.7, 49.6)	41.8 (37.0, 48.4)	0.524
RV EF (%)	67.6 (62.2, 72.1)	63.8 (60.7, 68.3)	**0.034**
FT RV GLS (%)	-22.9 (-20.1, -26.5)	-23.2 (-20.3, -26.6)	0.912
Right Atrium			
FT RA Es (%)	44.3 (35.5, 51.6)	45.2 (33.0, 49.4)	0.849
FT RA Ee (%)	22.1 (18.4, 31.3)	25.8 (16.0, 30.3)	0.508
FT RA Ea (%)	17.6 (13.8, 24.0)	20.8 (13.6, 23.4)	0.585

LV: left ventricular, EDV/ESV: end-diastolic/-systolic volume, SV: stroke volume, EF: ejection fraction, FT: Feature-Tracking, GLS/GCS/GRS: Global longitudinal/circumferential/radial strain, ROI: region of interest, ECV: extracellular volume, LA: left atrium, Es/Ee/Ea: atrial reservoir/conduit/booster pump function. Independent continuous parameters are presented as medians with interquartile ranges and were compared by using the Mann-Whitney U test. Bold p-values indicate statistical significance.

Table 4. Real-Time Cardiovascular Magnetic Resonance Imaging at rest and exercise-stress Time Volume Curves and Long Axis Strain

Variable	HFpEF	significance p rest vs stress	Non-cardiac dyspnea	significance p rest vs stress	significance p HFpEF vs non-cardiac dysnpea
Left Ventricle					
Total diastolic filling					
Rest (ml/m² BSA)	30.3 (25.3, 35.7)	**<0.001**	29.3 (23.8, 36.4)	**<0.001**	0.915
Stress (ml/m² BSA)	37.8 (31.6, 44.1)		41.8 (33.7, 45.0)		0.212
Early diastolic filling					
Rest (ml/m² BSA)	10.9 (8.1, 16.9)	0.257	11.2 (5.4, 16.2)	**0.032**	0.684
Stress (ml/m² BSA)	9.4 (6.7, 14.5)		7.9 (5.4, 12.2)		0.164
Diastolic filling slope					
Rest (ml/m² BSA)	2.1 (1.7, 2.5)	**<0.001**	2.3 (1.5, 2.8)	**<0.001**	0.792
Stress (ml/m² BSA)	5.2 (4.2, 5.6)		5.5 (5.1, 6.6)		**0.034**
LV LAS					
Rest (%)	13.5 (11.4, 15.4)	**0.012**	13.9 (12.0, 15.9)	**<0.001**	0.524
Stress (%)	14.9 (12.5, 18.0)		18.9 (15.7, 21.7)		**<0.001**
Left Atrium					
Total diastolic emptying					
Rest (ml/m² BSA)	-11.9 (-9.28, -11.9)	0.082	-10.7 (-8.82, -13.2)	**<0.001**	0.457
Stress (ml/m² BSA)	-12.3 (-9.57, -15.8)		-13.8 (-12.6, -15.9)		**0.033**
Early diastolic emptying					
Rest (ml/m² BSA)	-2.6 (-2.1, -4.1)	**0.022**	-2.1 (-1.3, -2.8)	**<0.001**	**0.021**
Stress (ml/m² BSA)	-2.2 (-1.5, -2.9)		-3.6 (-2.8, -4.5)		**<0.001**
Diastolic emptying slope					
Rest (ml/m² BSA)	-0.7 (-0.6, -1.0)	**<0.001**	-0.8 (-0.6, -1.2)	**<0.001**	0.379
Stress (ml/m² BSA)	-1.3 (-0.9, -1.9)		-2.1 (-1.7, -2.6)		**<0.001**
LA EF					
Rest (%)	34.2 (27.3, 38.5)	0.142	39.9 (35.4, 43.2)	**<0.001**	**0.002**
Stress (%)	32.2 (22.4, 38.0)		44.9 (39.4, 49.5)		**<0.001**
LA LAS					
Rest (%)	15.6 (11.0, 20.3)	0.939	22.7 (18.9, 29.6)	**<0.001**	**<0.001**
Stress (%)	15.7 (11.9, 18.8)		28.1 (25.0, 32.7)		**<0.001**

BSA: body surface area, LV: left ventricle, LA: left atrium, EF: ejection fraction, LAS: long axis strain. Continuous parameters are presented as medians with interquartile ranges and were compared using the Mann-Whitney U test if independent or the Wilcoxon signed-rank test if dependent. Bold p-values indicate statistical significance.

Figure Legends

Figure 1. Study Flow-Chart

LVEF: left ventricular ejection fraction, NYHA: New York Heart Association, CMR: cardiovascular magnetic resonance.

Figure 2. Atrial Time-Volume Curves

The graphs reflect atrial filling and emptying over one cardiac cycle. Atrial volume is displayed as percent volume increase during ventricular systole compared to minimal atrial volumes at the end of ventricular diastolic filling. The upper graph shows a patient with non-cardiac dyspnea, the lower graph a patient with heart failure and preserved ejection fraction (HFpEF).

Figure 3. Diagnostic accuracy of LV & LA LAS

The figure displays the diagnostic accuracy to detect heart failure with preserved ejection fraction as areas under the ROC curve (AUC) for the individual parameters of left ventricular (LV) and left atrial (LA) long axis strain (LAS) at rest and during exercise-stress.

Figure 4. Correlation of LA LAS and PCWP

The graphs show the correlation of left atrial (LA) long axis strain (LAS) with pulmonary capillary wedge pressures (PCWP) at rest (blue) and during exercise stress (red). The correlations between LA LAS and PCWP was assessed using Spearman rank correlation coefficients.