Circulation: Heart Failure

ORIGINAL ARTICLE

Insights Into Myocardial Oxygenation and Cardiovascular Magnetic Resonance Tissue Biomarkers in Heart Failure With Preserved Ejection Fraction

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BACKGROUND: The pathophysiology of heart failure with preserved ejection fraction is not well understood, but evidence strongly suggests involvement of microvascular dysfunction. We studied the myocardial oxygenation reserve as a direct marker of coronary vascular function and its relation to myocardial deformation and tissue characteristics by cardiovascular magnetic resonance (CMR).

METHODS: In a dual-center case-control study, patients with heart failure and preserved ejection fraction (>50%) and healthy controls older than 50 years underwent quantitative CMR for ventricular volumes and functional assessment with feature tracking, as well as tissue characterization (T1, T2, extracellular volume). Coronary vascular function was measured by oxygenation-sensitive (OS)–CMR of the myocardial oxygenation response to a vasoactive breathing maneuver.

RESULTS: Twenty-nine patients completed the CMR exam. Compared with cutoffs derived from 12 control subjects, circumferential peak strain was attenuated in 97% of patients. Native T1 was elevated in 93%, extracellular volume was elevated in 83%. Sixty-six percent of patients revealed either regional or global myocardial edema, defined by an increased myocardial T2. An attenuated global myocardial oxygenation reserve (<4.4%) was observed in 96% of the patients (1.7±3.9% versus 9.1±5.3% in controls, $P<0.001$). This was correlated with septal wall thickness (r=–0.54, $P=0.003$), edema (myocardial T2; β=–0.26% oxygenation-sensitive/ms [95% CI, –0.49 to –0.03], $P=0.029$), and reduced diastolic strain rate (β=1.50% oxygenation-sensitive/s^{-1} [95% CI, 0.06–2.90], $P=0.042$).

CONCLUSIONS: In patients with clinical heart failure with preserved ejection fraction, vascular dysfunction as measured by an attenuated myocardial oxygenation reserve is associated with myocardial edema, a thicker septum, and diastolic dysfunction. A quantitative comprehensive CMR exam including oxygenation-sensitive–CMR allows for comprehensive imaging-based phenotyping of heart failure with preserved ejection fraction.

Key Words: coronary artery disease ■ edema ■ heart failure ■ magnetic resonance imaging ■ oxygen

Heart failure with preserved ejection fraction (HFpEF) can be difficult to characterize due to heterogeneity in symptom presentation and varying phenotypes. Due to a normal left ventricular ejection fraction (LVEF), the severity of the condition including its progression of systolic dysfunction is often underappreciated. Importantly, however, the long-term rate of mortality is similar to patients with heart failure and reduced LVEF.[1]

The pathophysiologic hallmarks of HFpEF are not entirely understood. HFpEF evolution is commonly associated with stiffening of the ventricles, increased intraventricular filling pressures, and consecutive diastolic

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WHAT IS NEW?

- This study adds to our understanding of the pathophysiology of heart failure with preserved ejection fraction by implementing state-of-the-art imaging markers with novel techniques in a single exam. The results provide evidence for a close link between ventricular systolic and diastolic dysfunction (strain) with an increased interstitial space (increased T1 and extracellular volume), myocardial hypertrophy (septal wall thickness), coronary vascular function (myocardial oxygenation reserve), and myocardial edema (increased T2). This underscores the importance of microvascular dysfunction in heart failure with preserved ejection fraction. Moreover, it raises new evidence about a potential role of myocardial edema.

WHAT ARE THE CLINICAL IMPLICATIONS?

- A combined cardiovascular magnetic resonance (CMR) protocol including oxygenation-sensitive CMR (CMR) allows for a noninvasive assessment of key markers for morphology, ventricular function, myocardial tissue, and coronary vascular function and thus may serve as a very comprehensive test in clinical presentations suggestive of heart failure with preserved ejection fraction. Given the ability of CMR to differentiate ischemic from nonischemic heart failure, as well as identify other etiologies of heart failure, such a protocol could be used in combination with contrast-enhanced CMR sequences to characterize and phenotype this heterogeneous cohort.

Nonstandard Abbreviations and Acronyms

BNP	brain natriuretic peptide
CAD	coronary artery disease
CMR	cardiovascular magnetic resonance
ECV	extracellular volume
EF	ejection fraction
FT	feature tracking
HFpEF	heart failure with preserved ejection fraction
LV	left ventricular
NT-proBNP	N-terminal pro-brain natriuretic peptide
OS	oxygenation-sensitive

dysfunction. Multiple factors have been implicated in this process such as ventricular remodeling, myocardial fibrosis, myocardial edema, metabolic dysfunction, and myocardial ischemia.[2] An increasing body of evidence further points to coronary microvascular disease and diffuse myocardial injury as important underlying mechanisms of HFpEF.[3] These factors can lead to distinct pathophysiological phenotypes, which can be evaluated with noninvasive imaging.

Oxygenation-sensitive (OS)–cardiovascular magnetic resonance (CMR) is a diagnostic and prognostic[4,5] technique that assesses the function of the coronary vasculature by measuring the change of myocardial oxygenation induced by a vasoactive stimulus (myocardial oxygenation reserve).[6] OS-CMR exploits the signal attenuating effects of the local deoxyhemoglobin fraction as an endogenous contrast, primarily in the compartment of post-capillary myocardial venules.[6,7] A breathing maneuver consisting of a period of hyperventilation followed by a long voluntary breath-hold, triggers a vasoactive response with a myocardial oxygenation surplus.[8] An impaired response, shown by a blunted increase or even signal reduction below baseline, was shown to reflect coronary vascular dysfunction.[9] In addition to tissue characterization, myocardial strain imaging using feature tracking (CMR-FT) is becoming a diagnostic and prognostic tool for the assessment of ventricular function.[10,11] A combination of morphology, tissue characterization, myocardial oxygenation reserve, and ventricular function assessments would provide a simultaneous comprehensive view on the pathophysiology of HFpEF (Figure 1).

The aim of this study was to explore the relationship of the myocardial oxygenation reserve to indicators of myocardial edema and fibrosis and to systolic and diastolic function parameters in patients with HFpEF.

METHODS

Data Availability

The source data of our observations for this study are available from the corresponding author upon reasonable request. The corresponding author had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study Design and Enrollment

This was a dual-center study with a case-control design. We prospectively included patients with diagnosed or clinically suspected HFpEF as defined by the presence of heart failure symptoms (≥New York Heart Association II) and a normal ventricular function as defined by an LVEF ≥50% in previous imaging exams, and at least two of the following 3 features: diagnosis of heart failure or history of hospitalization for heart failure, presence of diastolic dysfunction, a BNP (brain natriuretic peptide) >100 pg/mL or NT-proBNP (N-terminal pro-brain natriuretic peptide) >360 pg/mL, as per European Society of Cardiology guidelines and consensus documents.[12] The H_2FPEF score was calculated post-recruitment using the data available in clinical records to estimate the probability of underlying HFpEF.[13] Patients were excluded if they had a history of heart transplantation, cardiomyopathies, previous chemotherapy treatment, percutaneous coronary intervention during the last 30 days, myocardial infarction, valve

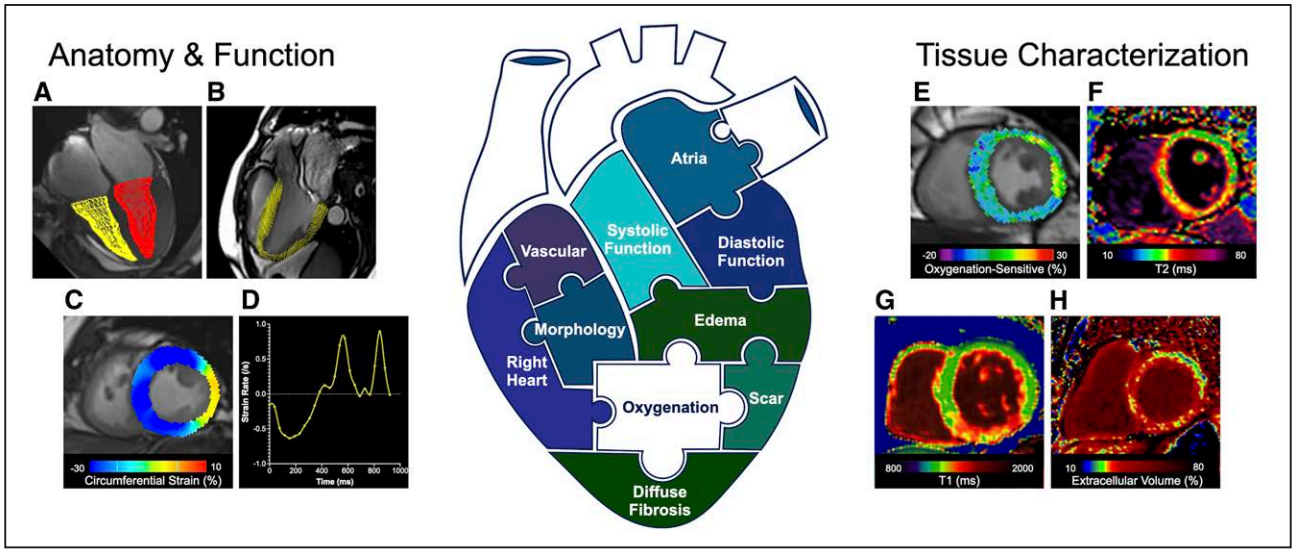

Figure 1. Using quantitative cardiovascular magnetic resonance (CMR) to decipher the puzzle of heart failure with preserved ejection fraction (HFpEF) presentation.

Using CMR, multiple functional and anatomic features (**A**–**D**) and tissue characterization of myocardial abnormalities (**E**–**H**) can be investigated to provide a comprehensive assessment of individual presentations of HFpEF. Right and left ventricular volumetry (**A**), (**B**) longitudinal strain, (**C**) peak circumferential strain and (**D**) strain rate by feature tracking, (**E**) oxygenation-sensitive, T2, T1, and extracellular volume mapping (**F**–**H**).

replacement, coronary artery bypass surgery within the last 90 days, current severe valve dysfunction, severe respiratory disorders, or contraindications to a contrast-enhanced CMR exam. To minimize imbalanced weighting of certain comorbidities, we prospectively limited the number of patients with diabetes, a history of coronary artery disease (CAD), or aortic valve disease to a maximum of one-quarter of the recruited population. Forty-three patients were recruited over a thirty-month period at Bern University Hospital, Inselspital in Bern, Switzerland, and the McGill University Health Centre in Montreal, Canada. Twelve healthy controls between the age of 50 to 70 years underwent a noncontrast enhanced CMR scan. Healthy controls were recruited through public advertisements and confirmed that they were nonsmokers and free of any cardiovascular or respiratory disease. The study was approved by both local ethics boards and complies with the Declaration of Helsinki. All subjects had given their written informed consent before enrollment into this study.

CMR Imaging

Before the CMR exam, participants were asked to refrain from consuming caffeinated beverages or food. Imaging was performed using a clinical 3T MRI system (MAGNETOM Skyra or Prisma; Siemens Healthineers, Erlangen, Germany). For ventricular and atrial volumes and function, images were acquired as a short-axis cine stack and in three long-axis views. The imaging protocol for tissue characterization included two short-axis slices of each, OS-CMR cine, T2 maps, and T1 maps. The latter were obtained for the assessment of extracellular volume (ECV) maps as a marker of diffuse fibrosis before and twenty minutes after an intravenous bolus of 0.1 mmol/kg gadobutrol (Gadovist, Bayer AG, Leverkusen, Germany). Standard late gadolinium enhancement images were acquired to assess focal fibrosis. The OS-CMR protocol for measuring the myocardial oxygenation reserve was performed with a vasoactive breathing maneuver. This involved baseline images and sixty seconds of paced hyperventilation at a rate of 30 breaths/min with a subsequent long breath-hold during which the heart was imaged continuously until the participant indicated the need to breathe.

Datasets were deidentified and split into 2 separate groups so that OS images were analyzed without knowledge of any information from the remaining images. Standard biventricular volumetry and tissue characterization analysis were performed. Using an FT algorithm, systolic and diastolic strain parameters were acquired, with diastolic strain rate separated for the early diastolic peak and for measuring late atrial contribution.[14] The myocardial oxygenation reserve was calculated as the percent signal intensity difference between the 30 s time point during the breath-hold in reference to the start of the breath-hold.[8] Detailed imaging and sequence parameters are provided in the Supplemental Material.

Statistical Analysis

To characterize the HFpEF population, mean values were compared to the healthy controls using a linear regression model accounting for sex and age as covariates. The frequency and percentage of the HFpEF population with abnormal CMR measurements were compared to reported[15] cutoffs or was based on the 95% CI of the median from the control cohort for less established measurements. This was performed to define global and regional abnormalities as detailed further in the Supplemental Methods. The association between myocardial oxygenation reserve, tissue characteristics, and functional data in patients with HFpEF were then investigated using mixed linear models fitted with the *lmer* function in R (*lme4* package). To allow for regional assessment, data were compared per myocardial segment, accounting for multiple measures per patient by including subject identification as a random intercept and reported as the β-coefficient with 95% CIs. Global measurements were used for comparison to volumetric and demographic variables. Statistical significance was defined with a

2-sided *P* value of <0.05. Statistical analyses were performed with GraphPad Prism version 9.0 (GraphPad Software, La Jolla, CA) and *R* software (version 3.5.0, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient Characteristics

Twenty-nine patients were eligible for analysis (Figure S1). Thirteen patients (45%) were female. Of the female patients; none had any history of macrovascular CAD, whereas a history of CAD was prevalent in half of the male population, with the majority having undergone reperfusion procedures (Table 1, Table S1). One patient had a stenosis visually assessed at 80% diameter reduction of the right coronary artery at the time of CMR. The majority of patients had mild heart failure symptoms (New York Heart Association II, 76%), with the rest in New York Heart Association classes III and IV. The H_2FPEF score[13] yielded no patients (0%) with a low likelihood (score 0–1) of HFpEF, 86% had an intermediate score (2–5), whereas 14% had a high confidence score (≥6). The age of healthy controls did not significantly differ from the patient group (56±5 years versus 61±11years, *P*=0.09), had a similar proportion of females (33% versus 45%, *P*=0.48), albeit a lower body mass index (24.4±2.1 versus 30.9±7.4 kg/m^2, *P*<0.001).

Myocardial Oxygenation Reserve

Four patients (14%) reported mild adverse effects during the vasoactive breathing maneuvers, specifically lightheadedness or headache (n=2) and tingling in the fingers during hyperventilation (n=2), all dissipating spontaneously within 60 s. The mean breath-hold time following hyperventilation was 42±21 s. One patient was unable to maintain a breath-hold for longer than 11 s, thus 28 were available for OS-CMR analysis. The overall mean myocardial oxygenation response in patients with HFpEF was +1.7±3.9% versus +9.1±5.3% in controls (*P*<0.001). All except for one patient (96%) demonstrated at least a regional oxygenation impairment, not achieving the normal oxygenation response of >4.4% during apnea, with a global impairment in 19 patients (68%, Table 2). A regional or global OS signal decrease to levels below individual baseline (<0%, indicating tissue deoxygenation) was evident in 21 patients (75%, Figure 2).

Tissue Characterization

There was no difference between groups for mean global T2 measures (Table 2). Using cutoff values (listed in Table 2), however, regionally prolonged T2 (>40.6 ms) was detected in 66% and global prolongation in T2 in 28% of the HFpEF group. Patients not only had a significantly

Table 1. HFpEF Characteristics

	Total (n=29)
Age, y	61±11
Body mass index, kg/m^2	30.6±5.6
Heart failure parameters	
H_2FPEF score	4.0 [3.0–5.0]
Low risk (0–1)	0 (0)
Intermediate risk (2–5)	25 (86)
High risk (6–9)	4 (14)
NYHA class	
NYHA II	22 (76)
NYHA III	6 (21)
NYHA IV	1 (3)
Diastolic dysfunction by echocardiography	
Grade 1	11 (38)
Grade 2	12 (42)
Grade 3	3 (10)
Unspecified diastolic dysfunction	3 (10)
Hypertension	15 (52)
Pulmonary hypertension	9 (31)
Dyslipidemia	16 (55)
Diabetes*	8 (28)
Sleep apnea syndrome	2 (7)
Smokers (past 6 mo)	5 (17)
History of CAD*	8 (28)
Myocardial infarction	3 (10)
PCI/CABG	7 (24)
Current coronary stenosis	1 (3)
History of valve disease	6 (21)
Aortic valve*	2 (7)
Mitral valve	4 (14)
Glomerular filtration rate, mL/(min·1.73 m^2)	71 [65–91]
BNP, pg/mL (n=8)	129 [51–203]
NT-proBNP, pg/mL (n=3)	1078 [140–1851]
Medication	
ACE inhibitors	9 (31)
Angiotensin II receptor blockers	6 (21)
Beta-blockers	16 (55)
Diuretics	9 (31)
Statins	19 (66)
Antiplatelets	19 (66)
Anticoagulants	6 (21)
Calcium channel blockers	3 (10)

Values are mean±SD, median [interquartile range], or frequency (percentage). ACE indicates angiotensin-converting enzyme; BNP, brain natriuretic peptide; CABG, coronary artery bypass graft; CAD, coronary artery disease; HFpEF, heart failure with preserved ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; and PCI, percutaneous coronary intervention.

*A preimposed limit of one-fourth of recruited patients with these comorbidities was implemented. Comparisons between males and females are provided in Table S1.

Table 2. Tissue Characterization and Feature Tracking in HFpEF

	Control	HFpEF	*P* value	Cutoff	HFpEF global abnormalities, n (%)	HFpEF regional abnormalities, n (%)
Tissue characterization						
Myocardial oxygenation (OS-CMR, %)	9.1±5.3	+1.7±3.9	<0.001	Impairment <+4.4%	19 (68)	27 (96)
				Deoxygenation <0 %	9 (32)	21 (75)
T2, ms	39.2±1.8	39.2±2.6	0.87	>40.6	8 (28)	19 (66)
T1, ms	1209±41	1273±49	0.001	>1241	20 (69)	27 (93)
ECV, %		28.8±3.5		>27.0	21 (72)	24 (83)
LGE, %		5.3±4.7		Present	7 (24)	…
Circumferential strain						
Peak strain, %	−19.1±1.8	−17.0±3.0	0.021	>−17.3	17 (59)	28 (97)
Time to peak strain, ms	344±37	343±43	0.61	>355	12 (41)	26 (90)
Early diastolic strain rate, /s	1.15±0.20	0.84±0.28	0.007	<1.07	26 (90)	26 (90)
e/a diastolic strain rate	1.84±0.48	1.80±1.90	0.73	<1.34	16 (55)	23 (79)
Longitudinal strain						
Peak strain, %	−16.8±1.3	−13.5±2.4	<0.001	>−15.3	22 (76)	23 (79)
Time to peak strain, ms	364±43	358±66	0.27	>391	7 (24)	21 (73)
Early diastolic strain rate, /s	0.75±0.19	0.59±0.19	0.09	<0.60	15 (52)	15 (52)
e/a diastolic strain rate	1.33±0.37	1.52±1.46	0.27	<1.04	14 (47)	25 (75)

Mean±SD is provided for the myocardial oxygenation reserve measured by OS-CMR, tissue characterization, and feature tracking strain measurements of both healthy controls and the HFpEF group. Proportions of HFpEF abnormalities, n (%), are provided if global left ventricular measures were outside of the reference range and for the presence of regional abnormalities. Cutoffs were defined by the 95% CI from the enrolled healthy controls, detailed in the Supplemental Material. ECV indicates extracellular volume; HFpEF, heart failure with preserved ejection fraction; LGE, late gadolinium enhancement; and OS-CMR, oxygenation-sensitive cardiovascular magnetic resonance.

higher native T1 than controls, consistent with fibrosis, but also edema or increased interstitial space due to other causes. The majority of patients (93%) revealed at least regionally increased T1 above the cutoff (>1241 ms). As a marker for diffuse fibrosis, an increased ECV was observed in 83% of patients (>27.0%, Figure 3), whereas regional/replacement fibrosis (late gadolinium enhancement) was less prevalent (24%, Figure 4).

Ventricular Morphology and Function

Forty-five percent of the patients had septal wall hypertrophy, and also 45% had a higher mass to end-diastolic volume ratio (Table S2). Despite preserved LVEF, the mean cardiac index in patients was 2.5±0.6 L/min/m^2, with 34% having a cardiac index below normal (<2.5 L/[min·m^2]). Gender-adjusted left atrial volume index was 35±15 mL/m^2. Right ventricular EF was 43±13% and was reduced (<50%) in 48% of the patients. Global systolic function as defined by abnormal myocardial strain values was attenuated longitudinally (global peak longitudinal strain) in 22 patients (76%; in reference to the cutoff values reported in Table 2). Additionally, 17 patients (59%) demonstrated compromised circumferential peak strain shortening (global peak circumferential strain, Figure 5). This proportion increased to 97% when taking regional dysfunction into account (Table 2). This resulted in prolonged global time to peak strain in 41% and 24%, for circumferential and longitudinal orientations. Furthermore, 90% of patients had a globally reduced early diastolic strain rate for circumferential and 52% for longitudinal fiber direction, indicating attenuated lusitropy.

Association Between Coronary Vascular Function, Tissue Characterization, and Ventricular Function

The myocardial oxygenation response (OS-CMR) decreased by −0.26% [95% CI, −0.49 to −0.03, %OS/ms] for every millisecond increase in T2 mapping (P=0.029). A poor OS-CMR was also linked to a prolonged longitudinal time to peak strain (β=−0.01%OS/ms [95% CI, 0.01–0.02], P=0.002) and a lower circumferential early diastolic strain rate (β=1.50%OS/s^{-1} [0.06–2.90], P=0.042). Furthermore, myocardial deoxygenation was correlated to increased septal wall thickness (r=−0.54, P=0.003, Figure 5). T2 mapping did not correlate with any functional parameters, whereas native T1 was associated with a reduction in multiple systolic and diastolic CMR-FT parameters (Tables S3 and S4). An increased ECV correlated with increased time to peak circumferential strain and with a reduced longitudinal diastolic strain rate. The association of CMR markers with patient characteristics including sex, CAD history, New York Heart Association, H_2FPEF scores, and echocardiography graded diastolic dysfunction are shown in Tables S5 through S7.

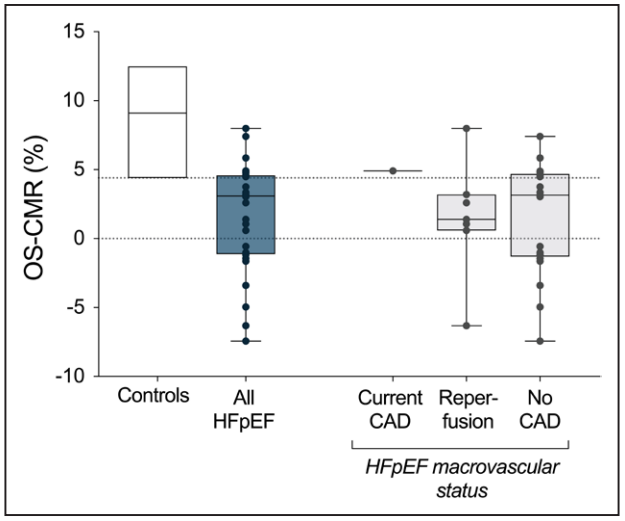

Figure 2. Myocardial oxygenation reserve in heart failure with preserved ejection fraction (HFpEF).
The distribution of the global myocardial vascular reserve measured by oxygenation-sensitive–cardiovascular magnetic resonance (OS-CMR) is shown for all heart failure with preserved ejection fraction (HFpEF) patients (dark), and further separated for the presence or absence of macrovascular disease in HFpEF, or status postreperfusion. Among patients, 31% of patients with HFpEF showed a net global tissue deoxygenation (<0%, lower line), even in the absence of coronary artery disease (CAD). The white box represents the mean and 95% CIs of a local reference population used to define the lower cutoff of 4.4% (upper line).

DISCUSSION

This study adds to the understanding of the pathophysiology of HFpEF by focusing on coronary vascular function, using the myocardial oxygenation reserve as a marker, and its relationship with parameters of morphology, function, and tissue. Furthermore, this data indicates that the breathing maneuver-elicited myocardial oxygenation reserve may serve as a clinical marker for coronary vascular function in conditions suggestive of HFpEF. The majority of patients with HFpEF (96%) demonstrated a subnormal myocardial oxygenation response, despite a lack of evidence for macrovascular CAD or recent adverse cardiovascular events. This supports the concept of microvascular dysfunction in HFpEF. A lower oxygenation reserve was also associated with diastolic dysfunction (strain) and myocardial edema. By combining OS-CMR with other tissue-derived and functional parameters, this comprehensive CMR protocol implemented several state-of-the-art imaging markers with novel parameters to characterize and phenotype this heterogeneous patient cohort (Figure 6).

Myocardial Oxygenation in the Absence of Macrovascular Disease

Oxygenation dysregulation secondary to coronary microvascular dysfunction has been implicated as an underlying factor of HFpEF.[16] Thus, noninvasive techniques that can quantitatively assess microvascular dysfunction are valuable. Albeit not a direct measure of oxygenation, nuclear perfusion imaging has demonstrated that myocardial flow reserve is significantly attenuated in patients with HFpEF even after adjusting for comorbidities,[17] and limited flow reserve has been linked to future major adverse cardiac events.[18] Abnormal flow reserve in the absence of CAD has been shown by CMR techniques as well as by first-pass perfusion imaging.[19] Löffler et al[20] reported that patients with HFpEF showed compromised myocardial perfusion, which was correlated with a higher ECV and attenuated maximal oxygen consumption. During right-heart catheterization, van Empel et al[21] measured impaired myocardial oxygen delivery in HFpEF by arterial and coronary sinus blood gas sampling during exercise testing and suggested microvascular dysfunction as a possible cause. Using nuclear 11C-acetate

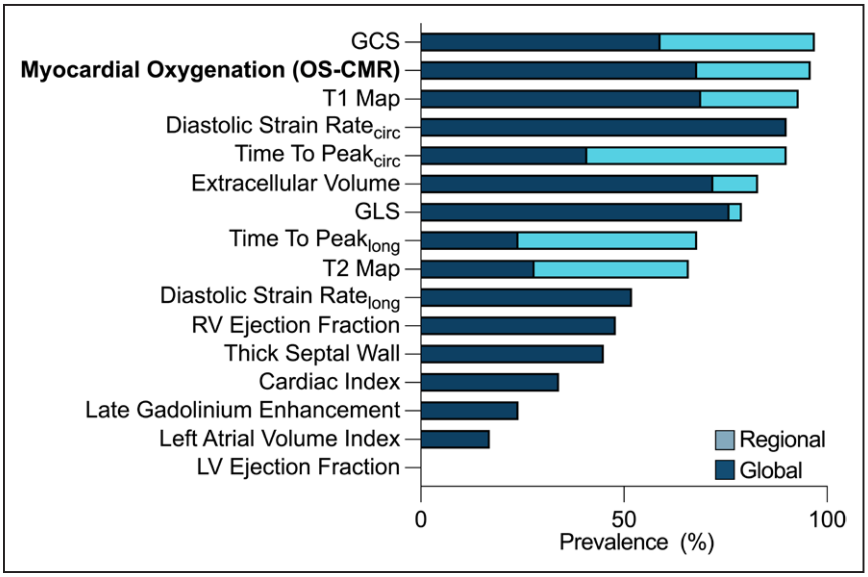

Figure 3. Prevalence of heart failure with preserved ejection fraction (HFpEF) abnormalities.
The proportion of patients with a cardiovascular magnetic resonance defined abnormality is ranked by prevalence as defined in Table 2 and Table S2. Dark blue represents patients with global abnormalities, and light blue represents the patients with normal global measurements but presented with regional abnormalities. Unless otherwise specified, markers refer to the left ventricle (LV). Circ indicates circumferential; GCS, global peak circumferential strain; GLS, global peak longitudinal strain; Long, longitudinal; OS-CMR, oxygenation-sensitive cardiovascular magnetic resonance; and RV, right ventricular.

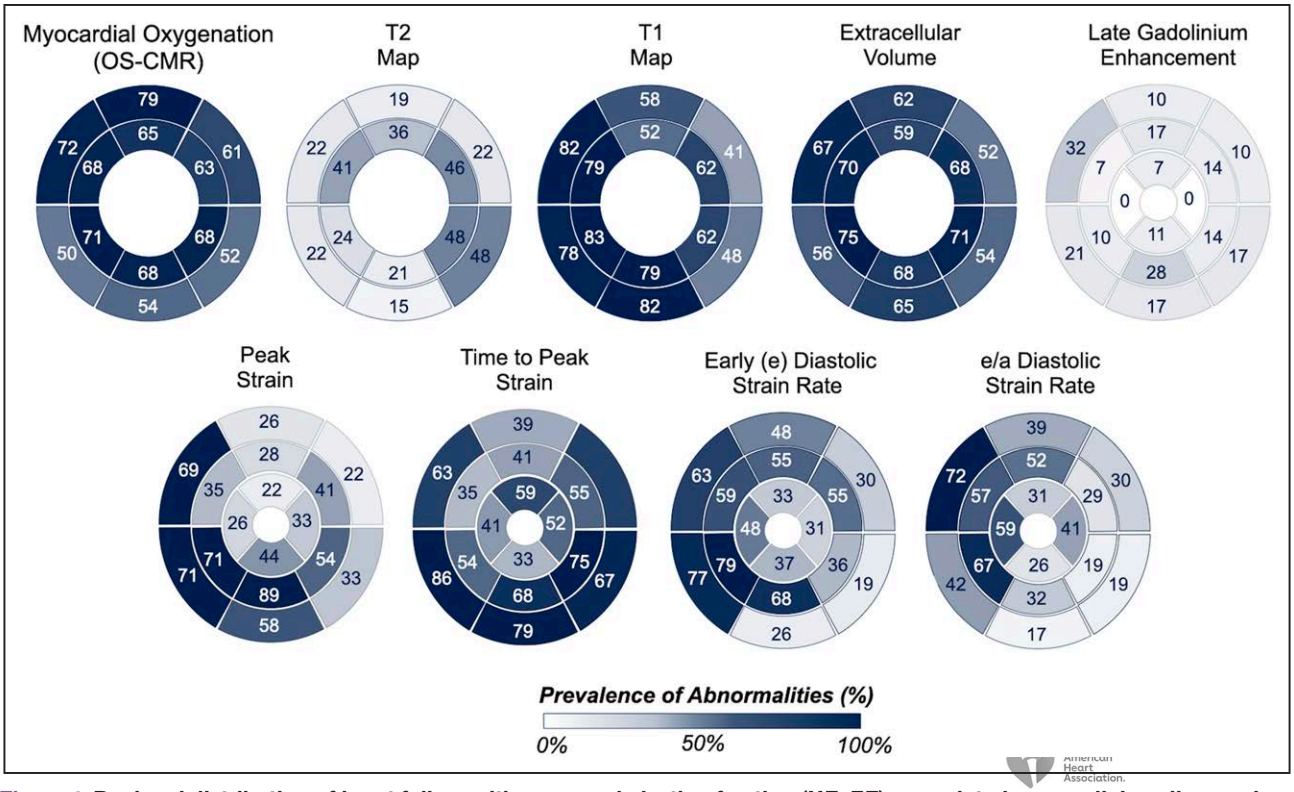

Figure 4. Regional distribution of heart failure with preserved ejection fraction (HFpEF)–associated myocardial cardiovascular magnetic resonance (CMR) abnormalities.

The proportion (%) of segments with myocardial abnormalities are shown for tissue characterization (top row) and for systolic (**bottom left**) and diastolic (**bottom right**) feature tracking strain measurements (circumferential orientation of short axis). Larger proportions are associated with darker shading. OS indicates oxygenation-sensitive.

positron emission tomography with dobutamine infusion, the concept of coronary microvascular dysfunction was strengthened by demonstrating an imbalance in myocardial energetics, diminished flow reserve, and impaired coupling to increased myocardial O_2 extraction.[22] Consistent with these results, the majority of our patients had at minimum a regionally attenuated oxygenation response to a vasodilatory stimulus induced by a standardized breathing maneuver, although all but one HFpEF patient had no known obstructive macrovascular disease. The role of microvascular dysfunction is also underlined by the fact that 32% of our patients even experienced a net global drop of myocardial oxygenation as a response to the vasoactive stimulus.

Myocardial Oxygenation and the Presence of Edema and Fibrosis

Poor myocardial perfusion or oxygenation reserve may be explained not only by impaired microvascular function but also by a reduction in the density of microvessels relative to the myocardial mass (capillary rarefication). This has been reported for HFpEF, where it was associated with myocardial fibrosis as shown by autopsy.[23] ECV mapping has been linked to markers of disease severity in HFpEF and other comorbidities such as infarct size, renal function, pulmonary vascular resistance, and poor clinical outcome.[24] We observed an ECV expansion in 83% of our HFpEF cohort, including 17 patients (59%) who were negative for late gadolinium enhancement. High water content and increased fibrotic load are both mechanisms that increase native T1, and prolonged T1 was at least regionally present in 93% of the participants. This supports the notion that HFpEF is strongly associated with altered myocardial tissue composition. A worsening myocardial oxygenation reserve was not linearly correlated with T1 or ECV. This lack of correlation with diffuse fibrosis has also been found in the iPOWER study (Improve Diagnosis and Treatment of Women with Angina Pectoris and Microvessel Disease) investigating women with suspected coronary microvascular disease, which found that myocardial blood flow reserve assessed by positron emission tomography was not correlated with ECV.[25]

However, in our sample, the oxygenation response was attenuated in the presence of a higher T2. We observed that 66% of this cohort had an elevated myocardial T2, in the absence of any known recent cardiac events that are commonly associated with edema. Diffuse edema could reflect not only mild inflammation but also venous congestion in the myocardium. Many comorbidities linked to HFpEF can increase myocardial water content such as volume overload,[26] and inflammation is associated with

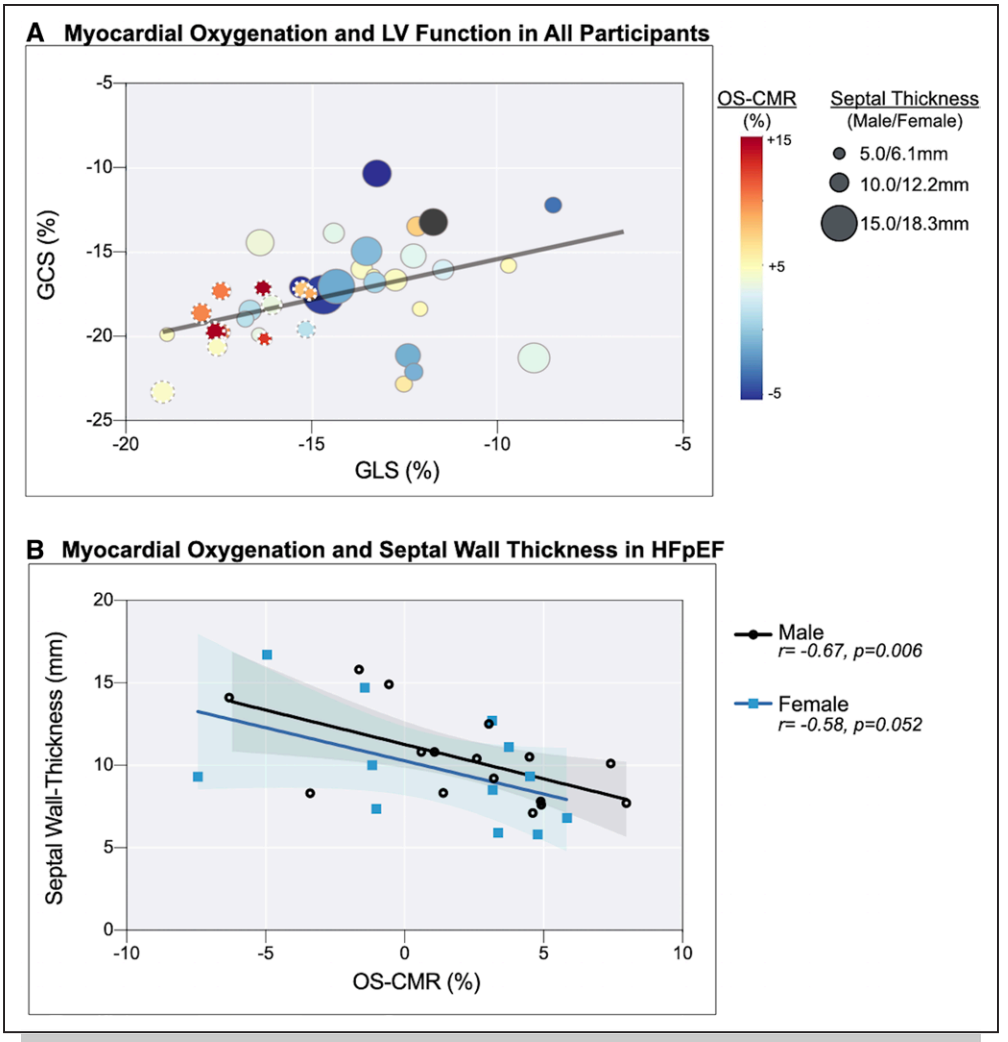

Figure 5. Myocardial oxygenation and left ventricle (LV) geometry.
A, Data for all heart failure with preserved ejection fraction (HFpEF, solid border) patients and healthy controls (dotted border) are plotted for global peak longitudinal (GLS) and circumferential (GCS) strain, with icon size representing end-diastolic wall thickness measured in the midcavity septum. The icon color indicates the myocardial oxygenation-sensitive–cardiovascular magnetic resonance (OS-CMR) response with luxury oxygenation depicted by red shades and myocardial deoxygenation by blue shades. Dark gray represents the patient who did not make the 30-second time point for the OS-CMR measure. **B**, Myocardial deoxygenation in patients with HFpEF is associated with septal wall thickness measured in end-diastole of the mid ventricle in the 4-chamber view.

pulmonary hypertension, arterial hypertension, stress-induced cardiomyopathy Takotsubo, and obesity.[27]

HFpEF phenotype groups displaying the most severe symptoms also have the highest levels of inflammatory biomarkers.[28] Multiple paradigms are being developed concerning the role of edema and inflammation in HFpEF. Paulus and Tschöpe[29] put forward a paradigm where a systemic proinflammatory state is induced by comorbidities, and this, in turn, leads to coronary microvascular endothelial inflammation and subsequent LV-remodeling, collagen deposition, and diastolic dysfunction. Another proposed paradigm involves similar mechanics but within a repetitive cycle, with myocardial inflammation as one of the features which lead to heart failure.[2] Edema may also be a result of repetitive ischemic events triggered by inadequate recruitment of blood flow under exertion due to microvascular dysfunction and recurrent mismatch of oxygen demand and supply. Myocardial edema can increase interstitial pressure and promote external microvascular compression, physically inhibiting vasodilation, whereas increased intraventricular pressure would impair subendocardial blood flow. Our data may, therefore, also shed new light on the potential role of myocardial edema as key component of heart failure. Although causality between edema and myocardial oxygenation is unclear so far, a quantitative link between the two mechanisms copresenting in patients with HFpEF is apparent and warrants further investigation.

Diastolic and Systolic Dysfunction

HFpEF has long been associated with impaired active early relaxation (lusitropy) and reduced compliance from

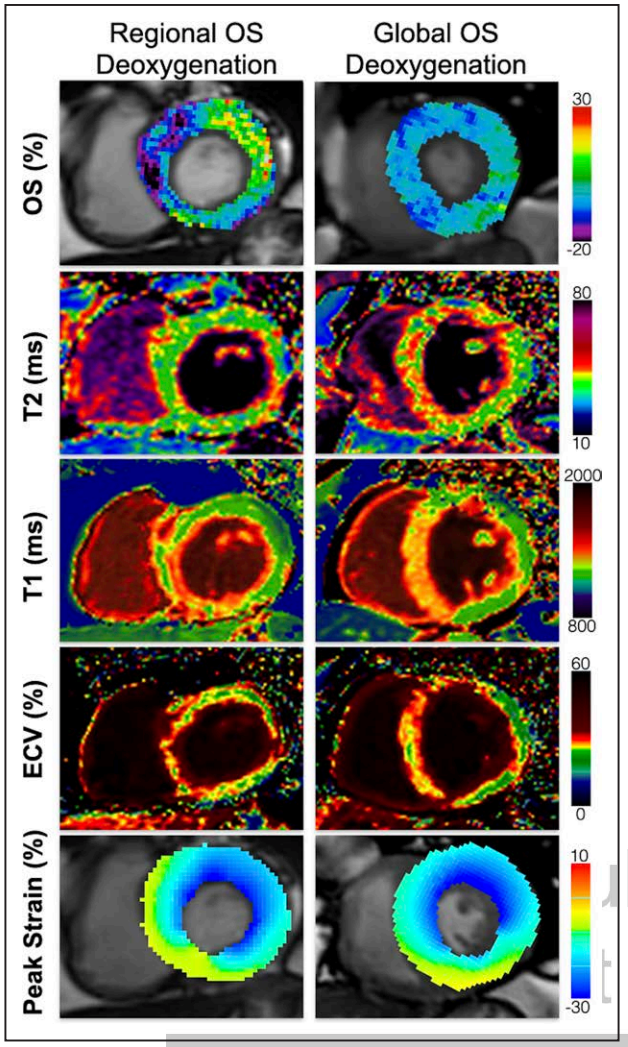

Figure 6. Quantitative cardiovascular magnetic resonance (CMR) in heart failure with preserved ejection fraction (HFpEF).
CMR images are presented for 2 patients with no history of macrovascular disease. On the **left** is a patient with a regional oxygenation-sensitive (OS) abnormality primarily in the septum with colocalized T1, extracellular volume (ECV), and peak circumferential strain abnormalities. On the **right** is a patient with a global OS abnormality with diffuse T2 abnormalities, along with septal T1, ECV, and peak strain abnormalities. For OS measurements, a normal reserve is indicated by green and yellow voxels, with deoxygenation marked by blue-purple. Normal myocardium is marked by green in T2, T1, and ECV images, with yellow-red voxels indicating elevated measurements, whereas a yellow-red overlay in the feature tracking images indicates worsening peak strain.

increased ventricular stiffness, resulting in diastolic dysfunction.[30–32] Mapping parameters of ECV and native T1, indicators of fibrosis and edema, were colocalized to reduced diastolic strain rate. Moreover, diastolic function is an early hallmark of myocardial ischemia as early active relaxation is highly energy-dependent. This study demonstrates for the first time that patients with reduced early diastolic strain rate at rest also mount a poor myocardial oxygenation response to a hypercapnic challenge.

In addition to diastolic dysfunction, increasing evidence points to coinciding, progressive systolic dysfunction in HFpEF.[33] When investigating subtle systolic dysfunction with CMR-FT strain analysis, we found that 59% of our patients with HFpEF had globally reduced global peak circumferential strain, and 76% had attenuated global peak longitudinal strain. As shown in Figure 3, none of our patients would have been attributed a subnormal systolic function based on LVEF alone. LV geometry plays a significant role in HFpEF.[34] It has been demonstrated that echocardiographic strain measures may better reflect contractility than EF because EF may remain preserved despite reduced longitudinal and circumferential shortening, especially in cases with small end-diastolic volume or increased ventricular wall thickness,[35] both of which are typical features of HFpEF.

Myocardial Oxygenation in Relation to Ventricular Geometry and Deformation

In patients with HFpEF, we observed a negative linear relationship between the myocardial oxygenation (vascular) response and wall thickness. Inducible perfusion deficits are recognized in hypertrophic cardiomyopathy, with regional hypoperfusion noted most in septal segments and territories with a greater wall thickness.[36] In addition to the impact of edema as described above, recognized mechanisms of ischemia in hypertrophic myocardium can include supply-demand mismatch of the increased tissue mass, compression of the epicardial vessels during systole, reduced coronary vasodilator response, and diffuse microvascular disease due to arteriole dysplasia.[36] HFpEF has a different pathophysiology than hypertrophic cardiomyopathy, although it is also associated with hypertrophy or borderline wall thickness. In a recent study using an animal model of HFpEF induced by LV pressure overload, the septum seemed to suffer more profoundly from circumferential diastolic myocardial stiffness than other myocardial segments.[37] We observed that oxygenation and abnormalities along with circumferential systolic and diastolic dysfunction were most prevalent in the septum (Figure 4), possibly representing earlier stages of the remodeling process.

Beyond peak strain measures, a prolonged time to peak strain correlated with myocardial oxygenation in the longitudinal orientation. Primary causes of prolonged time to peak strain are delayed contraction and postsystolic shortening, which itself is a sensitive marker for ischemia.[38] Abnormal function due to hypoperfusion or ischemia will likely be detected first in the longitudinal direction because the ischemia-sensitive subendocardium is primarily composed of longitudinal fibers, and these fibers are more exposed to increased intracavity pressures. OS-CMR was not solely linked to longitudinal measures, but we also observed relationships with circumferential diastolic function, whereas ECV, a marker

commonly associated with ventricular remodeling, is associated with both circumferential and longitudinal markers as well. In a porcine HFpEF model, collagen content increased but also fiber angle orientation changed during the disease process between longitudinal and circumferential orientations, which was associated with a rise in chamber stiffness.[37] Of note, both, circumferential and longitudinal orientation are of prognostic value in heart failure.[10] Moreover, such collagen deposition may lead to increasing microvascular dysfunction, which may further entertain the pathophysiologic spiral of HFpEF. Strain parameters derived from CMR-FT may allow more insight into various presentations of HFpEF and progressive deterioration of myocardial relaxation and ventricular compliance in relation to myocardial oxygenation. These feature tracking parameters might become useful as predictors of progression from diastolic to systolic dysfunction in HFpEF and of transition to reduced EF.

Comprehensive CMR

Our findings on characteristics of myocardial oxygenation as a marker of microvascular function, anatomic remodeling, ventricular dysfunction, and myocardial tissue abnormalities in HFpEF reflect the complexity of its phenotype(s). A comprehensive CMR protocol may be the most efficient and comprehensive approach to gain insights into the multifactorial process of HFpEF evolution and progression. The wide spectrum of information may also render CMR the method of choice for clinical decision-making, including quantitative T2 and T1 mapping along with OS-CMR. Kanagala et al[39] reported that including a standard perfusion exam with late gadolinium enhancement imaging resulted in the diagnosis of a new pathology in 27% of patients with HFpEF and that this combined model better predicted adverse outcomes. Mordi et al[40] incorporated CMR-based ECV measurements and strain analysis by speckle-tracking echocardiography to better differentiate HFpEF from a quite similar presentation in hypertensive patients. Even simultaneously acquired metadata such as the heart rate response to hyperventilation or pharmacological dilators can be incorporated into decision-making.[41,42] The use of a comprehensive CMR exam allows for an in-depth analysis of these patients, to help not only determine the adverse sequelae of HFpEF but also to determine the extent of other comorbidities such as stable CAD, myocardial hypertrophy, and amyloidosis.

Our data shows that while this technique is reliant on patient cooperation and their ability to perform breathing maneuvers, the majority (28/29) were able to complete the task. This sample was composed of obese patients with multiple comorbidities. Although patients are unlikely to maintain a maximal breath-hold as long as healthy controls, a 30 s time point is used, as it is where healthy myocardium appears to have reached a maximum myocardial oxygenation response but remains a feasible benchmark for patients to reach after a proper hyperventilation preparatory phase.[9] It is important to keep in mind that the duration of voluntary breath-holds is much longer if performed after a period of hyperventilation. This technique has been successfully implemented in patients with hypertension,[43] CAD,[9,44] heart transplant patients,[45] and women with ischemia and nonobstructive CAD.[46] In addition, OS-CMR has been compared to invasive blood and coronary flow measures in animals.[47–49] Nevertheless, as this is a developing technique further validation is required, along with additional comparisons to pharmacological stress testing.[8,44]

Limitations

This study is limited by its small sample size. We based inclusion on common HFpEF features: heart failure symptoms, diastolic dysfunction, and natriuretic peptides, although such criteria may not cover the entire spectrum of HFpEF. Thus, our findings do not account for multiple hypothesis testing with the correlation assessments, may still lack external validity, and may not be representative for other specific HFpEF populations. Categorical assignment of the presence of abnormalities is based on cutoff values derived primarily from our local controls, and values may, therefore, differ in other control populations and when other hardware, sequences, or software are used. Normal values will need to be validated further, particularly e/a diastolic strain ratio of myocardial tissue, which is inherently different from echocardiographic E/A transmitral inflow velocity ratio used in grading diastolic dysfunction (Table S6). The cutoff values used represent the threshold of healthy myocardium and, therefore, although in line with those reported in other control populations at 3T,[50] they may not necessarily reflect thresholds with prognostic value. Longitudinal follow-up of changes in HFpEF in a large patient sample are needed to investigate causal relationships between diagnostic markers and identify their prognostic utility. This analysis focuses on CMR markers, and the link to other diagnostic findings such as laboratory biomarkers, especially BNP measures, and cardiopulmonary exercise testing presents an interesting question that should be investigated in the future.

Conclusions

An abnormal coronary vascular response, provoked by a standardized hyperventilation-apnea maneuver and measured by the myocardial oxygenation response OS-CMR imaging, is highly prevalent in patients with HFpEF and is associated with hypertrophy, myocardial edema, and diastolic dysfunction. Future studies in larger samples are required to further elucidate these associations and

relationships between these novel markers and clinical HFpEF phenotypes.

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Disclosures

Dr Friedrich is a board member, advisor, and shareholder of Circle Cardiovascular Imaging Inc, the manufacturer of the software used for CMR image evaluation. Drs Fischer, Guensch, and Friedrich were inventors of but no longer hold the international patent: Measuring oxygenation changes in tissue as a marker for vascular function. Initial Filing Date: August 8, 2013. Patent issued: April 11, 2017. Application Number: 14/419877. Patent Number: 9615754. Continuation Filing Date: April 10, 2017. United States Patent Application No. 15/483712, Patent pending. As of April 2018, the patent rights were transferred to Circle Cardiovascular Imaging Inc, Calgary, AB, Canada. The other authors report no conflicts.

Supplemental Material

Supplemental Methods
Figure S1
Tables S1–S7

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