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Original Article

Cardiac Magnetic Resonance Postcontrast T1 Time Is Associated With Outcome in Patients With Heart Failure and Preserved Ejection Fraction

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Background—The underlying pathophysiology of heart failure with preserved ejection fraction (HFPEF) is incompletely understood, but myocardial extracellular matrix accumulation is thought to play a major role. Our aims were to estimate myocardial extracellular matrix using cardiac magnetic resonance T1 mapping and to assess the relationship between pathobiology/pathophysiology and prognosis.

Methods and Results—Patients with suspected HFPEF (n=100) were enrolled in this prospective, observational study. Confirmatory diagnostic tests, cardiac magnetic resonance imaging including T1 mapping, and invasive hemodynamic assessments were performed at baseline. Sixty-one patients with confirmed HFPEF entered a longitudinal outcome-monitoring phase (mean, 22.9±5.0 months), during which 16 had a cardiac event. Cardiac magnetic resonance T1 time (hazard ratio, 0.99; 95% confidence interval, 0.98–0.99; P=0.046), left atrial area (hazard ratio, 1.08; 95% confidence interval, 1.03–1.13; P<0.01), and pulmonary vascular resistance (hazard ratio, 1.01; 95% confidence interval, 1.00–1.01; P=0.03) were significantly associated with cardiac events. Patients with T1 times below the median (<388.3 ms) were at greater risk of cardiac events than the rest of the group (P<0.01). Extracellular matrix of left ventricular biopsies (n=9), quantified by TissueFAXS technology correlated with T1 time (R=0.98; P<0.01). T1 time also correlated with right ventricular–pulmonary arterial coupling (pulmonary vascular resistance: R=−0.36; P<0.01; right ventricular ejection fraction: R=0.28; P=0.01).

Conclusions—In the present preliminary study, cardiac magnetic resonance postcontrast T1 time is associated with prognosis in HFPEF, suggesting postcontrast T1 as possible biomarker for HFPEF. **(*Circ Cardiovasc Imaging*. 2013;6:00-00.)**

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Key Words: hypertension, pulmonary ■ magnetic resonance imaging ■ prognosis

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Almost half of the patients presenting with symptoms of heart failure are found to have a normal or near normal left ventricular ejection fraction (LVEF).[1] This condition has been labeled diastolic heart failure or heart failure with preserved ejection fraction (HFPEF).[2] Patients with HFPEF face adverse outcomes with respect to morbidity and mortality, and their prognosis is similar to that of patients with systolic heart failure.[3]

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Clinical Perspective on p XXX

The pathophysiology underlying HFPEF is still incompletely understood. Factors that seem to be contributory include arterial hypertension, coronary artery disease, and diabetes mellitus.[4] However, a common pathophysiological feature of HFPEF associated with all these underlying causes is the accumulation of extracellular matrix material and fibrosis within myocardial tissue.[5] Excessive extracellular matrix deposition is believed to be a major contributor to the impaired cardiac relaxation and stiffness that are the hallmarks of HFPEF.[6]

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Clinical evaluation of the presence and extent of extracellular matrix in the left ventricle is difficult. The gold standard for such evaluation is myocardial biopsy, which however is an invasive procedure with significant risks.[7] Cardiac magnetic resonance (CMR) T1 mapping has recently been developed as a noninvasive technique to estimate extracellular matrix,

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with validation against myocardial biopsies demonstrating a significant inverse correlation between myocardial postcontrast T1 time and myocardial collagen content.[8,9] In the present study, we used this novel technique and identified CMR markers associated with adverse outcomes in patients with an established diagnosis of HFPEF.

Methods

Study Design

This was a prospective, observational study performed at the Medical University of Vienna, approved by the local ethics committee (EK No. 796/2010). All participants gave written informed consent.

Patients

Consecutive patients with suspected HFPEF were invited to participate. HFPEF was suspected in the presence of the following: (1) symptoms or signs of heart failure; (2) normal or mildly reduced LV systolic function (LVEF >50%); and (3) evidence of abnormal LV relaxation or diastolic stiffness.[10] Reasons for exclusion were pacemaker or other conditions precluding patients from CMR, regional wall motion abnormalities, significant coronary artery disease, significant valvular or congenital heart disease, or glomerular filtration rate <30 mL/min.

Diagnostic Criteria

Patients underwent additional assessments to confirm the diagnosis of HFPEF (described below and summarized in Figure 1). On the basis of these assessments, the study population was divided into 2 groups: patients with a confirmed diagnosis of HFPEF and without a confirmed diagnosis.

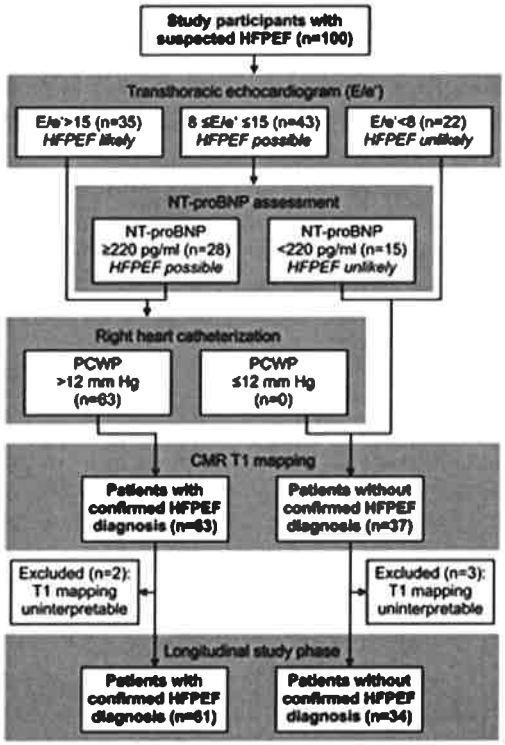

Figure 1. Study flow diagram. In all patients who underwent right heart catheterization (RHC) under the suspicion of heart failure with preserved ejection fraction (HFPEF), the diagnosis was confirmed. CMR indicates cardiac magnetic resonance; NT-proBNP, N-terminal pro–brain natriuretic peptide; and PCWP, pulmonary capillary wedge pressure.

First, LVEF and LV relaxation were assessed using transthoracic echocardiography with tissue Doppler analysis.[11] HFPEF was considered likely if E/e′ was >15. HFPEF was considered unlikely if E/e′ was <8. In intermediate cases with 8≤E/e′≤15, serum N-terminal pro–brain natriuretic peptide levels were determined. HFPEF was considered possible if N-terminal pro–brain natriuretic peptide levels were ≥220 pg/mL. Otherwise, HFPEF was considered unconfirmed.

If HFPEF was considered likely or possible after transthoracic echocardiography and N-terminal pro–brain natriuretic peptide assessment, right heart catheterization was performed. The hemodynamic diagnosis of HFPEF was confirmed if the pulmonary capillary wedge pressure exceeded 12 mm Hg.[10] Patients in whom HFPEF was not confirmed based on the noninvasive workup did not undergo further invasive assessment and were assigned to the group without confirmed HFPEF.

Outcome Measures

All patients underwent CMR imaging at baseline, including postcontrast T1 mapping. Amyloidosis and sarcoidosis were excluded in all study participants by late gadolinium enhancement imaging. Patients were then prospectively followed by ambulatory visits and telephone calls at 6-month intervals. The main outcome measure was a combined end point consisting of hospitalization for heart failure or death from cardiovascular causes. End points were ascertained by follow-up visits and phone calls and adjudicated by our internal adjudication committee consisting of D.B. and C.T., who were blinded to results of T1 mapping as well as hemodynamics and other patient characteristics.

Assessment Techniques

Transthoracic Echocardiography With Tissue Doppler Analysis

All transthoracic echocardiography studies were performed by board certified physicians using high-end scanners, such as GE Vivid 5 and Vivid 7 (GE Healthcare, Wauwatosa, WI). LVEF, mitral venous flow Doppler measures, and global longitudinal strain were assessed according to standard techniques.[12,13]

Right and Left Heart Catheterization

Pulmonary capillary wedge pressure, pulmonary arterial pressure, and cardiac output were determined. Cardiac output was measured by both the thermodilution method and Fick methods. Simultaneously, all patients underwent direct assessment of LV filling pressures, followed by coronary angiography. Derived hemodynamic parameters were calculated according to standard formulae.[14]

Histochemistry

Left heart biopsy was part of the protocol and was obtained from consecutive patients with confirmed HFPEF and 1 patient without confirmed HFPEF using Biopal 7 disposable biopsy forceps (Cordis Corporation, Bridgewater, NJ). Specimens were fixed in 7.5% PBS-buffered formalin. Modified Trichrome and Congo-red stains were performed.[15,16] Specimens from patients with confirmed diagnosis of cardiac amyloidosis were used as positive controls.

TissueFAXS and Collagen Quantification

Stainings were analyzed using a TissueFAXS microscopic system (version 3.5.5, TissueGnostics, Vienna, Austria). Each tissue section was scanned and automatically analyzed using HistoQuest software (TissueGnostics). Results were given as percentage connective tissue per millimeter squared of total specimen area.

Collagen quantification was performed as described.[17] Collagen content was expressed as a percentage of total protein.

Cardiac MRI

All patients underwent a CMR study on a 1.5-T scanner (Avanto, Siemens Medical Solutions, Erlangen, Germany). Studies consisted of functional and late gadolinium enhancement imaging, according to standard protocols.[18] Postcontrast T1 mapping was performed 15 minutes after intravenous injection of the contrast bolus (0.1 mmol/kg gadolinium-DTPA [Gadovist 1.0 macrocyclic;

Bayer Vital GmbH, Leverkusen, Germany]). A multiple breath-hold ECG-triggered segmented inversion recovery spoiled gradient echo sequence (fast low-angle shot [FLASH]; flip angle, 20°; voxel size, 2.2×1.6×8 mm³; parallel acquisition factor, 2) was used to acquire a stack of 8 images in the middle short-axis slice over a range of increasing inversion times from 115 to 900 ms.[8,19] For T1 time analysis, images were transferred to an external computer for off-line analysis (cmr42; Circle Cardiovascular Imaging, Calgary, Canada). The average T1 time of the myocardium was determined by fitting signal intensities at varying inversion times to the exponential curve.[8] Areas of focal fibrosis identified by late gadolinium enhancement were excluded. CMR studies were read by 2 independent observers blinded to clinical data.

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Statistical Analysis

Baseline characteristics were compared using the Fisher exact test for categorical variables and the Wilcoxon 2-sample test for continuous variables. Kaplan–Meier estimates were used to calculate cardiac event rates. Differences between Kaplan–Meier curves were analyzed using the log-rank test.

To identify variables associated with cardiac events, a univariate Cox regression model was performed for each influence factor (listed in Table 1), followed by a multiple Cox regression model with stepwise selection. In the stepwise selection, the threshold *P* value for inclusion of variables was set to 0.05. The multivariable Cox regression model accounted for all variables that were significant in the univariate analyses. Potential associations between parameters (listed

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Table 1. Baseline Characteristics of Study Participants

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Variable	Patients With Confirmed HFPEF (n=61)	Patients Without Confirmed HFPEF (n=34)	*P* Value
Age, y	70.5±7.6	69.1±8.1	0.39
	70.0 (67.0–76.0)	69.0 (67.0–74.0)	
AQ11 Sex, female/male	39/22	18/16	0.38*
Body mass index, kg/m²	30.4±5.3	28.4±4.5	0.06
	30.3 (25.8–33.9)	27.6 (25.5–30.8)	
Creatinine, mg/dL	1.15±0.31	1.01±0.20	**0.04** AQ12
	1.1 (0.9–1.3)	1.0 (0.9–1.1)	
GFR, mL/min	59.4±16.5	68.5±11.5	**0.01**
	59.3 (47.9–70.6)	67.8 (61.8–76.7)	
Hematocrit, g/dL	38.2±4.6	42.9±5.9	**0.02**
	38.0 (35.7–40.4)	40.9 (39.5–44.8)	
Heart rate, beats/min	67.2±12.4	66.0±12.2	0.71
	65.5 (61.0–72.0)	67.0 (56.0–73.0)	
NT-proBNP, pg/mL	1343±1178	198±105	**<0.01**
	1033.0 (557.0–1708.0)	174.6 (134.3–211.0)	
CMR data			
T1 time myocardium, ms	380.6±50.6	420.1±41.9	**<0.01**
	388.3 (349.1–422.3)	413.1 (401.1–447.4)	
T1 time blood pool, ms	261.7±36.5	269.2±40.1	0.56
	262.1 (235.5–287.7)	262.3 (238.5–297.6)	
LV ejection fraction, %	63.5±11.0	67.8±6.0	**0.04**
	65.0 (55.0–71.0)	69.0 (64.0–72.0)	
LV cardiac output, L/min	5.3±1.4	5.5±1.3	0.46
	5.2 (4.3–6.1)	5.6 (4.5–6.1)	
LV cardiac index, L·min⁻¹·m⁻²	2.7±0.8	2.8±0.5	0.31
	2.5 (2.2–3.2)	2.7 (2.5–3.1)	
LV end-diastolic diameter, mm	47.3±5.1	47.8±6.8	0.69
	48.0 (45.0–50.0)	46.5 (44.0–50.0)	
LV end-diastolic volume, mL	129.9±31.7	125.5±24.5	0.39
	125.0 (114.0–142.0)	117.5 (109.0–141.0)	
LV end-systolic volume, mL	79.3±21.3	84.9±17.4	0.33
	80.0 (66.0–94.0)	81.5 (73.0–92.0)	
RV ejection fraction, %	52.2±9.0	57.0±7.4	**0.01**
	54.0 (45.0–59.0)	57.0 (53.0–62.0)	
RV cardiac output, L/min	5.1±1.7	4.8±1.2	0.36
	4.9 (4.2–6.3)	4.7 (3.8–5.5)	

(*Continued*)

Table 1. Continued

Variable	Patients With Confirmed HFPEF (n=61)	Patients Without Confirmed HFPEF (n=34)	*P* Value
RV cardiac index, L·min^{-1}·m^{-2}	2.6±0.8	2.4±0.6	0.31
	2.4 (2.1–3.3)	2.4 (2.0–2.6)	
RV end-diastolic diameter, mm	39.1±6.0	0 37.2±3.7	0.14
	38.0 (36.0–42.0)	37.0 (35.0–40.0)	
RV end-systolic volume, mL	77.0±25.4	74.3±13.8	0.59
	75.0 (63.0–87.0)	76.0 (64.0–83.0)	
RV end-diastolic volume, mL	149.9±49.3	131.2±22.9	0.08
	140.0 (116.0–172.0)	131.0 (118.0–143.0)	
LA diameter, mm	63.9±9.8	55.9±6.4	**<0.01**
	65.0 (57.0–70.0)	55.0 (53.0–59.0)	
RA diameter, mm	63.7±9.3	55.7±6.6	**<0.01**
	63.0 (59.0–69.0)	55.0 (50.0–62.0)	
LA area, mm^2	30.5±8.3	24.6±5.1	**<0.01**
	30.0 (25.0–34.0)	24.0 (21.0–27.0)	
RA area, mm^2	27.6±8.6	22.6±3.8	**<0.01**
	25.0 (22.0–30.0)	22.0 (20.0–25.0)	
Septum thickness, mm	11.0±2.0	11.3±1.5	0.18
	11.0 (10.0–12.0)	11.0 (10.0–12.0)	
LV mass, g	117.1±36.0	116.0±31.2	0.86
	115.0 (92.0–134.0)	116.5 (92.0–140.0)	
LV mass index, g/m^2	59.5±17.7	58.1±12.3	0.81
	59.5 (50.0–70.7)	56.9 (47.3–69.1)	
RHC data			
PCWP, mm Hg	20.7±4.6	n.a.	...
	18.0 (16.0–23.0)		
PVR, dyn·s·cm^{-5}	200.2±118.5	n.a.	...
	189.5 (119.4–251.9)		
Mean PAP, mm Hg	31.3±11.1	n.a.	...
	30.0 (25.0–38.0)		
Cardiac output, L/min	5.1±1.2	n.a.	...
	5.1 (4.3–5.8)		
Cardiac index, L·min^{-1}·m^{-2}	2.6±0.6	n.a.	...
	2.6 (2.2–2.9)		

Values are given as mean±SD and medians (interquartile range). CMR indicates cardiac magnetic resonance; GFR, glomerular filtration rate; HFPEF, heart failure with preserved ejection fraction; LA, left atrial; LV, left ventricular; n.a., not applicable; NT-proBNP, N-terminal pro–brain natriuretic peptide; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RA, right atrial; RHC, right heart catheterization; and RV, right ventricular.

*P values were derived from Wilcoxon 2-sample test or Fisher exact test.

in Table I in the online-only Data Supplement) and T1 time were investigated using linear univariate regression models followed by a multivariable regression analysis accounting for the univariate significant parameters.

Interobserver variability was described as the mean of the within-patient SD over the 2 measurements (measured by 2 observers) as well as the corresponding proportion of the interobserver variability of the total variance.

Statistical analyses were performed with SAS version 9.1 (SAS Institute Inc., Cary, NC) and R 2.12.2 (The R Foundation for Statistical Computing, Vienna, Austria). A P value of <0.05 was considered to indicate statistical significance.

Results

Baseline Characteristics of Study Participants

The active enrollment was between September 2010 and August 2012. In total, 100 patients with suspected HFPEF were enrolled. The diagnosis of HFPEF was confirmed in 63 patients. Five patients (2 with and 3 without a confirmed diagnosis of HFPEF) had to be excluded because T1 mapping sequences were not interpretable because of artifacts. Thus, 95 patients entered the longitudinal study phase (Figure 1).

Baseline characteristics are shown in Table 1 (see also Table II in the online-only Data Supplement for echocardiographic data). Significant differences between the groups with confirmed and unconfirmed HFPEF were found with respect to T1 time ($P<0.01$), LVEF and right ventricular (RV) EF ($P=0.04$ and $P=0.01$, respectively), and atrial size (all $P<0.01$). Pulmonary hypertension (PH), defined as mean pulmonary arterial pressure ≥25 mm Hg, was present in 49 patients with HFPEF (80.3%). Twenty-eight patients (45.9%) presented with out-of-proportion PH (transpulmonary gradient >12 mm Hg).

Cardiac Outcomes

After baseline evaluation, patients were followed for a mean of 17.4±12.7 (range, 0.5–29.4) months. Among patients with HFPEF, 16 cardiac events occurred during a mean follow-up period of 22.9±5.0 (range, 0.5–28.4) months: 2 patients died from heart failure, 1 patient initially survived cardiac arrest but died shortly thereafter, and 13 patients were hospitalized for heart failure. One patient with HFPEF died from pancreatic cancer. No cardiac events were recorded among those without confirmed HFPEF. AQ14

Parameters Associated With Outcome in Patients With Confirmed HFPEF

In the cohort with confirmed HFPEF, baseline characteristics in patients with and without cardiac events were compared (Table 2). By multivariable analysis, however, only postcontrast T1 time (hazard ratio, 0.99; 95% confidence interval, 0.98–0.99; $P=0.046$), left atrial area (hazard ratio, 1.08; 95% confidence interval, 1.03–1.13; $P<0.01$), and pulmonary vascular T2

Table 2. Univariate Cox Regression Analyses in Patients With a Confirmed Diagnosis of Heart Failure With Preserved Ejection Fraction

Variable	Patients With Cardiac Event (n=16)	Patients Without Cardiac Event (n=45)	Hazard Ratio	95% Confidence Limit	*P* Value*
Age, y	70.6±10.3	70.5±6.5	1.00	0.93–1.07	0.99
	70.0 (65.0–79.5)	70.0 (67.0–76.0)			
Sex, female/male	10/6	29/16	0.90	0.33–2.49	0.84
Body mass index, kg/m²	30.8±5.3	30.3±5.4	1.03	0.94–1.13	0.53
	30.0 (27.7–35.9)	30.4 (25.6–33.8)			
Creatinine, mg/dL	1.3±0.3	1.1±0.3	2.61	0.68–10.05	0.16
	1.2 (1.1–1.4)	1.0 (0.9–1.2)			
GFR, mL/min	53.4±15.1	61.5±16.5	0.98	0.95–1.01	0.14
	55.7 (42.1–63.2)	63.4 (48.2–70.9)			
Hematocrit, g/dL	37.0±5.1	39.4±4.8	0.93	0.83;1.04	0.20
	37.2 (33.6–39.5)	38.9 (37.3–41.6)			
Heart rate, beats/min	67.8±11.3	67.0±12.7	1.00	0.96–1.05	0.87
	66.0 (62.0–74.0)	65.5 (60.0–72.0)			
NT-proBNP, pg/mL	2174.0±1752.5	1047.9±709.5	0.26	0.09–0.82	**0.02**
	1417.5 (1021.1–3318.5)	878.3 (447.2–1483.0)			
CMR data					
T1 time myocardium, ms	351.3±51.2	391.0±46.5	0.99	0.98–0.99	**0.01**
	352.2 (329.5–377.2)	396.4 (353.6–426.4)			
T1 time blood pool, ms	279.0±53.8	264.0±35.0	1.01	1.00–1.02	0.20
	270.8 (236.1–329.6)	261.1 (238.2–288.4)			
LV ejection fraction, %	63.1±14.5	63.7±9.7	0.99	0.94–1.04	0.59
	64.0 (54.5–75.0)	65.0 (56.0–71.0)			
LV cardiac output, L/min	5.4±1.4	5.3±1.5	0.99	0.70–1.41	0.96
	5.4 (4.9–6.3)	5.1 (4.3–6.0)			
LV cardiac index, L·min⁻¹·m⁻²	2.7±0.7	2.7±0.8	0.97	0.50–1.87	0.93
	2.6 (2.3–3.4)	2.5 (2.1–2.9)			
LV end-diastolic diameter, mm	47.6±4.2	47.2±5.5	1.02	0.92–1.12	0.77
	48.0 (45.5–48.5)	48.0 (43.0–50.0)			
LV end-diastolic volume, mL	130.8±37.4	129.6±29.9	1.00	0.99–1.02	0.89
	124.0 (97.0–161.5)	126.0 (115.0–140.0)			
LV end-systolic volume, mL)	77.6±24.6	79.8±20.3	0.99	0.97–1.02	0.58
	80.0 (60.5–95.5)	80.0 (66.0–91.0)			
RV ejection fraction, %	49.1±11.3	53.4±7.9	0.94	0.89–0.99	0.05
	44.5 (41.5–59.0)	54.0 (48.0–59.0)			

(Continued)

Table 2. Continued

Variable	Patients With Cardiac Event (n=16)	Patients Without Cardiac Event (n=45)	Hazard Ratio	95% Confidence Limit	*P* Value*
RV cardiac output, L/min	5.5±1.8	5.0±1.6	1.18	0.86–1.60	0.30
	5.6 (4.5–6.6)	4.5 (4.1–6.1)			
RV cardiac index, L·min^{-1}·m^{-2}	2.8±0.9	2.5±0.8	1.40	0.73–2.66	0.31
	2.8 (2.2–3.4)	2.4 (2.1–3.3)			
RV end-diastolic diameter, mm	40.6±7.2	38.6±5.5	1.06	0.97–1.14	0.20
	40.0 (36.0–44.5)	37.0 (36.0–41.0)			
RV end-systolic volume, mL	79.4±30.8	76.2±23.5	1.01	0.98–1.03	0.59
	74.0 (63.5–91.0)	76.0 (62.0–86.0)			
RV end-diastolic volume, mL	163.4±62.0	145.0±43.7	1.01	0.99–1.02	0.13
	153.5 (122.5–184.5)	136.0 (112.0–169.0)			
LA diameter, mm	67.3±10.4	62.7±9.4	1.04	0.99–1.10	0.10
	65.5 (60.0–71.5)	65.0 (56.0–70.0)			
RA diameter, mm	65.8±11.7	62.9±8.3	1.03	0.98–1.09	0.22
	62.5 (57.5–70.0)	63.0 (59.0–69.0)			
LA area, mm^2	35.8±11.0	28.6±6.3	1.08	1.03–1.13	**<0.01**
	34.0 (29.5–35.5)	28.0 (24.0–33.0)			
RA area, mm^2	28.5±9.6	27.3±8.3	1.02	0.96–1.07	0.56
	25.5 (22.0–29.5)	25.0 (22.0–30.0)			
Septum thickness, mm	11.3±1.8	10.9±2.1	1.06	0.85–1.32	0.59
	11.0 (10.0–12.5)	10.5 (10.0–11.5)			
LV mass, g	126.3±39.1	113.7±34.6	1.01	0.99–1.02	0.19
	130.0 (112.5–144.5)	110.0 (91.0–131.0)			
LV mass index, g/m^2	64.9±20.8	57.5±16.2	1.02	0.99–1.05	0.13
	61.5 (52.3–78.4)	57.6 (49.5–62.3)			
RHC data					
PCWP, mm Hg	23.8±5.2	17.9±6.8	1.06	1.01–1.12	**0.01**
	22.0 (19.0–27.5)	17.0 (13.0–20.0)			
PVR, dyn·s·cm^{-5}	270.6±129.9	175.2±104.7	1.01	1.00–1.01	**<0.01**
	281.6 (177.3–341.9)	185.7 (115.9–235.8)			
Mean PAP, mm Hg	38.4±9.8	28.8±10.5	1.06	1.02–1.09	**<0.01**
	38.0 (34.0–42.0)	27.0 (25.0–33.0)			
Cardiac output, L/min	4.9±1.0	5.2±1.2	0.77	0.48–1.23	0.27
	4.8 (4.1–5.6)	5.2 (4.4–5.9)			
Cardiac index, L·min^{-1}·m^{-2}	2.4±0.6	2.7±0.7	0.57	0.25–1.34	0.20
	2.5 (2.0–2.8)	2.6 (2.2–2.9)			

Values are given as mean±SD and medians (interquartile range). CMR indicates cardiac magnetic resonance; GFR, glomerular filtration rate; LA, left atrial; LV, left ventricular; NT-proBNP, N-terminal pro–brain natriuretic peptide; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RA, right atrial; RHC, right heart catheterization; and RV, right ventricular.

*P values were derived from univariate Cox regression models.

resistance (PVR; hazard ratio, 1.00; 95% confidence interval, 1.00–1.01; P=0.03) remained associated with outcome.

F2 Figure 2 shows Kaplan–Meier curves of patients with HFPEF stratified by median postcontrast T1 time (388.3 ms; P<0.01; Figure 2A), median left atrial area (30 mm^2; P<0.01; Figure 2B), and median PVR (189.5 dyn·s·cm^{-5}; P=0.19; Figure 2C).

Correlation of T1 Time With Variables Related to PH

Based on the hypothesis that LV stiffness triggers pulmonary vascular remodeling, we assessed the correlation between postcontrast T1 time and variables related to pulmonary hemodynamics in patients with confirmed HFPEF. Postcontrast T1 time was significantly correlated with E/e′ (P<0.01; R=−0.33; Figure 3A). Furthermore, T1 time showed a correlation with PVR (P<0.01; R=−0.36; Figure 3B) and with RVEF (P<0.05; R=0.28; Figure 3C). Patients with T1 times below the median (388.3 ms) had higher transpulmonary gradients (14.4±6.2 mm Hg) than those with T1 times equal to or greater than the median (10.4±5.1 mm Hg; P<0.05). F3

CMR T1 time interobserver SD on average was 11.37 ms over all patients and 10.74 ms within patients with confirmed HFPEF only, that is, a proportion of 4.6% (all patients) and 4.4% (patients with confirmed HFPEF only) of the total variance.

Mary	10/27/13	4 Color Fig: F4	23:34	Art:HCI000633

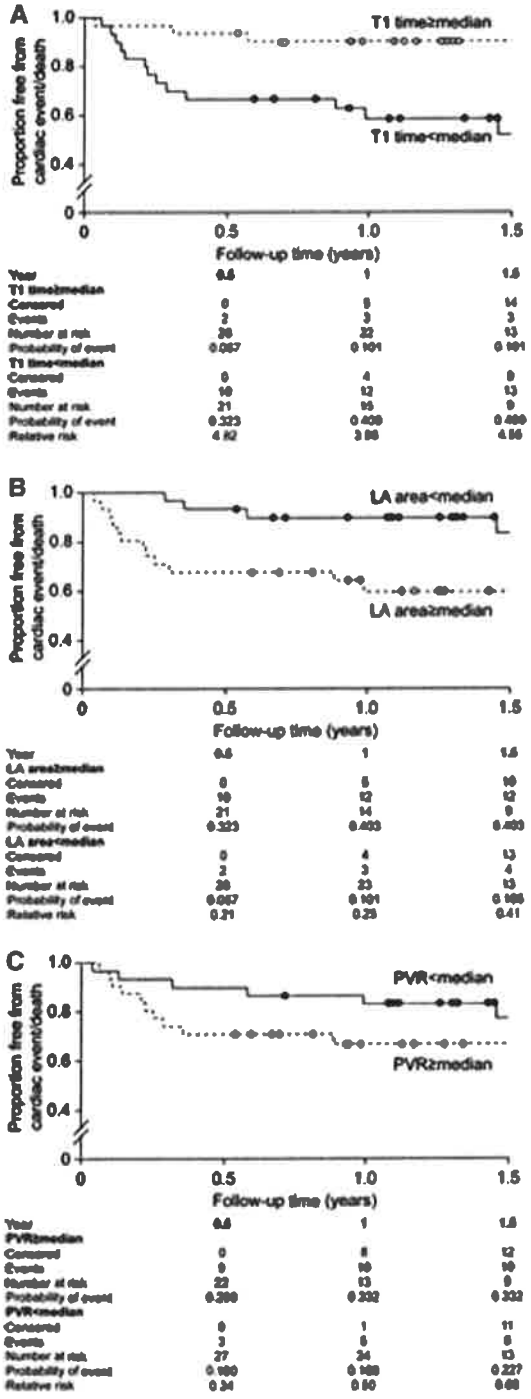

Figure 2. Kaplan–Meier curves showing cardiac outcomes in patients with heart failure with preserved ejection fraction. Patients were stratified by (**A**) median postcontrast T1 time (388.3 ms; log-rank $P<0.01$), (**B**) median left atrial (LA) area (30 mm^2; log-rank $P<0.01$), and (**C**) median pulmonary vascular resistance (PVR; 189.5 dyn·s·cm^{-5}; log-rank $P=0.19$). Event probabilities and relative risks are shown.

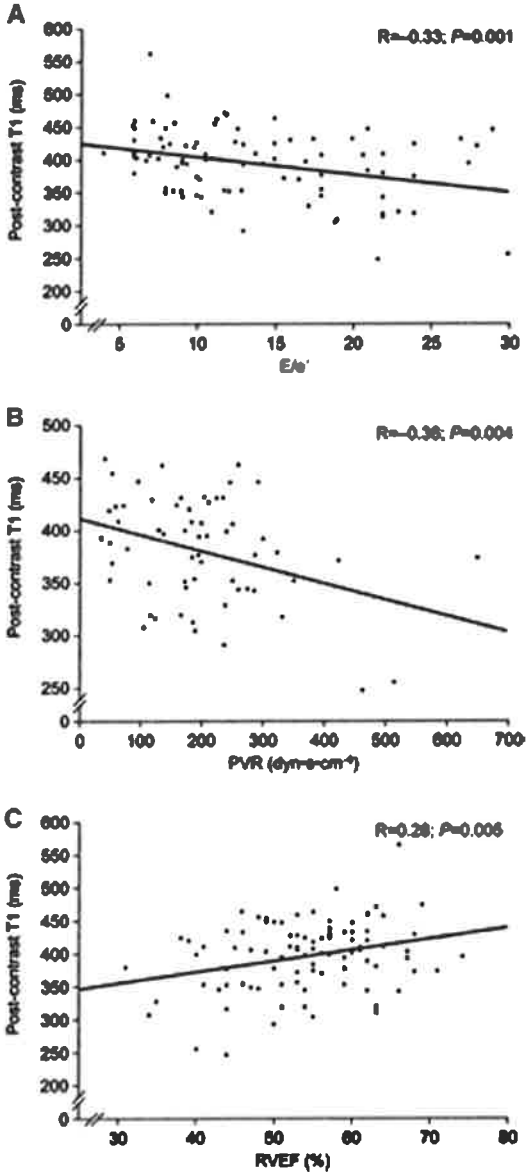

Figure 3. Correlation of postcontrast T1 time with (**A**) E/e′ ratio, (**B**) pulmonary vascular resistance (PVR), and (**C**) right ventricular ejection fraction (RVEF).

Histopathologic Analysis

Histological samples were obtained from 9 patients with confirmed HFPEF. Representative specimens are depicted in Figure 4. F4 In contrast to specimens from patients with cardiac amyloidosis, the extracellular substance did not stain for Congo-red. There was a correlation between the relative amount of extracellular matrix and postcontrast T1 time ($R=0.98$; $P<0.01$; Figure 5A). However, F5 there was no difference in collagen content between patients (10.2±7.2%) and controls (10.9±7.7%; $P=0.85$; Figure 5B).

Discussion

Our study elucidated pathobiology, pathophysiology, and their relations with outcome in a prospective cohort of patients with HFPEF. Postcontrast T1 time by CMR was identified as a potential disease biomarker. T1 time was significantly correlated with extracellular matrix area in LV biopsy samples as well as variables linked to RV coupling and was significantly associated with outcome.

HFPEF is a heterogeneous disease, with risk factors including old age, hypertension, diabetes mellitus, and obesity.[20] The

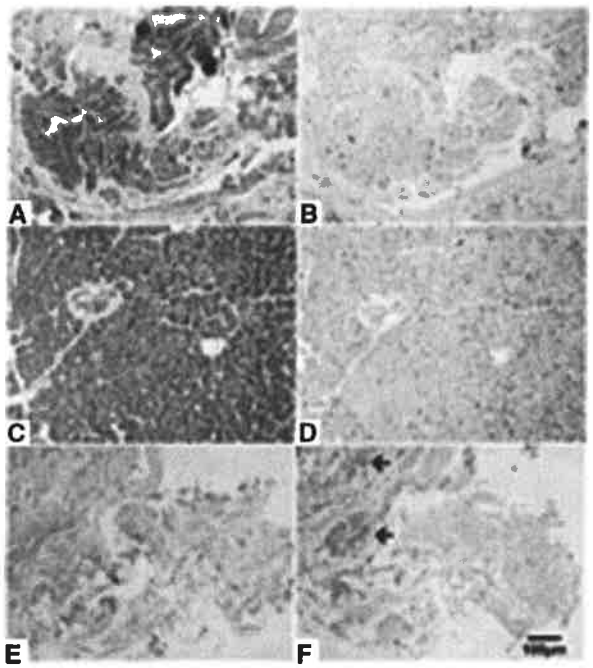

Figure 4. Parallel sections from representative myocardial biopsies of a patient with confirmed heart failure with preserved ejection fraction (HFPEF; **A** and **B**), a patient without HFPEF (**C** and **D**), and a patient with cardiac amyloidosis (**E** and **F**). **A**, **C**, and **E** have been subjected to modified Trichrome staining; **B**, **D**, and **F** were stained with Congo-red. In contrast to hearts of patients with amyloidosis (amyloid accumulation is indicated by black arrows; **F**), hearts of patients with HFPEF did not stain with Congo-red (**B**).

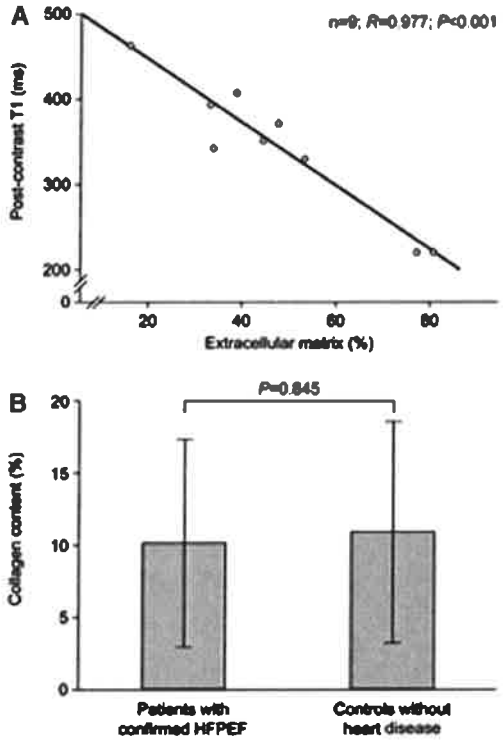

Figure 5. Extracellular matrix and collagen content in left ventricular biopsies. **A**, Correlation of postcontrast T1 time with myocardial extracellular matrix in patients with heart failure with preserved ejection fraction (HFPEF). **B**, Myocardial collagen content (mean±SD) in biopsies from patients with confirmed HFPEF (n=9) and controls (n=5).

underlying mechanisms that cause HFPEF are not yet fully understood. LV diastolic dysfunction is generally regarded as the main pathophysiological abnormality.[2,21,22] The heterogeneous nature of HFPEF poses a challenge for the development of treatments, and no specific therapy has yet demonstrated a convincing reduction in morbidity or mortality in affected individuals.[2]

Disease severity in HFPEF is difficult to assess. Several prognostic markers have been described that are primarily related to pulmonary hemodynamics and comorbidities.[23,24] However, all of them are either causes or consequences of the actual myocardial disease. Only recently have technical innovations enabled us to characterize the myocardial tissue composition by CMR T1 mapping.

Several T1 mapping methods have been used in the literature, including postcontrast T1 mapping,[8,19,25,26] calculation of extracellular volume fraction using MOLLI sequences,[27–29] and equilibrium contrast CMR.[9,30] Of these, only postcontrast T1 mapping and equilibrium contrast CMR have been validated with myocardial biopsies. Currently, no consensus exists on which is the most accurate mapping method. The method we chose has the advantage that it does not require an imaging sequence that is commercially unavailable at present, and it is relatively fast.[8,19,31]

As part of our protocol, we obtained LV biopsies in consecutive patients. We quantified extracellular matrix extent using TissueFAXS technology. These data were used for validation of the CMR T1 mapping technique but also provided new insights into the pathobiology of HFPEF. The amount of extracellular matrix in the biopsies was correlated with postcontrast T1 time, which in turn was related with outcome. However, T1 time was not related with measurements of collagen (Figure 5), confirming the notion that T1 time reflects extracellular substance rather than fibrosis in these patients.[32] Because of the limited number of biopsies obtained, we could not clarify whether the molecular composition of extracellular matrix varies depending on the cause of HFPEF. However, our results suggest that extracellular matrix accumulation could be a common denominator that drives prognosis in HFPEF of various causes.

In addition, our data show that T1 time correlates with pulmonary hemodynamics. A recent retrospective study demonstrated that elevated LV end-diastolic pressure was associated with PH in patients with HFPEF,[33] and a community-based study described a close connection between diastolic dysfunction and elevated systolic pulmonary arterial pressure in HFPEF.[24] That study found that the severity of PH could not be fully accounted for by postcapillary PH, suggesting the presence of a pulmonary arterial component (known as out-of-proportion or reactive PH). We found that postcontrast T1 time is associated with increased PVR and transpulmonary gradients as well as with impaired RVEF. Therefore, LV extracellular matrix deposition seems to be related to the development of out-of-proportion PH in HFPEF.

Limitations

Several factors have been identified as potential confounders of postcontrast T1 times, including renal function, heart rate, and

time of acquisition. In our study, postcontrast T1 images were consistently acquired 15 minutes postbolus, and no significant differences with respect to glomerular filtration rate, heart rate, and body mass index were encountered between outcome groups with confirmed HFPEF (Table 2). However, we did observe a significant association between creatinine levels and T1 time ($P<0.01$; Table I in the online-only Data Supplement). Kidney function has been shown to depend on RV performance.[34] Although highly speculative, the association between creatinine levels and T1 time could be explained by stiffening of the LV because of increased extracellular matrix, causing elevated LV filling pressures and eventually increasing PVR. This cascade could finally lead to RV uncoupling with renal damage attributable to venous congestion. However, we cannot entirely exclude that differences in renal excretion of gadolinium accounted for the differences in postcontrast T1 time.

Although our study demonstrated significant differences in T1 time between patients with and without confirmed HFPEF, and between patients with confirmed HFPEF with and without cardiac events, some overlap was observed. Therefore, the value of T1 time as a prognostic parameter in the individual patient remains to be established. However, for the time being, T1 time appears helpful in elucidating the pathophysiology of HFPEF in general.

Conclusions

In summary, we demonstrated a significant association between noninvasive CMR T1 time, validated against LV biopsies, and cardiac outcomes in patients with HFPEF. We furthermore found a correlation between postcontrast T1 time and variables related with LV filling pressures and out-of-proportion PH. Lack of precontrast T1 maps and incorporation of hematocrit that are needed for precise myocardial extracellular volume calculation is a significant limitation of this work. Future studies using this approach to characterize myocardium in HFPEF are warranted.

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Disclosures

None.

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CLINICAL PERSPECTIVE

This is the first study relating cardiac magnetic resonance T1 mapping to clinical characteristics and long-term outcomes in patients with heart failure and preserved ejection fraction. Postcontrast T1 time correlated with extracellular matrix content in left ventricular biopsies and event-free survival in a prospective cohort of patients with heart failure and preserved ejection fraction. Further research is warranted to determine the mechanistic link between extracellular matrix expansion and heart failure and preserved ejection fraction. If a direct link can be demonstrated, tissue characterization by T1 mapping may offer a powerful imaging tool to phenotype risk and potentially guide therapy.