Title Page

Full Title

Diffuse myocardial fibrosis evaluated by post-contrast T_1 mapping correlates with left ventricular stiffness

Brief Title

T_1 mapping and left ventricular stiffness

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Conflicts of Interest

The authors have no conflicts of interest nor relationships with industry.

Structured Abstract

Objectives

The purpose of this study was to utilize cardiac magnetic resonance (CMR) imaging and invasive left ventricular (LV) pressure-volume (PV) measurements to explore the relationship between diffuse myocardial fibrosis and indices of diastolic performance in a cohort of cardiac transplant recipients.

Background

The precise mechanism of LV diastolic dysfunction in the presence of myocardial fibrosis has not previously been established.

Methods

We performed CMR with T_1 mapping and obtained invasive LV PV measurements via a conductance catheter in twenty cardiac transplant recipients at the time of clinically-indicated coronary angiography.

Results

Both post-contrast myocardial T_1 time and extracellular volume fraction correlated with β, the load-independent passive LV stiffness constant ($r = -0.71$, $p = 0.001$ and $r = 0.58$, $p = 0.04$, respectively). Following multivariate analysis, post-contrast myocardial T_1 time remained the only independent predictor of β. No significant associations were observed between myocardial T_1 time and τ, the active LV relaxation constant, or other load-dependent parameters of diastolic function.

Conclusions

Diffuse myocardial fibrosis, assessed by post-contrast myocardial T_1 time, correlates with invasively-determined LV stiffness in cardiac transplant recipients. In patients with increased diffuse myocardial fibrosis, abnormal passive ventricular stiffness is therefore likely to be a major contributor to diastolic dysfunction.

Key Words

T_1 mapping; magnetic resonance imaging; myocardial fibrosis; diastolic dysfunction

Abbreviations List

CMR = cardiac magnetic resonance

LV = left ventricular

PV = pressure-volume

HFNEF = heart failure with a normal ejection fraction

ECV = extracellular volume

PCWP = pulmonary capillary wedge pressure

CC = conductance catheter

LVEDP = left ventricular end-diastolic pressure

LGE = late gadolinium enhancement

Introduction

Myocardial fibrosis is a fundamental event in the development of cardiac failure(1), regardless of its etiology(2,3). In animal models, myocardial fibrosis is associated with worsening ventricular systolic function, abnormal cardiac remodelling and increased ventricular stiffness(4). Myocardial fibrosis may be regional, as found in myocardial infarction due to coronary atherosclerosis, or diffuse, as observed in all forms of advanced cardiomyopathy. Diffuse myocardial fibrosis may be relevant in the pathogenesis of heart failure with a normal left ventricular (LV) ejection fraction (HFNEF), which accounts for up to 50% of all cases of heart failure and carries a comparable morbidity/mortality profile(5) to systolic heart failure. Whilst the detrimental effects of increasing myocardial fibrosis in heart failure still require further elucidation, a likely mechanism is diastolic dysfunction due to increased ventricular stiffness, which carries a poor prognosis in patients with cardiomyopathy who develop restrictive physiology(6).

Critical to our understanding of diffuse myocardial fibrosis and ventricular stiffness is the demonstration of a mechanistic link between these two observed phenomena. Using a histologically-validated cardiac magnetic resonance imaging (CMR) post-contrast T_1 mapping technique(7,8), we have previously observed in patients with advanced heart failure that increasing amounts of diffuse myocardial fibrosis, suggested by shortened post-contrast myocardial T_1 time, are accompanied by worsening diastolic function. Subsequent studies using a similar T_1 mapping technique have observed correlations between post-contrast myocardial T_1 time and non-invasive estimates of LV diastolic function in other disease states, including diabetes mellitus(9,10) and hypertrophic cardiomyopathy(11). Alternative T_1 mapping approaches, including non-contrast (native) and extracellular volume (ECV)

fraction techniques, have also been utilized to characterize myocardial tissue in other conditions such as cardiac amyloidosis(12), aortic stenosis(13) and systemic lupus erythematosus(14).

Whilst echocardiographic indices of diastolic function have been validated against invasive LV pressure measurement(15,16), these methods are sensitive to the effects of loading conditions. Furthermore it is virtually impossible to non-invasively ascertain the relative contributions of active ventricular relaxation, passive ventricular stiffness, volume loading and other extrinsic factors to diastolic dysfunction. However, with the aid of accurate invasive pressure-volume (PV) measurement, LV diastole can be broken up into two basic components; a decaying curve relating to active ventricular relaxation, and a passive filling pressure curve that increases monotonically with pressure. Tau (τ), the time constant of active LV relaxation, is prolonged in diastolic dysfunction, particularly in the presence of co-existent systolic dysfunction(17). Higher values of the passive LV stiffness constant (β), have been demonstrated in the presence of reduced ventricular compliance, consistent with intrinsic stiffening of the myocardium(18). In human subjects with diastolic dysfunction, derangements of both active relaxation and intrinsic stiffening have been implicated(19).

An investigation of the relationship between diffuse myocardial fibrosis and ventricular stiffness as a putative mechanism of diastolic dysfunction has not previously been described. We performed CMR with post-contrast T_1 mapping and obtained invasive LV PV measurements in a cohort of cardiac transplant recipients at the time of clinically-indicated coronary angiography, in order to relate change in myocardial tissue composition to intrinsic mechanical properties of the myocardium during diastole.

Methods

Patient selection

All research was performed at the Alfred Hospital, Melbourne, Australia. Twenty-seven consecutive cardiac transplant recipients referred for surveillance invasive coronary angiography were invited to participate. Exclusion criteria included chronic atrial fibrillation; histological evidence of allograft rejection; contraindications to CMR, including pacemaker and defibrillator implantation; and significant renal dysfunction (estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2). Informed consent was obtained from all participants and the study was conducted in accordance with the Alfred Hospital Ethics Committee's guidelines.

Cardiac catheterization protocol

For the measurement of right atrial pressure, right ventricular pressure, pulmonary artery pressure, and pulmonary capillary wedge pressure (PCWP), an introducer sheath was placed in the right femoral vein under local anesthesia and, under fluoroscopy, a balloon-tipped thermodilution catheter (7 F Arrow, Edwards Inc.) was introduced. The wedge position was confirmed fluoroscopically and by the profile of the accompanying pressure waveform and the mean PCWP was recorded at end-expiration. Cardiac output was measured using the thermodilution technique. Standard invasive coronary angiography was then performed via right femoral artery access.

A conductance catheter (CC) was utilized to record simultaneous LV PV measurements(20,21). A 7 F CC (CD Leycom, Zoetermeer, the Netherlands) was advanced via right femoral artery access into the LV under fluoroscopic guidance immediately following coronary angiography and connected to a PV signal processor (Inca, CD Leycom).

Real-time continuous LV pressure and volume signals were recorded for at least 30 seconds in the supine position. Volume calibration was performed using LV volumetric data obtained from the same-day CMR and CC data analysis was performed with dedicated software (Conduct NT, CD Leycom). Load-dependent LV diastolic function was assessed by LV end-diastolic pressure (LVEDP) and τ was calculated using a formula previously described by Weiss et al(17). Load-independent LV diastolic function was evaluated by β, using an equation representing the relationship of ventricular volume to pressure during passive filling(22);

$$P = P_B + Ae^{\beta V}$$

where P is LV diastolic pressure, P_B is the pressure asymptote, A and β are fitting constants, and V is LV diastolic volume. Curve-fitting to derive P_B, A and β was performed using a graphical software package (Origin 8.5, OriginLab, Massachusetts, USA).

CMR protocol

We performed CMR on all patients using a clinical 1.5-T scanner (Signa HD 1.5-T, GE Healthcare, Waukesha, Wisconsin, USA) on the same day as cardiac catheterization. All sequences were acquired during breath holds of 10–15 s. Initially, a contiguous short-axis steady-state free precession cine stack (repetition time [TR] = 3.8 ms, echo time [TE] = 1.6 ms, 30 phases) was acquired, extending from the mitral valve annulus to the LV apex (8 mm slice thickness, no gap), to enable volumetric analysis of the LV using the summation of disc method.

Late gadolinium enhancement (LGE) was evaluated 10 min after a bolus of gadolinium-

diethylene triamine penta-acetic acid (DTPA) (0.2 mmol/kg BW Magnevist, Schering, Germany) to identify regional myocardial fibrosis using a T_1-weighted inversion recovery gradient echo technique (TR 7.1 ms, TE 3.1 ms, inversion time [TI] individually determined to null the myocardial signal, slice thickness 8 mm, matrix 256 × 192, number of acquisitions = 2). To enable accurate nullification of healthy myocardium, a TI optimization sequence was performed 8 min post-gadolinium administration with a fast gradient echo, inversion recovery, gated, multi-phase acquisition, commencing at an inversion time of 150 ms and increasing in 25 ms increments to 250 ms, in a single mid-ventricular short-axis slice. LGE imaging was performed using standard long-axis views of the LV and a contiguous short axis stack from the mitral valve annulus to the LV apex. Regional fibrosis was identified by LGE within the myocardium, defined quantitatively by a myocardial post-contrast signal intensity 6 SD above that within a reference region of remote myocardium (without LGE) within the same slice(23). LGE was defined as being present only if it was identified in two orthogonal views.

To evaluate diffuse myocardial fibrosis, a histologically-validated post-contrast T_1 mapping sequence was used to cycle through acquisition of images obtained at the mid-LV short-axis level over a range of inversion times, as described previously(7). This electrocardiogram-triggered, inversion-recovery prepared, 2-dimensional fast gradient echo sequence employed variable temporal sampling of k-space (VAST)(24) (Global Applied Science Laboratory, GE Healthcare). Ten images at the mid-LV short-axis level were acquired sequentially at increasing inversion times, pre-contrast (for non-contrast myocardial T_1 time, TI range 75 to 1875 ms) and also 15 min after the bolus of gadolinium-DTPA (TI range 75 to 750 ms), and over a series of 3 to 5 breath-holds. Following image acquisition, the ten short-axis images of varying inversion times were transferred to an external computer for analysis using a

dedicated research software package with a curve fitting technique to generate T_1 maps (Cinetool, Global Applied Science Laboratory, GE Healthcare). For each short-axis image, a region of interest (ROI) was drawn around the entire LV myocardium (excluding regions of LGE for post-contrast images) to calculate myocardial T_1 time. To account for the potential effect of glomerular filtration rate on gadolinium pharmacokinetics, correction values(25) were used to normalize post-contrast myocardial T_1 times to a matched state (eGFR = 90 mL/min/1.73m^2). Non-contrast myocardial T_1 times were corrected for heart rate according to current recommendations(26). ECV, an alternative method of extracellular matrix expansion (ECM) quantification, was derived using the previously described formula(27); ECV = (1 – haematocrit) × ($\Delta R1_{myocardium}$ / $\Delta R1_{blood}$) where R1 = 1/T_1 time.

Echocardiography protocol

Transthoracic echocardiography with a standard clinical protocol was performed on all patients immediately prior to cardiac catheterization. Diastolic function was assessed by a combination of mitral inflow pattern (E to A ratio) and early mitral annular velocities (e', measured at the septal and lateral aspects of the mitral annulus in the apical 4-chamber view). Additionally, mitral E/e' (septal, lateral and mean) was chosen as an index of LV diastolic function. All measurements were made in accordance with the American Society of Echocardiography guidelines(28,29).

Data analysis

All echocardiogram and CMR images were interpreted by two experienced readers unaware of the subjects' clinical information and the results of other diagnostic tests. Endocardial and epicardial LV contours were drawn manually for each diastolic and systolic frame, excluding

papillary muscles. An experienced operator without knowledge of patients' other test results analyzed the CC data.

Statistical analysis

All data are expressed as mean ± standard deviation (SD) unless otherwise indicated. For all comparisons, a p value of < 0.05 was considered significant, and all reported p values are 2-tailed. Assuming a correlation coefficient between CMR measures of diffuse fibrosis (post-contrast T_1 time and ECV) and invasive measures of diastolic function (τ and β) of ≥ 0.55, a sample size of 20 was required to achieve a statistical power of 0.8 assuming a two-tailed p-value of < 0.05. Correlations of variables were determined by calculating the Pearson Product Moment. Multiple linear regression was used to determine the independence of correlations observed on simple linear regression. All analyses were conducted using Stata software version 11.1 (StataCorp, College Station, Texas).

Results

Clinical and demographic data

Twenty of twenty-seven patients were included during the study period and seven patients were excluded (five due to a retained pacing or defibrillator lead; one due to claustrophobia prior to CMR; and, one due to severe renal impairment). Baseline characteristics of the study cohort are presented in Table 1. Most patients were male (80%) and mean age was 49 ± 16 years. Median time elapsed since cardiac transplantation was 39 months (IQR, 13 – 61 months). Only seven patients (35%) experienced exertional dyspnea.

Cardiac catheterization data

Invasive cardiac measurements obtained during right heart catheterization and coronary angiography are detailed in Table 2. β was derived from CC data in seventeen patients (85%). In one patient, the aortic valve could not be crossed despite multiple attempts and ventricular ectopy resulted in an uninterpretable PV dataset in two patients. Seventeen patients had no discernible coronary artery disease, one patient had an obstructive coronary artery lesion requiring subsequent percutaneous coronary intervention, and two patients had subtotally occluded coronary arteries that were managed without revascularization.

CMR and echocardiography data

CMR and transthoracic echocardiography were completed in all twenty patients and results are displayed in Table 3. LGE was observed in three patients: two patients had subendocardially-based regional scar in the vascular distribution of a subtotally occluded coronary artery; and one patient had basal anteroseptal midwall LGE of unknown etiology. Post-contrast myocardial T_1 time was calculated in all twenty patients and, when corrected for eGFR, did not different significantly overall from uncorrected values (380 ± 82 ms vs.

375 ± 83 ms, p = 0.998). ECV could be determined in sixteen (80%) patients – in four patients, pre-contrast myocardial T_1 times could not be measured due to image artefact. ECV (26.8 ± 8.5%) and post-contrast T_1 time showed a strong negative correlation (r = -0.82, p = 0.0001, Figure 1).

Correlates of invasive measures or diastolic function

Linear regression modelling revealed no significant correlations between τ and patients' baseline characteristics, catheterization, CMR or echocardiography parameters. In particular, there was no correlation between τ and non-contrast myocardial T_1 time, post-contrast myocardial T_1 time, or ECV (p = non-significant for all comparisons).

Univariate linear regression demonstrated significant correlations between β and both post-contrast myocardial T_1 time (r = -0.71, p = 0.001, see Figure 2) and ECV (r = 0.58, p = 0.04) (see Table 4). There were trends toward increased PCWP and LVEDP with increasing β (r = 0.47, p = 0.06 and r = 0.39, p = 0.12, respectively). No correlation was observed between β and non-contrast myocardial T_1 time, nor with CMR-derived LV volumetric parameters or echocardiographically-determined measures of LV diastolic function. Given the strong correlation between post-contrast myocardial T_1 time and ECV, these variables were entered into separate multiple linear regression analyses. Following this analysis, only the correlation between β and post-contrast myocardial T_1 time remained significant.

Discussion

To our knowledge, this is the first study to demonstrate a physiologic link between diffuse myocardial fibrosis assessed by post-contrast myocardial T_1 time, and an invasively-determined index of LV diastolic stiffness. Myocardial T_1 time, obtained at a single time point after contrast administration, and ECV, calculated from pre- and post-contrast myocardial and blood pool signals, both correlated with β, the load-independent LV passive stiffness constant.

Post-contrast myocardial T_1 times have previously been shown to correlate with the quantity of diffuse myocardial fibrosis observed in endomyocardial biopsy specimens(7,8) and several T_1 mapping studies have observed associations between reduced T_1 times and LV diastolic dysfunction as assessed by echocardiography(9-11). However, because echocardiographic studies use integrated backscatter and Doppler techniques that reflect both structural and functional changes in the myocardium, the precise mechanism of diastolic impairment has not been established. Compared to echocardiography, T_1 mapping by CMR is a tissue-specific modality that allows the unique opportunity to directly assess the structural components of the myocardium contributing to altered diastolic function. In the present study, by performing invasive PV measurements, active relaxation, an energy-dependent process, and passive filling could be evaluated independently and then correlated with T_1 time.

In patients with LV systolic dysfunction and HFNEF, myocardial fibrosis is believed to contribute to increased passive LV stiffness(30). Given the diffuse nature of collagen deposition in cardiomyopathy, a non-invasive test for myocardial fibrosis is highly desirable,

not just in terms of disease stratification, but also in the evaluation of newer therapies aimed at minimising or reducing myocardial fibrosis in the treatment of heart failure. For example, therapies inhibiting the angiotensin II system may have anti-fibrotic properties(31,32) and T_1 mapping could theoretically be used to non-invasively monitor the amount of diffuse myocardial fibrosis present, allowing longitudinal assessment of the potential impact of such treatments on ventricular stiffness.

We observed correlations between post-contrast myocardial T_1 times and β, but not load-dependent measures of LV diastolic function such as LVEDP or the ratio of early mitral transmitral velocity to tissue Doppler mitral annular early diastolic velocity (E/e', by echocardiography). In addition, active LV relaxation (τ) did not correlate with CMR indices of diffuse myocardial fibrosis, suggesting that it is the intrinsic properties of the myocardium due to diffuse fibrosis and hence increased stiffness rather than perturbation of the energy-dependent active relaxation process that underlines the mechanism of diastolic dysfunction commonly observed in our patient cohort(33).

We found that whilst post-contrast myocardial T_1 time and ECV correlated with β, only the relationship between the post-contrast myocardial T_1 time and β remained statistically significant following multiple linear regression analysis. Non-contrast myocardial T_1 time exhibited no significant correlation with β. Post-contrast T_1 mapping times have been shown to correlate with the quantity of diffuse interstitial fibrosis seen on myocardial biopsy specimens(8) while non-contrast T_1 measurements, which are used to calculate ECV and native T_1 times, reflect a combination of both interstitial and myocardial signals. Therefore, precisely which altered tissue characteristics contribute to non-contrast values is uncertain. Various T_1 mapping approaches currently exist and are likely to provide different

information about myocardial tissue characteristics. Nevertheless, our data identify a clear relationship between post-contrast myocardial T_1 time and LV passive stiffness. It is possible that other T_1 mapping protocols may demonstrate differing degrees of correlation with β and future studies will be required to investigate this further.

Cardiac transplant recipients were chosen to form the study cohort because this enabled opportunities to obtain invasive PV measurements at the time of clinically-indicated coronary angiography. Additionally, diffuse myocardial fibrosis has been shown to occur in approximately 50% of cardiac transplant recipients(34), and the likelihood of pre-existing, and potentially confounding, cardiac conditions, such as hypertensive LV hypertrophy, significant valvular heart disease or cardiomyopathy, was low. However, the generalizability of our findings to other cardiac disease states will need to be confirmed with further studies. For instance, in patients with ischemic cardiomyopathy, impairment to the energy-dependent process of active relaxation may also contribute to diastolic dysfunction, without necessarily affecting T_1 time. Because only a limited number of cardiac transplants are performed, and a significant proportion of potentially eligible patients have contra-indications to CMR, our overall study cohort size is small. Additionally, all recruited patients had either absent or mild symptoms of LV diastolic dysfunction and overall intra-cardiac pressures were normal. Repeating our protocol in patients with more pronounced heart failure symptoms and higher intra-cardiac pressures would be of interest. The effect of various physiologic manoeuvres, such as exercise, on invasively-determined diastolic indices was also not investigated in this study and may represent a focus for future study.

Conclusions

Diffuse myocardial fibrosis, assessed by post-contrast myocardial T_1 time, correlates with invasively-determined LV stiffness in cardiac transplant recipients. In patients with increased diffuse myocardial fibrosis, abnormal passive ventricular stiffness is therefore likely to be a major contributor to diastolic dysfunction. The ability to non-invasively evaluate ventricular stiffness using T_1 mapping in a variety of cardiomyopathies may enhance our understanding of the pathogenesis and natural history of these conditions, and enable the therapeutic trials of putative anti-fibrotic agents.

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Figure Titles and Legends

Figure 1. Post-contrast myocardial T_1 time and Extracellular Volume Fraction

A significant negative correlation was observed between post-contrast T_1 time and extracellular volume fraction ($r = -0.82$, $p = 0.001$).

Figure 2. Post-contrast myocardial T_1 time and Passive LV Stiffness Constant (β)

A significant positive negative correlation was observed between post-contrast myocardial T_1 time and passive LV stiffness constant, β ($r = -0.71$ $p = 0.001$).

Tables

Table 1. Baseline Characteristics

Age, y	49 ± 16
Males, n (%)	16 (80%)
Body mass index, kg/m^2	27.9 ± 4.6
Time since transplant, months*	39 (13,61)
Exertional dyspnea	
NYHA class I	13 (65%)
NYHA class II	7 (35%)
NYHA class III or IV	0 (0%)
Medications, n (%)	
Beta-blocker	3 (15%)
Calcium channel blocker	6 (30%)
ACE inhibitor	8 (40%)
ARB	4 (20%)
Statin	18 (90%)
Loop diuretic	4 (20%)
Hematocrit	0.39 ± 0.04
eGFR, ml/min/1.73 m^2	66 ± 19

NYHA indicates New York Heart Association; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; and, eGFR, estimated glomerular filtration rate. *Values as median (quartiles).

Table 2. Cardiac Catheterization Data

Heart rate, beats/min	83 ± 14
Systolic blood pressure, mmHg	132 ± 24
Diastolic blood pressure, mmHg	79 ± 15
Cardiac index, L/min/m^2	3.2 ± 0.8
Right atrial pressure, mmHg	3.6 ± 3.2
Pulmonary artery pressure, mmHg	15.8 ± 4.2
Pulmonary capillary wedge pressure, mmHg	7.5 ± 3.2
Left ventricular end-diastolic pressure, mmHg	14.1 ± 8.2
Active ventricular relaxation constant (τ), ms	32.6 ± 7.4
Passive ventricular stiffness constant (β)	0.030 ± 0.016

Table 3. Cardiac Magnetic Resonance Imaging and Echocardiography Data

Cardiac magnetic resonance imaging	
LVEDV indexed, ml/BSA	81 ± 20
LV stroke volume, ml	100 ± 38
LVEF, %	62 ± 8
LV mass indexed, g/BSA	56 ± 12
Presence of LGE, n (%)	3 (15%)
Non-contrast myocardial T_1 time, ms	937 ± 158
Non-contrast blood pool T_1 time, ms	1435 ± 335
Post-contrast myocardial T_1 time, ms	380 ± 82
Post-contrast blood pool T_1 time, ms	229 ± 34
ECV, %	26.8 ± 8.5
Echocardiography	
Left atrial volume indexed, ml/m^2	59 ± 24
Mitral E velocity, cm/s	0.8 ± 0.2
Mitral A velocity, cm/s	0.4 ± 0.1
E/A ratio	1.9 ± 0.5
Deceleration time, ms	158 ± 31
Septal e', cm/s	7.9 ± 1.7
Lateral e', cm/s	12.4 ± 3.7
Mean e', cm/s	10.1 ± 2.1
Septal E/e' ratio	10.7 ± 2.4
Lateral E/e' ratio	7.1 ± 2.0

Mean E/e’ ratio	8.9 ± 1.7

LVEDV indicates left ventricular end-diastolic volume; BSA, body surface area; LVEF, left ventricular ejection fraction; LGE, late gadolinium enhancement; and ECV, extracellular volume fraction.

Table 4: Predictors of Passive LV Stiffness Constant (β) By Simple and Multiple Linear Regression

	Simple linear regression		Multiple linear regression (including post-contrast myocardial T_1 time)		Multiple linear regre (including ECV)	
	r	p value	β	p value	β	p value
Baseline characteristics						
Age	-0.21	0.4	0.11	0.7	-0.50	0.15
Body mass index	0.23	0.4	-0.15	0.5	0.18	0.5
NYHA class	0.07	0.8				
Time since transplant	0.29	0.3	0.29	0.18	0.32	0.3
Cardiac catheterization parameters						
Heart rate	0.16	0.5	-0.08	0.8	0.24	0.4
Systolic blood pressure	-0.22	0.4	-0.28	0.4	0.37	0.5
Diastolic blood pressure	-0.10	0.7				
RAP	0.24	0.4				
PCWP	0.47	0.06	0.07	0.8	0.39	0.4
LVEDP	0.39	0.12	0.29	0.3	-0.04	0.9
Cardiac magnetic resonance imaging parameters						
LVEDV indexed	-0.25	0.3				
LVEF	-0.02	0.9				
LV mass indexed	-0.16	0.6	-0.12	0.6	-0.51	0.3
Non-contrast myocardial T_1 time	0.25	0.4				

Post-contrast myocardial T_1 time	-0.71	0.001	-0.80	0.02		
ECV	0.58	0.04			0.51	0.19
Echocardiography parameters						
Left atrial volume indexed	-0.21	0.4				
Mean E/e' ratio	0.02	0.9				

LV indicates left ventricular; ECV, extracellular volume fraction; NYHA, New York Heart Association; RAP, right atrial pressure; PCWP, pulmonary capillary wedge pressure; LVEDP, left ventricular end-diastolic pressure; LVEDV, left ventricular end-diastolic volume; and LVEF, left ventricular ejection fraction.