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Progression of diffuse myocardial fibrosis assessed by cardiac magnetic resonance T₁ mapping

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Abstract

To evaluate long-term changes in diffuse myocardial fibrosis using cardiac magnetic resonance (CMR) with late gadolinium enhancement (LGE) and T₁ mapping. Patients with chronic stable cardiomyopathy and stable clinical status (n = 52) underwent repeat CMR at a 6 month or greater follow up interval and had LGE and left ventricular (LV) T₁ mapping CMR. Diffuse myocardial

fibrosis (excluding areas of focal myocardial scar) was assessed by post gadolinium myocardial T_1 times. Mean baseline age of 52 patients (66 % male) was 35 ± 19 years with a mean interval between CMR examinations of 2.0 ± 0.8 years. CMR parameters, including LV mass and ejection fraction, showed no change at follow-up CMR ($p > 0.05$). LVT_1 times (excluding focal scar) decreased over the study interval (from 468 ± 106 to 434 ± 82 ms, $p = 0.049$). 38 Patients had no visual LGE-, while 14 were LGE+. For LGE- patients, greater change in LV mass and end systolic volume index were associated with change in T_1 time ($\beta = -2.03$ ms/g/m², $p = 0.035$ and $\beta = 2.1$ ms/mL/m², $p = 0.029$, respectively). For LGE+ patients, scar size was stable between CMR1 and CMR2 (10.7 ± 13.8 and 11.5 ± 13.9 g, respectively, $p = 0.32$). These results suggest that diffuse myocardial fibrosis, as assessed by T_1 mapping, progresses over time in patients with chronic stable cardiomyopathy.

Keywords

Cardiac magnetic resonance imaging; Diffuse myocardial fibrosis; Late gadolinium enhancement; T_1 mapping; Non-ischemic and ischemic cardiomyopathy

Introduction

Myocardial fibrosis is an endpoint of myocardial tissue response and remodeling in response to physiological and pathological insults. Identification of ischemic myocardial fibrosis with late-gadolinium enhancement (LGE) using cardiac magnetic resonance (CMR) serves as a strong predictor for future cardiovascular events [1] as well as systolic and diastolic dysfunction [2–4].

Nonischemic cardiomyopathy may also be associated with LGE scar using CMR. Visually detected LGE in hypertrophic cardiomyopathy has been recently described as progressive and rapid [5]. However non-ischemic cardiomyopathy is frequently associated with diffuse myocardial fibrosis (DMF) that is often poorly detected using LGE CMR [6]. Invasive biopsy is the reference standard for identification of diffuse myocardial fibrosis, but it is subject to sampling error and assumes that the extracted sample of myocardium is representative of the entire myocardium. CMR T_1 mapping [7] has been shown to provide a noninvasive marker of DMF. The method has been validated in animal models [8] as well as human heart failure [9] and nonischemic cardiomyopathy [10], diabetes [11, 12], hypertrophic cardiomyopathy [13] as well as infiltrative cardiomyopathies such as amyloidosis.

The extent to which diffuse myocardial fibrosis changes over time is generally unknown. The purpose of this study was to investigate long-term changes in focal and diffuse myocardial fibrosis through serial LGE scar quantification and T_1 mapping (Fig. 1).

Materials and methods

Study population

This study was HIPAA compliant and approved by our institutional review board. Radiology imaging database was evaluated for patients who received two CMR scans

separated by at least 6 months from 2005 to 2011. In addition, patients were included only if there was no history of an acute event, such as myocardial infarction, hospitalization or cardiac procedure within 6 months of the baseline CMR. Patients with excessive artifact (e.g. pacemaker and/or motion artifact) that precluded visualization of the entire myocardium were excluded. Height, weight, heart rate, contrast dose, creatinine, and glomerular filtration rate (GFR) were recorded at the time of CMR.

CMR acquisition

CMR studies were performed on a 1.5 T MRI scanner (Avanto, Siemens, Erlangen, Germany). Left ventricular structure and function were assessed using a cine steady-state free-precession sequence (temporal resolution 50 ms, slice thickness 8 mm, in plane resolution 1.5×2 mm). Late gadolinium enhancement was assessed using gradient echo inversion recovery techniques with phase sensitive inversion recovery images. Gadolinium dose and patient weight were recorded at the time of CMR. T_1 measurements were obtained from a steady state free precession Look-Locker inversion recovery sequence in the 4-chamber view, starting 10 min after contrast injection. Imaging parameters were TR/TE 2.5/1.2 ms, flip angle = 50° , matrix size = 192×72 , FOV = 306×290 mm, slice thickness 8 mm, 30–45 phases with temporal resolution 30 ms. Use of this Look-Locker sequence and T_1 measurement method in a 4-chamber view has previously been demonstrated to have a good agreement with short-axis views and other CMR T_1 mapping sequences (18).

Focal scar quantification with LGE

Myocardial scars were classified as ischemic involving the subendocardium in a coronary artery distribution or non-ischemic (predominantly mid-wall or subepicardial location without subendocardial involvement in a non-coronary distribution). Myocardial mass was determined using ResearchMass (Leiden University Medical Center, Leiden, The Netherlands) by an experienced observer with seven years of CMR experience blinded to clinical parameters.

Interstitial fibrosis quantification with T_1 derivation

Multi phase Look Locker images were used to quantify the post-contrast T_1 values [10]. Endo and epicardial borders of the left ventricle excluding the papillary muscles were traced semi-automatically in 4-chamber views in all phases of the Look-Locker sequence. The T_1 values of pixels with χ^2 goodness of fit with level of significance $\alpha = 0.05$ were averaged for a final mean post-contrast T_1 value to reduce noise. T_1 values were then corrected for contrast dose, contrast relaxivity, post-contrast delay time, heart rate, and renal function as described by Gai et al. [14, 15]. Delay times after gadolinium injection were extracted from DI-COM headers. T_1 time was normalized to a dose of 0.15 mmol/kg gadopentetate dimeglumine. Post-contrast delay time was normalized to 15 min; heart rate was normalized to 60 beats per minute, 2 RR interval acquisition and GFR 90 mL/min/1.73 m². These normalizations were based on semi-empirical models using a custom Matlab algorithm [14, 15].

Statistical analysis

Statistical analysis was performed using SAS (SAS institute version 9.4, Carey, NC) statistical software. Continuous variables were expressed as mean $\pm$ standard deviation. D'Agostino-Pearson and Shapiro-Wilk tests were performed to assess for normality. Post-gadolinium T₁ times were compared using paired *t* test. Changes in T₁ were compared to change in relaxivity ($R_1 = 1/T_1$); correlation coefficients and regression coefficients showed no significant changes in the magnitude or direction of relationships between R_1 and T₁. Thus T₁ values rather than R_1 coefficients are shown in tables for easier data interpretation and by convention with prior studies. A generalized estimating equation approach was adopted to adjust for the correlations between repeated measures in those subjects without late gadolinium enhancement. Cox's proportional hazards model was employed to calculate hazard ratios for increases in diffuse myocardial fibrosis in each disease subgroup, stratified by age and gender. *p* values *italic*>0.05 were considered to be statistically significant.

Results

Of 53 patients meeting enrollment criteria, 1 patient was excluded due to the presence of amyloidosis. Of the remaining 52 patients, 14 patients (27 %) had visually identified enhancement on late gadolinium enhancement (LGE) images suggesting more advanced disease, and were classified as LGE+. LGE+ patients had primarily non-ischemic scar pattern (11/14). Thirty eight patients had no visually identified LGE (LGE-). The most common reasons for referral to CMR in the LGE- subgroup were nonspecific arrhythmia/rule out structural abnormality (*n* = 19), hypertrophic cardiomyopathy (*n* = 4), and myotonic dystrophy (*n* = 2). Thirteen additional patients had nonischemic cardiomyopathy (*n* = 13) without definitive classification by CMR or clinical diagnosis.

Tables 1 and 2 summarize demographic and CMR data at baseline and follow-up examinations. The mean interval between the baseline and the follow-up CMR scan was 2.0 $\pm$ 0.8 years. The interval between CMR scans was similar for LGE+ patients and LGE- patients (2.2 $\pm$ 1.0 and 1.9 $\pm$ 0.9 yrs, respectively, *p* = 0.20). No serious clinical cardiovascular events (i.e., interim myocardial infarction) were noted during the follow-up intervals.

The average LV ejection fractions at baseline and follow-up were similar (56.6 $\pm$ 13.6 and 57.0 $\pm$ 11.9 %, respectively, *p* = 0.78). In addition, the LV mass showed no significant change between baseline and follow up CMR (i.e., 143 $\pm$ 48 and 149 $\pm$ 58 g, respectively, *p* = 0.13). For the major LGE+ and LGE- subgroups, there were no significant differences between baseline and follow-up CMR parameters (Table 2). In the LGE+ subgroup, scar size was stable between CMR1 and CMR2 (10.7 $\pm$ 13.8 g at baseline vs. 11.5 $\pm$ 13.9 g at follow-up, *p* = 0.32).

Change in T₁ time at follow-up CMR versus baseline CMR

The mean post-gadolinium T₁ times for all evaluable patients (*n* = 52) was 468 $\pm$ 106 ms at baseline CMR and 434 $\pm$ 82 ms at the follow-up CMR scan (*p* = 0.049) after a mean duration of 1.9 years (N.B.: focal myocardial scar was excluded from the myocardial T₁

time determination) Twelve patients (23.5 %) had increased T_1 time at follow-up CMR, whereas 40 patients (78.4 %) had a lower T_1 time.

As indicated above, clinical parameters did not account for alterations in T_1 time. However, older LGE- subjects had greater decrease in T_1 time at follow-up CMR ($r = -0.42$, $p = 0.016$). In addition, change in LV mass was inversely related to change in T_1 time ($r = -0.40$, $p = 0.024$). In multivariable analysis, greater change in LV mass index remained significantly associated with lower T_1 time (-2.03 ms/g/m^2 , $p = 0.035$, Table 3). In addition, greater end systolic volume index at follow up was associated with higher T_1 time (2.1 ms/mL/m^2 , $p = 0.029$, Table 3). Similar results were seen for patients referred for assessment of presence of an arrhythmic substrate (Table 4).

For LGE+ subjects ($n = 14$), change in T_1 time was positively associated with increased stroke volume index (1.4 ms/mL/m^2 , $p = 0.03$), ejection fraction ($1.3 \text{ ms/\%}$, $p = 0.05$) and mass to volume ratio (73.3 ms/g/mL , $p = 0.03$) in minimally adjusted models for age and gender. Due to small sample size, further multivariable testing was not performed for this group.

Using a cut-off of 30 ms or greater T_1 time change at follow-up CMR as a threshold, we compared the LGE+ and LGE- groups. This analysis showed that the LGE+ group was approximately 4 times less likely than the LGE- group to experience a decrease in T_1 time over the study follow-up period (Hazard ratio for LGE+ = 0.25 [95 % CI, 0.064–0.99], $p < 0.05$).

Discussion

Long term changes in diffuse myocardial fibrosis are largely unknown. Prior to CMR, invasive myocardial biopsy has been needed to assess myocardial histology. To our knowledge, this is the first study that has used CMR to investigate longitudinal change in diffuse myocardial fibrosis in patients with stable cardiomyopathy. In myocardial tissue without visually evident late gadolinium enhancement, there was an average decrease in post-gadolinium myocardial T_1 times by 34 ms over approximately 2 years. These results suggest that diffuse myocardial fibrosis generally progresses even in patients who are otherwise clinically stable with and without focal myocardial scar. Using similar methods, in patients who underwent endomyocardial biopsy [10] we previously reported that a 30 ms decrease in T_1 time corresponds to an approximate 2 % greater degree of myocardial fibrosis.

Several prior studies have evaluated short term follow up of myocardial fibrosis by CMR. Over a 6 month interval, DMF was unchanged in patients with treated aortic stenosis, as assessed by the extracellular volume fraction (ECV) [16]. Reduction in size (remodeling) of acute myocardial infarction between 0 and 6 months has also been well described [17–19]. Remodeling of myocardial infarction corresponds to histological changes of acute myocardial necrosis, infarct involution and remodeling with scar size reduction [19]. Consistent with animal models, Chan et al. reported lower T_1 time in zones remote from the

acute infarction, thought to correspond to the expansion of the extracellular matrix due to myocardial overload, inflammation or other mechanisms [20, 21].

Regression analyses (Tables 3, 4, 5) were performed to determine if T_1 time was associated with clinical or functional cardiac parameters in each subgroup of this study. This analysis showed that greater LV mass and smaller end systolic volume were both predictors of greater myocardial fibrosis. These parameters suggest are consistent with adverse alterations in myocardial morphology in association with increased collagen deposition and stiffening of the myocardium. Lower stroke volume was also a predictor of greater fibrosis in the LGE + subgroup. In LGE subjects, lower ejection fraction was additionally associated with greater fibrosis.

Prior studies support the concept that early myocardial fibrosis is a dynamic process that may progress or regress, depending on the disease state. Lopez et al. found that while about 75 % of patients showed lower collagen volume fraction as a result of therapy, 25 % of patients showed increased collagen. [23, 24], Diez et al. studied patients treated with losartan for hypertension. Endomyocardial biopsy was performed at baseline and after 12 months of antihypertensive therapy, showing that collagen volume fraction generally decreased in patients with severe hypertension [22]. Biochemical markers of fibrosis (PIP, PIIP, and CITP) may also change after therapy [23, 24], indicating that myocardial fibrosis is a dynamic process. In our study, we showed a general trend towards decreased myocardial T_1 time, suggesting greater myocardial fibrosis. However, 23 % of subjects showed increased T_1 time, suggesting less fibrosis. We attribute this variation to variation in the natural history of different patients, with the degree of collagen deposition likely depending on factors such as age, disease state and treatment status.

In the current study, patients with advanced age showed greater decrease in T_1 time than younger patients, suggesting an interaction of age with disease progression. This may be reflective of disease duration: older patients on average may be likely to have a greater burden of disease than younger patients. Liu et al. demonstrated that the T_1 time of normal men is about 20 ms lower than that of younger men [25], while less marked differences occurred among women of different ages. By comparison, patients in the current study showed a more accelerated rate of change of T_1 times by about 17 ms/yr. The current study also suggests that changes in myocardial mass and volumes relate to altered T_1 time and thus to diffuse myocardial fibrosis. Structural alterations associated with changes in LV mass and interstitial fibrosis may constitute the substrate for arrhythmias both in ischemic [26, 27] and non-ischemic [28, 29] cardiomyopathies.

There are several limitations of this study. The study population was biased by the clinical need for a follow-up CMR examination, thus potentially selecting for study subjects with subclinical progression of cardiomyopathy. In addition, the lack of homogeneity of patient disease status along with the small sample size may limit generalizability of the results. Endomyocardial biopsy was not performed in this study population, so the presence of underlying fibrotic changes cannot truly be known. However, lower myocardial T_1 time after gadolinium administration is thought to reflect diffuse myocardial fibrosis [30, 31], although T_1 time is not a specific measure of collagen deposition [10, 32]. Finally, a

modified Look-Locker CMR pulse sequence may improve the reliability of T₁ mapping [33] but was not available over the duration of the study. Excellent agreement has been demonstrated with between the standard and modified Look-Locker sequence for post gadolinium T₁ values [15]. In addition, both intra and inter-observer agreement of T₁ values were excellent (ICC = 96.6 and 96.8 %, respectively), suggesting excellent reproducibility. However, T₁ mapping was performed on mid-slice 4 chamber view, and so the resulting T₁ value may not be entirely representative of disease in remote areas of myocardium. Native myocardial T₁ times and ECV (derived from pre- and post-gadolinium T₁ times) may also have clinical utility [34–36] but were unavailable in this study.

Conclusion

In conclusion, this study presents a longitudinal assessment of diffuse myocardial fibrosis by CMR post gadolinium T₁ time for patients with chronic, stable cardiomyopathy. An overall decrease in T₁ time was noted in the absence of changes in clinical and CMR parameters, suggesting progression of diffuse myocardial fibrosis. However, T₁ time is a nonspecific marker, and endomyocardial biopsy would ultimately be needed to establish the relationship of the T₁ changes to myocardial fibrosis. These results may provide the basis for further studies assessing subclinical progression of myocardial disease.

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Fig. 1. Progression of myocardial fibrosis. **a** 50 year old female with nonspecific cardiomyopathy with baseline CMR T₁ time of 363 ms. After 1.6 years, the CMR scan was repeated, showing a T₁ time of 326 ms. **b** 51 year old female with nonspecific cardiomyopathy with baseline CMR T₁ time of 391 ms. After 0.7 years, the CMR scan was repeated, showing a T₁ time of 251 ms

Table 1

Demographic/CMR parameters for All Subjects

	All subjects (n = 52)		
	CMR1	CMR2	p value
Age (years)	35 ± 19	37 ± 19	–
Time between CMR scans (yrs)	–	2.0 ± 0.8	–
Height (m)	1.72 ± 0.15	1.73 ± 0.13	0.36
Weight (kg)	77.7 ± 22.5	79.8 ± 22.3	0.11
BMI (kg/m ²)	25.9 ± 6.32	26.4 ± 6.71	0.40
HR(bpm)	69.9 ± 13.4	69.5 ± 14.4	0.81
CO (mL/min)	5,713 ± 2,010	5,750 ± 1,671	0.89
EDV (mL)	150.7 ± 52.1	154.0 ± 56.1	0.55
ESV (mL)	68.2 ± 40.5	69.6 ± 42.3	0.72
SV (mL)	82.5 ± 26.0	84.4 ± 24.7	0.55
EF (%)	56.6 ± 13.6	57.0 ± 11.9	0.78
LV mass (g)	143 ± 48	149 ± 58	0.13
LV mass/volume (g/mL)	0.99 ± 0.24	0.99 ± 0.29	0.99

CMR cardiac magnetic resonance, LV left ventricle, BMI body mass index, BSA body surface area, HR heart rate, CO cardiac output, EDV end diastolic volume, ESV end systolic volume, SV stroke volume, EF ejection fraction, LV left ventricle, g grams, bpm beats per minute, m meters

Table 2

Demographic/CMR parameters for LGE+ and LGE- subgroups

	LGE- (n = 38)			LGE+ (n = 14)		
	CMR1	CMR2	p value	CMR1	CMR2	p value
Age (years)	30 ± 18	32 ± 17	–	50 ± 16	52 ± 17	–
Time between CMR scans (years)	–	1.9 ± 0.8	–	–	2.2 ± 1.0	–
Height (m)	1.70 ± 0.16	1.71 ± 0.14	0.34	1.78 ± 0.06	1.78 ± 0.06	0.79
Weight (kg)	72.6 ± 21.9	75.7 ± 22.3	0.08	91.5 ± 18.3	91.0 ± 18.6	0.73
BMI (kg/m ²)	24.9 ± 6.5	25.6 ± 7.1	0.34	28.8 ± 5.2	28.6 ± 5.1	0.77
HR (bpm)	70.4 ± 13.3	68.0 ± 13.6	0.26	68.7 ± 14.1	73.4 ± 16.4	0.26
CO (mL/min)	5,790 ± 1,950	5,850 ± 1,710	0.84	6,079 ± 2,718	6,035 ± 1,957	0.94
Scar size (g)	–	–	–	10.7 ± 13.8	11.5 ± 13.9	0.32
EDV (mL)	139.9 ± 46.2	149.2 ± 56.7	0.06	173.9 ± 57.1	166.9 ± 59.4	0.58
ESV (mL)	56.2 ± 28.3	60.7 ± 29.6	0.19	86.9 ± 57.7	83.8 ± 55.7	0.77
SV (mL)	83.7 ± 27.7	88.5 ± 33.4	0.22	87.0 ± 26.8	83.1 ± 20.7	0.46
EF	60.9 ± 12.3	60.4 ± 9.3	0.78	52.8 ± 18.6	53.2 ± 18.1	0.84
LV mass (g)	130.2 ± 42.9	131.8 ± 40.6	0.63	180.4 ± 45.8	197.8 ± 73.9	0.09
LV mass/volume (g/mL)	0.96 ± 0.28	0.92 ± 0.23	0.29	1.08 ± 0.24	1.18 ± 0.37	0.24

CMR cardiac magnetic resonance, LV left ventricle, BMI body mass index, BSA body surface area, HR heart rate, CO cardiac output, EDV end diastolic volume, ESV end systolic volume, SV stroke volume, EF ejection fraction, LV left ventricle, g grams, bpm beats per minute, m meters

Table 3

Regression models for prediction of rate of change in T_1 for LGE- subjects

Parameter	Model 1: minimally adjusted*			Model 2: final Model		
	Regression coefficient (ms) [§]	95 % CI	p value	Regression coefficient (ms) [§]	95 % CI	p value
Age (years)	-0.07	[-1.53 1.39]	0.93	-	-	-
Gender (reference = female)	-23.4	[-72.4 25.6]	0.35	-	-	-
BMI (kg/m ²) [†]	-1.82	[-5.95 2.32]	0.39	-	-	-
End systolic volume index (mL/m ²) [‡]	0.45	[-0.59 1.50]	0.40	2.1	[0.2 4.0]	0.029 //
Stroke volume index (mL/m ²) [‡]	-0.59	[-2.36 1.19]	0.52	-	-	-
End diastolic volume index (mL/m ²) [‡]	0.05	[-0.66 0.77]	0.88	-	-	-
Ejection fraction (%)	-2.09	[-4.84 0.67]	0.14	-	-	-
LV mass index (g/m ²) [‡]	-0.44	[-1.60 0.72]	0.45	-2.03	[-3.91 -0.14]	0.035 //
M/V (g/mL) [‡]	-24	[-145 97]	0.70	-	-	-

* Adjusted for age and gender

[†] BMI = body mass index; M/V = Left Ventricular mass/volume ratio

[‡] Indexed parameters were normalized by BSA, which was calculated using DuBois formula

[§] Regression coefficient is expressed in (ms/g) for LV Mass, (ms/mL) for volume parameters, (ms/%) for EF, (ms/g/m²) for LV Mass Index

// Bold indicates $p < 0.05$

Table 4
Regression models for prediction of rate of change in T₁ for patients with non-specific arrhythmias

Parameter	Model 1: minimally adjusted [*]			Model 2: final Model		
	Regression coefficient (ms) [§]	95 % CI	p value	Regression coefficient (ms) [§]	95 % CI	p value
Age (years)	2.1	[0.64 3.6]	0.01//	-	-	-
Gender (Reference = Female)	4.7	[-58.6 67.9]	0.88	-	-	-
BMI (kg/m ²) [†]	10.7	[7.2 14.3]	<0.0001//	8.9	[5.6 12.2]	<0.0001//
End systolic volume index (mL/m ²) [‡]	-1.2	[-4.1 1.7]	0.43	3.4	[0.053 6.7]	0.05//
Stroke volume index (mL/m ²) [‡]	-2.4	[-4.5 -0.29]	0.03//	-	-	-
End diastolic volume index (mL/m ²) [‡]	-1.1	[-2.6 0.36]	0.14	-	-	-
Ejection fraction (%)	-2.8	[-6.0 0.49]	0.10	-	-	-
LV mass index (g/m ²) [‡]	-1.7	[-3.8 0.47]	0.13	-2.9	[-5.0 -0.78]	0.01//
M/V (g/mL) [‡]	57.1	[-41.8 156.1]	0.26	100.9	[-6.5 208.5]	0.07

^{*} Adjusted for age and gender

[†] BMI = body mass index; M/V = Left Ventricular mass/volume ratio

[‡] Indexed parameters were normalized by BSA, which was calculated using DuBois formula

[§] Regression coefficient is expressed in (ms/g) for LV Mass, (ms/mL) for volume parameters, (ms/%) for EF, (ms/g/m²) for LV Mass Index

// Bold indicates $p < 0.05$

Table 5Regression models for prediction rate of change in T₁ for LGE+ subjects

Parameter	Minimally adjusted model [*]		
	Regression coefficient (ms) [§]	95 % CI	p value
Age (years)	-0.69	[-2.1 0.71]	0.34
Gender (Reference = Female)	8.1	[-17.3 33.5]	0.53
BMI (kg/m ²) [†]	-0.45	[-3.4 2.5]	0.77
End systolic volume index (mL/m ²) [‡]	-0.68	[-2.1 0.70]	0.33
Stroke volume index (mL/m ²) [‡]	1.4	[0.14 2.6]	0.03 //
End diastolic volume index (mL/m ²) [‡]	-0.54	[-2.0 0.92]	0.47
Ejection fraction (%)	1.3	[0.01 2.5]	0.05 //
LV mass index (g/m ²) [‡]	0.35	[-0.25 0.96]	0.25

* Adjusted for age and gender

[†] BMI = body mass index; M/V = Left Ventricular mass/volume ratio

[‡] Indexed parameters were normalized by BSA, which was calculated using DuBois formula

[§] Regression coefficient is expressed in (ms/g) for LV Mass, (ms/mL) for volume parameters, (ms/%) for EF, (ms/g/m²) for LV Mass Index

// Bold indicates $p < 0.05$