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Relation of Myocardial Contrast-Enhanced T_1 Mapping by Cardiac Magnetic Resonance to Left Ventricular Reverse Remodeling After Cardiac Resynchronization Therapy in Patients With Nonischemic Cardiomyopathy

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Myocardial scar is known to be associated with limited left ventricular (LV) reverse remodeling after cardiac resynchronization therapy (CRT). However, the impact of diffuse myocardial interstitial fibrosis, as assessed with myocardial T_1 mapping cardiac magnetic resonance (CMR), has not been studied in patients with CRT. Therefore, we aimed at evaluating the association between diffuse myocardial interstitial fibrosis, in nonischemic cardiomyopathy patients, and LV reverse remodeling after CRT. A total of 40 patients (61 ± 11 years) with nonischemic cardiomyopathy who underwent CMR before CRT implantation were included. Myocardial T_1 mapping was performed using an inversion-recovery Look-Locker sequence after gadolinium injection. Myocardial contrast-enhanced T_1 time values were assessed from segments without delayed contrast enhancement and normalized for heart rate. At 6-month follow-up, LV reverse remodeling was assessed by the reduction in LV end-systolic volume. Before CRT implantation, mean myocardial contrast-enhanced T_1 time was 351 ± 46 ms. At 6-month follow-up, LV end-systolic volume decreased by 24 ± 21%. Myocardial contrast-enhanced T_1 time showed a significant correlation with LV reverse remodeling ($r = 0.5$, $p = 0.001$) together with hemoglobin level, renal function, LV dyssynchrony, and presence of delayed contrast enhancement. Multivariate regression analysis identified myocardial contrast-enhanced T_1 time (β −0.160, $p = 0.022$), LV dyssynchrony (β −0.267, $p = 0.002$), and renal function (β −0.334, $p = 0.021$) as independent associates of LV reverse remodeling. In conclusion, in nonischemic cardiomyopathy, diffuse interstitial myocardial fibrosis quantified with T_1 mapping CMR is independently associated with LV reverse remodeling after CRT and might, therefore, be used to optimize patient selection. **(Am J Cardiol 2017;119:1456−1462)**

Cardiac resynchronization therapy (CRT) is an established treatment for heart failure patients.[1] However, there is a spectrum of response to CRT, and subanalyses of randomized controlled trials have suggested that CRT might be more beneficial in patients with nonischemic compared with ischemic cardiomyopathy.[2] The superior efficacy of CRT in patients with nonischemic cardiomyopathy might be because of the absence of substantial myocardial scar, which has been shown to limit left ventricular (LV) reverse remodeling after CRT.[3−6] However, diffuse interstitial myocardial fibrosis might still be present in nonischemic cardiomyopathy and its impact on LV performance after CRT has not been evaluated. Recent advances in cardiac magnetic resonance (CMR) techniques with T_1 mapping sequences permit accurate assessment and quantification of diffuse interstitial myocardial fibrosis and have been validated with histologic studies.[7−12] The present study aimed at evaluating the association between diffuse interstitial myocardial fibrosis assessed with contrast-enhanced T_1 mapping CMR and LV reverse remodeling in patients with nonischemic cardiomyopathy who underwent CRT.

Methods

From 2004 to 2012, a total of 55 consecutive nonischemic cardiomyopathy patients who underwent successful CRT implantation and evaluated with CMR before the procedure were included in this analysis. After excluding 14 patients because of absence of contrast-enhanced Look-Locker sequence and 1 because of lack of echocardiographic follow-up, a total of 40 patients were included. The origin of heart failure was considered nonischemic in the absence of a previous myocardial infarction/revascularization or significant coronary artery disease on coronary angiography (>50% stenosis in ≥1 major epicardial coronary artery) and after excluding the diagnosis of other cardiomyopathies. The indication for CRT was based on previous and current

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CRT guidelines: heart failure symptoms New York Heart Association (NYHA) class II to IV despite optimal medical therapy, LV ejection fraction $\leq$35%, and a QRS duration $\geq$120 ms.[1] Cardiac devices were implanted as previously described.[13]

Before device implantation and at 6-month follow-up, all patients underwent extensive clinical evaluation and transthoracic echocardiography. Co-morbid conditions, medication, NYHA functional class, quality-of-life score, and 6-minute walk distance were assessed. At baseline, blood samples were obtained to evaluate hemoglobin level and renal function by estimated glomerular filtration rate (eGFR) using Modification of Diet in Renal Disease.[14] All data used for this study were acquired for clinical purposes and handled anonymously. Therefore, the institutional review board waived the need of written patient informed consent for this retrospective study.

All patients were scanned using a 1.5-T whole-body magnetic resonance imaging scanner (Gyroscan ACS/NT15; Philips, Best, The Netherlands), and images were digitally stored and analyzed off-line with dedicated quantitative software (MASS V2013-EXP; Leiden University Medical Center, Leiden, The Netherlands). The CMR protocol included standard acquisitions for the assessment of cardiac chamber dimensions and function and the administration of gadolinium-based contrast (gadolinium diethylenetriamine penta-acetic acid, 0.15 mmol/kg; Magnevist, Schering, Berlin, Germany) for delayed contrast-enhanced (DCE) imaging and quantification of global myocardial contrast-enhanced T_1 time. DCE images were acquired 15 minutes after a bolus injection of gadolinium-based contrast, with an inversion recovery gradient echo sequence with parallel imaging (SENSE, acceleration factor 2). The inversion time was determined by a T_1 scout (Look-Locker sequence) to null the normal myocardium signal. DCE images of the heart were acquired in 1 breath hold using 20 to 24 short-axis slices (depending on the heart size). The global myocardial contrast-enhanced T_1 time was quantified from the outlined short-axis Look-Locker sequence of varying inversion times and fitted iteratively using automatic pixel-by-pixel quantification in MASS as described earlier.[8,9] In summary, LV endo- and epicardial borders were outlined manually by a single reader in the mid-ventricular short-axis views in the end-systolic and end-diastolic images and every fourth image from the sequence. The remaining contours were generated using built-in contour interpolation algorithm in MASS and were carefully inspected to include only myocardium. From standard 17 LV segments model as recommended by the American Heart Association,[15] the 6 short-axis segments were analyzed. In fibrotic tissue, the washout time and volume distribution of gadolinium contrast agents are increased.[16,17] Hence, lower global myocardial contrast-enhanced T_1 time corresponds with increased diffuse interstitial myocardial fibrosis. The best fit for T_1 time value corresponding to the smallest fitting error was determined iteratively by inverting initial phases to a time corresponding to the zero crossing of the longest possible T_1 time value for each case. The built-in Levenberg-Marquardt algorithm in MASS was used to plot a nonlinear fit from the measured data. Only pixels with a significant goodness of fit (χ^2 test; level of significance of $\alpha = 0.05$) were included in the final average T_1 time value. The average global myocardial contrast-enhanced T_1 time was calculated automatically from T_1 times obtained from each individual pixel. Normal values for our laboratory for average global myocardial contrast-enhanced T_1 time are 504 $\pm$ 34 ms as previously published.[9] Figure 1 shows an example of myocardial wall contouring and T_1 time curve fitting. Only segments without evidence of DCE were used for the calculation of the global myocardial contrast-enhanced T_1 time (in case of DCE near to the border between 2 segments, both segments were excluded). Presence of DCE was defined as a signal intensity $\geq$35% of maximal myocardial signal intensity in 2 orthogonal views suggestive for macroscopic myocardial scar/fibrosis.[18,19]

Echocardiography was performed using a commercially available system (Vivid 7 and Vivid 9; General Electric Vingmed Ultrasound, Horton, Norway). Standard 2-dimensional and Doppler images were recorded and saved for off-line analysis (EchoPac, version 111.0.0; GE-Vingmed, Horton, Norway). Echocardiographic evaluation was performed according to the current recommendations and included quantification of LV volumes and LV ejection fraction by biplane Simpson's method.[20] LV dyssynchrony was quantified using apical 4-chamber view color-coded tissue Doppler imaging as the maximum delay between peak systolic velocities in the 2 basal segments (septal and lateral).[21]

Variables are presented as mean values $\pm$ SD or frequencies and percentages. Differences in baseline characteristics between the 2 groups were compared using unpaired Student *t* tests (continuous variables) and χ^2 (categorical data), as appropriate. The correlation between global myocardial contrast-enhanced T_1 time and heart rate was evaluated using linear regression analysis using Pearson correlation coefficient. Considering the observed linear dependence of global myocardial contrast-enhanced T_1 time on heart rate, normalization of T_1 time to a heart rate of 60 beats/min was performed using the slope of the regression line of heart rate versus global myocardial contrast-enhanced T_1 time with the following formula: normalized T_1 time = unadjusted T_1 time + α*(60 $-$ heart rate), where α equals -3.034 (slope of the regression line). A univariate linear analysis was performed to evaluate the association between baseline characteristics and LV reverse remodeling defined as the reduction in LV end-systolic volume at 6-month follow-up. Because of the small sample size of the population, in the linear regression analysis, LV reverse remodeling was introduced as continuous variable for optimal statistical power. To identify the independent associations, multivariate linear analysis followed including all clinical relevant parameters and parameters with a p value $\leq$0.10 in univariate analysis. All statistical analyses were performed using IBM PASW Statistics, version 20.0 (SPSS Inc., Chicago, Illinois). A $p < 0.05$ was considered statistically significant.

Results

Baseline patient characteristics are provided in Table 1. As assessed by echocardiography, LV volumes were severely enlarged and the LV function was impaired. The

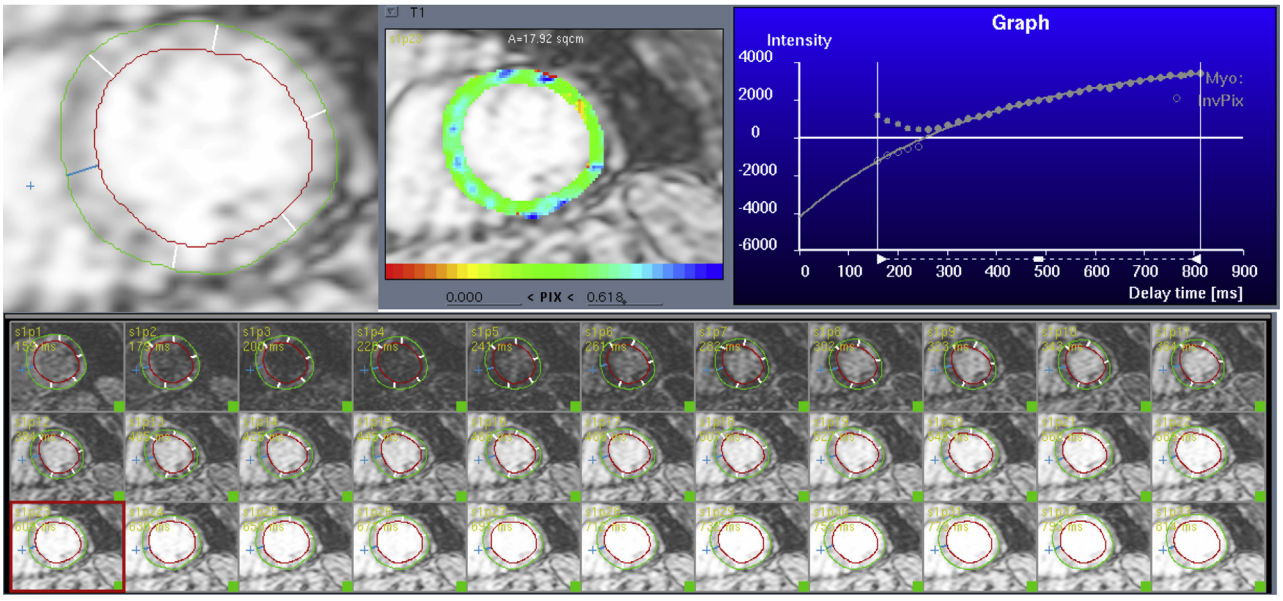

Figure 1. Example of global contrast-enhanced myocardial T_1 time using the Look-Locker CMR sequence in a patient with nonischemic cardiomyopathy before CRT implantation. In the lower panel, the left ventricular endo- and epicardial contours are outlined for 33 images, respectively, in *red* and *green*. The MASS software (MASS V2013-EXP; Leiden University Medical Center) automatically determined the myocardial signal intensity for every individual pixel from each image, performed curve fitting as shown in the graph *(upper right panel)* and calculated the unadjusted global contrast-enhanced myocardial T_1 time of 271 ms *(upper middle panel)*.

Table 1
Patient baseline clinical and echocardiographic characteristics

Variable	Total n=40
Age (years)	61±9
Men	26 (65%)
QRS duration (ms)	157±30
Left bundle branch block	31(78%)
NYHA functional class	2.6±0.7
Atrial fibrillation	5(13%)
Quality-of-life score	29±22
Six-minute walk distance (meter)	397±82
Diabetes mellitus	4 (10%)
eGFR (ml/min/1.73m^2)	80±22
Hemoglobin (mmol/L)	8.7±1.0
Left ventricular end-diastolic volume (ml)	207±81
Left ventricular end-systolic volume (ml)	156±73
Left ventricular ejection fraction (%)	27±8
LV dyssynchrony (ms)	63±37
Mitral regurgitation grades 0 and 1	25 (62%)
Mitral regurgitation grade 2	12 (30%)
Mitral regurgitation grade 3	3 (8%)
Unadjusted global contrast-enhanced myocardial T_1 time (ms)	325±67
Normalized global contrast-enhanced myocardial T_1 time (ms)	351±46

Values are mean ± SD or n.
eGFR = estimated glomerular filtration rate; LV = left ventricular; NYHA = New York Heart Association.

median time between CMR and CRT implantation was 0.98 months (interquartile range 0.20 to 1.47 months) and the median time between CMR and baseline echocardiography was 0.75 months (interquartile range 0.15 to 1.42 months).

In 16 patients (40%), DCE was observed (a total of 37 segments). These segments were excluded from the calculation of the mean global myocardial contrast-enhanced T_1 time. The mean global myocardial contrast-enhanced T_1 time was 324 ± 67 ms and a strong linear correlation with heart rate was observed (mean 70 ± 16 beats/min). The linear fit for T_1 time values and heart rate was determined (Pearson correlation coefficient $r = -0.729$, $p < 0.001$, Figure 2). Considering the dependence of global myocardial contrast-enhanced T_1 time on heart rate, an adjustment was performed to normalize values to a heart rate of 60 beats/min. After normalization, the mean global myocardial contrast-enhanced T_1 time was 351 ± 46 ms.

At 6-month follow-up, CRT resulted in significant improvement in clinical and echocardiographic parameters as shown in Figure 3. The functional capacity improved significantly: NYHA functional class decreased from 2.6 ± 0.7 to 1.9 ± 0.8 ($p < 0.001$), quality-of-life score improved from 29 ± 22 to 19 ± 20 ($p = 0.037$), and the 6-minute walking distance increased from 397 ± 82 to 459 ± 76 m ($p < 0.001$). Consistently, echocardiographic parameters improved with a significant decrease in LV volumes (LV end-diastolic volume from 207 ± 81 to 164 ± 77 ml, $p < 0.001$; LV end-systolic volume from 156 ± 73 to 119 ± 70 ml, $p < 0.001$; Figure 3) and LV ejection fraction increased from 27 ± 8 to 32 ± 11%, $p = 0.016$. Moreover, a significant reduction in LV dyssynchrony was observed from 63 ± 37 to 36 ± 29 ms, $p = 0.012$.

Significant correlations were observed between LV reverse remodeling and LV dyssynchrony ($r = 0.390$, $p = 0.013$) and normalized global myocardial contrast-enhanced T_1 time ($r = 0.500$, $p = 0.001$). To evaluate the association between normalized global myocardial

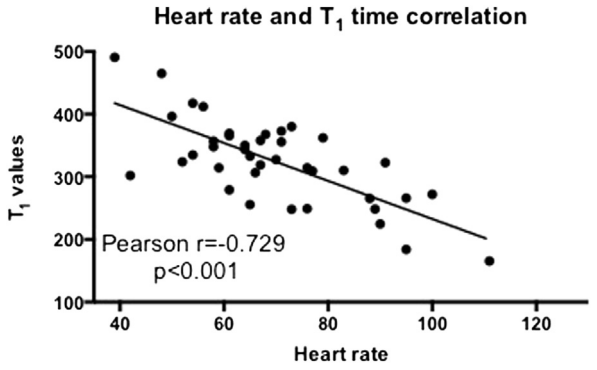

Figure 2. Correlation between heart rate and unadjusted global contrast-enhanced myocardial T_1 time.

contrast-enhanced T_1 time and the extent of LV reverse remodeling, univariate and multivariate linear regression analyses were performed (Table 2). In the univariate analysis, hemoglobin level, renal function, LV dyssynchrony, normalized global myocardial contrast-enhanced T_1 time, and presence of DCE showed important association with LV reverse remodeling. Including all these parameters, the multivariate analysis identified normalized global myocardial contrast-enhanced T_1 time (β −0.160 [SE 0.066], $p = 0.022$), LV dyssynchrony (β −0.267 [SE 0.077], $p = 0.002$), and eGFR (β −0.334 [SE 0.137], $p = 0.021$) as independently correlated parameters of LV reverse remodeling. In addition, multivariate analysis was re-performed considering change in LV end-systolic volume per 5% to confirm the results of the primary multivariate analysis even with bigger reduction in LV end-systolic volume that might be less dependent on the variability of the volumetric measurement by echocardiography. Also with this analysis, normalized global myocardial contrast-enhanced T_1 time (β −0.138 [SE 0.067], $p = 0.048$) was independently associated with LV reverse remodeling together with LV dyssynchrony (β −0.268 [SE 0.077], $p = 0.002$) and eGFR (β −0.323 [SE 0.138], $p = 0.026$).

Discussion

The present study explored in nonischemic cardiomyopathy patients, the potential impact of global myocardial contrast-enhanced T_1 time, a CMR measure of the burden of interstitial myocardial fibrosis on LV performance after CRT. LV reverse remodeling after CRT was independently associated with diffuse interstitial myocardial fibrosis, together with LV dyssynchrony and renal function.

Nonischemic cardiomyopathy is defined by the presence of reduced LV function in the absence of significant coronary artery disease. Without the typical ischemic distribution (endocardial or transmural) and with a limited extent, macroscopic myocardial fibrosis, as assessed by DCE CMR, can be observed in up to 40% of nonischemic cardiomyopathy patients.[16] However, DCE CMR visualizes only substantial macroscopic areas of myocardial fibrosis and is unable to identify diffuse reactive myocardial fibrosis, which also characterizes more homogenously the myocardium of nonischemic cardiomyopathy.[22] More recently, novel CMR T_1 mapping sequences allow the assessment of diffuse myocardial interstitial fibrosis,[8] and specifically, in nonischemic cardiomyopathy, histologic biopsy studies have demonstrated a strong inverse linear correlation between global myocardial contrast-enhanced T_1 time and the increase of percentage of myocardial fibrosis.[10–12] Interpretation of global myocardial contrast-enhanced T_1 time values, however, should be performed considering some variables that might affect this measure, such as heart rate and renal function.[8] Although data are contradictive among different studies, Gai et al recommended normalization of global myocardial contrast-enhanced T_1 time for heart rate, especially by elevated heart rates.[8,10] In the present study, a similar strong dependence was observed between global myocardial contrast-enhanced T_1 time and heart rate, and adjustment of the values using linear regression analysis coefficient was, therefore, performed. However, unadjusted values of global myocardial contrast-enhanced T_1 times in the present study were consistent with previous studies reporting the same measures in nonischemic cardiomyopathy patients using 1.5 T scanners.[10,23]

Despite specific indication criteria of the current guidelines, response to CRT may still significantly vary among patients in terms of beneficial effect on symptoms and LV function and ultimately on prognosis. Markers of LV dyssynchrony, such as QRS width and morphology, have been considered major determinants of CRT response, but other important clinical factors are suggested to affect the likelihood of a beneficial effect of CRT.[5,6,24,25] Nonischemic cardiomyopathy patients, in particular, have shown to have a relative greater magnitude of benefit from CRT than ischemic heart failure patients, probably because the absence of substantial myocardial scar, considering both the detrimental effect of the total burden of scar on LV function and/or the presence of scar at the targeted area for LV lead placement.[3–6,24,25] However, macroscopic myocardial fibrosis might still be present in nonischemic cardiomyopathy patients, although with limited extent, and several studies using DCE CMR demonstrated the prognostic value of myocardial fibrosis in these patients in terms of response to medical therapy, risk of arrhythmias, progression of heart failure, and ultimately in terms of long-term prognosis.[16,17,26,27] No extensive data have been published on the effect of macroscopic fibrosis on CRT response, and more importantly, the potential impact of diffuse interstitial myocardial fibrosis on LV reverse remodeling after CRT remained relatively unexplored. Including a mixed population of 27 ischemic cardiomyopathy and 21 dilated cardiomyopathy patients, Chen et al[28] described a nonsignificant correlation between CRT response and interstitial fibrosis assessed by T_1 mapping and suggested that mainly the presence of scar was predictive of CRT response. However, the small number of patients with dilated cardiomyopathy analyzed in that study prevents for drawing conclusion on the value of T_1 mapping analysis in this group of patients. The present study showed that both presence of DCE and lower global contrast-enhanced myocardial T_1 time (indicating extensive diffuse interstitial myocardial fibrosis) are strongly correlated with less LV reverse remodeling after CRT, suggesting that these measures may reflect irreversible damage of the myocardium less likely to be corrected by CRT implantation. Furthermore, multivariate analysis

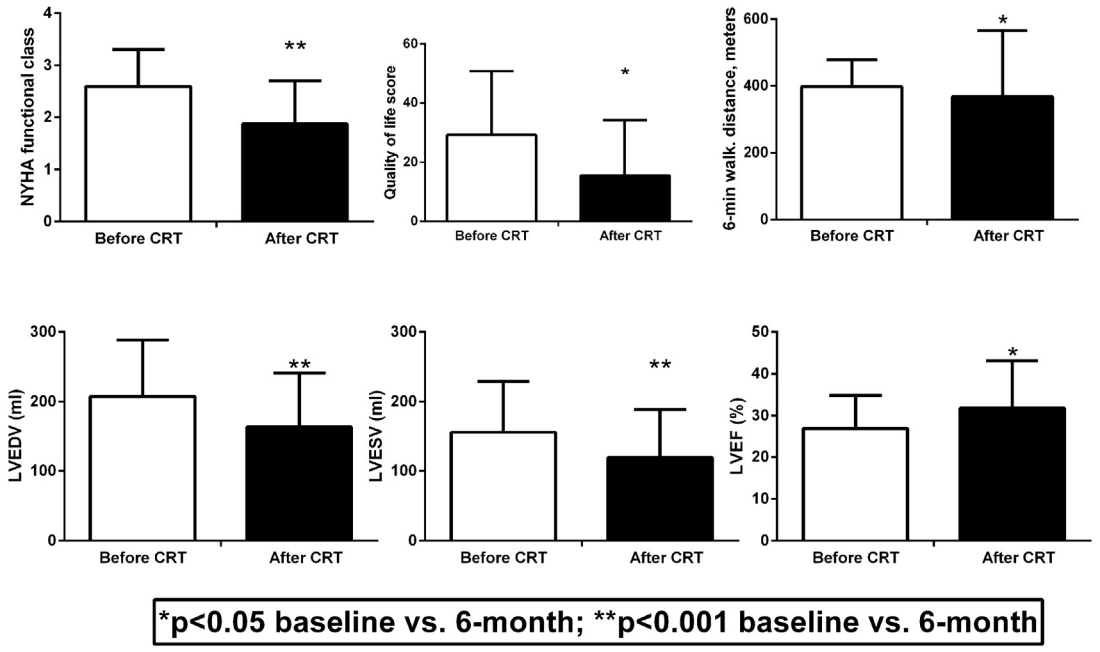

Figure 3. Changes in functional capacity (NYHA functional class, quality-of-life score, and 6-minute walk test) and echocardiographic parameters at 6-month follow-up. LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume.

Table 2
Univariate analysis evaluating the association between baseline characteristics and left ventricular reverse remodeling (reduction in left ventricular end-systolic volume at 6-month follow-up)

Variable	β (SE)	Univariate p-value
Age (per year)	0.287 (0.359)	0.429
Male gender	10.883 (6.713)	0.113
Diabetes mellitus	13.577(10.814)	0.217
Atrial fibrillation	–5.745(7.451)	0.446
NYHA functional class	1.364 (4.630)	0.770
QRS duration, per ms	–0.032 (0.110)	0.773
Left bundle branch block	–12.644(7.658)	0.107
Hemoglobin (per mmol/L)	–9.855(3.436)	**0.007**
eGFR (per ml/min/1.73m^2)	–0.361 (0.152)	**0.024**
Baseline left ventricular end-diastolic volume (per ml)	0.011 (0.041)	0.795
Baseline left ventricular end-systolic volume (per ml)	0.001 (0.046)	0.990
Baseline left ventricular ejection fraction (per %)	0.573 (0.416)	0.176
Mitral regurgitation per grade	5.395(3.495)	0.131
Baseline LV dyssynchrony, per ms	–0.217 (0.083)	**0.013**
Normalized global contrast-enhanced myocardial T_1 time, per ms	–0.223(0.063)	**0.001**
Presence of DCE	–14,370(6.343)	**0.029**

Bold p-values are statistically significant.

DCE = delayed contrast enhancement; eGFR = estimated glomerular filtration rate; LV = left ventricular; NYHA = New York Heart Association.

suggested the higher importance of diffuse myocardial fibrosis, identifying global contrast-enhanced myocardial T_1 time as independent determinant of LV reverse remodeling together with mechanical dyssynchrony, renal function, and hemoglobin level. Future larger prospective studies are needed to explore the impact of diffuse interstitial myocardial fibrosis on clinical outcomes after CRT in nonischemic cardiomyopathy and to evaluate the potential value of myocardial T_1 time CMR in improving patient selection for this device therapy.[29]

Several limitations of the present study should be mentioned. First, LV volumes and function before and after CRT were quantified with 2-dimensional echocardiography and not CMR because of the inability to re-evaluate after (CMR noncompatible) CRT device implantation. Furthermore, to use full statistical power because of relatively small sample size, LV reverse remodeling was not defined by a cut-off value (normally proposed of 15% reduction) but handled as a continuous variable. Considering the variability in volume measurements with echocardiography, the multivariate analysis was repeated with change in LV end-systolic volume per 5% and comparable results were observed. Second, global myocardial contrast-enhanced T_1 time was not validated with histologic data in the present study and a Look-Locker sequence instead of modified Look-Locker Inversion recovery (MOLLI) was used for T_1 mapping. Although previous studies showed good agreement between Look-Locker and MOLLI sequences, the derived global myocardial contrast-enhanced T_1 time from the present study is not directly comparable with studies that used different sequences/protocols. In particular, advances made in CMR technology have brought to more accessible and user-friendly sequences, such as ShMOLLI, SASHA, and SAPPHIRE.[30] Furthermore, pre-contrast T_1 mapping was not acquired in the present study.[7] Finally, global myocardial contrast-enhanced T_1 time was not adjusted for

renal function because of a lack of significant correlation between these 2 parameters in the present study. However, eGFR was found to be associated with LV reverse remodeling after CRT, and therefore, in the multivariate linear regression analysis, the strength of association between global myocardial contrast-enhanced T_1 time and LV reverse remodeling was adjusted for renal function.

Disclosures

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