Chapter 11

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

Ulaş Höke MD[a,b], Mand J.H. Khidir,[a] Rob J. van der Geest PhD[c], Martin J. Schalij MD PhD[a], Jeroen J. Bax MD PhD[a], Victoria Delgado MD PhD[a] and Nina Ajmone Marsan MD PhD[a]

[a]Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands.

[b]Interuniversity Cardiology Institute of the Netherlands (ICIN), Utrecht, the Netherlands.

[c]Department of Radiology, Leiden University Medical Center, Leiden, the Netherlands

Am J.Cardiol. 2017 May 1;119(9):1456-146

Cardiac resynchronization therapy (CRT) is an established treatment for heart failure patients.[1] However, there is a spectrum of response to CRT and sub-analyses of randomized controlled trials have suggested that CRT might be more beneficial in patients with non-ischemic as compared with ischemic cardiomyopathy.[2] The superior efficacy of CRT in patients with non-ischemic cardiomyopathy might be due to 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 non-ischemic 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 histological studies biopsies.[7-12] The current 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 non-ischemic cardiomyopathy undergoing CRT.

METHODS

From 2004 to 2012, a total of 55 consecutive non-ischemic cardiomyopathy patients who underwent successful CRT implantation and were evaluated with CMR before the procedure were included in this analysis. After excluding 14 patients due to absence of contrast-enhanced Look-Locker sequence and 1 due to lack of echocardiographic follow-up, a total of 40 patients were included. The etiology of heart failure was considered non-ischemic 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 CRT guidelines: heart failure symptoms New York Heart Association (NYHA) class II-IV despite optimal medical therapy, LV ejection fraction ≤35%, and a QRS duration ≥120 milliseconds (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 was 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 4th image from the sequence. The remaining contours were generated using built-in contour interpolation algorithm in MASS and were carefully inspected in order 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.[20,26] 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 α=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 Lab for average global myocardial contrast-enhanced T_1 time are 504±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 two segments, both segments were excluded). Presence of DCE was defined as a signal intensity ≥35% of maximal myo-

cardial signal intensity in 2 orthogonal views suggestive for macroscopic myocardial scar/fibrosis.[16,17]

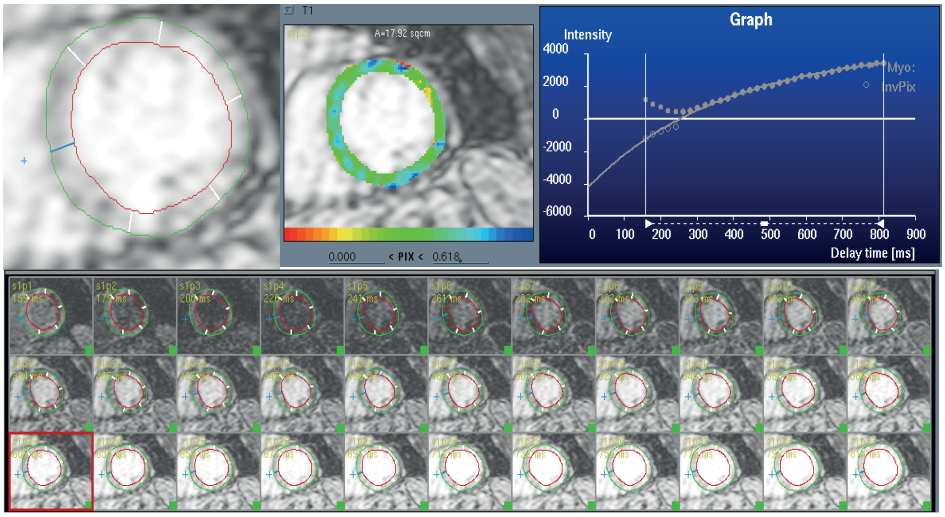

Figure 1. Example of global contrast-enhanced myocardial T_1 time using the Look-Locker CMR sequence in a patient with non-ischemic cardiomyopathy before CRT implantation.
In the lower panel, the left ventricular endo- and epicardial contours are outlined for 33 images respectively in red and green. The MASS software (MASS V2013-EXP, Leiden University Medical Center, Leiden, the Netherlands) 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 milliseconds (upper middle panel).

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.[18] LV dyssynchrony was quantified by using apical 4-chamber view color-coded tissue Doppler imaging as the maximum delay between peak systolic velocities in the 2 (septal and lateral) basal segments.[19]

Variables are presented as mean values±standard deviation, or frequencies and percentages. Differences in baseline characteristics between the 2 groups were compared using unpaired Student t-tests (continuous variables) and $\chi 2$ (categorical data), as appropriate. The correlation between global myocardial contrast-enhanced T_1 time and heart rate was evaluated using linear regression analysis by 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 per minute 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. Due to 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 of 0.10 or less in univariate analysis. All statistical analyses were performed by using IBM PASW Statistics, version 20.0 (SPSS Inc, Chicago, IL). A p-value of <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 median time between CMR and CRT implantation was 0.98 months (interquartile rage: 0.20-1.47 months) and the median time between CMR and baseline echocardiography was 0.75 months (interquartile rage: 0.15-1.42 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 per minute). 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 per minute. 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

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/1.73m²)	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

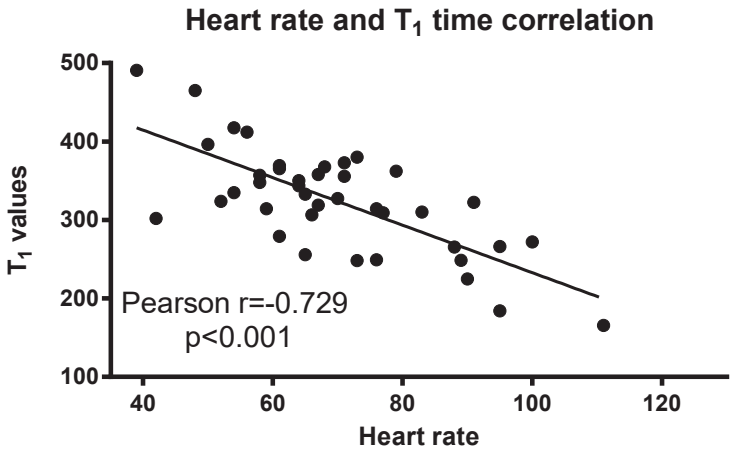

Figure 2. Correlation between heart rate and unadjusted global contrast-enhanced myocardial T_1 time.

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.

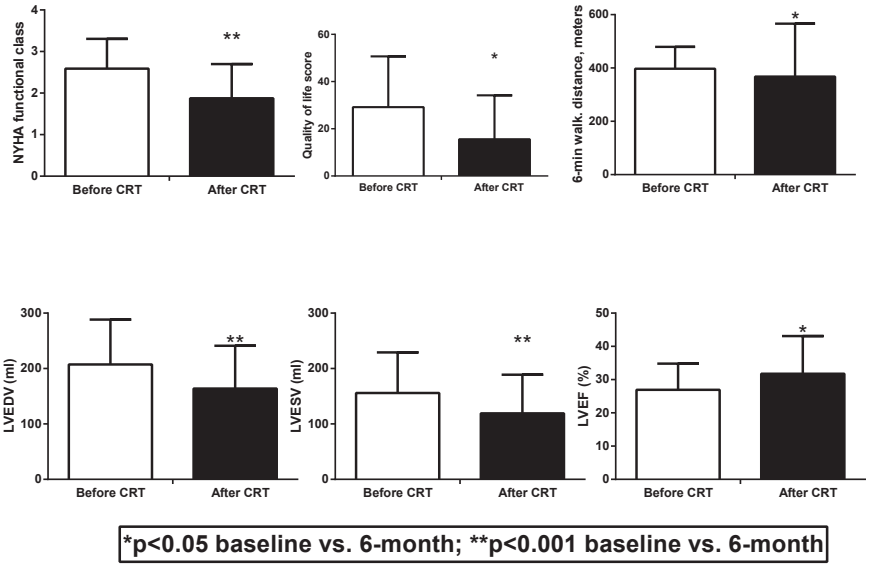

Figure 3. Changes in functional capacity (NYHA functional class, quality-of-life score and 6-minute walk test) and echocardiographic parameters at 6-month follow-up

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 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%, in order 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 to 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).

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).

Univariate		
Variable	**β (SE)**	**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/1.73m²)	-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

DISCUSSION

The current study explored in non-ischemic 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.

Non-ischemic 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 non-ischemic cardiomyopathy patients.[20] 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 non-ischemic cardiomyopathy.[21] More recently, novel CMR T_1 mapping sequences allow the assessment of diffuse myocardial interstitial fibrosis,[8] and specifically in non-ischemic cardiomyopathy, histological 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 which might affect this measure, such as heart rate and renal function.[8] Although data are contradictive among different studies, Gai and co-workers recommended normalization of global myocardial contrast-enhanced T_1 time for heart rate, especially by elevated heart rates.[8,10] In the current 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 co-efficient was therefore performed. However, unadjusted values of global myocardial contrast-enhanced T_1 times in the current study were consistent with previous studies reporting the same measures in non-ischemic cardiomyopathy patients using 1.5T scanners.[10,22]

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 impact the likelihood of a beneficial effect of CRT.[5,6,23,24] Non-ischemic cardiomyopathy patients in particular, have shown to have a relative greater magnitude of benefit from CRT than ischemic heart failure patients, probably due to 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.[3-6,23,24] However, macroscopic myocardial fibrosis might still be present in non-ischemic 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.[20,25-27] 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 popula-

tion of 27 ischemic cardiomyopathy and 21 dilated cardiomyopathy patients, Chen and co-workers described a non-significant 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.[28] 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 current 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 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 non-ischemic 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 current study should be mentioned. First, LV volumes and function before and after CRT were quantified with 2-dimensional echocardiography and not CMR due to inability to re-evaluate after (CMR non-compatible) CRT device implantation. Furthermore, in order to use full statistical power due to 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 histological data in current 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 due to lack of significant correlation between these 2 parameters in the current 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.

REFERENCES

1. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787-847.
2. Wikstrom G, Blomstrom-Lundqvist C, Andren B, Lonnerholm S, Blomstrom P, Freemantle N, Remp T, Cleland JG, investigators C-Hs. The effects of aetiology on outcome in patients treated with cardiac resynchronization therapy in the CARE-HF trial. Eur Heart J 2009; 30:782-788.
3. Bilchick KC, Dimaano V, Wu KC, Helm RH, Weiss RG, Lima JA, Berger RD, Tomaselli GF, Bluemke DA, Halperin HR, Abraham T, Kass DA, Lardo AC. Cardiac magnetic resonance assessment of dyssynchrony and myocardial scar predicts function class improvement following cardiac resynchronization therapy. JACC Cardiovascular imaging 2008;1:561-568.
4. Leyva F, Foley PW, Chalil S, Ratib K, Smith RE, Prinzen F, Auricchio A. Cardiac resynchronization therapy guided by late gadolinium-enhancement cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2011;13: 29.
5. Marsan NA, Westenberg JJ, Ypenburg C, van Bommel RJ, Roes S, Delgado V, Tops LF, van der Geest RJ, Boersma E, de Roos A, Schalij MJ, Bax JJ. Magnetic resonance imaging and response to cardiac resynchronization therapy: relative merits of left ventricular dyssynchrony and scar tissue. Eur Heart J 2009;30:2360-2367.
6. Ypenburg C, Roes SD, Bleeker GB, Kaandorp TA, de Roos A, Schalij MJ, van der Wall EE, Bax JJ. Effect of total scar burden on contrast-enhanced magnetic resonance imaging on response to cardiac resynchronization therapy. Am J Cardiol 2007;99:657-660.
7. Nacif MS, Turkbey EB, Gai N, Nazarian S, van der Geest RJ, Noureldin RA, Sibley CT, Ugander M, Liu S, Arai AE, Lima JA, Bluemke DA. Myocardial T1 mapping with MRI: comparison of look-locker and MOLLI sequences. J Magn Reson Imaging 2011;34:1367-1373.
8. Gai N, Turkbey EB, Nazarian S, van der Geest RJ, Liu CY, Lima JA, Bluemke DA. T1 mapping of the gadolinium-enhanced myocardium: adjustment for factors affecting interpatient comparison. Magn Reson Med 2011;65:1407-1415.
9. Ng AC, Auger D, Delgado V, van Elderen SG, Bertini M, Siebelink HM, van der Geest RJ, Bonetti C, van der Velde ET, de Roos A, Smit JW, Leung DY, Bax JJ, Lamb HJ. Association between diffuse myocardial fibrosis by cardiac magnetic resonance contrast-enhanced T(1) mapping and subclinical myocardial dysfunction in diabetic patients: a pilot study. Circ Cardiovasc Imaging 2012;5:51-59.
10. Iles L, Pfluger H, Phrommintikul A, Cherayath J, Aksit P, Gupta SN, Kaye DM, Taylor AJ. Evaluation of diffuse myocardial fibrosis in heart failure with cardiac magnetic resonance contrast-enhanced T1 mapping. J Am Coll Cardiol 2008;52:1574-1580.
11. Sibley CT, Noureldin RA, Gai N, Nacif MS, Liu S, Turkbey EB, Mudd JO, van der Geest RJ, Lima JA, Halushka MK, Bluemke DA. T1 Mapping in cardiomyopathy at cardiac MR: comparison with endomyocardial biopsy. Radiology 2012; 265:724-732.
12. aus dem Siepen F, Buss SJ, Messroghli D, Andre F, Lossnitzer D, Seitz S, Keller M, Schnabel PA, Giannitsis E, Korosoglou G, Katus HA, Steen H. T1 mapping in dilated cardiomyopathy with cardiac magnetic resonance: quantification of diffuse myocardial fibrosis and comparison with endomyocardial biopsy. Eur Heart J cardiovascular Imaging 2015;16:210-216.
13. Hoke U, Putter H, Van Der Velde ET, Schalij MJ, Delgado V, Bax JJ, Marsan NA. Left ventricular reverse remodeling, device-related adverse events, and long-term outcome after cardiac resynchronization therapy in the elderly. Circ Cardiovasc Qual Outcomes 2014;7:437-444.

14. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461-470.
15. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, Pennell DJ, Rumberger JA, Ryan T, Verani MS, American Heart Association Writing Group on Myocardial S, Registration for Cardiac I. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Circulation 2002;105:539-542.
16. Piers SR, Everaerts K, van der Geest RJ, Hazebroek MR, Siebelink HM, Pison LA, Schalij MJ, Bekkers SC, Heymans S, Zeppenfeld K. Myocardial scar predicts monomorphic ventricular tachycardia but not polymorphic ventricular tachycardia or ventricular fibrillation in nonischemic dilated cardiomyopathy. Heart Rhythm 2015;12:2106-2114.
17. Roes SD, Borleffs CJ, van der Geest RJ, Westenberg JJ, Marsan NA, Kaandorp TA, Reiber JH, Zeppenfeld K, Lamb HJ, de Roos A, Schalij MJ, Bax JJ. Infarct tissue heterogeneity assessed with contrast-enhanced MRI predicts spontaneous ventricular arrhythmia in patients with ischemic cardiomyopathy and implantable cardioverter-defibrillator. Circ Cardiovasc Imaging 2009;2:183-190.
18. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise J, Solomon S, Spencer KT, St John Sutton M, Stewart W, American Society of Echocardiography's N, Standards C, Task Force on Chamber Q, American College of Cardiology Echocardiography C, American Heart A, European Association of Echocardiography ESoC. Recommendations for chamber quantification. Eur J Echocardiogr 2006;7:79-108.
19. Bax JJ, Bleeker GB, Marwick TH, Molhoek SG, Boersma E, Steendijk P, van der Wall EE, Schalij MJ. Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy. J Am Coll Cardiol 2004;44:1834-1840.
20. Assomull RG, Prasad SK, Lyne J, Smith G, Burman ED, Khan M, Sheppard MN, Poole-Wilson PA, Pennell DJ. Cardiovascular magnetic resonance, fibrosis, and prognosis in dilated cardiomyopathy. J Am Coll Cardiol 2006;48:1977-1985.
21. Wu KC, Weiss RG, Thiemann DR, Kitagawa K, Schmidt A, Dalal D, Lai S, Bluemke DA, Gerstenblith G, Marban E, Tomaselli GF, Lima JA. Late gadolinium enhancement by cardiovascular magnetic resonance heralds an adverse prognosis in nonischemic cardiomyopathy. J Am Coll Cardiol 2008;51:2414-2421.
22. Han Y, Peters DC, Dokhan B, Manning WJ. Shorter difference between myocardium and blood optimal inversion time suggests diffuse fibrosis in dilated cardiomyopathy. J Magn Reson Imaging 2009;30:967-972.
23. van Bommel RJ, Bax JJ, Abraham WT, Chung ES, Pires LA, Tavazzi L, Zimetbaum PJ, Gerritse B, Kristiansen N, Ghio S. Characteristics of heart failure patients associated with good and poor response to cardiac resynchronization therapy: a PROSPECT (Predictors of Response to CRT) sub-analysis. Eur Heart J l 2009;30:2470-2477.
24. Sipahi I, Chou JC, Hyden M, Rowland DY, Simon DI, Fang JC. Effect of QRS morphology on clinical event reduction with cardiac resynchronization therapy: meta-analysis of randomized controlled trials. Am Heart J 2012;163:260-267 e263.
25. Leong DP, Chakrabarty A, Shipp N, Molaee P, Madsen PL, Joerg L, Sullivan T, Worthley SG, De Pasquale CG, Sanders P, Selvanayagam JB. Effects of myocardial fibrosis and ventricular dyssynchrony on response to therapy in new-presentation idiopathic dilated cardiomyopathy: insights from cardiovascular magnetic resonance and echocardiography. Eur Heart J 2012;33:640-648.
26. Looi JL, Edwards C, Armstrong GP, Scott A, Patel H, Hart H, Christiansen JP. Characteristics and prognostic importance of myocardial fibrosis in patients with dilated cardiomyopathy assessed by contrast-enhanced cardiac magnetic resonance imaging. Clin Med Insights Cardiol 2010;4:129-134.

27. Nazarian S, Bluemke DA, Lardo AC, Zviman MM, Watkins SP, Dickfeld TL, Meininger GR, Roguin A, Calkins H, Tomaselli GF, Weiss RG, Berger RD, Lima JA, Halperin HR. Magnetic resonance assessment of the substrate for inducible ventricular tachycardia in nonischemic cardiomyopathy. Circulation 2005;112:2821-2825.
28. Chen Z, Sohal M, Sammut E, Child N, Jackson T, Claridge S, Cooklin M, O'Neill M, Wright M, Gill J, Chiribiri A, Schaeffter T, Carr-White G, Razavi R, Rinaldi CA. Focal But Not Diffuse Myocardial Fibrosis Burden Quantification Using Cardiac Magnetic Resonance Imaging Predicts Left Ventricular Reverse Modeling Following Cardiac Resynchronization Therapy. J. Cardiovasc. Electrophysiol 2016;27:203-209.
29. Ling LH, Kalman JM, Ellims AH, Iles LM, Medi C, Sherratt C, Kaye DM, Hare JL, Kistler PM, Taylor AJ. Diffuse ventricular fibrosis is a late outcome of tachycardia-mediated cardiomyopathy after successful ablation. Circ Arrhythm Electrophysiol 2013;6:697-704.
30. Roujol S, Weingartner S, Foppa M, Chow K, Kawaji K, Ngo LH, Kellman P, Manning WJ, Thompson RB, Nezafat R. Accuracy, precision, and reproducibility of four T1 mapping sequences: a head-to-head comparison of MOLLI, ShMOLLI, SASHA, and SAPPHIRE. Radiology 2014;272:683-689.