Left ventricular wall thickness assessed by cardiac computed tomography and cardiac resynchronization therapy outcomes

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Aims	Up to 30% of selected heart failure patients do not benefit clinically from cardiac resynchronization therapy (CRT). Left ventricular (LV) wall thickness (WT) analysed using computed tomography (CT) has rarely been evaluated in response to CRT and mitral regurgitation (MR) improvement. We examined the association of LVWT and the ability to reverse LV remodelling and MR improvement after CRT.
Methods and results	Fifty-four patients scheduled for CRT underwent pre-procedural CT. Reduced LVWT was defined as WT <6 mm and quantified as a percentage of total LV area. Endpoints were 6-month clinical and echocardiographic response to CRT [New York Heart Association (NYHA) class, LV ejection fraction (LVEF), LV end-diastolic volume (LVEDV), and LV end-systolic volume (LVESV)], MR improvement and 2-year major adverse cardiac events (MACE). Patients were divided into three groups according to the percentage of LVWT <6 mm area: ≤20%, 20–50%, and ≥50%. At 6 months, 75%, 71%, and 42% of the patients experienced NYHA improvement in the ≤20%, 20–50%, and ≥50% group, respectively. Additionally, ≤20% group presented higher LVEF, LVEDV, and LVESV positive response rate (86%, 59%, and 83%, respectively). Both 20–50% and ≥50% groups exhibited a lower LVEF, LVEDV, and LVESV positive response rate (52% and 42%; 47% and 45%; and 53% and 45%, respectively). Additionally, ≥25% of LVWT <6 mm inclusive of at least one papillary muscle insertion was the only predictor of lack of MR improvement. Lastly, ≥50% group experienced significantly lower 2-year MACE survival free probability.
Conclusion	WT evaluated using CT could help to stratify the response to CRT and predict MR improvement and outcomes.
Clinical trial registration	NCT01097733.
Keywords	Heart failure • Cardiac resynchronization therapy • Response to cardiac resynchronization therapy • Mitral regurgitation • Computed tomography • Left ventricular wall thickness • Outcome

Introduction

Cardiac resynchronization therapy (CRT) improves mortality, morbidity, and quality of life in selected heart failure (HF) patients.[1,2]

Indeed, CRT implantation has been associated with left ventricular (LV) reverse remodelling and secondary mitral regurgitation (MR) improvement.[1,3] However, up to 30% of device recipients do not benefit clinically from CRT.[2] Among the factors influencing the

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What's new?

- Left ventricular wall thickness (LVWT) measured computed tomography could be associated with the response to cardiac resynchronization therapy (CRT).
- Cardiac resynchronization therapy candidates with a low percentage of LVWT <6 mm (≤20%) significantly improved their clinical status and echocardiography parameters compared to the groups with a larger proportion of reduced LVWT.
- An area ≥25% of LVWT <6 mm that including the insertion of at least one muscle limits the mitral regurgitation improvement after CRT implantation.
- Patients with ≥50% of LVWT <6 mm experienced poor outcomes 2 years of post-CRT implantation.

response to CRT, LV morphology and mitral valve (MV) geometry have been previously described. Indeed, LV fibrosis and MV apparatus geometry (analysed using cardiac magnetic resonance (CMR) or echocardiography, respectively) have been strongly correlated with poor LV function and MR enhancements after CRT implant.[3–5] Nonetheless, data regarding the impact of LV myocardial analysis using computed tomography (CT) on LV and MR functions after CRT are scarce.

Dual-source CT is an ideal non-invasive modality that provides pertinent information to guide the CRT implantation procedure.[6] Indeed, previous studies have demonstrated that CT can visualize the coronary venous anatomy, detect the presence of myocardial scar, and evaluate the LV mechanical dyssynchrony to guide physician for an optimal LV lead pacing site.[7,8] However, there is a paucity of data regarding the impact of LV wall thickness (WT) evaluated using CT on response to CRT. In this study, we sought to examine the association between LVWT and LV reverse remodelling and MR improvement after CRT in a prospective cohort.

Methods

Design of the study

The rationale and design of the Dual-Source Computed Tomography to Improve Prediction of Response to Cardiac Resynchronization Therapy (NCT01097733) have been previously published.[9] Briefly, 54 refractory HF patients with New York Heart Association (NYHA) functional Class II–IV, LV ejection fraction (LVEF) ≤35%, and electrocardiographic QRS duration >120 ms were prospectively enrolled for a CRT implantation procedure between 2010 and 2014. The CT scan protocol was previously described.[9] Of note, the distinction between ischaemic and non-ischaemic aetiology was based on the medical record of each patient and especially on the history of angina/myocardial infarction and coronary angiography findings. Patients with normal coronary angiography or with minor coronary lesion (<50% stenosis) not explaining the cardiomyopathy were classified as a non-ischaemic.

After CRT implantation, patients returned for regular clinic visits at 1, 3, 6 months, and annually thereafter. At each follow-up visit, NYHA class, global assessment, 6-min walk distance, and 12-lead electrocardiogram (ECG) were assessed. At the 6-month follow-up visit, a repeat echo and assessment for CRT response was performed. Study clinical follow-up ended at 2 years. Of note, the impact of LVWT on the response to CRT was assessed among the 54 enrolled patients and the impact of MR improvement was specifically evaluated among the patients with mild to severe MR at baseline (*n* = 38). The study protocol was approved by the institutional review board and all patients provided written informed consent.

Left ventricular wall thickness analysis

All CT images were retrospectively analysed using the ADAS-VT software (Galgo Medical, Barcelona, Spain) by an experienced observer, blinded to the clinical data. The performance and the inter- and intra-observatory reproducibility of the software has been previously described.[10,11] To create the model, CT images were exported in Digital Imaging and Communications in Medicine (DICOM) format and integrated in the software. A total of four landmarks were manually placed (centre of the aortic annulus, centre of the mitral annulus, LV apex, and centre of the tricuspid annulus). To adjust the model, the contours of the LV endocardium and epicardium were then manually drawn in three LV short-axis slices. Then, endocardial and epicardial borders were delimited with a semiautomatic segmentation algorithm. Lastly, a manual adjustment of the LV endocardial and epicardial boarders was required to fit the surface to the CT images in the short-axis, two chambers, and coronal planes. A three-dimensional visualization of the LV was then created and WT was defined using a colour threshold. As previously described, normal LV WT was defined as an end-diastolic WT >6 mm and WT <6 mm suggested reduced LVWT.[9,10,12] For quantitative analysis, the extent of total WT <6 mm burden was quantified as a percentage of total LV area. In this work, 10 CT images were used to evaluate the intra- and interobserver variance. The intraclass correlation coefficient was 0.97 (0.89–0.99) and 0.95 (0.82–0.99) for the intraobserver and interobserver variability for the total percentage of LVWT <6 mm, respectively.

Additionally, the LV was automatically segmented in 17 segments and each segment was considered with reduced WT in case of WT <6 mm area location. Depending on this segmentation, the LV was divided in three regions: postero-lateral (segments 4-5-10-11-15-16), antero-lateral (1-6-7-12-13), and septal (2-3-8-9-14). Patients were considered to have a thinned region if there was at least one segment with reduced WT in each region.

Regarding the MV apparatus analysis, papillary muscles (PMs) were manually tagged on DICOM images and then automatically segmented and extracted by the ADAS-VT software. Importantly, the implantation base of the PM was carefully tagged to accurately evaluate the WT below the insertion base. After this segmentation, each PM was added and superimposed on the three-dimensional LV model. PM was considered as inserted in a reduced WT area if the majority of the PM was implanted in a region with a WT <6 mm.

Endpoints

Endpoints included the clinical/echocardiographic response to CRT at 6 months, QRS duration decrease at 6 months, MR improvement at 6 months, and the occurrence of major adverse cardiac events (MACE) during 2 years of follow-up.

The clinical response to CRT endpoints included (i) change in the NYHA class at 6 months; and (ii) change in HF clinical status at 6 months using the patient global assessment. Of note, the global assessment score is a 7-point rating scale, allowing for the evaluation of the patient's own perspective of overall health compared with a previous point in time.[13] Patients exhibited HF clinical status response in case of markedly or moderately improvement.

The echocardiographic response to CRT endpoints included (i) change in left ventricular end-systolic volume (LVESV). Left ventricular end-systolic volume response was defined as reduction in LVESV by ≥15%; (ii) change in left ventricular end-diastolic volume (LVEDV). Left

ventricular end-diastolic volume response was defined as reduction in LVEDV by ≥10%; and (iii) LVEF improvement at 6 months. LVEF response was defined as improvement in LVEF by ≥5%.[14]

The intrinsic QRS durations at baseline (pre-CRT) were compared with the biventricular-paced QRS durations at 6 months; the delta QRS was defined as the intrinsic QRS duration (ms) at baseline minus the biventricular-paced QRS at 6 months.

Positive MR improvement at 6 months was defined as improvement by ≥1 class among patient with mild to severe MR at baseline. Of note, the MR was graded semi-quantitatively in an integrative fashion as none 0, trace (1), mild (2), moderate (3), or severe (4). All measurements were performed in accordance with the current guidelines.[15]

For the endpoint of 2-year MACE, we included the composite endpoint of death, LV assist device implantation, cardiac transplantation, and HF hospitalization.

Statistical analysis

Qualitative variables are summarized with frequencies (percentage); continuous data as mean ± standard deviation or median (interquartile range) depending on their distribution, which was assessed using the Kolmogorov–Smirnov test. Categorical variables were compared using the χ^2 test or Fisher's exact test. Continuous variables were compared using Student's t-test or the Mann–Whitney U test for two-group comparisons. Analysis of variance test or Kruskal–Wallis test was used to compare continuous variables among three or more groups. Multivariable analysis and odds ratio (OR) were determined using logistic regression. For the purposes of the multivariable analysis, variables with P-values <0.05 in univariate analysis were included. Of note, for the predictor of response to CRT, we used the LVESV parameter to define responder and non-responder patients (responder was defined as reduction in LVESV by ≥15%). Additionally, for the predictor of MR improvement, a receiver-operator curve analysis was used to categorize LVWT by selecting clinically-relevant cut-off, which were the closest to the optimal cut-off according to the maximum Youden's index (sensitivity + specificity). Survival rates were summarized using Kaplan–Meier estimates, and log-rank tests were used to compare groups. A P-value <0.05 was considered statistically significant. The analyses were performed with the SPSS statistical package, version 11.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

Among the 54 patients enrolled in the DIRECT study, the mean area of LVWT <6 mm was 62.6 ± 53.7 cm^2 per patient (30.2 ± 19.5% of the total LV area). To assess the impact of LVWT on the response to CRT, patients were divided into three groups according to the percentage of LVWT <6 mm related to the total LV area: ≤20% (low group = 21 patients); 20–50% group (moderate group = 21 patients); and ≥ 50% group (high group = 12 patients). Of note, to define these three groups, we used the tertiles of total percentage of LVWT <6 mm. Illustrative examples of patients with ≤ 20%; 20–50%; and ≥50% of LVWT <6 mm are shown in *Figure 1*. Baseline characteristics of the three groups were detailed in *Table 1*. Briefly, there was no difference regarding the age, gender, body mass index, and atrial fibrillation history. All groups have a mean QRS duration >150 ms without statistical difference in the QRS duration or morphology. Of note, there was a statistically increased gradient of N-terminal pro-brain natriuretic peptide (NT-proBNP) level between the three groups.

Regarding the echocardiography parameters, ≤20% group had higher LVEF at baseline without difference in LVEDV or LVESV but a non-significant increase in dilated LV from the ≤20% to the ≥50% group was noted. Additionally, the low LVWT area group had thicker interventricular septum. Regarding the LVWT <6 mm area location, there was a significant gradual number of postero-lateral segments with reduced LVWT from the ≤20% to the ≥50% group.

Of note, supplemental baseline characteristics between patients with ischaemic or non-ischaemic aetiology are presented in the Supplementary material online, *Table S1*. Briefly, ischaemic group was significantly older with worse renal function before CRT implantation. Importantly, both groups were similar according to the echocardiographic parameters and CT analysis at baseline.

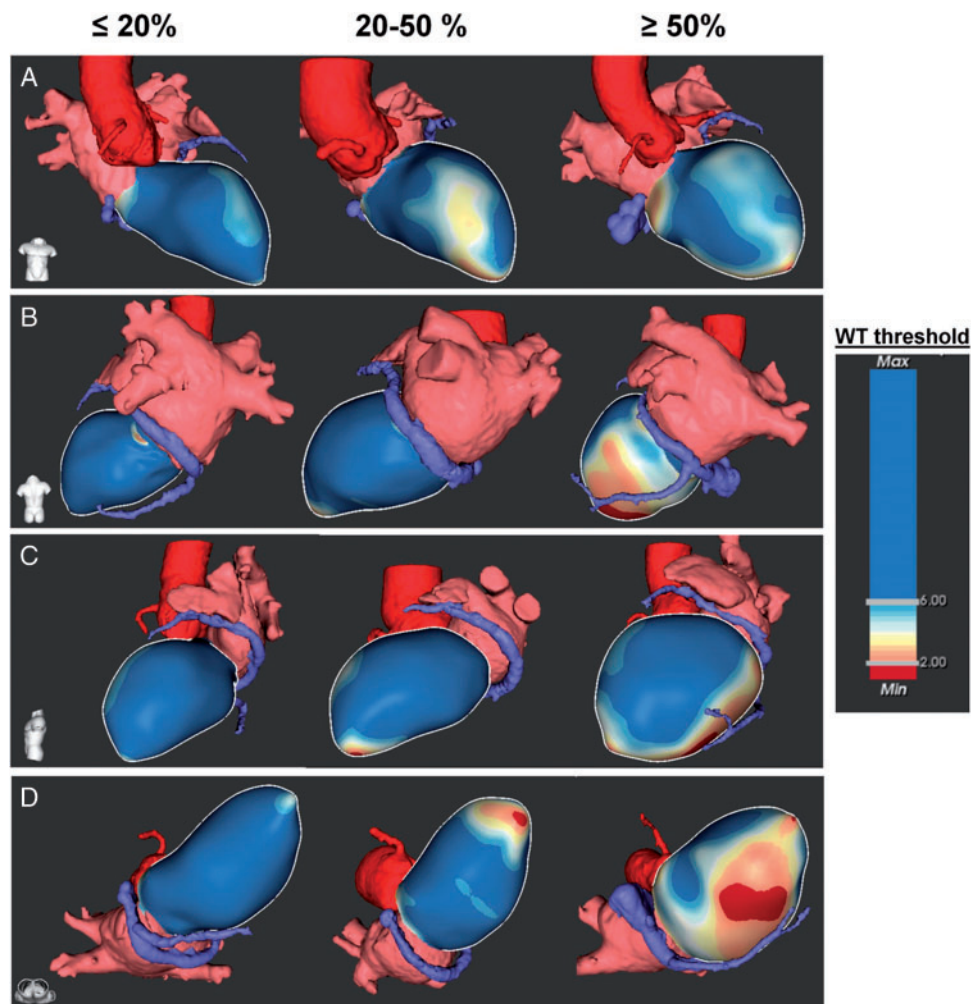## Left ventricular wall thickness and response to cardiac resynchronization therapy

At 6 months, 76%, 71%, and 42% of the patients experienced an improvement in NYHA class by ≥1 in the low, moderate, and high groups, respectively (*Table 2*). Additionally, a majority of patients included in the low and moderate groups (80% and 65%, respectively) had a significant improvement of their global assessment, whereas 42% in the ≥50% group experienced no change of worst global assessment (*Figure 2A*). However, despite a high rate of clinical response in the low and moderate LVWT area group, the 6-min walk distance was only significantly improved in the low group (*Figure 2B*).

Electrocardiographic and echocardiographic response is described in *Figure 3* and *Table 2*. Compared to baseline, biventricular pacing had significantly decreased the QRS duration in the ≤20% group (164.0 ± 14.3 vs. 145.7 ± 15.3, $P = 0.001$). In the 20–50% group, although we noted a QRS duration reduction (162.2 ± 26.7 vs. 148.9.1 ± 27.8, at baseline and 6 months, respectively), this improvement was not statistically significant ($P = 0.140$). Lastly, ≥50% group experienced no electrical remodelling, with no change in QRS duration at 6 months.

Regarding the echocardiographic response to CRT, patients in low LVWT area group have a significant improvement between baseline and 6 months in LVEF (27.2 ± 5.7 vs. 40.6 ± 9.5, respectively; $P < 0.001$) and LVESV (146.6 ± 82.9 vs. 93.3 ± 35.0, respectively; $P = 0.015$). Using the responder criteria for LVESV (≥15% relative reduction), LVEDV (≥10% relative reduction), and LVEF (≥5% absolute increase), positive echocardiographic responses to CRT were observed in 86%, 52%, and 81% of patients, respectively. Patients in the moderate area group experienced only LVEF significant improvement with a positive LVEF, LVEDV, and LVESV response rate of 52%, 52%, and 48%, respectively at 6 months. Lastly, patients with ≥50% of LVWT >6 mm experienced a lower rate of response to CRT at 6 months with 42%, 42%, and 25% of LVEF, LVEDV, and LVESV improvement using the CRT response definition.

Multivariate analysis for the predictor of response to CRT (based on the LVESV reduction at 6 months) showed that the total percentage of reduced WT area was the only predictors of response to CRT [OR 1.04 (1.003–1.08), $P = 0.032$] (Supplementary material online, *Table S2*).

Additionally, the response to CRT was evaluated depending on the underlying cardiomyopathy (Supplementary material online, *Table S3*). Importantly, both aetiologies in the <20% group had significant LVEF improvement and LVESV reduction. In the 20–50% and

Figure 1 Example of left ventricular wall thickness segmentation using the ADAS software in patients with ≤20%, 20–50%, and ≥50% of LV WT <6 mm, respectively. (*A*) Antero-posterior view. (*B*) Postero-anterior view. (*C*) Lateral view. (*D*) Inferior view. LV, left ventricular; WT, wall thickness.

>50% groups, there was no significant LVEF improvement and LV volumes reduction in both patient cohorts, i.e. with ischaemic and non-ischaemic cardiomyopathy. However, there is a trend towards less response in the ischaemic group using the LVEF, LVEDV, and LVESV criteria.

Changes in LVEF, LVEDV, and LVESV from baseline to 6 months were also evaluated depending on the location of the thinned WT in the postero-lateral, antero-lateral, and septal regions. Results are presented in the Supplementary material online, *Table S4*. Briefly, only patients with normal antero-lateral region experienced significant LVEF improvement from baseline to 6 months. Similarly, there was a non-significant trend towards a higher LVEDV and LVESV reduction in patients with normal postero-lateral region.

Mitral regurgitation improvement

Among the 54 patients, 38 (70.4%) had mild to severe MR at baseline and a total of 16 (42.1%) experienced MR improvement by ≥1 class at 6 months. Characteristics of patients with or without MR improvement were described in *Table 3*. Importantly, no difference was recorded regarding the LV dilation in both groups. However, patients

without MR improvement had significantly higher NT-proBNP level at baseline. Interestingly, patients without MR improvement had larger LVWT <6 mm area (41.5 ± 19.4 vs. 22.4 ± 16.1%, $P = 0.003$) associated with a higher number of PM inserted in the reduced LVWT area. Receiver-operator curve analysis for total percentage of LVWT <6 mm demonstrated that an optimal cut-off value of 25% differentiated patients with or without MR improvement {C-statistic of 0.77 [95% confidence interval (CI): 0.62–0.92]} Supplementary material online, *Figure* S1. In multivariable analysis, an area ≥25% of LVWT <6 mm including at least one PM insertion was the only predictor of no MR improvement at 6 months [OR 16.82 (95% CI: 1.72–164.2), $P = 0.015$]. Illustration of PM insertion in reduced LVWT is depicted in *Figure 4A* or *B*.

Lastly, as described in *Figure 4C*, patients with MR improvement had significant lower rate of basal segments with reduced WT (0.9 vs. 1.7, $P = 0.045$), especially in the lateral location. Additionally, results showed a trend toward fewer reduced WT segments in mid and apical locations among the 16 patients with MR improvement. Of note, patients with MR improvement exhibited a lower rate of postero-lateral WT <6 mm segments.

Table 1 Baseline characteristics

	≤20% (n = 21)	20–50% (n = 21)	≥ 50% (n = 12)	P-value
Computed tomography analysis				
LV area with WT <6 mm (cm^2)	9.8 (4.4–16.4)	34.9 (24.9–43.3)	55.4 (53.2–59.9)	**<0.001**
Postero-lateral LV segments with WT <6 mm	1.0 (0.0–2.0)	2.0 (1.0–3.0)	4.0 (2.5–4.5)	**<0.001**
Antero-lateral LV segments with WT <6 mm	0.0 (0.0–1.0)	2.0 (1.0–2.0)	3.0 (1.5–3.0)	**<0.001**
Age (years)	63.1 ± 10.4	63.2 ± 13.5	60.7 ± 10.1	0.810
Ischaemic cardiomyopathy	8 (38.1)	8 (38.1)	4 (33.3)	0.956
Male gender	14 (66.7)	17 (80.9)	9 (75.0)	0.570
Body mass index (km/m^2)	30.9 ± 6.8	27.5 ± 5.2	30.0 ± 3.9	0.148
Hypertension	12 (57.1)	9 (42.9)	6 (50.0)	0.651
Diabetes mellitus	9 (42.9)	3 (14.3)	1 (8.3)	**0.034**
Atrial fibrillation	4 (19.0)	1 (4.8)	3 (25.0)	0.227
Previous device				
Pacemaker	3 (14.3)	1 (4.8)	0 (0)	0.269
ICD	6 (28.6)	7 (33.3)	10 (83.3)	**<0.001**
NYHA functional class				0.556
II	3 (14.3)	5 (23.8)	1 (8.3)	
III	17 (80.9)	16 (76.2)	11 (91.7)	
IV	1 (4.8)	0 (0)	0 (0)	
6-min walk distance (m)	268.3 ± 130.7	341.1 ± 116.9	276.1 ± 131.7	0.177
Baseline medication				
Beta-blockers	20 (95.2)	19 (90.5)	11 (91.7)	0.833
ACEI/ARB	13 (61.9)	18 (85.7)	11 (91.7)	0.076
Spironolactone	8 (38.1)	5 (23.8)	7 (58.3)	0.141
Diuretics	13 (61.9)	13 (61.9)	10 (83.3)	0.381
Electrocardiogram				
Intrinsic QRS duration (ms)	164.0 ± 14.3	162.2 ± 26.7	152.7 ± 20.6	0.346
QRS morphology				0.559
LBBB	16 (76.2)	16 (76.2)	8 (66.6)	
RBBB	1 (4.8)	2 (9.5)	2 (16.7)	
Undetermined BBB	1 (4.8)	2 (9.5)	2 (16.7)	
Paced QRS	3 (14.3)	1 (4.8)	0 (0)	
Laboratory parameters				
Creatinine (mg/dL)	1.0 ± 0.9	1.1 ± 0.9	1.1±1.0	0.416
NT-proBNP (pg/mL)	361.0 (188.2–1113.0)	908.0 (630.7–1738.0)	1730.0 (1179.5–3438.5)	**<0.001**
Echocardiography				
LVEF (%)	27.2 ± 5.7	26.4 ± 6.8	21.2 ± 6.7	**0.031**
LVEDV (mL)	208.3 ± 93.0	235.7 ± 96.2	265.4 ± 81.8	0.149
LVESV (mL)	146.6 ± 82.9	172.5 ± 79.3	202.6 ± 69.4	0.145
Left atrial diameter (mm)	41.1 ± 6.6	44.5 ± 5.7	45.2 ± 4.2	0.082
Interventricular septum (mm)	10.6 ± 1.3	9.4 ± 1.5	9.4 ± 1.9	**0.036**
Posterior wall thickness (mm)	10.4 ± 2.3	10.3 ± 2.0	10.0 ± 1.7	0.836
Mitral regurgitation class				0.490
I	8 (38.1)	7 (33.3)	1 (8.3)	
II	9 (42.9)	7 (33.3)	4 (33.3)	
III	3 (14.3)	4 (19.0)	6 (50.0)	
IV	1 (4.8)	3 (14.3)	1 (8.3)	
LV lead location				
Non-apical location	19 (90.5)	21 (100)	10 (83.3)	0.190
Postero-lateral location	14 (66.7)	16 (76.2)	12 (100)	0.084
Biventricular pacing at 6 months (%)	99.0 (98.0–99.0)	99.0 (96.5–99.0)	98.0 (96.2–99.0)	0.392

A P-value < 0.05 was statistically significant are in bold. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BBB, bundle branch block; ICD, implantable cardioverter-defibrillator; LBBB, left bundle branch block; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; RBBB, right bundle branch block; WT, wall thickness.

Table 2 Echocardiographic and clinical response to CRT

Group	Parameters	Baseline	6 months	Change	P-value	Response definition	Response rate at 6 months (%)
≤20% (n = 21)	LVEF (%)	27.2 ± 5.7	40.6 ± 9.5	+13.5 ± 8.0	<0.001	≥5% absolute increase	86% (n = 18)
	LVEDV (mL)	208.3 ± 93.0	157.3 ± 54.2	−14.6 ± 25.6	0.100	≥10% relative reduction	52% (n = 11)
	LVESV (mL)	146.6 ± 82.9	93.3 ± 35.0	−28.6 ± 25.2	0.015	≥15% relative reduction	81% (n = 17)
	NYHA I/II/III/IV (%)	0/14/81/5	30/50/20/0	+1.0 ± 0.7	<0.001	≥1 class improvement	76% (n = 16)
20–50% (n = 21)	LVEF (%)	26.4 ± 6.8	31.3 ± 7.8	+4.9 ± 5.6	0.036	≥5% absolute increase	52% (n = 11)
	LVEDV (mL)	235.7 ± 96.2	202.7 ± 70.8	−5.6 ± 35.4	0.236	≥10% relative reduction	52% (n = 11)
	LVESV (mL)	172.5 ± 79.3	140.5 ± 61.4	−10.8 ± 34.3	0.173	≥15% relative reduction	48% (n = 10)
	NYHA I/II/III/IV (%)	0/24/76/0	23/48/29/0	+0.7 ± 0.7	0.004	≥1 class improvement	71% (n = 15)
≥50% (n = 12)	LVEF (%)	21.2 ± 6.7	24.2 ± 5.4	+3.1 ± 4.1	0.230	≥5% absolute increase	42% (n = 5)
	LVEDV (mL)	265.4 ± 81.8	246.9 ± 69.8	−5.6 ± 21.6	0.557	≥10% relative reduction	42% (n = 5)
	LVESV (mL)	202.6 ± 69.4	190.9 ± 58.6	−5.5 ± 23.1	0.669	≥15% relative reduction	25% (n = 3)
	NYHA I/II/III/IV (%)	0/8/92/0	17/42/33/8	+0.6 ± 0.9	0.038	≥1 class improvement	42% (n = 5)

CRT, cardiac resynchronization therapy; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association.
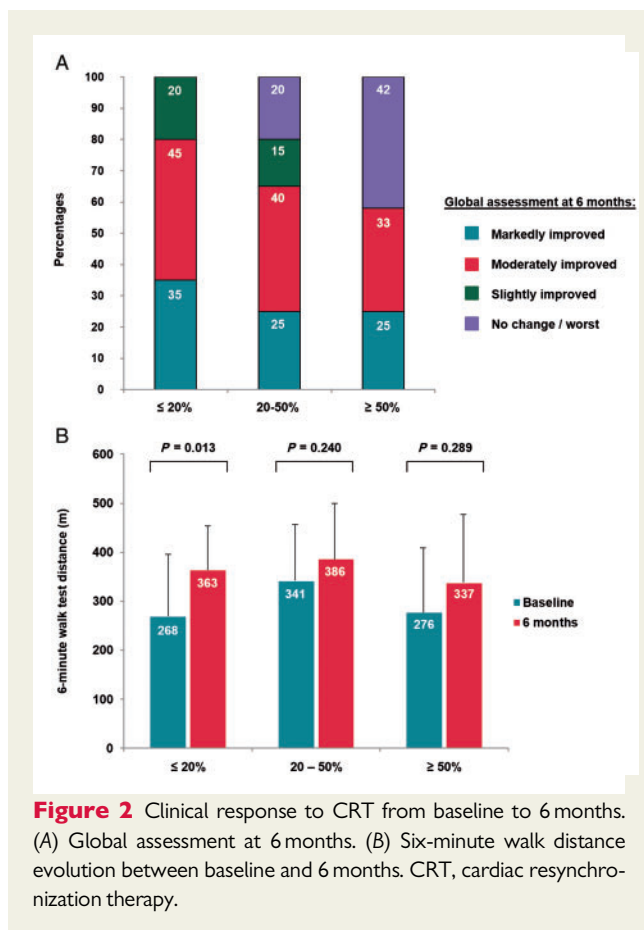
Figure 2 Clinical response to CRT from baseline to 6 months. (A) Global assessment at 6 months. (B) Six-minute walk distance evolution between baseline and 6 months. CRT, cardiac resynchronization therapy.

Left ventricular wall thickness and major adverse cardiac events outcomes

Among the 54 CRT recipients, MACE occurred in 9 (16.7%) patients after 2 years of follow-up. Among those, all experienced at least one HF hospitalization, one was subsequently implanted with a LV assist device and cardiovascular death occurred in five patients. None of these CRT recipients underwent heart transplantation. Of note, four patients who died were in the ≥50% group and death occurred 10.0 ± 6.8 months after CRT implantation. First MACE occurred after a mean time of 10.9 ± 5.9 months after CRT implantation and low and moderate area groups had higher MACE-free survival probability than the high area group (*Figure 5*).

Discussion

Main results

Our study is amongst the first to evaluate the role of CT in quantifying the extent of LVWT in prognosticating response to CRT. The main results of this study are: (i) LVWT could help to stratify the response to CRT and predicts MR improvement. (ii) Cardiac resynchronization therapy candidates with a low percentage of LVWT <6 mm (≤20%) significantly improved their clinical status and echocardiography parameters compared to the groups with a larger proportion of reduced LVWT. (iii) Patients without MR improvement had larger LVWT <6 mm area associated with a higher number of PM inserted in the reduced LVWT area. (iv) Lastly, patients with ≥50% of LVWT <6 mm were at higher risk of MACE.

Left ventricular morphology and response to cardiac resynchronization therapy

Among the factors influencing the response to CRT, LV myocardial morphology has been investigated in HF patients. Indeed, among 97 non-ischaemic patients, those with mid-wall fibrosis detected by CMR via late gadolinium enhancement were less likely to exhibit LV reverse remodelling.[16] Similarly, Taylor et al.[5] evaluated the impact of CMR among 89 CRT candidates and showed that LV lead deployment over non-scarred segments was associated with better
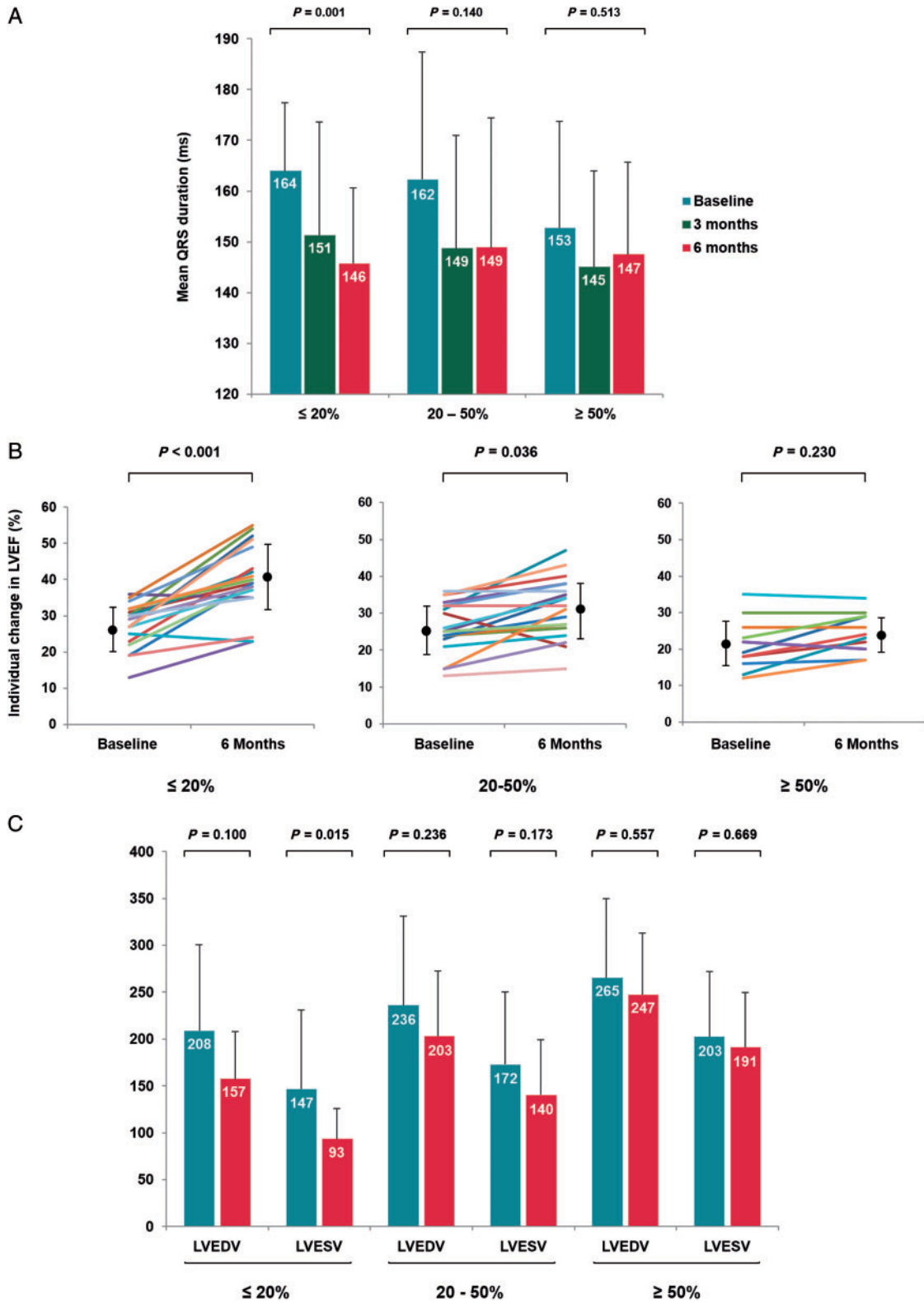
Figure 3 Electrocardiographic and echocardiographic response to CRT from baseline to 6 months. (*A*) QRS duration change from baseline to 6 months. (*B*) Individual changes in LVEF from baseline to 6 months. (*C*) Change in LVEDV and LVESV from baseline to 6 months. CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVEDV, left ventricular end-diastolic volume.

Table 3 Baseline characteristics between patients with or without MR improvement

	MR improvement by ≥1 class (*n* = 16)	No MR improvement (*n* = 22)	*P*-value
Age (years)	59.5 ± 10.1	65.7 ± 10.2	0.073
Male gender	12 (75.0)	16 (72.2)	0.829
Ischaemic cardiomyopathy	5 (31.2)	8 (36.4)	0.553
Body mass index (km/m^2)	28.3 (23.5–34.4)	27.4 (26.0–30.6)	0.657
Hypertension	4 (25.0)	12 (54.5)	0.137
Diabetes mellitus	1 (8.3)	4 (33.3)	0.374
Atrial fibrillation	2 (12.5)	4 (18.2)	0.981
NYHA functional class			0.425
II	4 (25.0)	3 (13.6)	
III	12 (75.0)	19 (86.4)	
IV	0 (0)	0 (0)	
Baseline medication			
Beta-blockers	15 (93.7)	19 (86.4)	0.624
ACEI/ARB	10 (62.5)	17 (77.3)	0.471
Spironolactone	6 (37.5)	10 (45.4)	0.875
Diuretics	10 (62.5)	18 (81.8)	0.267
Electrocardiogram			
QRS duration (ms)	171.5 ± 25.6	162.7 ± 20.7	0.251
LBBB morphology	11 (68.7)	14 (63.6)	0.985
Laboratory parameters			
Creatinine (mg/dL)	1.0 ± 0.2	1.1 ± 0.2	0.460
NT-proBNP (pg/mL)	813.0 (365.5–1243.5)	1651 (1100.0–3248.0)	0.007
Echocardiography			
LVEF (%)	26.2 ± 7.0	23.5 ± 7.4	0.268
LVEDV (mL)	246.8 ± 90.2	241.6 ± 106.0	0.873
LVESV (mL)	167.0 (124.0–251.0)	157.0 (107.2–206.0)	0.477
Left atrial diameter (mm)	45.9 ± 4.9	43.2 ± 6.2	0.144
Inter ventricular septum (mm)	9.7 ± 1.7	9.8 ± 2.2	0.867
Post-wall thickness (mm)	9.5 ± 2.5	10.1±1.5	0.428
MR class			0.547
II	10 (62.5)	10 (45.5)	
III	4 (25.0)	9 (40.9)	
IV	2 (12.5)	3 (13.6)	
LV computed tomography analysis			
Total of LV WT <6 mm (%)	22.4 ± 16.1	41.5 ± 19.4	0.003
Papillary muscle inserted in LV WT <6 mm			
0	13 (81.3)	6 (27.3)	0.004
1	3 (18.7)	14 (63.6)	
2	0 (0)	2 (9.1)	
Posterior MV pillar	3 (100)	13 (59.1)	0.031
Anterior MV pillar	0 (0)	5 (22.7)	0.061
LV lead location			
Non-apical location	15 (93.7)	19 (86.4)	0.624
Postero-lateral location	14 (87.5)	21 (95.4)	0.562
Biventricular pacing at 6 months (%)	99.0 (98.0–99.0)	98.0 (96.7–99.0)	0.388
Biventricular pacing QRS duration at 6 months (ms)	155.3 ± 22.8	152.1 ± 21.1	0.664

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ICD, implantable cardioverter-defibrillator; LBBB, left bundle branch block; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; MV, mitral valve; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; RBBB, right bundle branch block; WT, wall thickness.
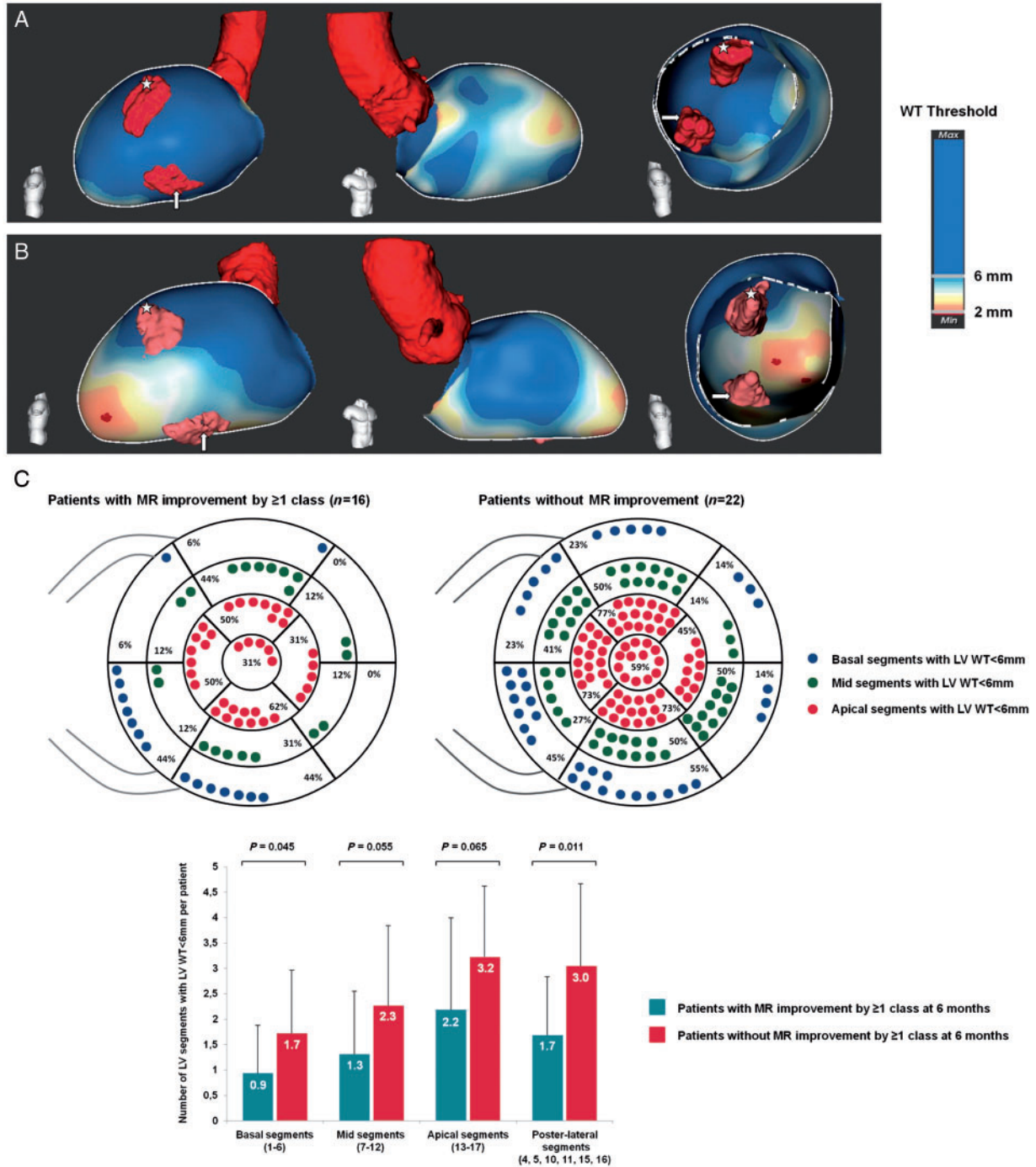
Figure 4 (A and B) Illustrative examples of WT segmentation and PM insertion. (A) Patient with 45% of LVWT <6 mm and PM insertion in normal WT area who experienced MR improvement at 6 months. (B) Patients with 46% of LVWT <6 mm and posterior PM inserted in reduced WT area without MR improvement. (C) LV segmentation and location of each reduced WT segments in a patient with or without MR improvement. Star indicates anterior PM insertion; Arrow indicates posterior PM insertion. LVWT, left ventricular wall thickness; MR, mitral regurgitation; PM, papillary muscle; WT, wall thickness.

response and clinical outcomes after CRT. However, data regarding LV CT analysis and CRT benefit are unclear.[9] Variability in the measurement of WT (i.e. end-diastole or end-systole) can impact it predictive value. WT measured during maximal systolic thickening could possibly under-estimate the real burden of reduced WT area

compared to end-diastole measurement. Indeed, a recent editorial has suggested that the quantification of reduced WT is more accurate during the end-diastole.[12] In our study, we observed a graded enhanced response to CRT with increasing WT. Similarly, WT as a marker for adverse events in CRT recipients has been evaluated
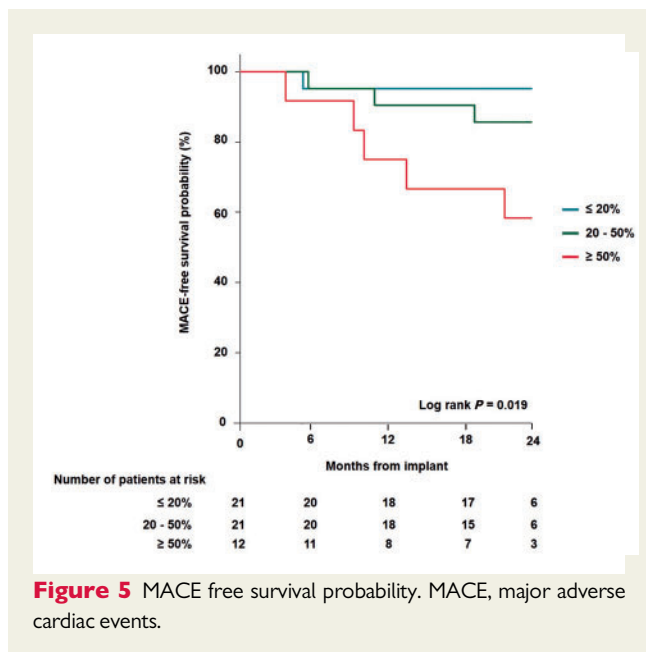
Figure 5 MACE free survival probability. MACE, major adverse cardiac events.

among the patients enrolled in the MADIT-CRT study.[17] In this work, relative WT at baseline was the best echocardiographic predictor for ventricular tachyarrhythmia events compared with commonly used echocardiographic measurements and rightfully suggested that WT can mirror the extent of LV fibrosis and scarring on one hand and the extent of the remodelling process on the other hand.[17] In the current study, advanced deleterious remodelling process could explain poor response to CRT in patients with a larger baseline area of WT <6 mm. Indeed, moderate (20–50%) and high (≥50%) groups had both numerical higher LVEDV and LVESV at baseline compared to the low area patients. However, the moderate group experienced more favourable response to CRT than the high group and higher fibrosis and more scar response in these patients may explain that they less likely experienced LV reverse remodelling. Notably, we found that patients within the ≥50% group had no QRS reduction after CRT compared to baseline ECG, thereby explaining the LV function improvement, as previously described.[18]

Left ventricular wall thickness and mitral regurgitation improvement after cardiac resynchronization therapy

In our current study, we observed that PM insertion site is probably crucial. Indeed, patients without MR improvement had larger LVWT <6 mm area associated with a higher number of PM inserted in the reduced LVWT area. This result possibly highlighted the critical link between the LV morphology at the site of MV apparatus insertion and suggests that normal WT could promote a MV apparatus remodelling after CRT. Our result is supported by previous work that demonstrated that the lack of scar at the PM insertion sites using echocardiography was associated with MR improvement.[19] Lastly, we observed that patients without MR improvement had larger area of reduced WT in the basal segments. Similarly, previous study showed that CRT enhanced the mitral annular deformation by resynchronizing LV basal segments.[20] Consequently, normal WT

adjacent to the MV annulus could potentially improve mitral annulus deformation in CRT recipients, leading to a decrease of the annular diameter.

Computed tomography as a tool to predict outcomes in cardiac resynchronization therapy candidates

In our study, we show that patient with ≥50% area of LVWT <6 mm had poor 2 years of outcomes compared to ≤20% and 20–50% groups. Of note, this result is consistent with a previous study that demonstrated that CRT patients with low relative WT at baseline had significantly higher risk for ventricular arrhythmias and death.[17] Additionally, advanced deleterious remodelling process could explain the worse outcomes in patients with a larger area of WT <6 mm. Indeed, we showed that this subgroup of patients had lower LVEF and higher NT-proBNP level at baseline.

Clinical implications

These results bring important information and could be helpful in daily clinical practice. First, in contrast to other cardiac imaging technique, CT provides some benefit. Indeed, compared to CMR, CT can be much more easily and quickly performed in patients previously implanted with a device (pacemaker or implantable cardioverter-defibrillator) and who require an upgrade to CRT. Additionally, echocardiography measurement requires a relatively high image quality, depends more heavily on operator experience and cannot provide an extensive description of the WT compared to CT. Second, LVWT using CT analysis could stratify the response to CRT in HF patients, depending on the total area with WT < 6 mm (≤20%, 20–50%, and ≥50%) and may assist the physician to optimize the HF management. Indeed, patient with low or moderate percentages of LVWT <6 mm (≤20% and 20–50%) experience few MACE during 2 years of follow-up compared to patients with a larger area of LVWT <6 mm, who exhibited 33.3% of cardiac death. Physicians should consequently carefully manage this last group associated with probably low chance of long-term CRT benefit expected but only temporary HF status stabilization.

Limitations

The limited sample size makes our study hypotheses generating, and will require validation in larger studies. The relationship between WT and fibrosis is difficult to define and will require evaluation through studies using multi-modality imaging (i.e. CMR and CT). Lastly, due to the small number of MACE, we were not able to provide a multivariate analysis to evaluate the impact WT on the outcomes.

Conclusion

Left ventricular wall thickness evaluated using cardiac CT could help to stratify the response to CRT and MR improvement in HF patients. This needs to be further validated in a larger cohort of patients receiving CRT.

Supplementary material

Supplementary material is available at Europace online.

Funding

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Corrigendum

Corrigendum to: Lyme carditis atrioventricular block: management strategies [*Europace* 2019;**21**:1280–2]

In Figure 1 from the Letter to the Editor entitled "Lyme carditis atrioventricular block: management strategies",[1] the treatment for Lyme carditis was presented as "Continue intravenous antibiotics for 10-14 days, followed by oral antibiotics for 4-6 weeks". However, this should have read "Continue intravenous antibiotics for 10-14 days", follow by oral antibiotics for a total course of 14-21 days". Therefore, the figure in the online version of the Letter has been amended.

Reference

1. Crinion D, Yeung C, Baranchuk A. Lyme carditis atrioventricular block: management strategies. *Europace* 2019;**21**:1280–2.