Tohoku J. Exp. Med., 2020, **251**, 69-79

Cardiac Resynchronization Therapy for Improving Non-Uniform Thickening of Left Ventricular Wall: Assessment by Quantitative Gated Myocardial Perfusion SPECT

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Cardiac resynchronization therapy (CRT) improves cardiac dyssynchrony in heart failure patients with a wide QRS electrocardiogram (ECG). Assessment of left ventricular (LV) dyssynchrony using echocardiography or other imaging modalities is important to predict CRT effectiveness. In this study, we retrospectively evaluated cardiac nuclear imaging of ECG-gated myocardial perfusion single-photon emission computed tomography (SPECT) with ^{99m}Tc-sestamibi for CRT candidate (n = 120) with severe heart failure and wide QRS (> 120 msec) in ECG. To analyze LV non-uniformity, we used the quantitative gated SPECT (QGS) software to calculate changes in regional LV wall thickness during a cardiac cycle (i.e., wall thickening scores). Cardiac events (heart failure, ventricular arrhythmias and cardiac death) after CRT during 38 ± 22 (SD) months were also evaluated. In 97 of 120 patients who underwent QGS before and 6 months after CRT, CRT homogenized non-uniform wall thickening between septal and lateral of the LV especially in CRT responders. This observation was indicated as increase in the lateral deflection (X_{WT}) of wall thickening scores before CRT and its decrease after CRT. In 120 patients with QGS before CRT, the larger X_{WT} before CRT (≥ 16.5) predicted better prognoses after CRT. This finding was similarly observed even in patients with narrower baseline QRS (≤ 140 msec; n = 41 of 120), who usually have less benefits from CRT. In conclusion, CRT improved non-uniformity of wall thickening between the LV septal and lateral regions evaluated using QGS, which is predictive of better prognosis in the chronic phase after CRT.

Keywords: cardiac resynchronization therapy; dyssynchrony; heart failure; nuclear imaging; quantitative SPECT
Tohoku J. Exp. Med., 2020 June, **251** (2), 69-79.

Introduction

Cardiac resynchronization therapy (CRT) is a promising non-pharmacological treatment using bi-ventricular pacing for severe heart failure patients with cardiac dyssynchrony (Abraham et al. 2002; Kass 2003). Although a wider QRS duration using the electrocardiogram (ECG) as a marker of cardiac *'electrical'* dyssynchrony is used to select CRT candidates (Hunt et al. 2005; Swedberg et al. 2005), it is known that measurements of intra-left ventricular (LV) *'mechanical'* dyssynchrony are important for predicting the efficacy of CRT (Kass 2003). Although cardiac echocardiography (Yu et al. 2002; Chung et al. 2008; Seo et al. 2011) has been used to assess mechanical dyssynchrony in patients subjected to CRT, there are no definite criteria for dyssynchrony to predict CRT responders (Chung et al. 2008; Seo et al. 2011).

Other modalities of cardiac imaging have been developed and used supplementary for the evaluation of CRT using echocardiography (AlJaroudi et al. 2011). In nuclear imaging with single-photon emission computed tomography (SPECT), the quantitative gated SPECT software

Received September 10, 2019; revised and accepted April 29, 2020. Published online June 4, 2020; doi: 10.1620/tjem.251.69.
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(QGS) is widely used to analyze global and regional myocardial perfusion and LV function in the clinical situation (Germano et al. 1997). However, there is no promising or convenient method to evaluate cardiac dyssynchrony or CRT response using the nuclear imaging.

In this study, we report the importance of LV-wall thickening analysis using QGS to evaluate the effectiveness of CRT. The non-uniformity of the regional LV-wall thickening assessed by QGS is a convenient and useful parameter to predict the effects and prognosis after CRT.

Materials and Methods

Study patients

In this study, we retrospectively evaluated 120 heart failure patients who received CRT from July 2003 to August 2011 and underwent ECG gated SPECT before the CRT (pre CRT). The indication of CRT was considered according to the major randomized trials (Abraham et al. 2002; Bristow et al. 2004) and guidelines (Hunt et al. 2005; Swedberg et al. 2005) of CRT as follows; QRS duration ≥ 120 msec (both intrinsic QRS and right ventricular (RV) pacing) and New York Heart Association (NYHA) class II to IV, LV ejection fraction (EF) ≤ 35%. In this study, patients with both sinus rhythm and chronic atrial fibrillation were included. Although patients with atrial fibrillation were excluded in the major randomized trials of CRT (Abraham et al. 2002; Bristow et al. 2004), we included these patients because CRT was clinically effective in these patients in some extent. LV dyssynchrony assessed by echocardiography (Yu et al. 2002; Chung et al. 2008; Seo et al. 2011) was considered for the selection of CRT candidates. In a part of these patients, the follow-up SPECT was repeated at 2 weeks (n = 106) and 6 months (n = 97) after CRT implantation during biventricular pacing to elucidate the effectiveness of CRT at the acute and chronic phase in the QGS analysis.

This study was discussed and approved by the ethics committee at Tohoku University (December 19, 2005) for scientific presentation or publication as a clinical retrospective observational study, especially in terms of the repeat examination using a nuclear agent. The patients provided their written informed consent including the CRT implantation and the accompanying several examinations of cardiac imaging including the gated SPECT before the treatment.

CRT system is composed of a bi-ventricular pacing system, i.e., an ordinary pacemaker system (right atrial and ventricular pacing) and an LV pacing. An LV pacing lead was transvenously implanted around the LV lateral region through the lateral branch of coronary vein (n = 114) or the anterior region through the great cardiac vein due to anatomical reasons (n = 2). When the transvenous approach through coronary vein was unsuccessful, the LV lead was surgically implanted around the LV lateral wall (n = 4). After CRT implantation, the atrio- and inter-ventricular delays were optimized using echocardiography. Medications were also optimized and all patients were able to tolerate β-blockers or angiotensin converting enzyme inhibitors/angiotensin receptor blockers after the CRT. In patients with atrial fibrillation, the heart rates were reduced to achieve biventricular pacing (≥ 90% of total beats) using digoxin, β-blockers or amiodarone. In the 3 patients with drug-resistant tachycardia of atrial fibrillation, an atrio-ventricular nodal ablation was performed.

Gated SPECT

In the clinical setting, the QGS analysis using ECG-gated SPECT is widely used to assess cardiac global (i.e., LV volume and EF) and regional LV function (i.e., wall thickening) and coronary perfusion (i.e., myocardial viability) in heart failure patients with ischemic heart disease, cardiomyopathy, and so on. In this study, we used almost the same protocol as that in the clinical setting as follows.

The acquisition of the ECG-gated SPECT at rest was started 60 minutes after an injection of 600 MBq of ^{99m}Tc-sestamibi using a double-head gamma camera (E-CAM, Siemens, Germany) equipped with high-resolution collimators, a 180° rotation arc, 32 projections, and 64 × 64 matrices. Gated images were acquired for 40 beats in 20 steps over 180° orbits at 16 frames per cardiac cycle.

The commercially available QGS program, which was originally described by Germano in Cedars-Sinai Medical Center (Germano et al. 1997), semi-automatically determined the 3-D endocardial and epicardial surfaces of the LV (see Fig. 1B) in the gated images during the cardiac cycle and calculated the LV end-diastolic (EDV) and end-systolic volumes (ESV) and EF. We performed the follow-up SPECT at 6 months after CRT in 97 (81%) of 120 patients. CRT responders were defined as patients who had a ≥ 10% decrease in the ESV at 6 months after the CRT.

In addition, the regional myocardial perfusion and regional wall thickening (i.e., changes in regional wall thickening during the cardiac cycle) were quantified and scored in 26 divided LV segments as shown with bull's eye mapping (see Fig. 2A). The algorithm of the QGS for calculating the wall thickening scores was based on the methodology by Germano et al. (1997), where the wall thickening scores were calculated as an increase in the wall thickening from end-diastole to end-systole and was expressed as the percentage of the maximum in the 26 LV segments.

Wall thickening analysis evaluated by QGS

In order to assess the regional LV function, the regional wall thickening scores analyzed by QGS as described above were used in this study. Except for the apex, we averaged the wall thickening scores in 8 LV circumferential segments of the bull's eye map, that were composed of 2 segments each from the anterior (A1, A2), lateral (L1, L2), inferior (I1, I2), and septal (S1, S2) regions of the LV (see Fig. 2B).

We studied the distribution of the wall thickening scores in the 8 circumferential LV segments and calculated the average wall thickening scores by summing the ampli-

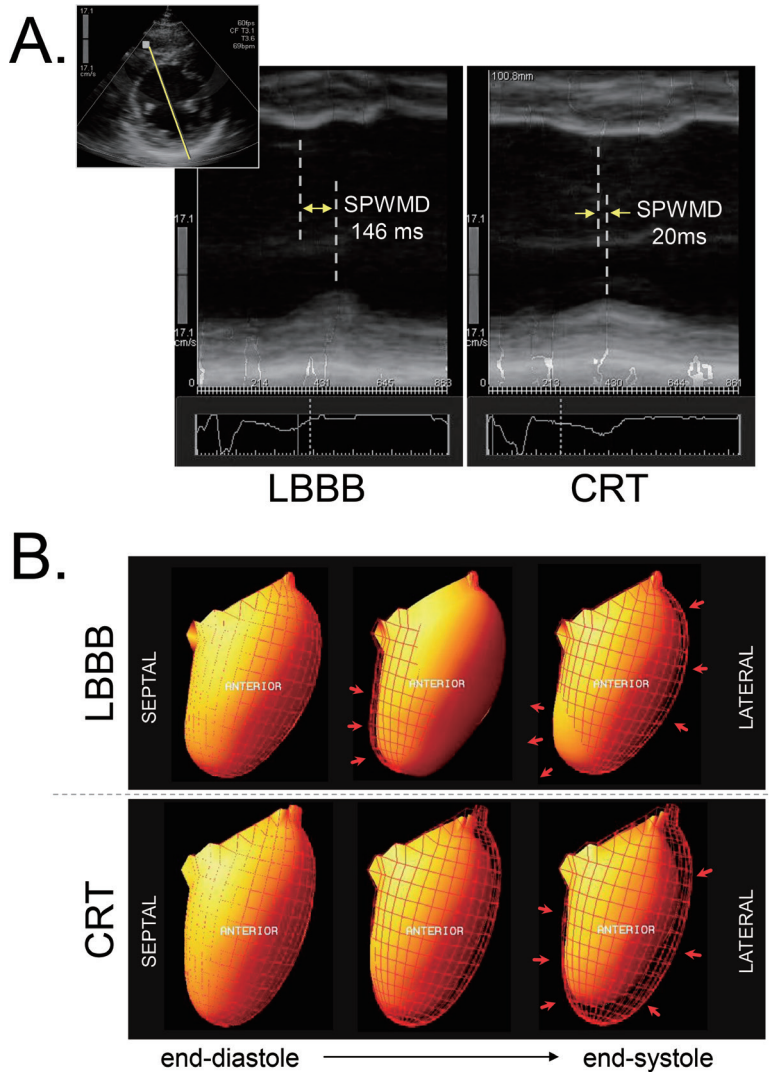

Fig. 1. Typical example of cardiac dyssynchrony.
A. Representative results of M-mode echocardiography in a dilated cardiomyopathy patient with LBBB, showing 146 msec of SPWMD. CRT improved LV dyssynchrony, resulting decrease in SPWMD.
B. Reconstructed left ventricular endocardial surface movies using QGS, showing dyssynchronous wall motion during LBBB and its improvement during CRT. The septal wall moved inward early during systole and then bulged outward during end-systole due to late activation of the LV lateral wall during LBBB, whereas the septal and lateral wall simultaneously moved inward during CRT.
LBBB, left bundle branch block; CRT, cardiac resynchronization therapy; SPWMD, septal-to-posterior wall motion delay.

tudes as vectors toward the 8 LV segments in the bull's eye map based on the angular distribution (see Fig. 2C) as in the following calculations:

$$X_{WT} = A1*\cos(5/8\pi) + A2*\cos(3/8\pi) + L1*\cos(1/8\pi) + L2*\cos(-1/8\pi) + I1*\cos(-3/8\pi) + I2*\cos(-5/8\pi) + S1*\cos(-7/8\pi) + S2*\cos(7/8\pi)$$

$$Y_{WT} = A1*\sin(5/8\pi) + A2*\sin(3/8\pi) + L1*\sin(1/8\pi) + L2*\sin(-1/8\pi) + I1*\sin(-3/8\pi) + I2*\sin(-5/8\pi) + S1*\sin(-7/8\pi) + S2*\sin(7/8\pi).$$

The summed vector of the wall thickening scores was expressed as a coordinate point (i.e., X_{WT} and Y_{WT}; see Fig. 2C). X_{WT} was the lateral deflection of the averaged wall thickening as a marker of the wall thickening non-uniformity between the septal and lateral regions, and Y_{WT} was the deflection of the averaged wall thickening between the LV anterior and inferior regions.

Follow-up

The patients were followed up for 38 ± 22 (SD, standard deviation) months on average after the CRT implantation. Cardiovascular deaths, hospitalizations due to worsening of heart failure, introduction of LV assist systems, and occurrence of ventricular tachy-arrhythmias including appropriate defibrillator shocks were defined as major

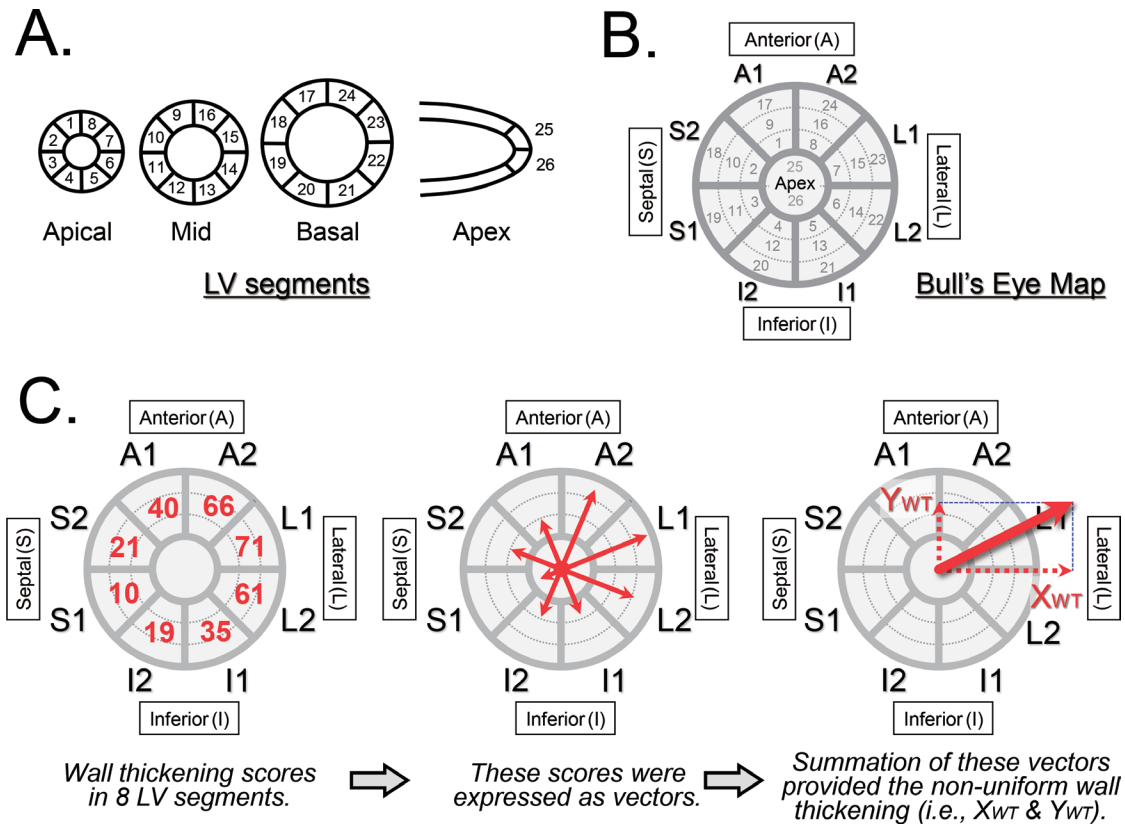

Fig. 2. Evaluation LV wall thickening using QGS.
A. Schema of the perfusion SPECT of the LV segments assigned as no.1 to 26.
B. Schema of the bull's eye polar map of SPECT, showing the score of each 26-LV segment.
C. An example of the averaged wall thickening scores in the 8 left ventricular (LV) circumferential segments on the basis of the Bull's eye map calculated using the QGS analysis (*left panel*). The wall thickening scores in the 8 LV circumferential segments were expressed as vectors (*middle panel*). The summation of those vectors of the wall thickening in the 8 LV segments provides a coordinate point (i.e., X_{WT} and Y_{WT}; *right panel*). The X_{WT} was used as a marker of septal-to-lateral non-uniformity of the wall thickening.

adverse cardiac events (MACE).

Statistical analysis

The results were expressed as the mean ± SD. The Pearson's chi-squared test was used for discrete variables, and the Wilcoxon signed rank test for continuous variables among the patient groups. Multiple comparisons between variables were performed by the post-hoc Bonferroni test. Survival curves from MACE were constructed according to the Kaplan-Meier methods and the differences between curves were analyzed by the log-rank test. $P < 0.05$ was considered to be statistically significant. All analyses were performed with SPSS-based software (version 11.0).

Results

Patient characteristics and responses to CRT

The characteristics of the patients in this study before the CRT are shown in Table 1. In 97 of 120 patients who had baseline and 6-month SPECT data, 63 patients (65%) were diagnosed as CRT responders with LV reverse remodeling (≥ 10% decrease in the ESV at 6 months), while the remaining 34 patients (35%) were non-responders as has been shown previously (Abraham et al. 2002; Bristow et al. 2004). CRT responders frequently had a left bundle branch block (LBBB) morphology (including RV apical pacing) in the baseline ECG and exhibited longer QRS widths than the non-responders. There was no difference in the NYHA class between the 2 groups although lower plasma levels of the brain natriuretic peptide (BNP) before the CRT were observed in responders.

Table 2 shows the LVEDV, ESV, and EF evaluated by QGS. The baseline LV volume and EF were comparable between the responders and non-responders. By definition, the EDV and ESV were decreased even at 2 weeks and further decreased at 6 months after the CRT in responders. In contrast, those were markedly increased at 6 months the non-responders.

Evaluation of dyssynchrony using QGS

Fig. 1A shows representative results of an M-mode echo in a patient with dilated cardiomyopathy. Before the CRT during LBBB, the septal wall thickening began early during the systolic phase and exhibited biphasic movement due to delayed activation of the posterolateral wall, with a

Table 1. Baseline patients characteristics.

	All patients (n = 120)	Responders (n = 63)	Non-responders (n = 34)	P values[1)]
Age, years	62 ± 12	62 ± 13	60 ± 13	P = 0.61
Male	81 (68)	40 (63)	27 (79)	P = 0.11
Ischemic etiology	23 (19)	10 (16)	9 (26)	P = 0.21
NYHA class	2.9 ± 0.5	2.9 ± 0.5	3.0 ± 0.4	P = 0.31
QRS, msec	160 ± 33	171 ± 31	147 ± 35	P < 0.01
LBBB[2)]	76 (63)	52 (83)	13 (38)	P < 0.01
BNP, pg/dl	661 ± 615	525 ± 447	840 ± 754	P < 0.05
Prior ICD	19 (16)	6 (10)	7 (20)	P = 0.13
History of VT/VF	25 (21)	11 (17)	8 (24)	P = 0.47
AF	41 (34)	21 (33)	12 (35)	P = 0.84
RV pacing	40 (33)	27 (43)	8 (24)	P = 0.06
Medication				
β-blockers	102 (85)	55 (87)	28 (82)	P = 0.51
ACEI / ARB	107 (89)	58 (92)	29 (85)	P = 0.30
Diuretics	107 (89)	57 (90)	31 (91)	P = 0.91
Digitalis	44 (37)	27 (43)	12 (35)	P = 0.47
Aldosterone blockers	72 (60)	37 (59)	23 (68)	P = 0.39
Class III AAD	43 (36)	18 (29)	15 (44)	P = 0.12
Pimobendan	27 (23)	12 (19)	9 (32)	P = 0.39

The results are expressed as the mean ± SD or number, with percentages in parentheses.
ICM, ischemic cardiomyopathy; NYHA, New York Heart Association; LBBB, left bundle branch block; BNP, brain natriuretic peptide; ICD, implantable cardioverter defibrillator; VT/VF, ventricular tachycardia and fibrillation; AF, atrial fibrillation; RV, right ventricular; ACEI/ ARB, angiotensin converting enzyme inhibitors / angiotensin receptor blockers; AAD, anti-arrhythmic drugs.
[1)]Comparison of responders and non-responders.
[2)]LBBB morphology including right ventricular apical pacing.

146-msec wall motion delay. CRT synchronized such abnormal wall thickening delay.

Using the 3D LV surface displays constructed by QGS (Fig. 1B), dyssynchronous wall motion was recognized during LBBB and was improved during CRT. The septal wall moved inward early during systole and then bulged outward during end-systole due to late activation of the LV lateral wall during LBBB, whereas the septal and lateral wall simultaneously moved inward during CRT. These findings were consistent with those observed with M-mode echo.

Effects of CRT on regional perfusion and wall thickening

We evaluated the effects of CRT on the regional LV myocardial perfusion and wall thickening in the bull's eye map using QGS. In Fig. 3A, CRT did not affect the distribution of the regional LV perfusion, whereas that of the regional wall thickening clearly changed after biventricular pacing in the responder. During LBBB, the wall thickening in the septum decreased and that in the lateral LV segment became enhanced in the responder. The wall thickening became homogeneous especially between the septal and lateral regions after the CRT. In contrast as shown in Fig. 3B, the non-responder had little non-uniformity of the LV wall thickening before CRT and no improvement after CRT.

The average distribution of the regional myocardial perfusion demonstrated that CRT did not affect the regional perfusion in either the responders or non-responders (Fig. 4A). In contrast, CRT affected the distribution of the regional wall thickening especially in the responders as shown in Fig. 4B. The average wall thickening scores in the responders strikingly demonstrated a lateral shift before CRT and its centralization after CRT. These observations were indicated by a significant reduction in the X_{WT} (Fig. 4C; a positive value indicates a lateral deflection) from +54 ± 52 (pre) to –5 ± 43 and –12 ± 40 (2 weeks and 6 months; both $P < 0.01$ vs. pre), respectively. In contrast, in the non-responders, there was little change in the wall thickening scores before CRT (Fig. 4B, C).

Determinants of LV reverse remodeling and the prognosis

As shown in Fig. 5A, the X_{WT} before the CRT was significantly correlated with the percent changes in the ESV (% ESV) at 6 months after the CRT ($R = 0.465$, $P < 0.01$; $n = 97$). The changes in the plasma BNP level at 6 months after the CRT were also linearly correlated with the % ESV ($R = 0.58$, $P < 0.01$; $n = 97$, data not shown here). These results

Table 2. Analysis of the left ventricular global function using QGS.

	All patients (n = 120)	Responders (n = 63)	Non-responders (n = 34)	P values[1)]
EDV				
pre CRT, ml	249 ± 114	239 ± 97	289 ± 143	P = 0.07
2 weeks, ml	234 ± 116	206 ± 80	289 ± 147	P < 0.01
6 months, ml	216 ± 132	163 ± 72**	311 ± 159	P < 0.01
%Δ *2 weeks*, %	–11 ± 14**	–17 ± 10**	–1 ± 9	P < 0.01
%Δ *6 months*, %	–16 ± 25**	–31 ± 17**	+9 ± 15**	P < 0.01
ESV				
pre CRT, ml	192 ± 106	184 ± 88	233 ± 134	P = 0.06
2 weeks, ml	183 ± 110	154 ± 74	240 ± 141	P < 0.01
6 months, ml	164 ± 127	110 ± 65**	260 ± 152	P < 0.01
%Δ *2 weeks*, %	–11 ± 17**	–20 ± 13**	+2 ± 17	P < 0.01
%Δ *6 months*, %	–21 ± 32**	–40 ± 20**	+14 ± 19 **	P < 0.01
EF				
pre CRT, %	26 ± 11	26 ± 11	23 ± 10	P = 0.26
2 weeks, %	26 ± 11	27 ± 10	21 ± 11	P < 0.01
6 months, %	31 ± 15**	37 ± 14**	20 ± 10	P < 0.01
Δ *2 weeks*, %	+1 ± 6**	+3 ± 6*	–2 ± 5	P < 0.01
Δ *6 months*, %	+6 ± 11**	+12 ± 10**	–3 ± 6*	P < 0.01

The results are expressed as the mean ± SD.
QGS, quantitative gated perfusion SPECT; EDV and ESV, end-diastolic and end-systolic volume of left ventricle; EF, ejection fraction; %Δ, percent changes of values; Δ, absolute changes of values.
[1)]Comparison of responders and non-responders.
*P < 0.05, **P < 0.01 vs. pre CRT.

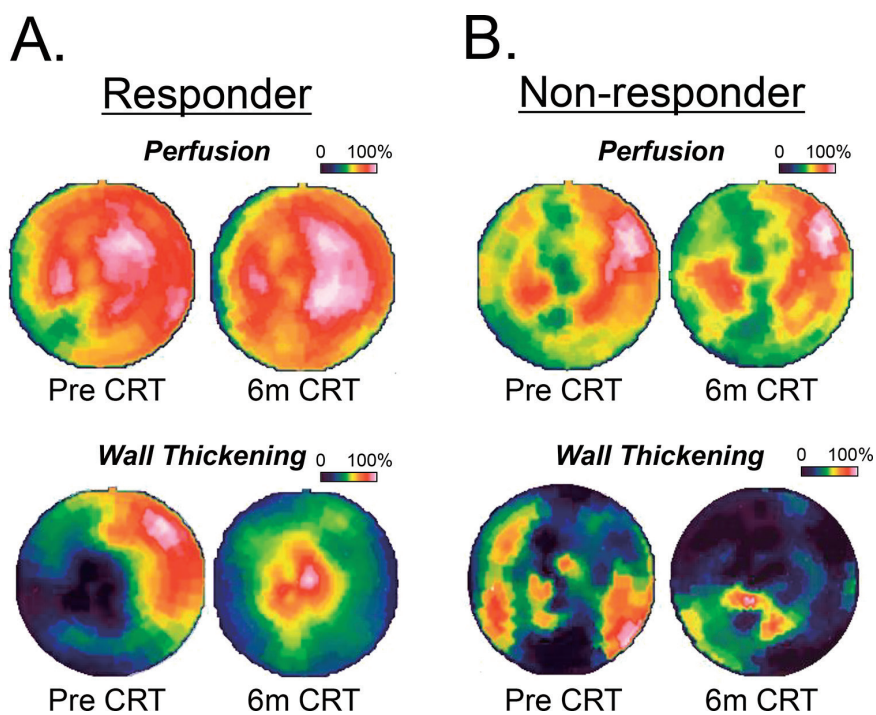

Fig. 3. Typical examples of myocardial perfusion and wall thickening evaluated by QGS.
A. Bull's eye maps of the myocardial perfusion (*upper panels*) and wall thickening (*lower panels*) before the cardiac resynchronization therapy (*pre CRT; left*) and at 6 months after the CRT (*6m CRT; right*) in a CRT responder with dilated cardiomyopathy (the same patient as in Fig. 1).
B. Bull's eye maps of the perfusion and wall thickening in a non-responder patient with dilated cardiomyopathy.

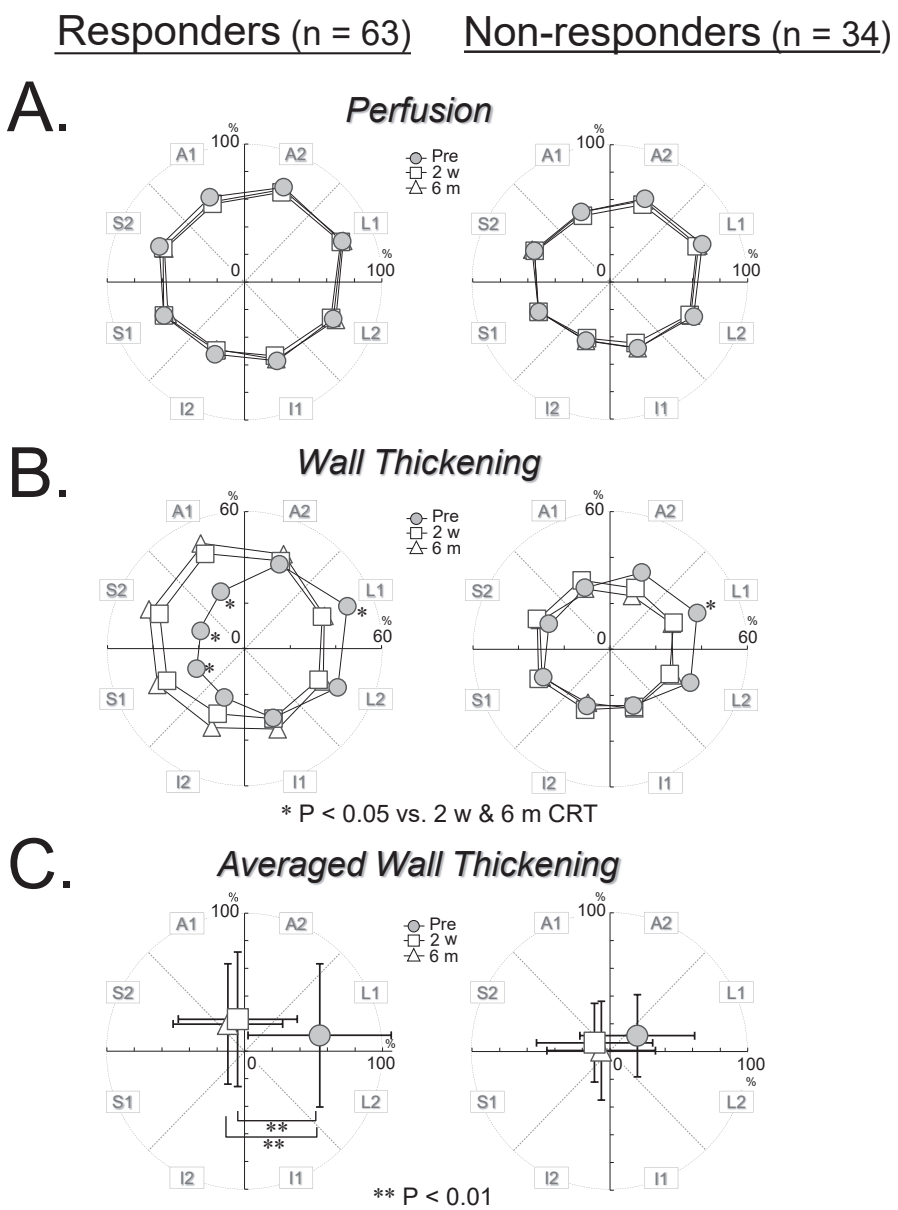

Fig. 4. Summary of the regional perfusion and wall thickening.
A. Summary of the perfusion scores in 8 circumferential LV segments.
B. Summary of wall thickening scores in 8 circumferential LV segments.
C. The average of the wall thickening scores was calculated as a sum of the vectors toward the 8 circumferential LV segments.
Left panels: results in CRT responders; Right panel: results in CRT no-responders.

suggest that LV reverse remodeling after CRT was closely related with the improvement of heterogeneous LV wall thickening and also the status of heart failure. In the receiver-operating characteristics (ROC) curve analysis, the area under the curve for detecting CRT responders was 0.66 (95% CI; 0.55 - 0.78; $P < 0.01$) for the X_{WT} before the CRT (Fig. 5B). Using the ROC curve analysis, we determined the cut off values for the X_{WT} (16.5; sensitivity 0.76, specificity 0.50).

Using the cutoff value, we evaluated the prognosis in all patients who had baseline QGS (n =120) with an occurrence of a MACE after the CRT during the 38 ± 22 month follow-up period. The Kaplan-Meier analysis revealed a significant decrease in the MACE in the responders compared with the non-responders ($P < 0.01$; Fig. 5C). Importantly, the cutoff value of the X_{WT} (≥ 16.5) predicted a better prognosis after the CRT (Fig. 5D). This result suggested that the patients with a septal-to-lateral non-uniformity (i.e., larger X_{WT} before CRT) in the wall thickening detected by QGS received larger benefits from the CRT.

QGS evaluation in the patients with a relatively narrow QRS duration

We further studied whether the QGS evaluation was

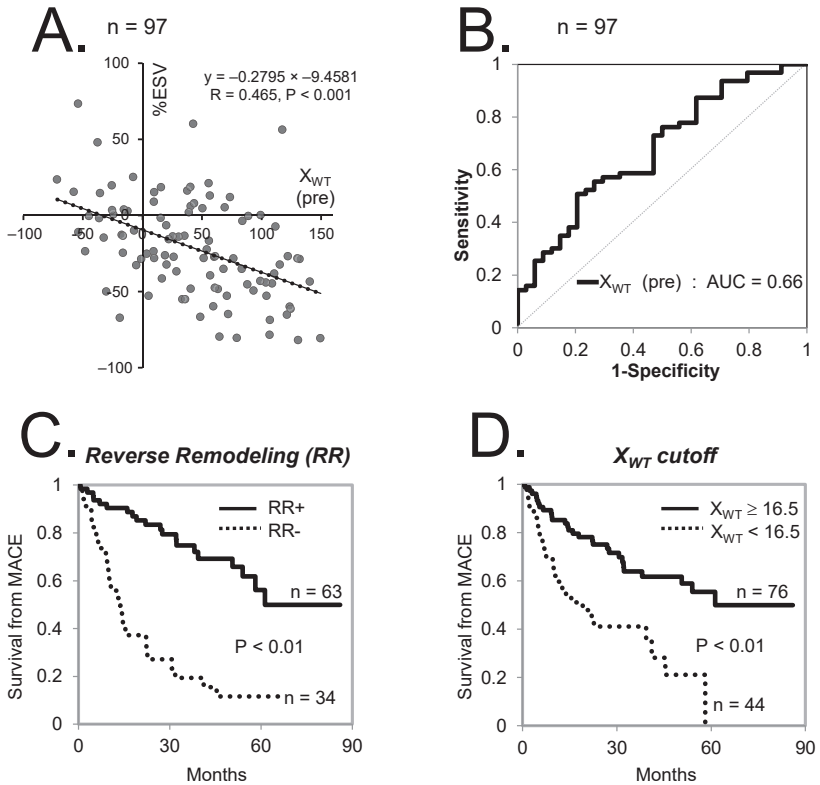

Fig. 5. Predictors of LV reverse remodeling and the long-term outcome after CRT.
A. Correlation between the %ESV and X_{WT} before the CRT.
B. The ROC curves for the X_{WT} before the CRT to detect CRT responders, providing the cutoff value (i.e., X_{WT} = 16.5).
C. The Kaplan-Meier curves for the survival after CRT from major adverse cardiac events (MACE). The patients were divided into two groups using the existence of reverse remodeling (RR) at 6 months after the CRT.
D. The Kaplan-Meier curves for the survival after CRT from MACE, showing better prognosis using cutoff values of the $X_{WT} \geq 16.5$.
AUC, the area under the curve for the detection of CRT responders.

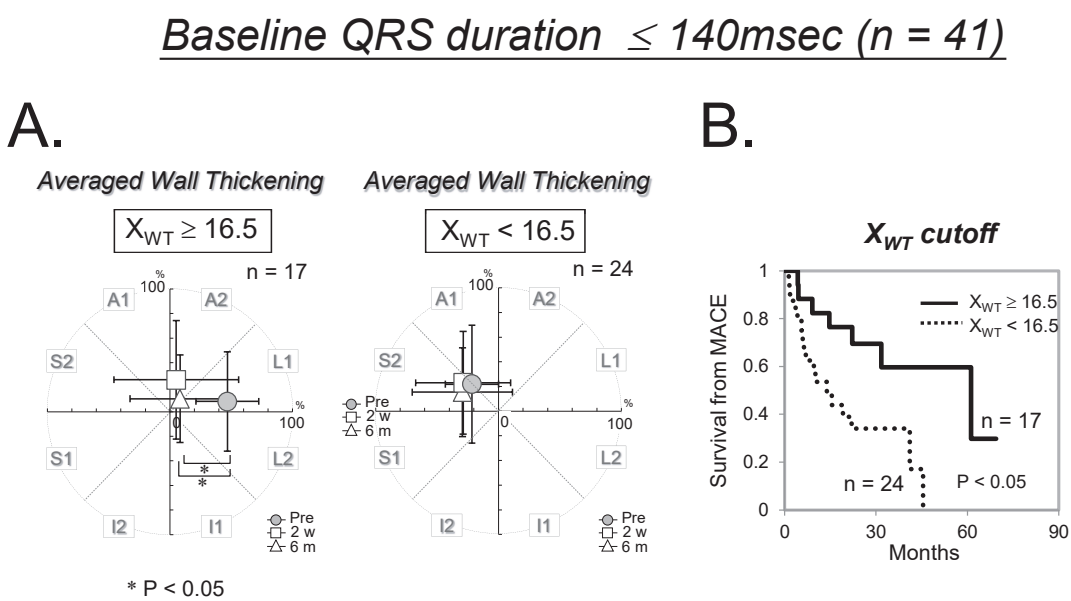

Fig. 6. Effects of CRT on the wall thickening in patients with a relatively narrow baseline QRS.
A. Summary of the wall thickening scores in the 8 circumferential LV segments in patients with baseline QRS of ≤ 140 msec.
Left panel: $X_{WT} \geq 16.5$; Right panel: $X_{WT} < 16.5$ before the CRT.
B. The Kaplan Meier analysis using the cutoff values of the X_{WT} in patients with baseline QRS of ≤ 140 msec.

useful in patients with a relatively narrow QRS complex (≤ 140 msec; n = 41), because these patients are reported to get less benefits from CRT compared with those with QRS of more than 150 msec (Peterson et al. 2013).

Fig. 6 shows the QGS analysis of the regional wall thickening in the patients with a QRS duration of ≤ 140 msec. Using the cutoff value of $X_{WT} \geq 16.5$ as described above, CRT significantly decreased the X_{WT} at 2 weeks and 6 months after the CRT only in the patients with an $X_{WT} \geq 16.5$ (i.e., baseline septal-to-lateral wall thickening non-uniformity) as shown in Fig. 6A (pre: 47 ± 26 vs. 2 weeks: 5 ± 51 and 6 months: 8 ± 41, $P < 0.05$; n = 17). Importantly, the cutoff value of the X_{WT} could predict a better prognosis even in patients with a relatively narrow QRS complex (Fig. 6B). These results suggested that the wall thickening analysis using QGS in this study could be applicable in patients with relatively narrow QRS that usually have less CRT benefits than those with wider QRS (≥ 150 msec).

Discussion

Cardiac dyssynchrony has been shown to depress the cardiac function by worsening the coordination of the LV regional contractions especially in patients with a wide QRS electrocardiogram of LBBB (Kass 2003). CRT improves the delay in the wall motion of the LV free wall, which is usually detected by echocardiography (Yu et al. 2002; Chung et al. 2008; Seo et al. 2011). In addition, other imaging modalities including cardiac nuclear imaging have been developed to evaluate CRT (AlJaroudi et al. 2011). Under this clinical background, we studied the 3-D evaluation of cardiac synchronization after CRT using the regional wall thickening measured by a semi-automatic QGS program based on gated myocardial perfusion SPECT. In this study, we demonstrated that the non-uniformity of wall thickening between the LV septal and lateral regions is predictive of reverse remodeling and a better prognosis in the chronic phase after CRT, even in patients with narrower baseline QRS (≤ 140 msec).

Gated SPECT in LBBB patients

It has been reported that perfusion defects in the interventricular septum can be observed in LBBB patients without coronary artery stenosis as a false positive for ischemic heart disease (Sugihara et al. 1997; Kasai et al. 2004; Nowak et al. 2004). However, in this study, there were no remarkable changes in the regional myocardial perfusion before and after the CRT irrespective of the clinical response to CRT (Figs. 3, 4A), probably due to the end-diastolic gating in our QGS system (Sugihara et al. 1997).

In contrast to the small changes in the regional myocardial perfusion, changes in the regional wall thickening were clearly affected by CRT, especially in CRT responders (Figs. 3, 4). It has been previously reported that LBBB patients have decreased wall thickening in the septum using gated perfusion SPECT (Sugihara et al. 1997) and positron emission tomography (Nowak et al. 2004), even in those with a normal cardiac function (Kasai et al. 2004). In typical LBBB patients (Fig. 1), regional myocardial contractions occur first in the RV and interventricular septum. The early-activated septum causes pre-stretch of the LV lateral wall, resulting in relative enhancement of the wall thickening in the LV lateral wall (Kass 2003). As a result of the late activation of the LV lateral wall, the septal wall thickening exhibits a biphasic (or paradoxical) pattern, leading to the attenuation of the septal wall thickening at end-systole. Consequently, the LBBB patients have a septal-to-lateral non-uniformity in the LV wall thickening as observed in this study (Figs. 3, 4).

Evaluation of the CRT effectiveness using a wall thickening analysis

Although echocardiography is widely used to evaluate LV dyssynchrony, the current methodology for the detection of cardiac dyssynchrony is not promising for selecting CRT responders (Chung et al. 2008; Seo et al. 2011). In a part of heart failure patients, the pathophysiology underlying cardiac dyssynchrony is complicated because of heterogeneous myocardia as a result of the existence of focal myocardial damage, Ca^{2+} overload, myocardial ischemia, and/or myocardial scar. Such diseased myocardium exhibits non-uniform contraction patterns and thus a reduced cardiac function (Wakayama et al. 2005; ter Keurs et al. 2006). The presence of myocardial scar detected using MRI has been reported to affect the response to CRT (Bleeker et al. 2006). These diseased conditions in CRT patients may make it difficult to predict a CRT response.

In this study, we evaluated the uniformity of the wall thickening in CRT patients from the aspect of the 3-D LV configuration using QGS. The approach in this study was thought to be essential for evaluating the CRT effectiveness because a uniform contraction or wall thickening in the LV is equivalent to a uniform stress or strain in the LV wall as has been previously reported using tagging MRI (Kass 2003; AlJaroudi et al. 2011). The phase analysis of the wall thickening using gated perfusion SPECT in patients with LV dyssynchrony has been reported (Boogers et al. 2009; AlJaroudi et al. 2011), suggesting the usefulness of gated SPECT in CRT patients in spite of its lower temporal and spatial resolution than the echo-based evaluation. Although our approach is not a direct evaluation of the temporal dyssynchrony, the evaluation of the non-uniform magnitude of the wall thickening and its improvement using QGS in this study was closely related to the initial and chronic effectiveness of CRT. Therefore, the direct measurement of the regional wall thickening using QGS may be supplemental for selecting CRT candidates, although it has less temporal information in terms of dyssynchrony.

Prediction of LV reverse remodeling using gated SPECT

Evaluation of cardiac dyssynchrony between LV lateral and septal regions is important for predicting the clinical response and LV reverse remodeling after CRT (Yu et

al. 2002; Seo et al. 2011). In this study, the nuclear imaging-based evaluation of the non-uniformity in the regional wall thickening also predicted the CRT response and prognosis (Figs. 5, 6). We used a parameter for the non-uniformity of LV lateral-to-septal wall thickening (i.e., X_{WT}), which was similar to the echo-based evaluation of dyssynchrony (Yu et al. 2002; Chung et al. 2008; Seo et al. 2011). Our results suggested that the lateral-to-septal non-uniformity in the wall thickening (i.e., X_{WT}) was an excellent predictor of cardiac events after CRT (Fig. 5). These results were applicable to the patients with a relatively narrow (≤ 140 msec) QRS complex (Fig. 6). These observations were reasonable because biventricular pacing fundamentally improved the lateral delay in the LV wall movement that was detected as the lateral-to-septal non-uniformity in the wall thickening in our study.

The QGS-based 3-D evaluation provided both the LV volume and function (Fig. 1B, Table 2) and had an advantage over the echo-based 2-D evaluation in the presence of dyskinesis or dyssynchrony. Cine MRI can provide excellent calculations for the LV volume and wall thickening (AlJaroudi et al. 2011), but it is limited only in patients with a MRI-conditional device. Thus, the present nuclear imaging-based method was useful for the selection and follow-up of CRT patients as a complementary method to the echo-based evaluation.

Limitations of the study

Several limitations should be mentioned for this study. First, this study was a retrospective observational study in a single center. Second, in this study, we evaluated the RI count-based regional cardiac function, but not the temporal differences in the regional motion. The temporal resolution of the 16-interval gated SPECT is estimated as ~ 54 msec when the heart rate is ~ 70 bpm. This is relatively low temporal resolution compared to the evaluation by echocardiography. Third, the non-responders had relatively narrow QRS morphology, suggesting that a selection bias might exist in the clinical setting of this study because CRT is known to be effective to patients with wide QRS of LBBB. Therefore, we confirmed the effectiveness of the wall thickening analysis in patients with relatively narrow QRS of less than 140 msec (Fig. 6), but further studies in patients with narrow QRS of less than 120 msec may be needed. Finally, this study was performed in the early stage of CRT in Japan. We therefore used only unipolar or bipolar LV lead system, which may affect the effectiveness of CRT, although the recent quadripolar LV lead system is thought to be provide better CRT effectiveness (Leyva et al. 2017).

Conclusions

In conclusion, we emphasize the usefulness of the wall thickening analysis of QGS in evaluation of the effectiveness of CRT. The non-uniformity of regional LV-wall thickening assessed by QGS is a convenient and useful parameter to detect the effects and prognosis after CRT. It is noteworthy that these results are applicable for marginal CRT candidates with relatively narrow QRS of less than 140 msec. The QGS analysis may be supplemental approach to select appropriate CRT candidates even in patients with a relatively narrow QRS complex.

Acknowledgments

A part of this work was presented in the annual scientific meeting of Japanese Circulation Society in 2013 at Yokohama, Japan.

This work was supported in part by the Grants-in-Aid (19659193 and 19790510) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

Conflict of Interest

The authors declare no conflict of interest.

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