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ORIGINAL ARTICLE

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Association of corrected QT dispersion with symptoms improvement in patients receiving cardiac resynchronization therapy

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Abstract Cardiac resynchronization therapy (CRT) is theoretically expected to affect repolarization as well as depolarization. We studied the effects of CRT on corrected QT (QTc) dispersion in association with symptomatic improvement. QTc dispersion was analyzed in 26 consecutive patients (67 ± 6 years old, 18 men and 8 women) who underwent CRT. CRT responders and nonresponders were defined as patients showing and not showing ≥1 class New York Heart Association symptomatic improvement 3 months after CRT, respectively. QTc interval, QRS width, and QTc dispersion were measured automatically from digital data using an analyzing system. There were 18 CRT responders and 8 nonresponders among the patients. CRT responders showed significantly larger QTc dispersion than CRT nonresponders before CRT (102 ± 26 vs 40 ± 12 ms, $P < 0.01$). A significant decrease in QTc dispersion by CRT was observed in responders (102 ± 26 to 52 ± 15 ms, $P < 0.01$). In contrast, QTc dispersion was not decreased by CRT in nonresponders (40 ± 12 to 39 ± 11 ms, not significant). The difference observed before CRT was thus abolished after CRT (52 ± 15 vs 39 ± 11 ms, not significant). Baseline values and changes in QRS width or QTc, as well as asynchrony of wall motion determined by tissue Doppler imaging, were not different between CRT responders and nonresponders before CRT. The present study with a small number of patients shows the potential utility of QTc dispersion for distinguishing CRT responders from CRT nonresponders before CRT, and warrants further study with a greater number of patients.

Key words Heart failure · Pacing · Electrocardiography · Repolarization · Asynchrony

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Introduction

Cardiac resynchronization therapy (CRT) has been introduced as a treatment for congestive heart failure patients with prolonged QRS duration, i.e., conduction delay, based on the concept of improving dyssynchronous conduction of the heart by biventricular pacing. Left ventricular reverse remodeling is an objective endpoint that is thought to contribute to the symptomatic benefits of CRT[1] and may improve long-term survival.[2–4] Although data on the beneficial effects of CRT on clinical endpoints and cardiac function are of paramount importance, nonresponse to the therapy has been consistently observed in about one third of patients, which is troubling.[1,5,6]

Electrocardiogram (ECG) criteria, including the presence of left bundle branch block (LBBB) and QRS duration, are poor predictors because they may underestimate intraventricular dyssynchrony.[7,8] A number of ultrasound studies have proposed several parameters to identify CRT responders.[1,6,9–14] The specificity and accuracy of these parameters for distinguishing responders to CRT from nonresponders were, however, inadequate. This indicates that an alternative method of dyssynchrony assessment other than QRS duration or ultrasound parameters is the key to identifying appropriate patients for CRT and predicting a favorable response.[1,15]

Regarding ECG indices, duration of repolarization (QT duration), as well as QRS duration, theoretically reflects cardiac wall contraction. QT dispersion has been reported to reflect local left ventricular damage in acute myocardial infarction.[16] CRT can be theoretically predicted to affect repolarization as well as depolarization. However, little is

known about the effect of CRT on ventricular repolarization.[17,18] Some studies indicated that greater QT dispersion might reflect a dispersion of repolarization, suggesting asynchrony of ventricular wall motion.[19,20] Based on these considerations, we hypothesized that CRT would improve QT dispersion. QT dispersion is assumed to be small in hearts with normal synchronous wall motion and in advanced failing hearts without dyssynchronous wall motion. In contrast, dyssynchrony is likely to be large when QT dispersion is large. We thus hypothesized that in order to benefit from CRT, patients would need to have relatively large QTc dispersion before CRT. Accordingly, to test this hypothesis, we measured QTc dispersion to distinguish responders to CRT from nonresponders.

Patients and methods

Patients

We retrospectively studied 26 consecutive patients with congestive heart failure who underwent CRT. Clinical characteristics and underlying disorders in these patients are listed in Table 1. All patients suffered chronic heart failure and were refractory to optimal and maximally tolerated medical therapy (i.e., diuretics, angiotensin-converting enzyme inhibitors, beta-blockers, digitalis, etc.). No drugs were changed before or for 3 months after the CRT in any of the patients. All patients were classified as functional class III or IV [New York Heart Association (NYHA)] and had a left ventricular ejection fraction (LVEF) determined by left ventriculography <35%. Replacement of DDD pacing by biventricular pacing was performed in three patients with dilated cardiomyopathy. There were no patients with pacing cardiomyopathy. The remaining 23 patients showed QRS duration >130 ms. Their heart failure conditions were relatively stable without ischemic attacks requiring coronary revascularization. The exclusion criteria were (1) acute heart failure, (2) a history of permanent atrial fibrillation, (3) coronary artery bypass graft surgery or myocardial infarction within the previous 3 months, and (4) primitive and hemodynamically significant valve disease. The present study complied with the rules of the Helsinki Declaration,[21] informed consent was obtained, and the study was approved by our institutional ethics committee for human research.

Table 1. Baseline characteristics of the study patients

	Responders	Nonresponders	*P* value
Number	18	8	
Age (years)	69 ± 8	65 ± 12	NS
Male/Female	11/7	7/1	<0.05
Underlying disorder			
DCM/OMI	14/4	6/2	NS
AF (Ablate&Pace)	1	2	
DDD upgrade	2	1	
NYHA	3.3 ± 0.5	3.4 ± 0.5	NS
LVEF (%)	30 ± 6	22 ± 9	<0.05
MR (I–IV grade)	1.6 ± 1.0	1.2 ± 0.7	NS
BNP (pg/ml)	616 ± 431	635 ± 605	NS

DCM, dilated cardiomyopathy; OMI, old myocardial infarction; AF, atrial fibrillation; NYHA, New York Heart Association Functional class; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; BNP, B-type natriuretic peptide; DDD, DDD pacemaker; NS, not significant

Pacemaker implantation

The CRT device with a biventricular pacemaker (Medtronic Insync III 8040 or 4193, Medtronic, Minneapolis, MN, USA) was implanted according to essentially the established methods reported previously.[6] Transvenous left ventricular pacing was performed in all cases. Under the guidance of coronary sinus angiograms, a unipolar lead was introduced into the lateral or posterolateral cardiac vein. The final position was determined visually with the right and left anterior oblique views. Atrioventricular (AV) coupling affects left ventricular (LV) pump dysfunction.[22] Optimization of the AV delay was thus carefully determined using Doppler echocardiography (Vivid 7, General Electric, Milwaukee, WI, USA) 1 day after CRT device implantation in 24 patients.[23] In the remaining two patients, the AV delay interval was optimized hemodynamically in accordance with methods reported previously.[24] The biventricular pacing rate was determined as the rate that produced all biventricular pacing.

Definition of CRT responders and nonresponders

CRT responders and nonresponders were defined as patients who showed or did not show a decrease ≥1 class in NYHA functional classification 3 months after CRT, respectively. Patients who suffered cardiac death during the follow-up periods were defined as nonresponders.

Measurement of QT dispersion

QT measurements were performed by two investigators who were blinded to the other clinical data. A 12-lead ECG was recorded using a computerized ECG machine (FDX-6521, Fukuda Denshi, Tokyo, Japan) before and 1 day after CRT device implantation. QT interval and QT dispersion measurements were determined from averaged complexes on the digital ECGs using interactive software (QTD-1, Fukuda Denshi) that detected QRS onset and T-wave offset: the reliability and accuracy were previously demonstrated.[25] The QT intervals and corrected QT intervals (QTc) for each lead and QTc dispersion were calculated automatically. Briefly, the QT intervals were measured by averaging beats from similar cycles. A global QRS onset and T-wave offset were determined in all 12 leads, and then an individual QT interval was measured for each lead. When a U wave was present, QT was measured at the nadir of the T–U curve. The QT intervals were corrected automatically for heart rate using Bazett's formula.[26] The QTc dispersion was defined as the difference between the minimal and maximal QTc in any of the 12 ECG leads in

which the QTc could be reliably determined.[27] Further, manual determination was also performed in every ECG to confirm the accuracy of the automatic QT measurements. The QTc dispersion was obtained using the same methods for pacing ECGs in patients with a DDD pacemaker before CRT and was analyzed in accordance with previous studies.[17,18]

None of the patients showed a U wave superimposed on the end of the T wave. Consequently, QT dispersion was determined in all patients. QT intervals were measured in all 12 leads. The range (mean ± SD) for the controls for QTc dispersion was 46.8 ± 10.4 ms. The JT interval (from the J point to the end of the T wave) was also determined using the equation JT = QT – QRS. JTc dispersion was also obtained as maximal – minimal JTc.

Tissue Doppler imaging to assess LV dyssynchrony

Tissue Doppler imaging (TDI) has been reported to be highly sensitive at detecting reverse remodeling of the left ventricle compared with strain-rate imaging (SRI).[28,29] In addition to the conventional echocardiographic examination, TDI was therefore performed to assess LV dyssynchrony before and 1 day after CRT device implantation in accordance with previously reported well established methods in 24 of 26 patients.[30,31] The delay in peak velocity between the septum and the LV lateral wall was calculated as an indicator of LV dyssynchrony.

Statistics

The Student *t*-test was used to compare data between the two groups. The significance of changes in QTc dispersion, as well as other factors, before and after CRT was determined using the paired *t*-test. All values are expressed as mean ± SD, and *P* values of less than 0.05 were considered significant.

Results

There were 18 CRT responders and 8 nonresponders among the patients. In accordance with the definition of responders, the NYHA functional class improved from 3.3 ± 0.5 to 2.2 ± 0.4 in responders, while it was unchanged in nonresponders (3.4 ± 0.5 to 3.4 ± 0.5). There were no significant differences in the NYHA functional class, plasma B-type natriuretic peptide (BNP) level, or grade of mitral regurgitation before CRT between responders and nonresponders (Table 1). Although there was a statistically significant difference in LVEF before CRT between responders and nonresponders, differences were not large and considerable overlap values were noted between the two groups when compared with the QTc dispersion described below. The difference in LV ejection fraction (EF) could not discriminate between responders and nonresponders. There were no significant differences in LV dimension or thickness of septal and posterior wall between the CRT responders (larger QTc dispersion) and nonresponders. On ECG indices other than QTc dispersion, there were no significant differences in heart rate, maximal QRS duration, QRS dispersion, maximal QTc length, maximal JTc duration, or JTc dispersion before CRT between responders and nonresponders (Table 2).

QTc dispersion

Acceptable agreement in QT duration measurements from 100 randomly selected QRS-ST-T complexes of 12-lead ECG between manual and automatic methods was demonstrated by Bland and Altman plots. The maximal difference in QT interval between manual and automatic measurements was 8 ms, which was acceptably small.

Representative results of QTc dispersions in a responder and a nonresponder are shown in Figs. 1 and 2, respectively. Responders showed significantly larger QTc dispersion than nonresponders (102 ± 26 vs 40 ± 12 ms, $P < 0.01$) (Fig. 3). Moreover, there were no overlapping values in QTc dispersion between responders and nonresponders. A significant decrease in QTc dispersion after CRT was observed in responders (before vs after, 102 ± 26 vs 52 ± 15 ms, $P < 0.01$). In contrast, nonresponders showed no significant decrease in QTc dispersion after CRT (40 ± 12 vs 39 ± 11 ms). Furthermore, QTc dispersion obtained only from precordial leads, V1 to V6, was larger in responders than in nonresponders (Fig. 4). To exclude the effect of QRS width, JTc and JTc dispersions were measured. JTc showed the same performance as QTc and QTc dispersion.

For the other ECG indices, QRS duration and QRS dispersion were not different between responders and nonresponders (Table 2). In addition, no differences in changes in QRS duration or QRS dispersion after CRT were observed between responders and nonresponders.

Tissue Doppler imaging

The measurements of absolute difference in time to peak systolic strain rate between the basal septal and basal lateral walls from SRI were significantly shortened in both the responder and nonresponder groups after CRT. There were, however, no differences in the time lag of peak systolic strain from the intraventricular septum and lateral wall before CRT between the two groups (Table 2).

Discussion

The present study suggests that QTc dispersion has potential as a useful marker for distinguishing CRT responders from CRT nonresponders before the CRT procedure. We measured QT interval and QT dispersion automatically in digital ECGs with interactive software. The validity of the system used has been reported.[25,27,32] In fact, the maximal difference in QT interval between manual and automatic

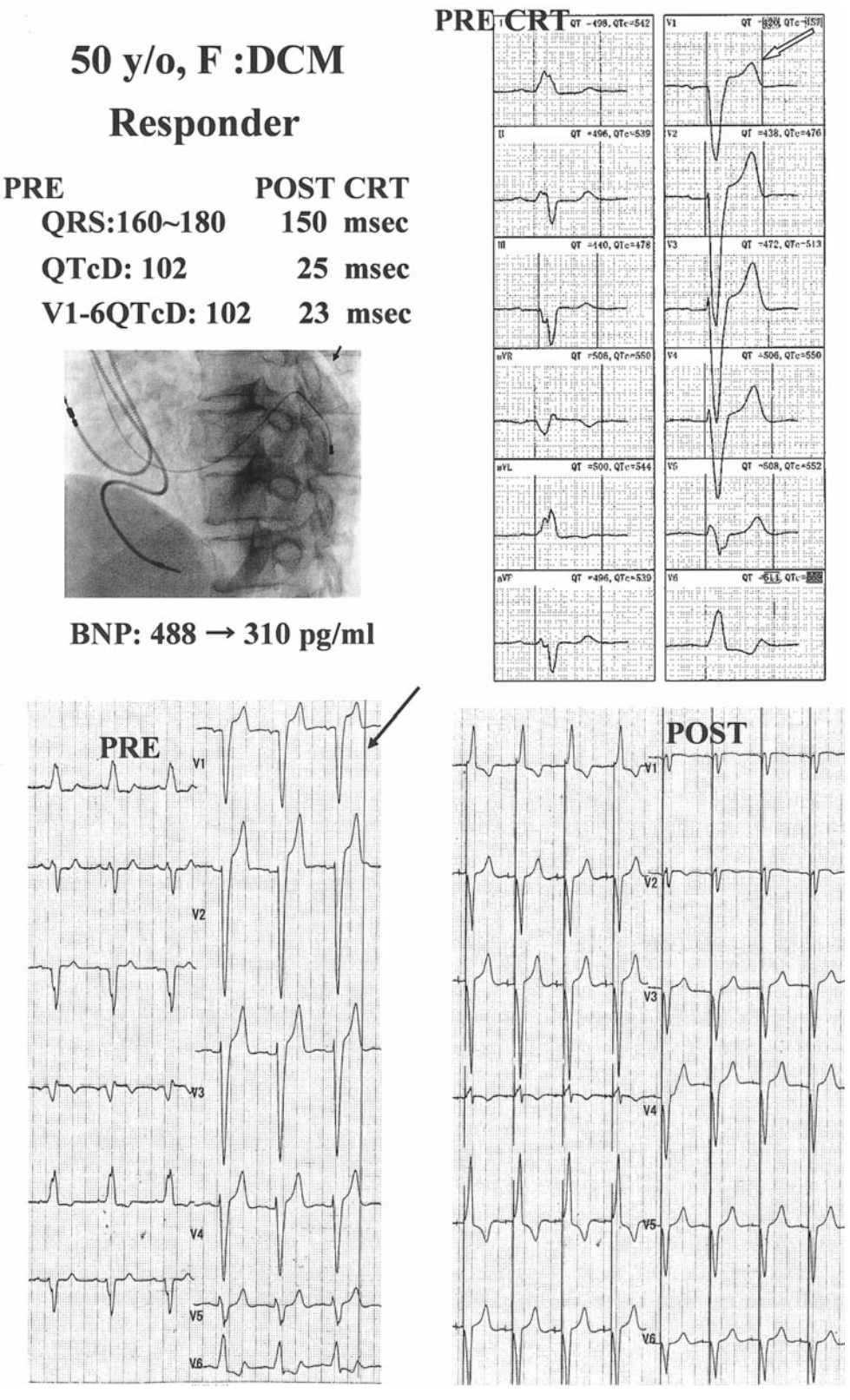

Fig. 1. Representative results in a 50-year-old responder. An ECG before cardiac resynchronization therapy (*CRT*) showed a large corrected QT dispersion (*QTcD*) of 102 ms obtained from both 12 leads and leads V1 to V6. *Upper right panel* shows averaged ECG from digital ECG recordings for automatic measurements of QTc. *Lower panel* shows ordinary 12-lead ECG before and after CRT. Lines indicated by *open arrows* show end of QT by automatic detection. Lines indicated by *closed arrows* indicate the QT dispersion visually. *F*, female; *DCM*, dilated cardiomyopathy; *BNP*, B-type natriuretic peptide

measurements was 8 ms, which was acceptably small. The present methods for the measurement of QT interval and QT dispersion were thus valid. New York Heart Association functional class was used to define responders to CRT in the present study. There is no still reliable definition that distinguishes responders from nonresponders, and published studies have used acute hemodynamic changes and chronic left ventricular reverse remodeling, as well as intermediate or long-term clinical response, to classify them. We did not perform right-sided heart catheterization (RHC)

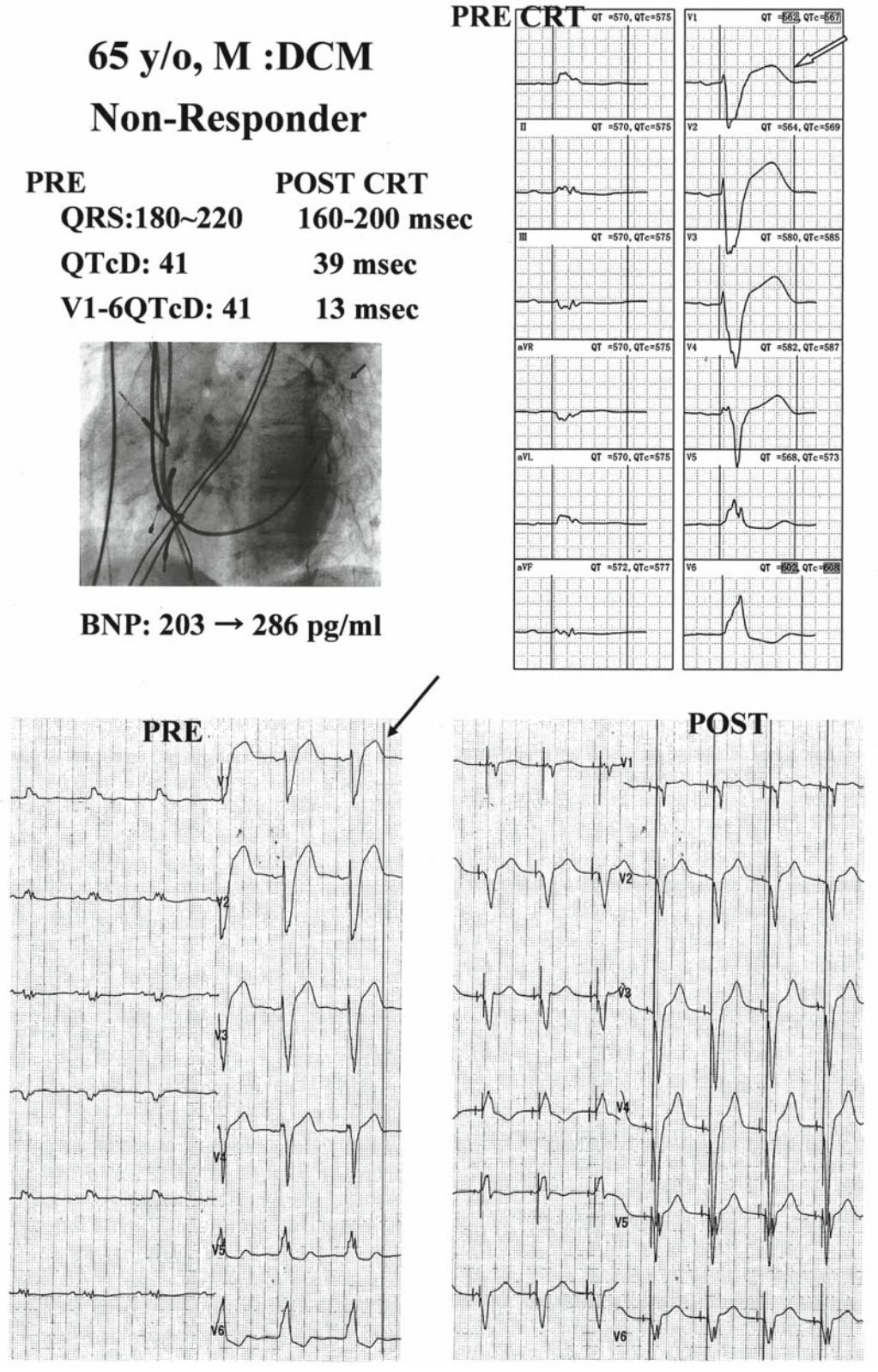

Fig. 2. Representative results in a 65-year-old nonresponder. An ECG before cardiac resynchronization therapy (*CRT*) showed a small corrected QT dispersion (*QTcD*) of 41 ms obtained from both 12 leads and leads V1 to V6. *Upper right panel* shows averaged ECG from digital ECG recording for automatic measurements of QTc. *Lower panel* shows ordinary 12-lead ECG before and after CRT. Lines indicated by *open arrows* show the end of QT by automatic detection. Lines indicated by *closed arrows* show the QT dispersion visually. *M*, male; *DCM*, dilated cardiomyopathy; *BNP*, B-type natriuretic peptide

just before and after biventricular pacemaker implantation for CRT, because a Swan–Ganz catheter for RHC interferes with the introduction and position of the pacemaker lead for the right ventricle. Indexes obtained from RHC were therefore not used to determine responders. Each method to discriminate responders from nonresponders has limitations and there is no consensus at present on which clinical criteria should be selected to define nonresponders. We determined NYHA functional class 3 months after CRT. Although a placebo effect might have affected the

Table 2. ECG characteristics and other measurements before and after CRT

	Responders (n = 18)			Nonresponders (n = 8)			
	before CRT	3 months after CRT	before vs after P value	before CRT	3 months after CRT	before vs after P value	baseline: responder vs nonresponder P value
Heart rate (beats/min)	71 ± 15	80 ± 17	/	69 ± 17	75 ± 11	/	/
Duration of max QRS (ms)	178 ± 47	158 ± 16	NS	158 ± 42	176 ± 19	NS	NS
QRS dispersion (ms)	30 ± 18	18 ± 13	NS	30 ± 11	33 ± 15	NS	NS
Duration of max. QTc (ms)	569 ± 52	546 ± 43	NS	526 ± 73	535 ± 63	NS	NS
QTc dispersion (ms)	102 ± 26	52 ± 15	$P < 0.0001$	40 ± 12	39 ± 11	NS	$P < 0.0001$
QTc dispersion of V1–6 (ms)	96 ± 28	36 ± 17	$P < 0.0001$	34 ± 13	25 ± 17	NS	$P < 0.0001$
Duration of max. JTc (ms)	393 ± 26	382 ± 28	NS	374 ± 78	360 ± 50	NS	NS
JTc dispersion (ms)	98 ± 24	54 ± 18	$P < 0.0001$	49 ± 11	47 ± 16	NS	$P < 0.0001$
Plasma BNP level (pg/ml)	616 ± 431	245 ± 194	$P < 0.05$	635 ± 605	688 ± 651	NS	NS
Tissue Doppler imaging (n = 24)		n = 16			n = 8		
Time lag of IVS–lateral wall (ms)	161 ± 87	65 ± 47	$P < 0.0001$	138 ± 103	55 ± 33	$P < 0.02$	NS

CRT, cardiac resynchronization therapy; BNP, B-type natriuretic peptide; IVS, intraventricular septum; NS, not significant

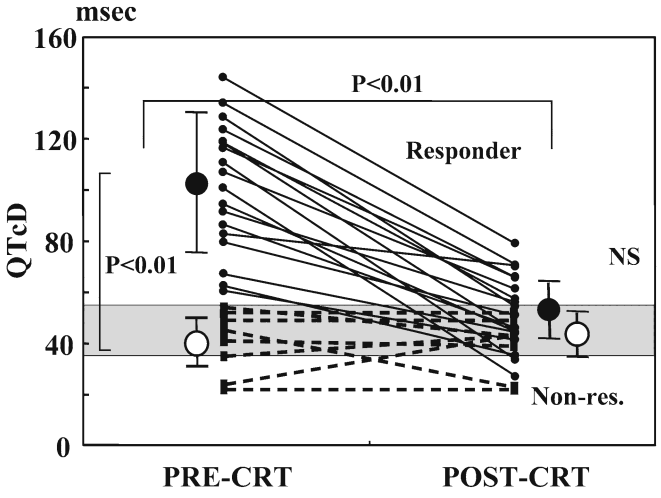

Fig. 3. Corrected QT dispersion (*QTcD*) determined from 12-lead ECG in responders and nonresponders before and 3 months after cardiac resynchronization therapy (*CRT*). *Closed circles* and *solid lines* indicate responders. *Open circles* and *dotted lines* indicate nonresponders. *Bars* indicate standard deviations

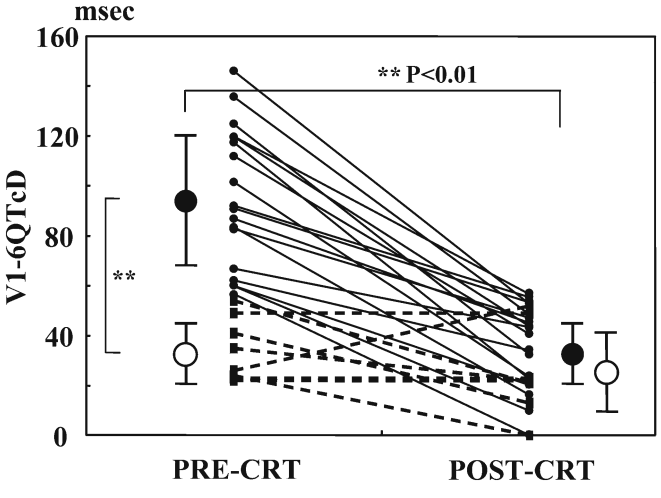

Fig. 4. Corrected QT dispersion (*QTcD*) determined from leads V1 to V6 in responders and nonresponders before and 3 months after cardiac resynchronization therapy (*CRT*). *Closed circles* and *solid lines* indicate responders. *Open circles* and *dotted lines* indicate nonresponders. *Bars* indicate standard deviations

present NYHA functional class improvement, the NYHA functional class has been widely used and its reliability has been well demonstrated. For these reasons, we used the NYHA functional class to differentiate responders from nonresponders to CRT. The fact that plasma BNP levels were significantly improved only in responders strongly supports the notion that our definition of responders was reliable.

We used QTc dispersion as a sensitive indicator of LV dyssynchrony. QT dispersion has been reported to reflect LV remodeling and function.[16,19,20,38–40] Based on the reported results, it can be assumed that QT dispersion is large when cardiac pathological changes occur heterogeneously, causing dyssynchrony of LV wall contraction. Otherwise, QT dispersion can be reasonably assumed to be associated with LV dyssynchrony. In addition, it is known that diastolic function is more strongly influenced by asynchronous motion than systolic function.[41] Harjai et al.[38] suggested that spherical distortion of the LV was associated with increased QT dispersion, as shown by the increased heterogeneity of myocardial repolarization observed using echocardiography in 60 patients with dilated cardiomyopathy. Based on theoretical considerations and the reported evidence, we hypothesized that QT dispersion would be large in association with dyssynchrony of LV wall motion, and patients with large QT dispersion would thus be predicted to have a good response to CRT. Conversely, patients without large QT dispersion would not have a good response to CRT. These patients with normal QT dispersion, despite their severe cardiac dysfunction, have relatively uniform cardiac damage, and consequently do not show large QT dispersion, but rather "pseudo-normalization."

In a study that examined QT interval in relation to CRT, Berger et al.[18] found that QT dispersion increased during right ventricular, and decreased during biventricular, pacing as compared to sinus rhythm in patients with complete left

bundle branch block. Their results were in good agreement with the present results. In contrast, there is a report that QT dispersion was increased after CRT.[42] The reason for the discrepancy between results by Berger et al. as well as our findings and other reported results remains obscure. QT dispersion before CRT was smaller in that series than it was in either our study or the study by Berger et al., and the underlying electrophysiological conditions of the patients in the former report might have been different from those in the latter two studies. Further discussion would be inappropriate because the present study lacked any direct data concerning this issue.

There is no study that compares the effect of CRT on QT dispersion between responders and nonresponders before CRT. Our findings that responders showed larger QTc dispersion compared with nonresponders and that there was a decrease in QTc dispersion only in responders cannot therefore be compared with previous reports. We found QT dispersion obtained by precordial leads V1–V6 showed similar results to that obtained by 12-lead ECG. One study[43] indicated that QT dispersion obtained by precordial leads was reliable at reflecting the moment of local activity. Determination of QT dispersion from precordial leads was easier than that from all 12 leads. Furthermore, QT dispersion was estimated with a vertical line drawn at the end of the T wave from precordial leads as indicated in Figs. 1 and 2, not from 12 leads. The present results indicated that QT dispersion may provide clinically useful information with respect to estimating the effects of CRT.

Although EF could not discriminate between responders and nonresponders, there were statistically significant, but small, differences with considerable overlap values in EF between responders and nonresponders. This suggests that when the myocardium is severely irreversibly disturbed, effects of CRT may be minimal. Further discussion about EF is inappropriate due to a lack of direct data to explain this issue. The present study also showed that TDI failed to distinguish responders from nonresponders before CRT, although TDI has been reported to be highly sensitive at detecting reverse remodeling of the left ventricle when compared with SRI.[28,29] The time delay between the intraventricular septum and lateral wall motions improved significantly after CRT delay measured from TDI. The delay was not significant before CRT in responders or nonresponders. Among various TDI indices, only the standard deviation of time to peak myocardial velocity during the ejection phase in 12 LV wall segment (Ts-SD) has been reported to be a predictor of reverse LV remodeling in response to CRT.[10] Responders were defined as having a reduction in LV end-diastolic volume of >15%, and the rate of nonresponders was high (42%). It is questionable why only Ts-SD has been selected as an indicator for responders. In one study, the judgment of efficacy and its predictive power was made using the same geometrical factors. The results were therefore unconvincing. The reason for the present finding that QT dispersion was superior at identifying responders before CRT than TDI was not clear. TDI only uses the peak velocities of two points, that is, the septum and the LV lateral wall, to determine LV dyssynchrony, and may lose other parameters regarding the LV wall and dyssynchrony. In contrast, ECG determines the pathophysiological conditions of the whole heart with multiple leads. Furthermore, it is well known that changes in ECG occur earlier than changes in ventricular geometry and contraction status. Various possible mechanisms to explain the differences in behavior between QTc dispersion and TDI in CRT could be proposed, but further discussion of this issue is inappropriate here because of the lack of data.

There are several limitations to the present study. First, it included only a small number of patients. There are, however, reports using a similar number of patients.[17,18] Although differences in QTc dispersion before CRT between responders and nonresponders were considerably large, examination of a large number of patients is required to confirm the present results. Second, QTc dispersion was not measured sequentially after CRT. We measured QTc dispersion using software and confirmed the accuracy of QTc dispersion measurements before CRT. Therefore, the lack of sequential measurements of QTc dispersion after CRT was not a major limitation. Third, long-term follow-up data are not yet available and the incidence of major arrhythmic and cardiac events could not be analyzed, although a variable relation of these events and QT dispersion has been reported previously.[44,45] In conclusion, the results showed a significantly larger QTc dispersion in CRT responders than in CRT nonresponders before CRT. The present study suggests that QTc dispersion has the potential to distinguish CRT responders from CRT nonresponders before CRT, and warrants further study with a greater number of patients to confirm its potential.

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