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ORIGINAL ARTICLE

Impact of interlead distance on immediate and mid-term response to cardiac resynchronization therapy

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Abstract

Objectives. It is currently recommended that the left ventricular (LV) lead be placed at the posterolateral or lateral wall of heart during cardiac resynchronization therapy (CRT). The aim of our study is to evaluate the influence of interlead distance on immediate and mid-term response to CRT with altered right ventricular (RV) pacing site. *Design.* A total of 35 consecutive patients underwent CRT for standard indications. RV pacing site was altered from RV outflow tract (RVOT) to RV apex (RVA) in the course of implantation, permitting assessment of a "poorer response" and a "better response" site based on intraprocedural aortic velocity time integral (aVTI). LV–RV interlead distances were compared between these sites during operation. We also made a comparison of the interlead distances between responders and non-responders 6 months after CRT. *Results.* In the process of CRT implantation, the better response site showed significantly larger interlead distance ($16.5 \pm 4.4 \text{ cm vs.} 12.4 \pm 5.6 \text{ cm}, p = 0.001$) as well as its vertical component ($9.8 \pm 4.8 \text{ cm vs.} 4.3 \pm 2.8 \text{ mm}, p = 0.001$) on lateral fluoroscopy view as compared with the poorer response site. Furthermore, RVA proved more likely to be the "better response" site than RVOT (91% vs. 9%, p = 0.001). At 6-month -up, responders demonstrated larger direct interlead distance ($18.1 \pm 4.5 \text{ cm vs.} 14.8 \pm 3.5 \text{ cm}, p = 0.011$) and horizontal interlead distance ($14.1 \pm 6.6 \text{ cm vs.} 8.3 \pm 6.1 \text{ cm}, p = 0.004$) on the lateral radiograph in comparison with non-responders with great significance. *Conclusions.* Larger interlead distance on lateral fluoroscopy view is associated with more favorable immediate and mid-term response to CRT. Use of these findings may help to maximize the benefit derived from CRT.

Key words: cardiac resynchronization therapy, heart failure, interlead distance

Introduction

Nowadays cardiac resynchronization therapy (CRT) is widely performed in patients with pharmacological refractory heart failure, and has been proved to be quite effective in appropriately selected patients (1,2). However, about 20–40% of the patients show poor response to CRT (3). A number of factors including etiology of heart failure, renal function, atrial fibrillation and QRS morphology play an important role in the clinical outcome of CRT (4–7). With regard to left ventricular (LV) stimulation, a posterolateral or lateral tributary of the coronary venous system has been reported to be the most optimal pacing site (8,9). Given that CRT is intended to improve ventricular synchrony by coordinating LV and right ventricle (RV) contraction, efforts to

maximize RV to LV electrode separation have been advocated (10). Since the LV lead positioning is often restricted due to anatomical variations, unacceptable electrical parameters, phrenic nerve stimulation or other technical problems, can we choose an appropriate RV lead position to maximize CRT response, which could be more easily selected by operators? The goal of the present study is to investigate the association of immediate and mid-term response to CRT with LV–RV lead distances.

Methods

Study population

Thirty-five consecutive patients admitted for CRT from January 2011 to June 2012, were studied. All

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patients had New York Heart Association (NYHA) heart failure functional Class III or IV with reduced LV ejection fraction (\leq 35%) and prolonged QRS duration (\geq 120 ms) after optimal medical therapy for at least 3 months, including β-blocker, angiotensinconverting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), aldosterone antagonist, diuretics and digoxin if necessary. Etiologies included ischemic and non-ischemic cardiomyopathy. Before device implantation, all subjects underwent history inquiry, physical examination, 12 lead-electrocardiogram (ECG) and transthoracic echocardiography. A written informed consent was also obtained from each patient before the implantation.

12 Lead-electrocardiogram

All ECGs were recorded at a 50 mm/s sweep speed. QRS duration was measured using hand-held calipers, on the lead showing the widest complex (11). Paced QRS duration was measured from the pulse signal to the end of complex, on the lead with the widest complex. Complete left bundle branch block (CLBBB) is defined as a QRS duration of \geq 120 ms with a monophasic QS or RS complex in lead V₁ and a monophasic R wave in lead V₆, and complete right bundle branch block (CRBBB) is defined as a QRS duration of \geq 120 ms with a secondary R wave (R') in lead V₁ which is greater than the initial R wave (rsR') and a wide deep terminal S wave in leads II, V₅ and V₆ (7).

Echocardiography

All the echocardiographic parameters were obtained by one echocardiologist using Phillip IE 33 (S5-1) cardiac ultrasound machine. LV end-diastolic diameter (LVEDD) and end-systolic diameter (LVESD) were measured by M-mode echocardiography in the parasternal long-axis view. As for LV ejection fraction (LVEF), we first derived the left ventricular enddiastolic volume (LVEDV) and left ventricular endsystolic volume (LVESV), LVEF was calculated from the conventional apical 2- and 4-chamber images, using the biplane Simpson's technique. The severity of tricuspid or mitral valve regurgitation was graded semi-quantitatively from color flow Doppler in the parasternal long axis and apical four-chamber images. The regurgitation was graded on a 3-point scale: mild (jet area/atrial area < 20%), moderate (jet area/ atrial area 20-45%) and severe (jet area/atrial area >45%) (12). In order to evaluate LV dyssynchrony, tissue Doppler imaging (TDI) was acquired in 12 basal- and mid-ventricular segments from the apical 2-, 3- and 4-chamber views with high frame rate (>80 frames/s). Myocardial velocity curves were

obtained and the time to peak velocity during ejection phase (Ts) was measured in each segment, using QRS onset as a reference. Then the standard deviation (SD) of Ts of all 12 segments (Ts-SD) was computed to assess globle LV synchronicity (13,14). The aortic velocity was recorded just above the aortic valve using pulsed wave Doppler and the aortic velocity time integral (aVTI)of at least three beats was measured and averaged, with the purpose of gaining hemodynamic assessment (Figure 1) (15,16).

CRT protocol and acute hemodynamic assessment

Pacemaker implantation was performed with standard techniques via left subclavian vein, and devices were manufactured by Medtronic, Biotronik or St Jude Cooperations. Intraoperatively, coronary sinus angiography was performed using a balloon catheter and a target vein was identified. We placed the LV lead in a lateral or posterolateral tributary of coronary vein as far as possible. If there was no accessible lateral or posterolateral tributary, an anterior or inferior lead position was selected. Wherever the LV lead was placed, it produced an acceptable pacing threshold without phrenic nerve stimulation. The atrial lead was routinely placed in right auricle. The RV lead was first placed at right ventricular outflow tract (RVOT) septum, getting a satisfactory pacing threshold. Then we paced LV and RV simultaneously in VOO mode at a rate of 90 bpm with a suitable output which assured that both ventricles were captured. Afterwards, the 12-lead ECG was performed. Transthoracic echocardiography was performed after 3 min of pacing when a relatively stable hemodynamic parameter could be obtained. The Ts-SD was calculated as asynchrony of LV, and aVTI was measured as the acute hemodynamic effect of CRT. After that, we preserved the fluoroscopy in a posteroanterior (PA) and a left lateral view, with the atrial lead, RV lead and LV lead contained. Then the RV lead was placed at right ventricular apex (RVA) with optimal pacing threshold. Then the same procedure was carried out as above. Both the ECG and echocardiography were carried out with the caution that the operation site should not be contaminated. In the end, we implanted the RV lead at the place where a higher aVTI was acquired, which was defined as a "better response"site. In contrast, another RV pacing site which provided a lower aVTI was defined as a "poorer response"site. Finally all leads were connected to the pulse generator conventionally.

Interlead distance measurements

As is mentioned above, we preserved the fluoroscopy in a PA and a left lateral view for both "better



Figure 1. Echocardiography taken during implantation. aVTI of at least three beats were averaged (A). Myocardial velocity curves obtained and Ts measured in each segment from 4-chamber view (B).

response" and "poorer response" sites for each patient. The interlead distance was measured on a digital radiology work station by one cardiologist who was unaware of the hemodynamic results of the study. The direct RV-LV electrode tip distance and its horizontal and vertical components (defined as horizontal distance and vertical distance) were measured from the PA and left lateral fluoroscopy views, taking a tip-ring distance of atrial lead for reference,

which was provided by the manufacturer. All patients underwent preprocedure PA chest radiography for measurements of a cardiothoracic ratio (CTR), which was defined as the ratio of the width of the cardiac silhouette to the width of the thoracic cavity measured at the level of the diaphragm. All interlead distances, including direct distance (DD), horizontal distance (HD) and vertical distance (VD), were divided by the cardiothoracic ratio to account for different cardiac and thoracic sizes between patients, thus creating the corrected interlead distances (3,10,17). Theoretically, vertical interlead distance ought to be of the same value whether measured from PA or lateral views. Slight differences between VD measurements may be attributed to respiration and cardiac contraction of the patients (Figure 2). In addition, the LV lead tip position was defined as anterior (within the great cardiac vein), lateral or posterolateral (within the posterolateral cardiac vein) and inferior (within the middle cardiac vein) according to the PA and left anterior oblique (LAO) fluoroscopy views.

Mid-term follow-up

All patients were interviewed 6 months after CRT implantation. Physical examination, ECGs, pacemaker interrogation, and transthoracic echocardiography were performed. Response was defined as a decrease of $\geq 15\%$ in LVESV measured by echocardiographic ultrasound at 6-month follow-up. The remaining patients were considered as nonresponders. A comparison of the interlead distance was made between responders and non-responders.

Statistical analysis

Continuous variables are expressed as mean \pm SD. Categorical data are summarized as frequencies and percentages. The categorical characteristics were compared using χ^2 and Fisher's exact tests for cell count <5. The paired Student's *t*-test was used to compare the continuous data between the "better response" and "poorer response" sites in CRT procedure. Differences between variables in responders versus non-responders were evaluated by grouped Student's *t*-test. For all analysis, p < 0.05 was considered statistically significant. SAS 8.2 (SAS Institute Inc, USA) was applied to accomplish all the analysis.

Results

Patient characteristics

Baseline characteristics of the 35 patients included in this study are summarized in Table I. Eight cases suffered from ischemic cardiomyopathy and 27 from non-ischemic cardiomyopathy. All baseline ECGs showed sinus rhythm and a CLBBB QRS morphology with a mean ORS duration of 164 ± 28 ms. Patients had severely depressed LV function with a mean LVEF of $29 \pm 7\%$ and obvious LV dyssynchrony, as indicated by a mean Ts-SD of 42 ± 12 ms, thus meeting the typical indications for CRT. Almost all patients received an ACEI or ARB (97%) and 94% were on beta blocker therapy. In addition, CRT-ICD (CRT-D) was implanted in 22 patients while CRT-P was implanted in 13 patients. No significant difference was noted between responders and nonresponders on baseline clinical features.

CRT/CRT-D implantation

Device implantation was successful in all patients without procedure-related complications being reported. Though the desired LV lead position was the posterolateral vein, the LV pacing leads were positioned in the lateral or posterolateral region in 32 patients (91%). Two patients received an LV lead in the inferior region and one patient in the anterior region due to anatomical variations of cardiac vein or other technical difficulties. The RV lead position was determined by intraprocedural aVTI, which was placed where a higher aVTI could be acquired. As a



Figure 2. Interlead distance measured as DD, HD and VD on posteroanterior (A) and left lateral (B) fluoroscopy views.

Table I. Baseline characteristics of responders versus non-responders (n = 35).

| | Total (n = 35) | Responder $(n=18)$ | Non-responder $(n = 17)$ | P value |
|---------------------------------------|-------------------|--------------------|--------------------------|---------|
| Age (years) | 63.0 ± 12.9 | 63.3 ± 14.1 | 62.8 ± 12.1 | 0.938 |
| Gender (male/female) | 23/12 | 12/6 | 11/6 | 0.903 |
| Etiology (ischemic/non-ischemic) | 8/27 | 3/15 | 5/12 | 0.369 |
| Systemic hypertension | 11 (31%) | 7(39%) | 4 (24%) | 0.328 |
| Diabetes mellitus | 5 (14%) | 3(17%) | 2 (12%) | 0.679 |
| NYHA functional class (III/IV) | 20/15 | 9/9 | 11/6 | 0.380 |
| Systolic blood pressure (mmHg) | 114 ± 13 | 112 ± 11 | 116 ± 16 | 0.428 |
| Diastolic blood pressure (mmHg) | 70 ± 7 | 70 ± 7 | 71 ± 7 | 0.762 |
| QRS duration (ms) | 164 ± 28 | 168 ± 27 | 159 ± 30 | 0.429 |
| LVEF (%) | 29 ± 7 | 27 ± 7 | 32 ± 7 | 0.140 |
| LVEDD (mm) | 77 ± 11 | 75 ± 11 | 78 ± 10 | 0.422 |
| LVESD (mm) | 65 ± 10 | 65 ± 12 | 66 ± 10 | 0.889 |
| MV regurgitation (moderate-to-severe) | 22 (63%) | 12 (67%) | 10 (59%) | 0.631 |
| TV regurgitation (moderate-to-severe) | 9 (26%) | 4 (22%) | 5 (29%) | 0.627 |
| aVTI (cm) | 10.8 ± 1.8 | 10.6 ± 1.6 | 11.0 ± 2.0 | 0.578 |
| Ts-SD (ms) | 42 ± 12 | 44 ± 10 | 39 ± 13 | 0.311 |
| Medication | | | | |
| ACEI/ARB | 34 (97%) | 18 (100%) | 16 (94%) | 0.296 |
| β-blocker | 33 (94%) | 18 (100%) | 15 (88%) | 0.134 |
| Diuretics | 32 (91%) | 17 (94%) | 15 (88%) | 0.512 |
| aldosterone antagonist | 29 (83%) | 16 (89%) | 13 (77%) | 0.330 |
| Digoxin | 17 (49%) | 10 (56%) | 7 (41%) | 0.395 |
| CRT-D/CRT-P | 22/13 | 10/8 | 12/5 | 0.358 |

NYHA, New York Health Association; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; MV, mitral valve; TV, tricuspid valve; Ts-SD, standard deviation of the time to peak velocity; aVTI, aortic velocity time integral; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRT-D, cardiac resynchronization therapy accompanied with implantable cardioverter defibrillator.

result, 32 patients had a RV lead at RVA, while only 3 patients had a RV lead at RVOT septum. In the latter three patients, LV leads were positioned in the inferior and anterior regions.

Immediate echocardiographic assessment and interlead distance during implantation

As is mentioned, the "better response" and "poorer response" sites were defined according to intraprocedural aVTI. The better response site had a significantly larger direct interlead distance (which had been corrected) on the lateral film (p = 0.001), so was the corrected vertical interlead distance on both lateral and PA films (Table II). In the present study, a better response was achieved with the RV lead more frequently localized at RVA (p = 0.001). Only three patients showed a better response with RVOT pacing, in whom the LV lead was anteriorly or inferiorly positioned. Though previous studies showed that RV apical pacing produced a wider QRS duration than RVOT septum, this is not the case with the combination of RV and LV pacing. The better the response was, the narrower the QRS complex seemed to be, in accordance with interlead separation (p < 0.05).

Response to CRT at 6-month follow-up

At 6 months of follow-up, 18 (51%) patients were rated as responders with a reduction in LVESV \geq 15%. No patient died 6 months after CRT. Compared with non-responders, responders significantly had a larger

Table II. Comparison of interlead distance with different RV lead positioning.

| | Better response site | Poorer response site | p value |
|-----------------------------|----------------------------|----------------------------|---------|
| aVTI (cm) | 15.9 ± 2.3 | 14.7 ± 2.3 | 0.001 |
| Ts-SD (ms) | 33 ± 7 | 37 ± 6 | 0.009 |
| QRS duration (ms) | 145 ± 21 | 156 ± 24 | 0.047 |
| Localization of RV lead | | | 0.001 |
| Apex | 32 (91%) | 3 (9%) | |
| RVOT septum | 3 (9%) | 32 (91%) | |
| Interlead distance/CTR (cm) | | | |
| DD on P-A view | 11.9 ± 4.7 | 9.7 ± 3.4 | 0.057 |
| HD on P-A view | 6.1 ± 4.2 | 7.8 ± 3.6 | 0.078 |
| VD on P–A view | 9.6 ± 4.7 | 4.4 ± 2.8 | 0.001 |
| DD on lateral view | 16.5 ± 4.4 | 12.4 ± 5.6 | 0.001 |
| HD on lateral view | 11.3 ± 7.0 | 11.1 ± 5.8 | 0.779 |
| VD on lateral view | 9.8 ± 4.8 | 4.3 ± 2.8 | 0.001 |

RVOT, right ventricle outflow tract; CTR, cardiothoracic ratio; DD direct interlead distance; HD, horizontal interlead distance; VD, vertical interlead distance. corrected interlead distance, together with its horizontal component, on the lateral X-ray. In the PA radiograph, no significant difference of interlead distance was found between responders and nonresponders (Table III).

Discussion

As is widely known, response to CRT is associated with the diminishing of the septal-to-lateral delay, which is determined, in a great part, by the LV lead position. Though several studies (3,10,17) have revealed that interlead distance on the lateral thoracic X-ray correlates with CRT response, most of those interlead distance diversities resulted from different LV lead positions and were measured postprocedurally on thoracic X-ray. While in the present study, we altered the RV lead position intraprocedurally and carried out immediate hemodynamic assessment by means of echocardiography. To the best of our knowledge, the present study is the first of this kind to investigate the relationship between LV-RV interlead distance and immediate CRT response more accurately with the exclusion of baseline cardiac function, long-term medication therapy during follow-up and unsuitable life patterns. As a result, we not only found the relationship between the LV-RV interlead distance and immediate hemodynamic response, but also put it into clinical use just in the course of implantation.

Previous studies have elicited that LV–RV interlead distance on lateral radiograph, especially its horizontal component, is closely associated with both acute and mid-term hemodynamic response to CRT. Our results are in consistence with the available studies concerning mid-term response to CRT. However, the immediate hemodynamic effect in the present study proved to be mostly correlated with the vertical component of interlead distance (no matter from the PA view or from a lateral view) and a direct interlead distance on lateral fluoroscopy view. Whereas we should take into consideration

Table III. Comparison of interlead distance between responders and non-responders at 6-month follow-up.

| Interlead distance/ CTR (cm) | Responder $(n = 18)$ | Non-responder $(n = 17)$ | P value |
|---------------------------------|----------------------|--------------------------|---------|
| DD on P–A view | 11.1 ± 4.4 | 12.9 ± 4.7 | 0.168 |
| HD on P-A view | 5.8 ± 2.6 | 6.3 ± 5.3 | 0.568 |
| VD on P-A view | 9.1 ± 4.8 | 10.3 ± 4.4 | 0.377 |
| DD on lateral view | 18.1 ± 4.5 | 14.8 ± 3.5 | 0.011 |
| HD on lateral view | 14.1 ± 6.6 | 8.3 ± 6.1 | 0.004 |
| VD on lateral view | 9.4 ± 4.8 | 10.2 ± 4.96 | 0.570 |

CTR, cardiothoracic ratio; DD direct interlead distance; HD, horizontal interlead distance; VD, vertical interlead distance.

that in previous studies, the horizontal interlead distance on the lateral film became progressively greater due to the anterolateral to the lateral to the posterolateral LV lead positions compared with the anteriorly positioned RV lead in different cases. It is not surprising that such kind of association could be found given that a number of studies have demonstrated improved outcomes with lateral and posterolateral LV pacing compared with anterior pacing sites (18-20). While in our study we altered RV pacing site for each individual during the procedure. resulting in different interlead distances especially on the vertical plane instead of horizontal plane. Hence, a larger vertical interlead distance could be observed with the "better response"site in contrast with the aforementioned studies. From this viewpoint, we could conclude that the LV-RV interlead distance on the lateral chest radiograph correlated well with hemodynamic response to CRT, no matter it was driven by its horizontal or vertical component.

It is worth mentioning that neither immediate nor mid-term CRT response had correlation with the interlead distance on PA view, including its horizontal component. Now that a large part of left ventricle is just behind the right ventricle on PA radiograph, their spatial distance may overlap to a certain extent. Therefore, this projection scarcely reflects the real location. In the present study, even a shorter horizontal distance on a PA view tended to get a better response (not significantly).

In our study, 91% of the subjects had the LV lead placed in a lateral or posterolateral region, while 9% received the LV lead in a different location. It should be realized that obtaining the LV electrode site for best resynchronization is sometimes difficult because of the characteristics of coronary venous anatomy, unacceptable electrical parameters, phrenic nerve stimulation, or other technical difficulties. Nevertheless, the RV electrode site could be chosen more freely by operators. As is shown in our study, 32 cases displayed a better response with the RV lead placed at RVA, while another 3 cases showed a better response with the RV lead at RVOT septum. Buck et al. (3) also found that non-responders more frequently had the RV lead localized in the RVOT. On the contrary, more studies (21-23) showed no significant positive effect on CRT response of altering the RV lead position. Those studies discussed the impact of RV lead position on a 6-12-month follow-up using unpaired Student's t-test; while in the present study, we made an immediate hemodynamic assessment using a paired Student's t-test for each individual. Besides, previous studies discussed the effect of RV lead position regardless of LV lead location; our study carried out a self-contrast analysis, minimizing the confounding variables. For the 3 cases that showed a better response with the RV lead at RVOT septum, the LV lead happened to be anteriorly or inferiorly positioned, much closer to RV apex. Possibly, a larger interlead separation is created by placing the RV lead in the apex while LV lead is posterolaterally positioned; In contrast, RVOT septum pacing contributes to maximize interlead distance when LV is positioned close to apex. Thus we were able to conclude that CRT outcome resulted from a composite effect of LV and RV pacing site, rather than the LV or RV lead alone. The optimal RV lead location somewhat varied depending on the LV lead.

It needs to be pointed out that most candidates for CRT showed a CLBBB morphology on ECGs. The LV lead position is naturally most important. As mentioned, a lateral or posterolateral LV lead positioning is usually preferable, while an optimal RV lead helps to maximize the interlead distance on a lateral fluoroscopy view, adding to CRT benefits.

Limitations

The main limitation of our study is the small number of patients. Another limitation relates to the nonrandom selection of the patients. However, paired Student's *t*-test may have reduced the variance. After all, for individuals, the larger the interlead distance on lateral view is, the better one may respond to CRT.

Conclusions

The present study highlights that larger interlead distance on lateral fluoroscopy view is associated with better response to CRT, both intraprocedurally and at mid-term follow-up. In addition, RVA pacing is generally superior to RVOT pacing during biventricular pacing, especially when the LV lead is posterolaterally or laterally positioned.

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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