Comparison of segmental and global markers of dyssynchrony in predicting clinical response to cardiac resynchronization

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Aims Cardiac resynchronization therapy (CRT) reduces inter- and intraventricular dyssynchrony and shortens total isovolumic time (t-IVT). We compared the extent to which the values of ventricular dys-synchrony and t-IVT predict clinical benefits of CRT.

Methods and results Ventricular dyssynchrony was assessed in 39 patients with heart failure before and 6 months after CRT. Segmental dyssynchrony was identified from time to onset and peak systolic velocity of wall motion. T-IVT (s/min) was derived as \( [60 - (\text{total ejection time} + \text{total filling time})] \). The difference between ventricular pre-ejection periods (D-PEP) was calculated. Outcome measures were fall in New York Heart Association (NYHA) class and increase in cardiac output (CO). Following CRT, NYHA class fell in 29/39 patients, CO increased (by 1.0 L/min, \( P < 0.001 \)), and intraventricular delay (Intra-VD), interventricular delay (Inter-VD), t-IVT, and D-PEP shortened (by 25 ms, 72 ms, 6 s/min, and 38 ms, \( P < 0.01 \)). NYHA class and CO were unchanged with CRT in 10/39, and Intra-VD, Inter-VD, t-IVT, and D-PEP lengthened (by 43 ms, 52 ms, 7 s/min, and 35 ms, \( P < 0.05 \)). Though univariate predictors of CO increment with CRT were Intra-VD, Inter-VD, t-IVT, and D-PEP, only pre-CRT values of CO (\( P < 0.001 \)), t-IVT (\( P < 0.001 \)), and D-PEP (\( P = 0.025 \)) were independent.

Conclusion Global, rather than segmental, measures of ventricular dyssynchrony are powerful, independent predictors of clinical response to CRT.

Introduction

Cardiac resynchronization therapy (CRT) is a treatment of intractable heart failure with intraventricular conduction disturbances. Clinical trials have demonstrated the benefits of CRT on symptoms, exercise capacity, quality of life, heart failure hospitalization, and long-term prognosis.\(^1\)\(^-\)\(^4\) However, individual responses may vary; indeed, up to 30% of patients receiving CRT fail to respond clinically.\(^5\) Widened QRS complex on the surface electrocardiogram, baseline New York Heart Association (NYHA) function class, age, sex, and ejection fraction (EF) correlate poorly with outcome.\(^6\)\(^-\)\(^7\) In contrast, the predictive value of direct measures of segmental dyssynchrony using a variety of outcome measures based on different imaging types such as M-mode,\(^8\) Doppler,\(^9\) tissue Doppler,\(^9\)\(^-\)\(^11\) tissue synchroni-zation\(^12\) and strain-rate analysis\(^13\) have demonstrated predictive accuracies of 85–100%. However, segmental measures of mechanical dyssynchrony do not necessarily reflect the overall effect of CRT on global cardiac function.

Segmental dyssynchrony decreases peak rates of left ventricular (LV) pressure rise and fall,\(^1\(^4\)\) but also prolongs total isovolumic time (t-IVT: time in the cardiac cycle when the LV is neither ejecting nor filling).\(^1\(^5\)\) In patients with coronary artery disease, t-IVT prolongs as mechanical dyssynchrony increases during dobutamine stress\(^15\) and shortens with surgical revascularization.\(^16\) CRT also shortens t-IVT.\(^17\) Our working hypothesis was that when correction of dyssynchrony increases cardiac output (CO), it does so by shortening t-IVT. We therefore compared the predictive value of t-IVT in identifying responders to CRT with that of several global and segmental measures of LV dyssynchrony. We aimed not only to identify patients most likely to benefit clinically from CRT but also to predict its extent.

Methods

Study population

We retrospectively studied 39 patients with end-stage heart failure who received clinically indicated CRT during the period 2003–04. All patients included in the study fulfilled the AHA/ACC/NASPE criteria for resynchronization, that is, symptomatic NYHA classes III–IV, drug-refractory heart failure, stable sinus rhythm, LVEF ≤35%, dilated cardiomyopathy (LV end-diastolic diameter ≥55 mm), and prolonged QRS complex (≥130 ms). Ischaemic or non-ischaemic heart disease was defined by the WHO criteria.\(^18\) Exclusion criteria were acute heart failure, unstable angina, coronary artery bypass surgery, severe atrial fibrillation, mitral regurgitation, or severe conduction disturbances that preclude CRT implantation.

Aims Cardiac resynchronization therapy (CRT) reduces inter- and intraventricular dyssynchrony and shortens total isovolumic time (t-IVT). We compared the extent to which the values of ventricular dys-synchrony and t-IVT predict clinical benefits of CRT.

Methods and results Ventricular dyssynchrony was assessed in 39 patients with heart failure before and 6 months after CRT. Segmental dyssynchrony was identified from time to onset and peak systolic velocity of wall motion. T-IVT (s/min) was derived as \( [60 - (\text{total ejection time} + \text{total filling time})] \). The difference between ventricular pre-ejection periods (D-PEP) was calculated. Outcome measures were fall in New York Heart Association (NYHA) class and increase in cardiac output (CO). Following CRT, NYHA class fell in 29/39 patients, CO increased (by 1.0 L/min, \( P < 0.001 \)), and intraventricular delay (Intra-VD), interventricular delay (Inter-VD), t-IVT, and D-PEP shortened (by 25 ms, 72 ms, 6 s/min, and 38 ms, \( P < 0.01 \)). NYHA class and CO were unchanged with CRT in 10/39, and Intra-VD, Inter-VD, t-IVT, and D-PEP lengthened (by 43 ms, 52 ms, 7 s/min, and 35 ms, \( P < 0.05 \)). Though univariate predictors of CO increment with CRT were Intra-VD, Inter-VD, t-IVT, and D-PEP, only pre-CRT values of CO (\( P < 0.001 \)), t-IVT (\( P < 0.001 \)), and D-PEP (\( P = 0.025 \)) were independent.

Conclusion Global, rather than segmental, measures of ventricular dyssynchrony are powerful, independent predictors of clinical response to CRT.

KEYWORDS

Cardiac resynchronization therapy; Interventricular delay; Intraventricular delay; Total isovolumic time

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Comparison of segmental and global markers of dyssynchrony

Echocardiographic assessment

Transthoracic echocardiography was performed using a Phillips Sonos 5500 echocardiograph and a multifrequency transducer (Andover, MA, USA). Standard two-dimensional parasternal long- and short-axis views and apical four-, five-, and two-chamber views were performed. Cross-sectional two-dimensional guided M-mode recordings of the LV minor axis were obtained. EF and end-systolic volume (ESV) were calculated by Simpson’s method. Mitral regurgitation (MR) was recorded using colour-flow Doppler and continuous-wave Doppler in the apical four- and two-chamber views, and its duration, expressed as percentage of the RR interval, was calculated.

Subaortic flow velocity was obtained by pulsed-wave Doppler from the apical five-chamber view, with the sample volume placed in the LV outflow tract, 1 cm below the aortic cusps. LV ejection time (ET) was measured using leading edge methodology as the interval between the onsets of forward aortic flow and aortic valve closure artefact. Stroke distance was calculated as the time integral of aortic velocity, stroke volume as the product of stroke distance and subaortic area, and CO as stroke volume multiplied by heart rate. A pre-determined increment in CO of ≥15% was used to signify an increase in CO after CRT.

Transmitral flow velocities were recorded from the apical four-chamber view using pulsed-wave Doppler. Isovolumic relaxation time (IVRT: the interval between A2 and the onset of mitral flow) and peak E (early diastolic) and A (atrial) velocities were obtained in all patients. Filling time (FT) was measured using leading edge methodology from the onset of the E-wave to the end of the A-wave. Isovolumic contraction time (IVCT) was calculated by subtracting the sum of IVRT (ms), ET (ms), and FT (ms) from RR interval.

Total LV ejection and filling periods were derived as the product of the corresponding time interval and heart rate, expressed in s/min, e.g. total ET (s/min) = ET (ms)*heart rate/1000. T-IVT, also in s/min, was derived as [60 – (total ET + total FT)]15-17 (Figure 1).

LV pre-ejection period (LV-PEP) and RV pre-ejection period (RV-PEP) were measured from the onset of the QRS complex to the onsets of aortic and pulmonary flow, respectively. With CRT, the pacing artefact was taken as the onset of ventricular activation. The difference (D-PEP) was calculated as LV-PEP minus RV-PEP.

LV long axis M-mode and pulsed-wave tissue Doppler recordings were obtained with the cursor positioned at the lateral, septal, and posterior angles of the mitral ring and at the lateral ring of the tricuspid valve for the RV. A Doppler velocity range of ±30 cm/s displayed systolic and early diastolic velocities. Intraventricular delay (Intra-VD) and interventricular delay (Inter-VD) were calculated using the following two methods.

HR = 64 bpm

**Figure 1** Measurement of t-IVT. Total ET and total FT are derived as the product of the corresponding time interval and heart rate, expressed in s/min. t-IVT is calculated as (60 – [total ET + total FT]).

**M-mode imaging**

Segmental electromechanical delay was measured from the onset of the QRS to the onset of long-axis shortening (TSD) (Figure 2, top). Intra-VD (TOS-Intra-VD) was calculated as the difference between the longest and shortest regional electromechanical coupling time (irrespective of site). Inter-VD (TOS-Inter-VD) was calculated as the difference between regional electromechanical coupling time at the RV free wall and the most delayed LV site (i.e. longest regional electromechanical coupling time).

**Tissue Doppler imaging**

Tissue Doppler imaging was used to measure the time to peak systolic velocity (Tts), taken from the onset of the QRS complex to the peak velocity during ejection (Figure 2, bottom). Intraventricular (Tts-Intra-VD) delay was calculated as the difference between the longest and shortest time to peak systolic velocity (irrespective of site), and Inter-VD (Tts-Inter-VD) as the difference between time to peak systolic velocity at the RV free wall and the most delayed LV segment.

**Pacemaker implantation**

Seventeen of 39 patients were implanted with a biventricular pacemaker (Guidant Contak TR CHFD, Guidant Inc., St. Paul, MN, USA), Medtronic InSync ICD 7040, Medtronic Inc., Minneapolis, MN, USA, or Guidant Contak CD CHFD or Contak Renewal, Guidant Inc., or Medtronic InSync ICD 7272, Medtronic Inc.). Implantation was performed as previously described and was uncomplicated in all cases. The final LV lead position was lateral (in 23 cases), posterolateral (in 10 cases), and posterior (in six cases). The biventricular pacing mode was programmed in DDD, and the lower rate set at 40 bpm. The ativoventricular interval was optimized for maximal diastolic filling by Doppler echocardiography while ensuring...


Time to onset of shortening ($T_{OS}$)

Time to peak ejection velocity ($T_S$)

Figure 2 Time to onset of long-axis shortening ($T_{OS}$) was measured from onset of QRS complex to onset of long-axis shortening (top). Time to peak systolic velocity ($T_S$) was measured from onset of QRS complex to peak systolic velocity (bottom).

Data analysis

Statistical analyses were performed using Statview 4.5 (Abacus Concepts, Berkley, CA, USA) and S Plus 6.2 (Insightful, Seattle, WA, USA). Normally distributed continuous variables were expressed as mean ± standard error. Continuous variables within and between groups were compared using two-tailed paired and unpaired Student’s t-tests. Categorical variables were expressed as number (percentage) and compared using a χ² or Fisher’s exact test as appropriate. Agreement between reduction in NYHA class, improvement in CO, and reduction in ESV was assessed using the kappa statistic. The influence of t-IVT vs. a number of pre-determined global and segmental measures of LV dyssynchrony in predicting the increase in CO with CRT was assessed with multiple-regression analysis (ANCOVA). Correlation was performed by linear-regression analysis.

A significance level of $P < 0.05$ was employed throughout the study.

Results

Thirty-nine patients (aged 65 ± 10 years, QRS duration 154 ± 18 ms, 30 male) were studied before (median 2.0 months, interquartile range (IQR) 0.5–2.5 months) and after (median 6.3 months, IQR 4.2–8.9 months) pacemaker implantation. Before pacing, 37/39 patients were in NYHA class III and two were in NYHA class IV. NYHA class fell by ≥1 functional class with CRT in 29/39 patients (‘responders’) and did not change in 10 (‘non-responders’).14 The demographic, clinical, and therapeutic characteristics of the patient population are presented in Table 1. Half of all responders and 90% of non-responders had an ischaemic aetiology ($\chi^2 = 5.3$, $P < 0.03$). There was no difference in LV lead placement between responders vs. non-responders (lateral LV lead: 66 vs. 50%, posterolateral lead in 10 vs. 20%; posterior lead: 24 vs. 30%, all $P = NS$). Similarly, there was no difference in medical therapy or in the programmed resting atioventricular interval between responders (89 ± 19 ms) and non-responders (93 ± 19 ms, $P = 0.77$).

Relation between changes in NYHA class, CO, and ESV

Resting CO increased with CRT in 31/39 patients (in whom NYHA class fell ≥1 class in 29/31). ESV fell by >15% in 32/39 patients (in whom NYHA class fell ≥1 class also in 29/31). The agreement between fall in NYHA class and increase in CO (>15%) was associated with a kappa statistic of 0.85 ($P < 0.001$); similarly, fall in NYHA class and reduction in ESV (>15%) were associated with a kappa statistic of 0.78 ($P < 0.001$). In the event, we used post-implantation CO as a quantitative measure to determine the predictors of clinical response to CRT.

Comparison between responders and non-responders at baseline

When compared with non-responders, responders had lower baseline values for mitral E-wave velocity (by 35 cm/s, $P < 0.001$) and longer values for t-IVT, LV-PEP, and D-PEP (by 7 s/min, $P < 0.001$; 33 ms, $P = 0.008$; 50 ms, $P < 0.001$, respectively; Table 2). Segmental dyssynchrony was more pronounced at baseline in responders (Table 3), with Intra-VD and Inter-VD up to 51 and 71 ms longer, respectively, than that in non-responders (both $P < 0.001$).

Effect of CRT on global LV function

Responders With CRT, there were significant mean (±SE) increases in CO (by 1.0 ± 0.1 L/min), EF (by 10 ± 2%), and total LV FT (by 5 ± 1 s/min), and significant mean (±SE) reductions in ESV (by 58 ± 31 mL), MR duration (by 10 ± 7%), and IVCT (by 50 ± 39 ms, all $P < 0.001$, Table 2). The combination of shorter IVCT and longer FT resulted in a significant fall in t-IVT (by 6 ± 4 s/min, $P < 0.001$). D-PEP shortened in responders (by 38 ± 23 ms, $P < 0.001$).

Non-responders

There were no significant mean changes in resting CO, EF, or duration of MR with CRT (Table 2), and ESV decreased by 30 ± 21 mL ($P < 0.05$ compared to responders). In contrast to responders, IVCT lengthened (by 73 ± 95 ms, $P = 0.037$) and FT shortened (by 5 ± 4 s/min, $P = 0.024$), so that t-IVT increased (by 7 ± 4 s/min, $P = 0.001$). D-PEP increased with CRT in non-responders (by 35 ± 12 ms, $P < 0.001$).
**Effect of CRT on segmental LV function**

**Responders**

The LV lead was placed at the site of longest electromechanical delay in 76% of patients. Intra-VD and Inter-VD fell with CRT in responders (Table 3): $T_{05}$-Intra-VD and $T_{05}$-Inter-VD both shortened (by $25 \pm 42$ ms, $P = 0.003$ and $72 \pm 37$ ms, $P < 0.001$ respectively), as did $T_{5}$-Intra-VD and $T_{5}$-Inter-VD (by $25 \pm 76$ ms, $P = 0.043$ and $51$ ms, $P < 0.001$ respectively).

**Non-responders**

The LV lead was placed at the site of longest electromechanical delay in 70% of patients ($P = NS$ compared with responders). Intra-VD and Inter-VD increased with CRT in non-responders (Table 3): $T_{05}$-Intra-VD and $T_{05}$-Inter-VD both increased (by $43 \pm 13$ ms $P = 0.015$ and $52 \pm 10$ ms $P < 0.001$ respectively), as did $T_{5}$-Inter-VD (by $28 \pm 18$ ms $P < 0.001$). Mean $T_{5}$-Intra-VD was unchanged.

**Predictors of the extent of increase in CO with CRT**

Other than baseline values of CO, there were several univariable predictors of the CO increment with CRT: $T_{05}$-Intra-VD, $T_{05}$-Inter-VD, D-PEP, t-IVT, total FT, IVCT, LV-PEP, and T-Inter-VD (Table 4). After adjusting for baseline values of CO, the only independent variables that predicted CO-increment with CRT were t-IVT ($P < 0.001$) and D-PEP ($P = 0.025$, Table 4). The combination of pre-CRT values for CO, t-IVT, and D-PEP explained $87\%$ ($R^2 = 0.87$) of the total variance in observed CO with CRT (Figure 3), considerably more than any of these variables singly. Overall, responders tended to have longer t-IVT and D-PEP before CRT (Figure 4A) and shorter t-IVT and D-PEP with CRT (Figure 4B). The reverse was true for non-responders.

**Reproducibility**

We have previously published the reproducibility of measurements used in our analysis; reproducibility,
expressed as root mean square, was 3.5 s/min for t-IVT, 1.26 L/min for CO, and 11 ms for ESV.

Table 3 Effect of CRT on segmental dyssynchrony

<table>
<thead>
<tr>
<th>Variable</th>
<th>Responders (n = 29)</th>
<th>Non-responders (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-CRT</td>
<td>CRT</td>
<td>P-value</td>
</tr>
<tr>
<td>T\textsubscript{05} -Intra-VD (ms)</td>
<td>82 ± 5</td>
<td>57 ± 15</td>
</tr>
<tr>
<td>T\textsubscript{05} -Inter-VD (ms)</td>
<td>123 ± 6</td>
<td>51 ± 6</td>
</tr>
<tr>
<td>T\textsubscript{l} -Intra-VD (ms)</td>
<td>97 ± 11</td>
<td>72 ± 7</td>
</tr>
<tr>
<td>T\textsubscript{l} -Inter-VD (ms)</td>
<td>133 ± 10</td>
<td>82 ± 6</td>
</tr>
</tbody>
</table>

Discussion

The principal aim of CRT is to improve clinical outcome or to prolong prognosis. We thus chose an independently determined, previously validated, clinical marker of response to CRT (fall in NYHA class ≥1 grade) as an endpoint to identify clinical responders to CRT. There was a close agreement between fall in NYHA class (clinical response to CRT) and increase in resting CO and reduction in ESV (echocardiographic response). Fall in NYHA class agreed with an increase in CO with a higher kappa statistic than that for reduction in ESV, which lent credence to using CO increase with CRT as an endpoint. Measurement of CO is a clinically valid and reliable outcome measure in patients with end-stage heart failure, with the advantage of eliminating any placebo effect on NYHA class.

Findings

Our results demonstrate that patients who responded to CRT with a fall in NYHA class and rise in resting CO had more pronounced segmental dyssynchrony and greater values for t-IVT and D-PEP before implantation when compared with non-responders. A positive clinical response to CRT was also accompanied by shortening of t-IVT, as previously demonstrated in the MUSCITIC trial, and of D-PEP, as previously demonstrated in the CARE-HF trial, compatible with lessening of the degree of segmental dyssynchrony. Indeed, resynchronization by CRT augmented stroke volume to the extent that resting CO increased, despite a significant reduction in heart rate after pacing. In contrast, segmental dyssynchrony became more apparent after pacing in non-responders, in whom t-IVT and D-PEP both increased.

In line with previous studies, we found that patients who responded to CRT had more pronounced segmental dyssynchrony, whether measured by M-mode or tissue Doppler. Furthermore, their baseline values proved to be significant univariate predictors of response to CRT. However, these segmental measures of dyssynchrony were subsumed in multivariate analysis, and the only independent predictors of CO increment with CRT were baseline values of CO, t-IVT, and D-PEP. Indeed, the combination of baseline values of CO, t-IVT, and D-PEP accounted for 87% of the variance in CO increment with CRT. Moreover, combining t-IVT and D-PEP in a simple two-dimensional display demonstrated clustering of patients with almost complete separation between responders and non-responders (Figure 4).

Mechanisms

It is clear from Figure 4 that responders were patients in whom pre-implantation values of both t-IVT and D-PEP were greatly and abnormally prolonged. We have previously shown that t-IVT is prolonged by segmental dyssynchrony and shortens as a result of reduction of dyssynchrony with CRT. We have also previously shown that it is a powerful predictor of peak VO\textsubscript{2} in patients with dilated cardiomyopathy, which might explain its significance in predicting the clinical response to CRT. The reason why D-PEP is as sensitive to t-IVT, as well as being synergistic with it, is not entirely clear. We previously demonstrated that dysynchronous LV contraction is a determinant of PEP in patients with LV disease. Owing to uncertainty in determining the onset of the QRS on the surface ECG in some patients with LBBB, this correlation is apparent only as prolonged D-PEP, rather than in absolute values of LV-PEP in isolation. We assume, therefore, that D-PEP, like t-IVT, can be regarded as an index of the overall effects of dyssynchrony on LV function.
In keeping with previous investigations, ~25% of our patients were non-responders. From Figure 4, it is clear that in all non-responders, values of t-IVT and D-PEP were within the normal range prior to implantation. This strongly suggests that in these patients, failure to respond to CRT was associated with pre-existing coordinate contraction rather than dyssynchrony uncorrected by biventricular pacing, caused, for instance, by inappropriate positioning of the LV lead due to unfavourable coronary sinus anatomy. Furthermore, it was disquieting to observe that in nearly every non-responder, implementation of CRT was associated with prolongation of both t-IVT and D-PEP to values well outside the normal range. The possibility that CRT had actually induced dyssynchrony was reinforced in these patients by the observation that measures of segmental dyssynchrony had also deteriorated (Table 3).

Limitations

Although the study sample size was relatively small, the results are compatible with previous conclusions that the absence of baseline dyssynchrony is the main basis for non-response. Similar to other studies,14,20 only basal LV sites were interrogated; this may have led to the loss of precision in localizing intraventricular dyssynchrony, thereby favouring t-IVT and D-PEP on multivariate analysis. However, potential intraventricular dyssynchrony at mid-cavity or apical level would have been reflected in reciprocal dyssynchrony at the base of the heart which we studied. Furthermore, basal segmental function is closely related to global cardiac function (EF), so basal intraventricular dyssynchrony, if present, would be more likely to have an effect on global cardiac function than dyssynchrony elsewhere in the myocardium. We chose a clinical rather than an echocardiographic marker of response to CRT (reduction in LV ESV), as the aim of our study was to predict clinical, not echocardiographic, improvement with CRT. Although the assessment of NYHA class may be subjective, there was a good agreement between clinical and echocardiographic
response to CRT on an individual patient basis. As in all CRT studies, the possibility exists of spontaneous improvement, independent of pacing, which may confound the results. Finally, the statistical analysis implicitly assumes that the effects of CRT are constant with time (i.e. patients do not have an initial improvement and subsequently decline).

Clinical implications

To be of value in a clinical setting, any measurement should be easy to quantify and interpret. Individuals with pronounced evidence of global LV dysynchrony (long t-IVT and D-PEP) are more likely to respond clinically to CRT, regardless of baseline demographics, QRS duration, NYHA class, or EF. T-IVT and D-PEP can be measured rapidly and compared with those on a display as in Figure 4, allowing a clinical decision to be made. Using these simple intervals avoids multiple determinations of segmental function, which may be time consuming to perform. Furthermore, we have previously demonstrated the close association between resting t-IVT and peak VO$_2$; the shorter the t-IVT, the greater peak VO$_2$. This might explain the favourable clinical outcome in patients who responded to CRT. The contrasting observation that CRT may apparently induce dysynchrony in patients with coordinate contraction requires further investigation.

Conclusion

The consequence of segmental dysynchrony in patients with end-stage heart failure appears to be reflected in simple measurements of timing within the cardiac cycle, namely t-IVT and the difference between the ventricular pre-ejection periods. These measures of global LV function, which can readily be made in routine clinical conditions using simple and well-validated techniques, independently predict the extent of clinical response to biventricular pacing and together afford the possibility of predicting the outcome of CRT in individual patients with some precision.

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Conflict of interest: None declared.

References