Cardiac resynchronization therapy : determinants of patient outcome and emerging indications

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Chapter 17

Diverse patterns of longitudinal and radial dyssynchrony in patients with advanced systolic heart failure

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ABSTRACT

Background: Little was known about the impact of QRS duration and etiology of heart failure on the pattern of left ventricular long- and short-axis dyssynchrony. This was investigated in the current study by using tissue Doppler imaging (TDI) and two-dimensional (2D) speckle-tracking imaging.

Methods: 448 heart failure patients (65±12years, 75% males) with ejection fraction ≤35% from the 2 cardiac centers were examined for the occurrence of longitudinal dyssynchrony by TDI and radial dyssynchrony by 2D speckle-tracking imaging. Region(s) of the latest mechanical contraction were also determined.

Results: Longitudinal dyssynchrony was identified in 263 (59%) patients while radial dyssynchrony in 186 (42%). There were 125 (28%) patients who had both longitudinal and radial dyssynchrony, 138 (31%) had only longitudinal, 61 (13%) had only radial, and 124 (28%) had neither form of dyssynchrony. By using TDI, the single most delayed segment was the septal, lateral, anterior, inferior, anteroseptal and posterior wall in 12%, 27%, 12%, 19%, 7% and 13% of patients while multi-segmental delay occurred in 10% of patients. These figures were 10%, 8%, 5%, 10%, 12%, 14% and 41% by using 2D speckle-tracking. When compared between patients with wide and narrow QRS complexes, both longitudinal (63% vs. 53%) and radial (49% vs. 36%) dyssynchrony parameters were slightly more frequently positive in the wide QRS group defined by QRS duration ≥120 ms (both $p<0.05$). When compared between non-ischemic and ischemic patients, the prevalence of longitudinal dyssynchrony was comparable (61% vs. 57%, $p = 0.467$), while radial dyssynchrony was marginally more common in the non-ischemic group (47% vs. 37%, $p = 0.049$). However, the distributions of the most delayed segment between the sub-groups were highly similar when assessed by the same echocardiographic method.

Conclusions: In patients with advanced systolic heart failure, the patterns of longitudinal and radial dyssynchrony are heterogeneous, and mechanical dyssynchrony is slightly more prevalent in the wide QRS group or the non-ischemic group.

INTRODUCTION

Systolic dyssynchrony has been recognized as a common mechanical phenomenon in patients with advanced heart failure. It not only occurs in heart failure with electrical conduction delay as evidenced by a wide QRS complex, but also exists in those with a normal QRS duration.[1,2] With the development of advanced and quantitative echocardiographic imaging techniques, mechanical dyssynchrony could further be investigated for different components according to the axis of left ventricular (LV) motion. Among various echocardiographic techniques, tissue Doppler imaging (TDI) has been validated for assessing the timing of regional myocardial motion along the LV longitudinal axis, while two-dimensional (2D) speckle-tracking imaging has been adopted for measuring radial axis dyssynchrony.[3,4,5]

Cardiac resynchronization therapy (CRT) is an established device therapy for patients with refractory heart failure who have electromechanical delay.[6,7,8,9] While the QRS duration on surface ECG failed to predict a favorable response, the assessment of dyssynchrony by echocardiographic techniques showed a close relationship with improvement after CRT.[10,11,12,13] Furthermore, it has recently been suggested that identifying the location of the latest mechanical activation might provide insight into the optimal location of the LV pacing lead, apart from deploying it at the postero-lateral wall.[14,15] Therefore, in the current study, we examined the occurrence of longitudinal and/or radial dyssynchrony and the pattern of the latest contraction in heart failure patients with LV ejection fraction (LVEF) ≤35% despite optimal medical therapy.

METHODS

Patients

From Jan, 2006 to Jan, 2009, patients who presented congestive heart failure with an LVEF ≤35% despite optimal medical therapy were recruited from 2 cardiac centers (CUHK and LUMC). Patients were excluded from the study if they had a previous pacemaker implantation and/or chronic atrial fibrillation. Ischemic etiology of heart failure was confirmed by a history of myocardial infarction and/or a positive result by coronary angiogram. The study protocol was approved by the ethic committees of the 2 institutions and informed consent was obtained from each participant.

Comprehensive echocardiography with two-dimensional (2D), Doppler and TDI was performed in each patient (Vivid 7, Vingmed-General Electric, Horten, Norway). At least 3 consecutive beats were stored and the images were analyzed offline with the aid of a customized software package (EchoPac PC, version 7.0.0; Vingmed-General Electric, Horten, Norway). LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV) and LVEF were calculated from the apical 4- and 2-chamber views, using the biplane Simpson's method.[16]

Color TDI images were acquired in the apical 4-chamber, 2-chamber and 3-chamber views for assessing LV longitudinal motion. The myocardial velocity curve was reconstituted offline in each segment of the 6-basal, 6-mid LV model, where the time to peak systolic velocity during ejection phase (Ts) was measured.[17] Longitudinal systolic dyssynchrony was calculated as the standard deviation of Ts among the 12 LV segments (Ts-SD) and a cut-off value of ≥33ms was adopted as previously described.[18] The segment(s) with the latest contraction was determined by the longest Ts.

Gray-scale 2D images at the mid-cavity level of LV short-axis view were analyzed for radial deformation by using 2D speckle-tracking technology. The myocardial radial strain curves were reconstituted in each of the 6 mid-LV segments from which the time to maximal radial strain was measured. Radial dyssynchrony was calculated as the time difference between the anteroseptal and posterior segment (anteroseptal-to-posterior delay) and a cut-off of ≥130 ms was adopted to identify significant dyssynchrony.[18,19] The most delayed segment(s) was that with the longest time to maximal radial strain.

Statistical analysis

Statistical analysis was performed using SPSS 13.0 (SPSS, Inc., Chicago, Illinois, USA). Parametric variables are expressed as mean±SD while categorical variables are expressed as numbers and percentages. The paired sample t-test or McNemar test was adopted when appropriate in comparisons between longitudinal and radial dyssynchrony. The distributions of most delayed segment between longitudinal and radial dyssynchrony were compared by Chi-square test. The Chi-square test or unpaired sample t-test was used when appropriate to compare between sub-groups, including wide vs. narrow QRS and non-ischemic vs. ischemic heart failure. A p-value <0.05 was considered statistically significant.

RESULTS

Demographics of the study population

A total of 448 patients were recruited in this observational study. All patients were put on optimal medical therapy for heart failure which included diuretics, angiotensin converting enzyme inhibitors or angiotensin receptor blockers, β-blockers and Spironolactone. Table 1 shows baseline characteristics of the study population.

Table 1. Baseline characteristics of the study population (n = 448)

Age	65 ± 12years
Gender (male)	75%
Heart rhythm (sinus)	100%
NYHA class, II / III / IV	27 (6%) / 403 (90%) / 18 (4%)
Etiology of heart failure (ischemic)	250 (56%)
QRS duration ≥120 ms	241 (54%)
Left bundle branch block	174 (39%)
Right bundle branch block	30 (7%)
Intraventricular conduction delay	37 (8%)
LV end-diastolic volume (ml)	191 ± 71
LV end-systolic volume (ml)	141 ± 60
LV ejection fraction (%)	27 ± 7

Prevalence and pattern of systolic dyssynchrony in heart failure

By using TDI assessment, the mean Ts-SD of the study population was 37.7±16.9 ms and significant longitudinal dyssynchrony occurred in 263 (59%) patients. In contrast, by using 2D speckle-tracking imaging, the mean anteroseptal-to-posterior delay was 136±115 ms and significant radial dyssynchrony occurred in 186 (42%) patients. Therefore, longitudinal dyssynchrony parameter was significantly more frequently positive than radial dyssynchrony parameter (χ^2 = 29.4, p<0.001). Furthermore, there were 125 (28%) patients who had both longitudinal and radial dyssynchrony, 138 (31%) patients had only longitudinal dyssynchrony, 61 (13%) patients had only radial dyssynchrony, and 124 (28%) patients had neither form of dyssynchrony. The occurrence of longitudinal and radial dyssynchrony is concordant in 249 (56%) of the study patients.

By using TDI, the single most delayed segment was found in the septum for 52 (12%) patients, in the lateral wall for 120 (27%) patients, in the anterior wall for 55 (12%) patients, in the inferior wall for 85 (19%) patients, in the anteroseptum for 30 (7%), and in the posterior wall for 60 (13%) patients. Forty-six (10%) patients had multi-segmental delay. Conversely, by using 2D speckle-tracking imaging, these figures were 45 (10%), 36 (8%), 22 (5%), 45 (10%), 54 (12%), 63 (14%) and 183 (41%) patients, respectively (Figure 1). A concordance in the most delayed segment between TDI and 2D speckle-tracking methods was found in 134 (30%) patients.

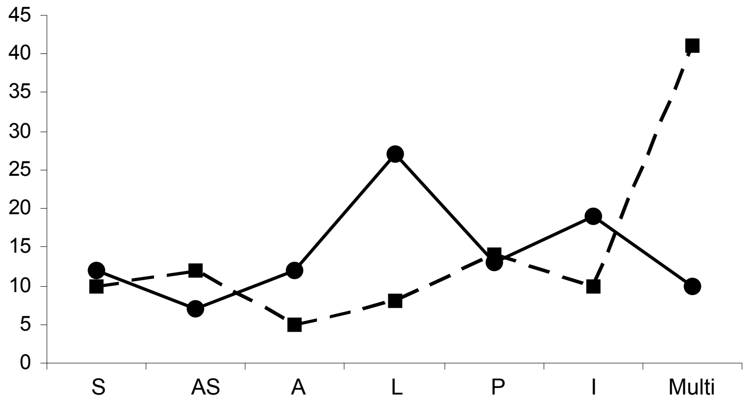

Figure 1. Distributions of the most delayed segment detected by tissue Doppler imaging (———) and two-dimensional speckle-tracking imaging (– – – – –) in the whole study population. S = septum; AS = anteroseptum; A = anterior segment; L = lateral segment; P = posterior segment; I = inferior segment, Multi = multi-segmental delay.

Pattern of systolic dyssynchrony in heart failure with wide vs. narrow QRS complexes

When comparing between patients with wide and narrow QRS complexes, the wide QRS group had a larger LVEDV (198±79 ml vs. 182±60 ml, p = 0.014), LVESV (148±68 ml vs. 132±50 ml, p = 0.005) and a lower LVEF (26.4±7.6% vs. 28.1±7.1%, p = 0.019). The wide QRS group also had a more prolonged dyssynchrony indices of TDI (Ts-SD: 39.2±16.0 ms vs. 36.0±17.8 ms, p = 0.044) and 2D speckle-tracking (anteroseptal-to-posterior delay: 151±122 ms vs. 118±104 ms, p = 0.003) methods. The difference in the occurrence of positive longitudinal dyssynchrony parameter in the wide QRS group, when compared to narrow QRS group, was marginally significant (63% vs. 53%, p = 0.043). Similarly, radial dyssynchrony parameter was slightly more frequently positive in wide QRS group (49% vs. 36%, p = 0.039).

In the wide QRS group, the most delayed segment using TDI was the septum in 30 (12%) patients, the lateral wall in 67 (28%), the anterior wall in 27 (11%), the inferior wall in 50 (21%), the anteroseptum in 17 (7%), and the posterior wall in 34 (14%). Multi-segmental delay was found in 16 (7%) patients. These figures were similar in the narrow QRS group, which were 22 (11%), 53 (26%), 28 (14%), 35 (17%), 13 (6%), 26 (12%) and 30 (14%) patients, respectively (p = 0.173). Similar distributions between the wide and narrow QRS groups were also found using 2D speckle-tracking (p = 0.511) (Figure 2A&2B).

Figure 2A

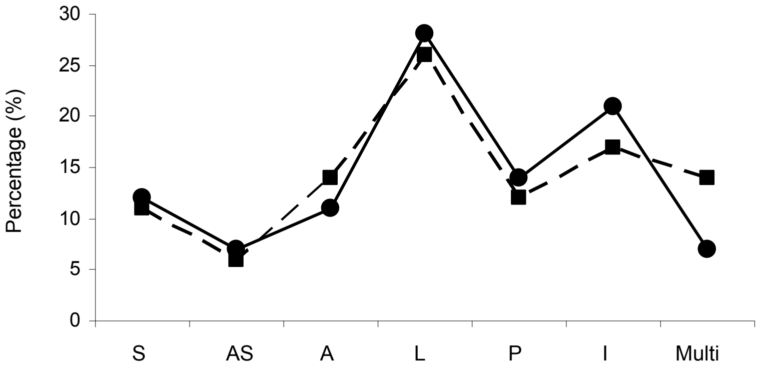

Figure 2B

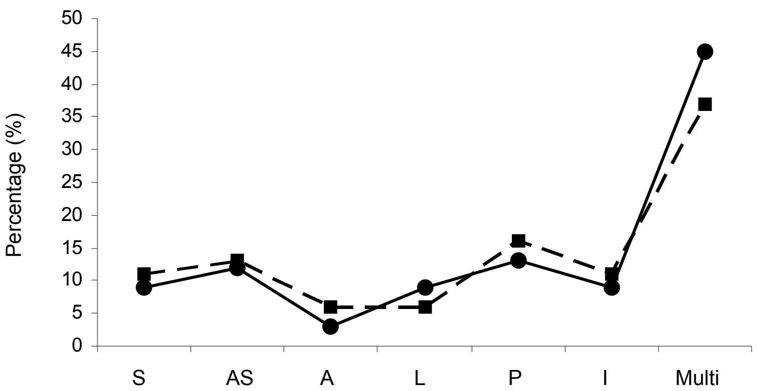

Figure 2. Distributions of the most delayed segment detected by tissue Doppler imaging (**A**) and two-dimensional speckle-tracking imaging (**B**) in the wide QRS (solid line) and narrow QRS (dashed line) sub-groups.
S = septum; AS = anteroseptum; A = anterior segment; L = lateral segment; P = posterior segment; I = inferior segment, Multi = multi-segmental delay.

Pattern of systolic dyssynchrony in ischemic vs. non-ischemic patients

When comparing between non-ischemic and ischemic patients, there was no significant difference in the LVEDV (194±74 ml vs. 182±67 ml, p = 0.391), LVESV (144±65 ml vs. 138±57 ml, p = 0.272) and LVEF (26.6±7.6% vs. 27.6±7.2%, p = 0.637). A wide QRS complex was found in 111 (56%) patients in the non-ischemic group and in 130 (52%) patients in the ischemic group ($\chi^2 = 0.733$, p = 0.392). Although dyssynchrony index by TDI was not different between the 2 groups (38.3±17.0 ms vs. 37.2±17.0 ms, p = 0.504), the anteroseptal-to-posterior delay by 2D speckle-tracking imaging was more prolonged in non-ischemic group (153±125 ms vs. 122±104 ms, p = 0.005). Longitudinal dyssynchrony by TDI was identified in 120 (61%) patients in the non-ischemic group and 143 patients (57%, p = 0.467) in the ischemic group. In contrast, radial dyssynchrony by 2D speckle-tracking imaging was identified in 93 (47%) patients in the non-ischemic group and 92 patients (37%, p = 0.049) in the ischemic group.

In the non-ischemic group, TDI identified the most delayed segment as the septum in 27 (14%), the lateral wall in 54 (27%), the anterior wall in 19 (10%), the inferior wall in 43 (21%), the anteroseptum in 10 (5%), and the posterior wall in 29 (15%) patients. Multi-segmental delay was observed in 16 (8%) patients. The figures were 25 (10%), 66 (26%), 36 (14%), 42 (19%), 20 (8%), 31 (12%) and 30 (11%) patients respectively in the ischemic group (p = 0.220). Similarly, 2D speckle-tracking demonstrated no difference in the prevalence of delay in the septum, lateral wall, anterior wall, inferior wall, anteroseptum, posterior wall and multi-segmental delay between the non-ischemic (13%, 11%, 6%, 11%, 10%, 15% and 34%) and ischemic (8%, 5%, 4%, 9%, 14%, 14% and 46%) groups (p = 0.128) (Figure 3A&3B).

Figure 3A

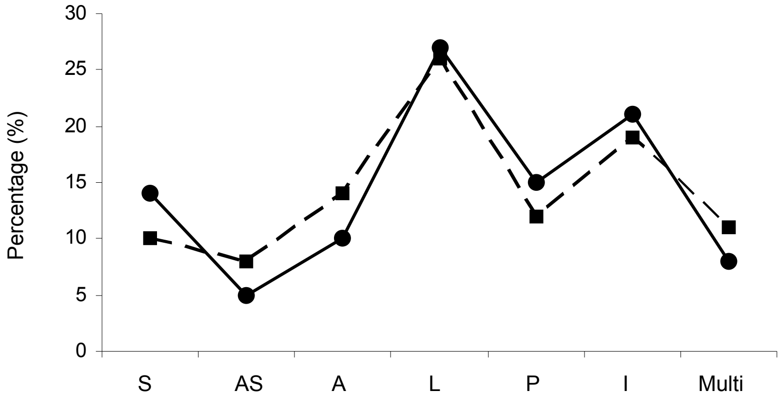

Figure 3B

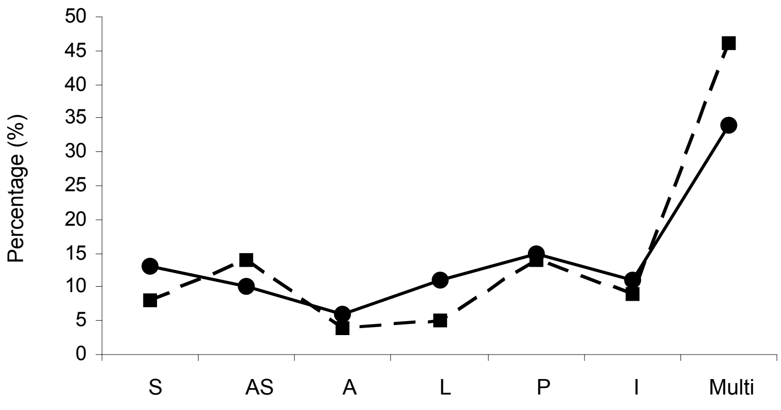

Figure 3. Distributions of the most delayed segment detected by tissue Doppler imaging (**A**) and two-dimensional speckle-tracking imaging (**B**) in the non-ischemic (solid line) and ischemic (dashed line) sub-groups. S = septum; AS = anteroseptum; A = anterior segment; L = lateral segment; P = posterior segment; I = inferior segment, Multi = multi-segmental delay.

DISCUSSION

In this study we show that longitudinal and radial dyssynchrony, as defined by two previously published and most commonly used parameters, was present in 59% and 42% of patients with heart failure and LV ejection fraction of ≤35%. However, the concordance of dyssynchrony, as defined by these two parameters, was modest and occurred in only slightly more than half of the patients. Interestingly, when the two methods were compared in their ability to detect single most delayed segment, the concordance occurred in about one-third of the patients. Of note, dyssynchrony parameters were positive in patients with both narrow and wide QRS complex, although this was slightly more frequent in the presence of wide QRS complex, a finding which is consistent with our previous observation.[20] Finally, heart failure etiology (ischemic vs. non-ischemic) only marginally affected dyssynchrony parameters or the detection and location of the most delayed segment.

Longitudinal vs. radial dyssynchrony

The current study chose 2 previously validated parameters, namely Ts-SD by TDI and anteroseptal-to-posterior delay by 2D speckle-tracking, to investigate the occurrence of longitudinal and radial dyssynchrony simultaneously in a large number of heart failure patients.[17,19] TDI has been widely used for assessment of LV longitudinal dyssynchrony, which has shown a close agreement with cardiac magnetic resonance imaging (MRI).[21] Furthermore, a number of TDI dyssynchrony parameters have been suggested helpful in predicting favorable response to CRT.[18] 2D speckle-tracking imaging is an angle-independent tool where the derived radial dyssynchrony has been found being able to identify CRT responders.[19] The diverse pattern of longitudinal and radial dyssynchrony displayed in the current study indicates the complex nature of mechanical dyssynchrony in heart failure as cardiac motion *per se* is complex and contains various components of action. The use of different echocardiographic technologies which can track longitudinal and radial motions is likely to provide comprehensive and incremental information on the extent of LV dyssynchrony. Interestingly, the wide QRS group had a higher prevalence of both longitudinal and radial dyssynchrony than the narrow QRS group, which probably reflected the additional impact of electrical propagation abnormalities within the LV of the former group.[22] On the other hand, the lack of difference in the prevalence of longitudinal dyssynchrony between etiologies of heart failure corroborates the findings of previous studies in patients undergoing CRT. These studies demonstrated a similar response rate in terms of LV reverse remodeling at 3-month follow up between ischemic and non-ischemic heart failure patients.[23] Of note, in heart failure patients with a wide QRS complex, the simultaneous assessment of longitudinal dyssynchrony by TDI and radial dyssynchrony by speckle-tracking resulted in a higher CRT responder rate of 93% than that of only assessing either parameter in which the responder rate was only 57%.[24] This study and our findings in the present study suggest that developing a robust scheme of dyssynchrony assessment which including different cardiac axes would provide complementary information and potentially assist future decision making.

Diversity of the most delayed segments

In a few small-scale CRT studies, identification of the segment with the latest contraction by 2D speckle-tracking imaging was suggested to be helpful in identifying an optimal position for the LV pacing lead.[15,25] However, it remains controversial whether this echocardiography-guided implantation would result in a better response to CRT, when compared with conventional placement of the LV lead at the LV postero-lateral wall. The present study demonstrated a diverse pattern of the most delayed segments in both longitudinal and radial dyssynchrony, as illustrated in Figure 1. There was also a trend of more patients with postero-lateral wall delay by TDI (about 40% in all the sub-groups), while by 2D speckle-tracking imaging the trend was in favor of more patients with multi-segmental delay. Intriguingly, within each sub-group of wide and narrow QRS complex or ischemic and non-ischemic etiology, the patterns of delay by TDI or 2D speckle-tracking imaging were distinctively concordant, as illustrated in Figures 2 and 3. These findings could have been consistent with previous single-center observations that CRT resulted in a similar early volumetric responder rate for patients with wide and narrow QRS complexes who had a similar extent of systolic dyssynchrony,[26,27] although it was not demonstrated in the multi-center RethinQ study.[28]

Study limitations

The current study was the first one of this kind to describe the prevalence and pattern of longitudinal and radial dyssynchrony simultaneously within a large heart failure population. However, it was not envisaged to explore the underlying pathophysiological processes leading to the development of different components of mechanical dyssynchrony, nor to demonstrate the correlation between longitudinal or radial dyssynchrony and prognosis in a cross-sectional observational study where no follow up data available. Meanwhile, the inclusion of much fewer patients in NYHA class II or IV made it impossible to correlate the echocardiographic findings with clinical parameters. Hopefully, our understanding of the complex relations between the different forms of cardiac dyssynchrony would be improved with the assistance of other advanced imaging techniques such as contrast-enhanced MRI, and with the data from prospective clinical trials.

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