Original Article

Comparison of Echocardiographic Markers of Cardiac Dyssynchrony and Latest Left Ventricular Activation Site in Heart Failure Patients with and without Left Bundle Branch Block

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Abstract

Background: *Several echocardiographic markers have been introduced to assess the left ventricular (LV) mechanical dyssynchrony. We studied dyssynchrony markers and the latest LV activation site in heart failure patients with and without left bundle branch block (LBBB).*

Methods: *Conventional echocardiography and tissue velocity imaging were performed for 78 patients (LV ejection fraction ≤ 35%), who were divided into two groups: LBBB (n = 37) and non-LBBB (n = 41). Time-to-peak systolic velocity (Ts) was measured in 12 LV segments in the mid and basal levels. Seven dyssynchrony markers were defined: delay and standard deviation (SD) of Ts in all and basal segments, septal-lateral and anteroseptal-posterior wall delay (at the basal level), and interventricular mechanical delay (IVMD).*

Results: *The LBBB patients had significantly higher QRS duration and IVMD. The posterior wall was the latest activated site in the LBBB and the inferior wall was the latest in the non-LBBB patients. The most common dyssynchrony marker in the LBBB group was the SD of Ts in all segments (73%), whereas it was Ts delay in the basal segments in the non-LBBB group (48.8%). Ts delay and SD of all LV segments, septal lateral delay, septal-to-posterior wall delay by M-mode, pre-ejection period of the aortic valve, and IVMD were significantly higher in the LBBB group than in the non-LBBB group. Also, 29.3% of the non-LBBB and 10.8% of the LBBB patients did not show dyssynchrony by any marker. The number of patients showing dyssynchrony by ≥ 3 markers was remarkably higher in the LBBB patients (73% vs. 43.9%, respectively; p value = 0.044).*

Conclusion: *The LBBB patients presented with a higher prevalence of dyssynchrony according to the frequently used echocardiographic markers. The latest activation site was different between the groups.*

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Introduction

Cardiomyopathy is characterized by the progressive remodeling of the ventricles and affects the conduction pathway. Disturbances in cardiac bundles and fascicles cause a delay in the onset of right and left ventricular (LV) contractions, named dyssynchrony. Dyssynchronous contraction of a diseased heart reduces the ejection of blood volume. Patients diagnosed with asynchronous contraction are candidates for cardiac resynchronization therapy (CRT).

Several echocardiographic methods (conventional and tissue velocity imaging) have thus far been introduced to assess the LV mechanical dyssynchrony in patients with heart failure.[1-6] Different cut-off values for each echocardiographic parameter have been proposed, which permit an estimation of the prevalence of mechanical dyssynchrony. Although according to the PROSPECT study, the sensitivity and specificity of the different echocardiographic parameters to predict response to CRT vary widely[7] and no single echocardiographic measure of dyssynchrony may be a marker of improvement after CRT, recent studies have focused on the prevalence of dyssynchrony when a multi-parametric echocardiographic approach is taken in the same patient.[8-10] Another aspect for response to CRT is the role of identifying the most delayed LV site[1, 11, 12] in predicting the improvement in the systolic function or the LV reverse remodeling after CRT.

The present study sought to compare the prevalence of cardiac dyssynchrony detected by different previously described echocardiographic markers and the most delayed activation site between two groups of cardiomyopathy patients: those with and without LBBB.

Methods

Between January 2006 and December 2008, a total of 78 patients at a mean age of 51.23 ± 14.00 years (range = 14 to 74 years) with cardiomyopathy and low left ventricular ejection fraction (LVEF ≤ 35%) and the New York Heart Association (NYHA) functional class ≥ III were referred to the Echocardiography Department of Tehran Heart Center, Tehran, Iran, to be evaluated from the point of suitability for CRT.

Complete and incomplete form of left bundle branch block (LBBB) was diagnosed in 12-lead surface electrocardiography (ECG) using previous definitions.[13] The patients were divided into two groups according to the presence or absence of persistent LBBB: the LBBB group consisted of 37 (47%, 3 of them had incomplete LBBB, mean EF = 22.96 ± 19.74%) and the non-LBBB group was comprised of 41 (53%, mean EF = 19.74 ± 6.46%) patients.

The research protocol was approved by Tehran Heart Center's Review Board. Patients with concomitant right bundle branch block were excluded. Conventional echocardiography and tissue Doppler imaging were performed in each patient by an expert physician, blinded to what was shown in the 12-lead ECGs.

Standard two-dimensional and M-mode echocardiographic examinations were performed for all the study subjects in a maximum interval of one week after the ECG. Echocardiographic data were acquired with a digital ultrasound machine commercially available (VIVID 7, Vingmed-General Electric, Horten, Norway), using a 3.5-MHZ phased array transducer. The patients were asked to lie in the left decubitus position to optimize the echocardiographic image. The measurements were taken according to the guidelines of the American Society of Echocardiography.[14] The LVEF was evaluated eyeball and with the Simpson method via the multi-plane modality of a four-dimensional probe.

The opening and closing times of the aortic and pulmonic valves were also measured using the systolic blood flow via pulsed Doppler, with the sample volume placed at the level of the aortic and pulmonic annulus. The aortic pre-ejection time was measured from the beginning of the QRS complex to the beginning of the aortic flow velocity curve recorded by pulsed-wave Doppler in the apical view. Also, the pulmonary pre-ejection time was measured from the beginning of the QRS complex to the beginning of the pulmonary flow velocity curve recorded in the left parasternal shor-axis view. Interventricular mechanical delay (IVMD) was defined as the difference between the aortic and pulmonary pre-ejection times. A cut-off value of 40 msec was employed to indicate IVMD.[15]

M-mode tracing was recorded from the parasternal long-axis view. The time between the anteroseptal and posterior wall contractions was calculated as the shortest interval between the maximal posterior displacement of the anteroseptal and the maximal displacement of the left posterior wall. The septal-to-posterior wall motion delay (SPWMD) was also obtained using an M-mode recording from the parasternal long-axis view. Patients with a difference of > 130 ms in the SPWMD were considered as having dyssynchrony.[16]

Time-to-peak myocardial systolic velocity (Ts) of 6 basal and 6 middle LV segments was measured using tissue velocity imaging under the guidance of tissue synchronization imaging (Figure 1) in the four-, three-, and two-chamber apical views. Gain and filters were adjusted as needed to eliminate background noise and allow for a clear spectral display. The measurements were recorded at a sweep speed of 100 mm/s and digitally stored. Offline analysis of 3 consecutive beats at the end of expiration was performed, and the results were averaged.

The following indices, which were previously reported as LV dyssynchrony markers, were calculated: (the predictive cut-off values for positive response to CRT are shown in parentheses prior to the reference number): All segments delay (Ts-delay all segments): delay between shortest and

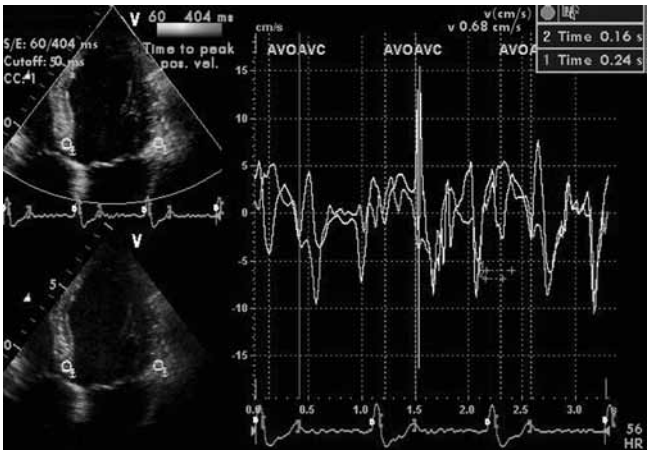

Figure 1. Time-to-peak systolic velocity measurement in the left ventricular septal basal and lateral basal segments by tissue Doppler imaging under guidance of tissue synchronization imaging in a dilated cardiomyopathy patient with left bundle branch block

longest Ts in 12 LV segments (105 msec);[4] Basal segments delay (Ts-delay basal segments): delay between shortest and longest Ts in LV basal segments (78 msec);[4] All segments standard deviation (Ts-SD all segments): SD of the time-to-peak myocardial systolic velocity of 12 LV basal and mid segments (34.4 msec);[4] Basal segments SD: (Ts-SD basal segments) SD of the time-to-peak myocardial systolic velocity of 6 LV basal segments (34.5 msec);[4] Septal-lateral delay: maximum delay between peak systolic velocities between the basal interventricular septum and the lateral wall (60 msec);[17] and Anteroseptal-posterior delay: absolute difference in Ts between the basal posterior and anteroseptal segments (65 msec).[18]

A patient was considered as having cardiac dyssynchrony if he/she showed dyssynchrony by at least one previously introduced index (six tissue-derived indices as was mentioned above or IVMD by conventional echocardiography), and the number of indices showing dyssynchrony in each patient is expressed as the number of positive markers.

Inter- and intraobserver variability for Ts in our lab was 13 ± 11% and 18 ± 20%, respectively.[19]

The Statistical Software Package (SPSS for Windows, version 13, SPSS Inc., Chicago, Illinois, USA) was used for the statistical analyses. The continuous variables are presented as mean ± SD, and the categorical variables are expressed by percentages. The continuous variables were compared using the Student t-test, or the Mann-Whitney test if needed. The categorical variables were compared using the chi-square or the Fisher exact test. Probability values of a p value ≤ 0.05 were considered statistically significant.

Results

The patients' characteristics in each group are summarized in Table 1. All the 78 patients (81.8% male) had complete data sets, including baseline echocardiography measurements and dyssynchrony analysis, except for 16 patients, whose measurement of the SPWMD was not possible. The mean age of the LBBB group was significantly higher than that of the non-LBBB group. The LBBB patients had also a significantly higher pre-ejection period of the aortic valve and the QRS duration.

There were 16 ischemic, 19 dilated, and 2 valvular cardiomyopathies in the LBBB group, and the non-LBBB group had 23 ischemic, 17 dilated, and one valvular cardiomyopathy patients. The Ts of 12 LV segments is summarized in Table 2. According to Table 2, all the 12 individual segments in the LBBB group showed a significantly lower mean Ts than the corresponding segments in the non-LBBB group. (The p value for Ts of the mid-lateral segment was trend.)

The mean value for the difference between the longest and shortest Ts in all the LV segments was significantly higher in the LBBB group: 121.89 ± 344.39 vs. 99.15 ± 42.66 msec (Table 3). The means of septal-lateral delay, Ts-all-SD, Ts-basal-SD, and IVMD were also remarkably higher in the LBBB than in the non-LBBB group (Table 3).

In the LBBB group, the most frequently observed positive marker of dyssynchrony was Ts-all-SD (73%) and the lowest was septal-lateral delay (35.1%), whereas in the non-LBBB group, Ts-basal-delay was the most frequently seen positive marker (48.8%) and septal-lateral delay was the lowest (22%) (Table 4).

In the LBBB group, 10.8% of the patients had no positive marker, 8.1% had 7, and the remaining patients presented with a number of positive markers between 0 and 7. In the non-LBBB group, 29.3% of the patients had no positive marker and none of the patients had 7 positive markers.

The number of patients with positive markers ≥ 3 was remarkably higher in the LBBB group than in the non-LBBB group (73% vs. 43.9%, respectively; p value = 0.009). In the 78 study patients, the agreement rate between the markers was evaluated as follows: the highest agreement rate (50%) was observed between the 3 markers of Ts-delay all, Ts-SD all, and Ts-SD basal segments. This rate for the 4 positive markers of Ts-delay all, Ts-delay basal, Ts-SD all, and Ts-SD basal segments was 42.3%. The rate of these agreements was not different between the LBBB and non-LBBB groups.

In the LBBB group, the site of earliest activation was the anteroseptal wall in 37.8% of the patients and the posterior wall was the latest activation site in 48.6% of the patients. In the non-LBBB group, the anterior wall was the first activated site in 36.6%, and the inferior wall was the latest in 34.1% of the patients.

Measurement of the SPWMD was possible for 32 patients in the LBBB and 30 cases in the non-LBBB groups. The mean value of the SPWMD was remarkably higher in the LBBB group: 174.09 ± 88.77 msec in the LBBB vs. 108.03

± 38.3 msec in the non-LBBB patients; p value < 0.001. Using this marker, 12 (40%) patients in the non-LBBB and 22 (68.8%) in the LBBB group had dyssynchrony; this difference was statistically significant (p value = 0.023).

The mean QRS duration was not different between the patients with and without dyssynchrony in each study group: 122.38 ± 29.97 vs. 112.00 ± 11.22 msec in the non-LBBB and 159.06 ± 30.36 vs. 164.50 ± 25.52 msec in the LBBB patients.

The correlation between widening of QRS and IVMD in the LBBB patients was significant but poor (r = 0.372, p value = 0.030), and non-significant in the non-LBBB patients (r = 0.287, p value = 0.072). However, there was no significant correlation between the QRS duration and the presence of dyssynchrony in either group (r = 0.059, p value = 0.734 for LBBB and r = 0.183, p value = 0.253 for non-LBBB).

Table 1. Comparison of the patients' characteristics in the two study groups*

	LBBB (n=37)	Non-LBBB (n=41)	P value
Age (y)	55.70±12.08	49.17±13.03	0.054
Male sex	27 (73.0)	34 (82.9)	0.411
LVEDV (ml)	205.26±93.44	198.89±67.01	0.721
LVESV (ml)	163.47±89.62	156.97±66.64	0.729
PAP (systolic) (mmHg)	42.73±18.80	49.82±17.30	0.144
QRS duration (msec)	159.67±29.58	119.34±26.19	< 0.001
Pre-ejection period of aortic valve (msec)	140.57±36.58	120.05±53.52	0.050
Pre-ejection period of pulmonary valve (msec)	95.42±24.90	98.76±45.57	0.694

Data are presented as mean±SD or n (%)
LVEDV, Left ventricular end diastolic volume; LVESV, Left ventricular end systolic volume; LVEF, Left ventricular ejection fraction; PAP, Pulmonary artery pressure

Table 2. Mean of time-to-peak systolic velocity using tissue Doppler imaging in twelve left ventricular segments*

	LBBB (n=37)	Non-LBBB (n=41)	P value
Septal basal (ms)	194.32±55.15	170.83±50.45	0.047
Septal mid-portion (ms)	200.81±55.35	176.83±44.35	0.024
Lateral basal (ms)	203.24±63.95	159.63±47.94	0.001
Lateral mid-portion (ms)	191.35±66.67	162.32±50.25	0.059
Anterior basal (ms)	191.35±72.58	155.75±53.00	0.021
Anterior mid-portion (ms)	185.41±74.22	149.13±50.46	0.013
Inferior basal (ms)	203.51±49.00	176.59±41.93	0.014
Inferior mid-portion (ms)	219.46±51.26	181.22±37.50	< 0.001
Anteroseptal basal (ms)	190.00±56.96	162.25±47.26	0.025
Anteroseptal mid-portion (ms)	186.24±57.76	161.22±44.68	0.050
Posterior basal (ms)	228.11±66.95	175.12±53.25	< 0.001
Posterior mid-portion (ms)	218.11±71.99	175.98±58.39	0.006

*Data are presented as mean±SD
LBBB, Left bundle branch block

Table 3. Comparison between cardiomyopathy patients with and without LBBB regarding TDI and conventional echocardiography dyssynchrony indices*

	LBBB	Non-LBBB	P value
Delay in all LV segments (ms)	121.89±34.39	99.15±42.66	0.004
Delay in basal LV segments (ms)	98.65±37.80	84.76±39.87	0.098
Septal lateral delay (ms)	64.05±36.24	40.00±29.58	0.003
Anteroseptal posterior delay (ms)	55.41±39.20	44.75±37.14	0.241
Ts-SD all segments (ms)	42.33±11.82	33.97±13.44	0.002
Ts-SD basal segments (ms)	40.64±13.96	33.41±14.49	0.021
Interventricular mechanical delay (ms)	47.08±31.60	25.90±1-9.02	0.001

*Data are presented as mean±SD
LBBB, Left bundle branch block; TDI, Tissue Doppler Imaging; LV, Left ventricular; Ts-SD, Standard deviation of time to peak systolic velocity

Table 4. Frequency of cardiac dyssynchrony in two groups of cardiomyopathy patients with and without LBBB with respect to TDI and conventional echocardiography cut-off values of different markers

	LBBB (%)	Non-LBBB (%)	P value
Delay in all LV segments	67.6	39	0.012
Delay in basal LV segments	67.6	48.8	0.094
Septal lateral delay	35.1	22.0	0.196
Anteroseptal posterior delay	43.2	27.5	0.148
Interventricular mechanical delay	54.1	26.8	0.014
Ts-SD all segments (ms)	73.0	43.9	0.017
Ts-SD basal segments (ms)	64.9	41.5	0.039

*Data are presented as mean±SD
LBBB, Left bundle branch block; TDI, Tissue Doppler imaging; LV, Left ventricle; Ts-SD, Standard deviation of time to peak systolic velocity

Discussion

According to the results of our study on cardiomyopathy patients, 29.3% of the non-LBBB and 10.8% of the LBBB patients had no marker of dyssynchrony, regardless of the etiology of cardiomyopathy in each group. The most frequently observed dyssynchrony marker was Ts-all-SD in the LBBB and Ts-basal-delay in the non-LBBB group. The posterior wall was the latest activated site in the LBBB and the inferior wall was the latest in the non-LBBB patients.

We found 73% dyssynchrony according to the cut-off value for Ts-SD of all segments in the LBBB group, but a lower percentage of 43.9% in the non-LBBB patients. Faletra et al.[10] also reported 69% dyssynchrony according to these criteria among 63 patients with heart failure. In our study, the dyssynchrony rate of the basal LV segments was 67.6% for the LBBB and 48.8% for the non-LBBB patients with a cut-off of 78 msec. Bax et al.[17] reported intra-LV dyssynchrony > 65 ms (maximum delay of Ts between septal, lateral, anterior, or inferior walls in the basal level) as the only marker that could predict responders (74%) among 85 patients with heart failure and LBBB, which is relatively close to what is observed in the present study.

Identifying the most delayed LV site could have practical implications for increasing the effect of CRT. In line with a previous study,[20] the present study showed that the last activated site was located in the posterior wall (posterior-basal) in the LBBB group and in the inferior wall (inferior mid-portion) in the non-LBBB group. Our study also demonstrated that the anteroseptal wall as the most frequent first activated wall in the LBBB group and the anterior wall as the most frequent first activated wall in the non-LBBB patients. These findings are compatible with the results of the Badano et al. study,[20] which introduced the anterior septum and anterior wall as the first activated LV walls and the posterior wall as the last activated wall in LBBB patients. In contrast, Ansalone et al.[1] found the lateral wall as the most delayed site (35%) among 31 patients with non-ischemic heart failure and LBBB. A study on 56 patients with heart failure and QRS duration > 120 msec in the form of either bundle branch block or intraventricular conduction delay showed that the most common site of most severe delay was the inferior wall (in 45% of patients).[3]

In a more recent study conducted by Lafitte et al.,[9] a multi-parametric echocardiographic strategy based on the association of conventional criteria was a better indicator of CRT response than single parametric approaches. With respect to this issue, we also investigated agreement between different TDI markers of the LV dyssynchrony. The highest agreement rate was observed between the Ts-basal-delay, Ts-all-SD, and Ts-basal-SD of the basal segments. When we entered the fourth marker, the highest agreement rate was found for Ts-all-delay, Ts-basal-delay, Ts-all-SD, and Ts-basal-SD. It was notable that the agreement rates were not different between the LBBB and non-LBBB groups; however, our study was not set up to evaluate validation of different combinations of TDI markers in predicting response to CRT.

The mean QRS duration was not different between the patients with and without dyssynchrony in each study group, and nor was there any significant correlation between the QRS duration and the presence of dyssynchrony in either group. This may show that LBBB and non-LBBB patients may have criteria of dyssynchrony, irrespective of the QRS duration, although our previous report,[21] with a much larger sample size, found a higher prevalence of both inter- and intraventricular dyssynchrony indices in the patients with wide QRS than in those with narrow QRS durations.

For the first time, Pitzalis et al.[16] described the SPWMD and reported a mean of 192 msec for this marker in severe heart failure patients with LBBB. Although due to technical reasons, measurement of the SPWMD[22] was not possible in all of our study population, the value was significantly different between the patients with and without LBBB. In our study, the mean SPWMD was 174 msec in the LBBB and 108 msec in the non-LBBB patients.

Our analysis was mainly focused on the study of the pattern and prevalence of dyssynchrony in two groups of cardiomyopathy patients: those with and without LBBB. Although we observed that the mean QRS duration was not different between the patients with and without dyssynchrony in each study group, the inadequate number of patients with QRS < 120 msec did not allow for further analysis.

Conclusion

There was a delay of activation in all LV segments in the LBBB compared to the non-LBBB patients with impaired systolic function. A higher prevalence of cardiac dyssynchrony was found in the LBBB patients, independent of the etiology of cardiomyopathy. The most frequent dyssynchrony marker and the site of the latest activation were different between the two groups.

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