Indian Heart Journal 70 (2018) 387–393

Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Original Article

Three-dimensional echocardiographic evaluation of mechanical dyssynchrony in systolic heart failure with narrow QRS complex

Anupam Bhambhani[a,c,*], Nelson John[b,c], B. Kumar[a,c], Amalu Mathew[a,c]

[a] Department of Cardiology, India
[b] Department of Community Medicine, India
[c] Vydehi Institute of Medical Sciences and Research Centre, Whitefield, Bangalore, 560066, India

ARTICLE INFO

Article history:
Received 29 July 2017
Accepted 24 October 2017
Available online 28 October 2017

Keywords:
Left ventricular mechanical dyssynchrony
Systolic dyssynchrony index
Three-dimensional echocardiography

ABSTRACT

Objectives: To investigate the role of three-dimensional echocardiography (3DE) in evaluation of left ventricular mechanical dyssynchrony (LVMD) in heart failure (HF) patients with narrow QRS.
Methods: 143 subjects (70 with HF and narrow QRS, 23 with HF and LBBB and 50 controls) were subjected to 3DE, evaluating global and regional dyssynchrony using systolic dyssynchrony index, maximum segmental dyssynchrony and opposite segment dyssynchrony. Spatial distribution of LVMD was studied in each patient using 3DE derived regional time volume curves. Extent of LVMD in HF patients with narrow QRS was compared to those with left bundle branch block (LBBB).
Results: Frequency of LVMD was similar in HF patients with narrow QRS or LBBB (55.7% vs. 47.8%, p = NS). There was no difference in the severity of LVMD between these two groups (10.7 ± 6.7% vs. 12.1 ± 7.4%, p = NS). Both HF groups had significantly more dyssynchrony than controls. A scattered pattern of distribution of asynchronous segments was seen in narrow QRS patients; 33.96% of them had their earliest contracting segment, instead of delayed segment, located in areas conventionally targeted for LV pacing i.e. anterolateral, inferolateral or inferior segments.
Conclusions: 3DE confirmed significant dyssynchrony in >50% HF patients with narrow QRS as demonstrated by other imaging methods. 3D distribution patterns of asynchronous segments indicate possibility of left ventricular mechanics related reasons responsible for lack of CRT responsiveness, an observation that generates hypothesis on possible reasons of CRT non-responsiveness.

1. Introduction

Cardiac resynchronization therapy (CRT) is an established treatment for advanced heart failure (HF) patients having wide QRS of left bundle branch block (LBBB) morphology[1] with unequivocal benefits in terms of quality of life[2] as well as survival.[3] Substantial proportion (~50%) of HF patients has evidence of left ventricular mechanical dyssynchrony (LVMD) despite narrow QRS.[4] Studies conducted about a decade back suggested that significant benefit could be obtained from CRT in this subset of patients[5] and some investigators even cautioned against not considering CRT for such patients just because of normal QRS duration.[6] These suggestions were substantiated by the background evidence indicating that the main predictor of CRT responsiveness was LVMD rather than electrical dyssynchrony,[7–9] and therefore it was expected to be effective in narrow QRS patients with evidence of echocardiographically determined LVMD.[10] However, later studies did not support this concept[11,12] and recent data even suggested worsening of prognosis by CRT in HF with narrow QRS.[13] Reasons for unresponsiveness to CRT in these trials could be limitations of used imaging methods in terms of assessment of magnitude of LVMD and also in the identification of most asynchronous part of left ventricle (LV), thereby causing poor achievement of spatial concordance between the LV lead position and most delayed segment.[10,14] Although, targeted lead placement strategy is already supported by data in wide QRS patients with HF,[15,16] it is likely to be more relevant in LV dysfunction patients with narrow QRS because, as they don't have fixed sequence of myocardial depolarization vectors determined by specific bundle branch blocks, they are expected to have more unpredictable spatial distribution of asynchronous or delayed LV segments. Considering these facts, three-dimensional echocardiography (3DE) is expected to have strong potential in guiding CRT in terms of selection of most eligible patients (i.e. with higher magnitude of LVMD), targeting of most appropriate LV segment for

* Corresponding author at: Department of Cardiology, Vyhehi Institute of Medical Sciences & Research Centre, #82 EPIP Area, Whitefield, Bangalore, 560066, India.
E-mail address: anupam.bhambhani@yahoo.in (A. Bhambhani).

https://doi.org/10.1016/j.ihj.2017.10.013

lead placement and for post procedure device optimization. By its ability to interrogate whole LV simultaneously, it can not only recognize patients unlikely to benefit from CRT but also can help understand the factors related to LV mechanics that make them unresponsive and probably can provide insights into future modifications needed in the device implantation methods that can make CRT effective in these patients.

We conducted this study investigating whether the novel 3DE technique can provide new insights into the LVMD, which can be useful in HF treatment. Our study investigated the frequency and magnitude of LVMD using 3DE in HF patients having left ventricular ejection fraction (LVEF) $\leq$35% and narrow QRS ($<$120 ms); comparing them to HF patients with wide QRS complexes ($\geq$120 ms) of LBBB morphology and to normal controls. We also evaluated the 3D distribution pattern of asynchronous segments. Although, a couple of earlier studies have addressed these issues using tissue Doppler imaging[17,18] or speckle tracking methods[16] but the data using 3DE on this subject are scarce.

2. Methods

2.1. Study design & subjects

It was a prospective, single center study that recruited 143 eligible subjects including 50 normal controls and 93 HF patients found to have LVEF $\leq$35%, who presented to our noninvasive cardiology unit from December 2016 to April 2017. Out of 93 HF patients, 70 had narrow QRS complexes (group 1) and 23 had wide QRS complexes of LBBB morphology (group 2). Controls (group 3) had no historical, clinical, 12-lead electrocardiogram (ECG) related or 2D echocardiographic (2DE) evidence of heart disease. Baseline demographic characters were noted. Ischemic etiology for LV dysfunction was decided by presence of at least one epicardial coronary stenosis of 70% or more or historical or ECG evidence of angina or myocardial infarction. The exclusion criteria were poor echocardiographic window and/or presence of atrial fibrillation or any other persistent arrhythmia likely to interfere with 3DE imaging, or presence of primary valvular or structural heart disease. All patients and controls were subjected to 12-lead ECG recording and routine 2D and Doppler echocardiography. This was followed by 3DE recording of LV full volume loops as described below.

2.2. Echocardiography

2D and Doppler echocardiography were performed using standard protocols for screening the subjects and allocating them to their respective study groups. Following this, they were subjected to ECG gated 3DE imaging in apical 4 chamber view, recording LV full volume loops on commercial iE33 equipment (Philips Medical Systems, Andover, MA, USA) using X5-1matrix array transducer. The sector width and depth were optimized to obtain maximum possible frame rate and gain settings were adjusted to obtain best possible endocardial definition. In order to get highest resolution with minimal stitch artifacts, we used 2-beat 3DE recordings in all patients to obtain full volume loops. The loops were analyzed to assess left ventricular end diastolic volume (LVEDV), left ventricular end systolic volume (LVESV), LVEF and finally the magnitude and spatial pattern of LV intra-ventricular dyssynchrony by following semi automated method: after selecting left ventricular end diastolic as well as end systolic frames, the appropriate reference points were marked for the sequence analysis. The endocardial borders were confirmed in 3D short axis view. Wherever appropriate, the 3D tracking points were edited by manually adding extra points on endocardial border. On initiating "sequence analysis" the software automatically calculates LVEDV, LVESV and LVEF. Final group allocation was decided by the 3DE readings of LVEF.

For assessing dyssynchrony, six basal and six mid LV level segments were selected. Three dimensional systolic dyssynchrony index (SDI) was assessed using Philips Q-lab software, which automatically quantifies SDI for the selected LV segments as: standard deviation of time to attain minimum systolic volume (Tmsv) of selected LV segments, which is expressed as percentage of cardiac cycle length (12-segment Tmsv-%R–R). SDI value of $>$10% was considered as suggestive of significant dyssynchrony in accordance with observations reported by investigators who introduced and validated this parameter.[19] These authors had reported that CRT responsiveness correlated with SDI of 16.1 $\pm$ 5.1%.

In addition, regional time volume curves (Fig. 1) were constructed using the same software and spatial pattern of dyssynchrony was identified for every patient, both qualitatively and quantitatively. The qualitative assessment consisted of identification of the latest contracting LV segment (most delayed segment). The quantitative inter-segmental dyssynchrony was defined by two methods – (a) Maximum segmental dyssynchrony (MSD) – maximum difference in time to attain minimum systolic volume among 12 selected LV segments i.e. difference in time-to-minimum systolic volume (Tmsv) of earliest contracting and latest contracting LV segments; and (b) Opposite segment dyssynchrony (OSD) – maximum Tmsv difference observed between diagonally opposite LV segments. Since there are no validated cut-off values for MSD and OSD, we arbitrarily considered a value of $\geq$130 ms as suggestive of severe LVMD. The reason for this cut-off was based on the fact that if not similar, OSD and MSD are physiologically analogous to dyssynchrony assessment using time to peak radial strain analysis wherein a value of $\geq$130 ms has been found associated with CRT responsiveness.[20]

Color coded "bull's eye" maps generated by Q-lab software were further analyzed for spatial distribution of LV segments with minimum or maximum "time to minimum systolic volume (Tmsv)". Here, blue and red colors indicate earliest and latest contracting segments, respectively (Fig. 1).

Finally, patients with ischemic and non-ischemic etiologies for HF were compared in for the extent and pattern of dyssynchrony.

All 3DE analyses were done by a single investigator having 15 years' experience in echocardiography and one and a half years' experience in 3DE.

2.3. End points

1. Frequency of 3DE determined dyssynchrony in HF patients with LV dysfunction and narrow QRS (group 1) in comparison to group 2 (LBBB) and group 3 (controls);
2. Relative magnitude of 3DE determined LVMD in group 1, group 2 & group 3 as assessed by four criteria: 12-segment Tmsv-%R–R (SDI), 12-segment Tmsv (i.e. without correction for R–R duration), MSD and OSD (as defined above).
3. 3D spatial distribution patterns of most asynchronous segments in group 1.

The institutional ethics committee approved this project and written consent was taken from all subjects for participation in the study.

2.4. Statistical analysis

The data were analyzed using SPSS Statistics Software Version 21.0.0.0. All qualitative data are expressed as frequencies and percentages. The baseline quantitative data are expressed as

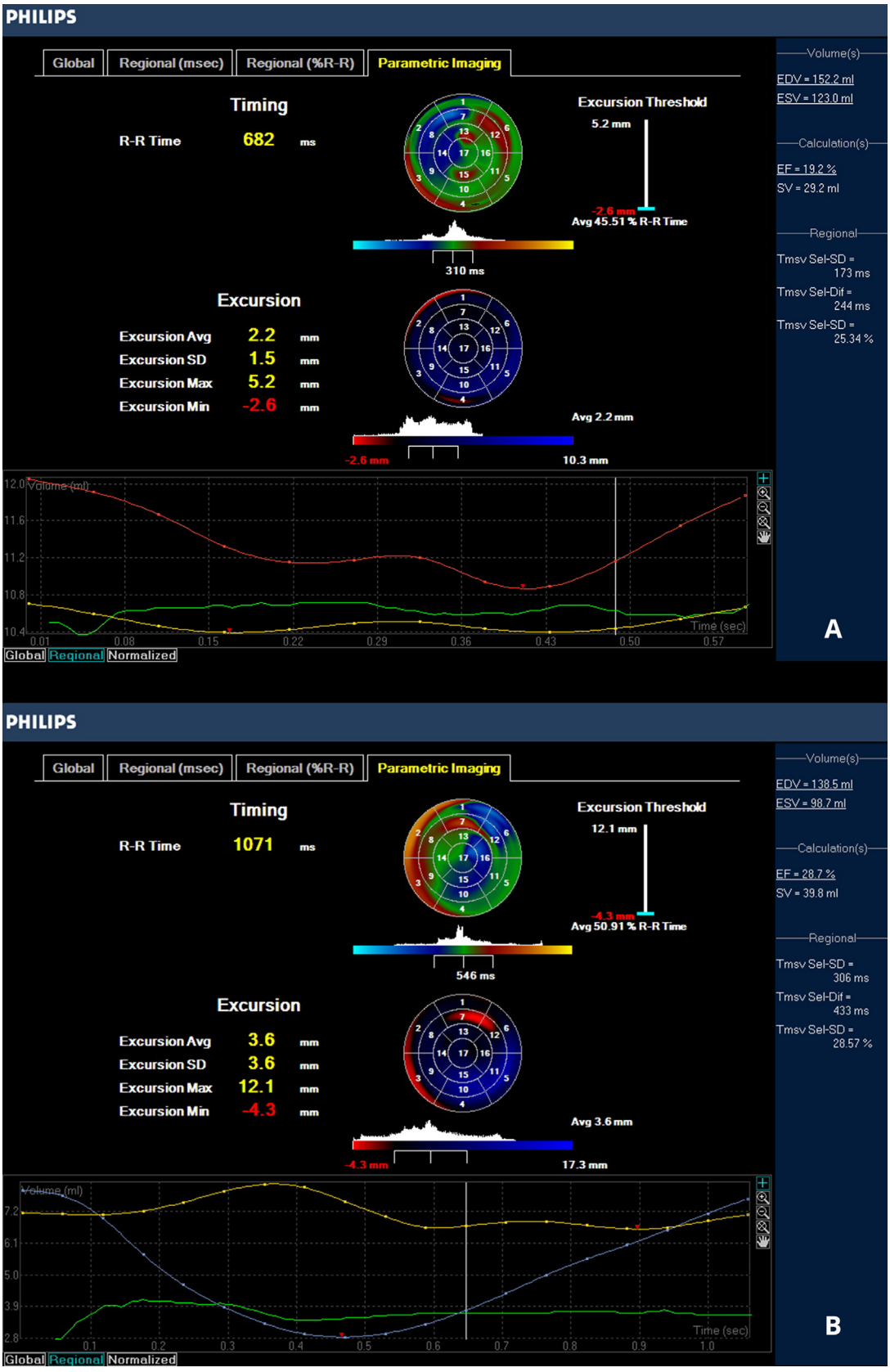

Fig. 1. (A & B). Color coded Bull's eye maps in two different patients (A & B) showing time to achieve minimum systolic volumes for 17 standard left ventricular segments (upper polar maps). Blue color indicates earliest contracting segment; red color indicates latest contracting (most asynchronous) segment. A – mid antero-lateral segment (12) is most asynchronous. B – basal antero-septal segment (2) is most asynchronous while mid antero-lateral segment (12) is earliest in achieving minimum volume. Lower part of the figure shows regional time volume curves for earliest and most delayed segments; red arrowheads indicate minimum systolic volume for each segment.

mean ± standard deviation. The results are expressed as medians with inter-quartile ranges (IQR). For comparison of two or more categorical variables, Chi square test was used. For comparison of two continuous variables, Mann Whitney *U* test was applied. To assess the relationship between two variables, Spearman's rank correlation was applied. Stepwise multiple linear regressions were used to examine the effect of baseline variables on four pre-defined parameters of intraventricular dyssynchrony. P value <0.05 was considered statistically significant.

3. Results

3.1. Dyssynchrony indices in controls

Before analyzing HF patients, we evaluated normal 3DE reference ranges of dyssynchrony indices in our normal population, obtaining four pre-decided dyssynchrony parameters in 50 control subjects. Expressed as: medians with IQR, the 12-segment Tmsv-%R–R was 1.6%, IQR 1.2; 12-segment Tmsv was 13 ms, IQR 12; MSD was 32 ms, IQR 34 & OSD was 15 ms, IQR 20.

3.2. Dyssynchrony in heart failure patients

Of 93 patients with HF, 70 (80% men) had narrow QRS (group 1) and 23 (70% men) had wide QRS of LBBB morphology (group 2). All patients had significant LV dysfunction with mean LVEF 26.6 ± 6.6% and 29.3 ± 5.9% in group 1 and group 2, respectively (p = NS). As shown in Table 1, group 1patients were younger compared to group 2; Mean QRS duration was significantly more in group 2 (146.4 ± 20.2 ms vs. 85 ± 10.4 ms). Other baseline demographic and echocardiographic parameters were well matched between these two groups.

3.3. Frequency of dyssynchrony in HF patients

Using any of the pre decided criteria in this study, LVMD was observed with equal frequencies in HF patients with narrow or wide QRS (Table 2). While assessing SDI, LVMD was present in 55.7% of narrow QRS patients and 47.8% of LBBB patients (p = NS). Corresponding values for OSD & MSD were 44% vs. 56% (p = NS) and 74% vs. 70% (p = NS) for narrow QRS and LBBB groups, respectively.

3.4. Magnitude of dyssynchrony

Magnitude of LVMD was assessed and compared in controls as well as group 1 and group 2 HF patients. As explained while describing study methods, four 3DE dyssynchrony indices were used for this purpose. Table 3 summarizes the observed medians with IQRs for these four indices in groups 1–3 and their statistical comparisons. It can be seen that when extent of LVMD was assessed by any of the four dyssynchrony indices, there was no statistically significant difference between narrow QRS and LBBB patients; however, both HF groups were found to have significantly more dyssynchrony than controls.

On analyzing the effect of baseline clinical, ECG and echocardiographic variables on dyssynchrony in narrow QRS group, the Univariate model revealed significant inverse correlation between SDI and LVEF (Table 4a). As expected, for other LVMD indices that are not corrected for R–R interval i.e. Tmsv, MSD and OSD, heart rate was found to be a predictor of dyssynchrony. In the stepwise multi regression model, none of the baseline variables predicted SDI in narrow QRS group (Table 4b). No gender based differences were seen. For non R–R corrected indices, HR was the only independent predictor of LVMD (Table 4b). QRS duration was not a predictor of any of the LVMD indices either in Univariate or Multivariate analyses.

3.5. Spatial distribution of most asynchronous LV segments in HF patients with narrow QRS

A scattered pattern of distribution of most asynchronous (most delayed) segments was seen in narrow QRS patients, i.e. asynchronous segments could be found in any of the 6 basal and 6 mid LV segments (Fig. 2). This pattern was observed irrespective of ischemic or non-ischemic etiologies.

While studying the bull's eye map of distribution of earliest & latest contracting segments (Fig. 1), we noticed that amongst patients in whom mechanical dyssynchrony was demonstrated by at least one of the four LVMD indices used in this study, 33.96% patients in narrow QRS group had their earliest contracting segment located in either of the antero-lateral, infero-lateral or inferior part of LV (i.e. areas conventionally targeted for LV pacing by coronary sinus lead).

Intra-observer variability evaluation revealed good agreement of dyssynchrony parameters between two observations made by same investigator at two different points in time (Table 5).

Table 1
Baseline characteristics of HF patients with narrow QRS or LBBB.

Clinical characteristics	Narrow QRS	LBBB	Chi square	P value
Age (Years)	52.8 ± 12	60 ± 9.3		0.004
Male:female (%)	80:20	70:30	0.35	NS
QRS duration (ms)	85 ± 10.4	146.4 ± 20.2		<0.001
Etiology (%)				
Ischemic	53	39	2.7	NS
Non ischemic	47	61		
NYHA class (%)				
Class 2	10	9	0.10	NS
Class 3 or 4	90	91		
LV End diastolic volume (ml)	139.5 ± 38.3	151.1 ± 54.3		NS
LV End systolic volume (ml)	102.2 ± 30	107.2 ± 41		NS
LVEF (%)	26.6 ± 6.6	29.3 ± 5.9		NS

(Data expressed as mean ± SD or percentages).

4. Discussion

Data from several studies conducted about a decade ago, suggested that significant benefit could be obtained from CRT in narrow QRS HF patients[5] but recent trials refuted the beneficial role of resynchronization in this group.[13] This discrepancy in results could be due to limitations of the two dimensional or Doppler based imaging techniques used in those trials in guiding therapy. Because of its ability to interrogate the whole LV volume simultaneously, 3DE is likely to be more accurate and efficient in providing relevant information regarding extent and pattern of LVMD. In this study, we investigated the role of 3DE in assessment of LVMD in HF patients with narrow QRS, exploring whether this technique can provide new insights useful in the treatment of advanced HF.

4.1. Magnitude of LVMD

In order to assess relative extent of LVMD, we determined the 3DE frequency and magnitude of dyssynchrony in HF patients having narrow QRS, comparing them to controls as well as to those with LBBB. The number of patients in LBBB group was much smaller than that in narrow QRS group because during the study period, only 24.73% of the patients presenting with HF were found to have LBBB. Similar proportions (20–30%) have been reported by other investigators also.[19,21] In order to assess the severity of global and regional LVMD separately, we used four different indices as already described.

Table 2
Frequency of significant mechanical dyssynchrony in HF patients with narrow QRS or LBBB expressed as percentage of patients having abnormal indices.

3D echocardiographic dyssynchrony indices	Narrow QRS (group 1)	LBBB (group 2)	Chi square value	p value
12-segment Tmsv-%R–R	55.7%	47.8%	5.3	NS
Opposite segment dyssynchrony (OSD)	44%	56%	0.43	NS
Maximum segmental dyssynchrony (MSD)	74%	70%	0.27	NS

Table 3
Magnitude of mechanical dyssynchrony in controls, narrow QRS and LBBB patients.

MD criteria	Group 1 (Narrow QRS) (n = 70)	Group 2 (LBBB) (N = 23)	Group 3 (Controls) (n = 50)	p value (1 vs. 3)	p value (2 vs. 3)	p value (1 vs. 2)
SDI (Tmsv-%R-R)	10.6 (7.5)	9.7 (13.5)	1.6 (1.2)	<0.001	<0.001	NS
Tmsv (ms)	69 (57)	73 (95)	13 (12)	<0.001	<0.001	NS
MSD (ms)	152.5 (135)	173 (267)	32 (34)	<0.001	<0.001	NS
OSD (ms)	80 (125)	100 (166)	15 (20)	<0.001	<0.001	NS

Data are expressed as median (inter-quartile range).

Table 4a
Correlation between mechanical dyssynchrony indices and baseline clinical or echocardiographic variables in narrow QRS HF patients (Univariate model).

Variables	SDI (Tmsv-%R–R)		Tmsv		MSD		OSD	
	r	p value	r	p value	r	p value	r	p value
Age	0.19	NS	0.25	0.03	0.21	NS	0.23	NS
HR	-0.09	NS	−0.34	0.003	−0.36	0.002	−0.32	0.007
QRS duration	0.03	NS	0.02	NS	0.08	NS	0.07	NS
LVEF	-0.27	0.02	−0.21	NS	−0.20	NS	−0.21	NS
End diastolic LV vol abnormal	-0.13	NS	−0.10	NS	−0.06	NS	−0.09	NS
End systolic LV volume	0.005	NS	0.01	NS	0.04	NS	0.008	NS
NYHA class	−0.18	NS	−0.12	NS	−0.13	NS	−0.09	NS

Table 4b
Stepwise multiple regression analysis for correlation of mechanical dyssynchrony indices and baseline clinical & echocardiographic variables in HF patients with narrow QRS.

Variables	SDI (Tmsv-%R–R)		Tmsv		MSD		OSD	
	β	p value	β	p value	β	p value	β	p value
Age	0.09	NS	0.11	NS	0.07	NS	0.11	NS
HR	−0.20	NS	−0.44	<0.001	−0.45	0.001	−0.45	<0.001
QRS duration	−0.09	NS	−0.08	NS	−0.04	NS	−0.02	NS
LVEF	−0.07	NS	−0.09	NS	−0.003	NS	−0.12	NS
LVEDV	−0.86	NS	0.61	NS	0.86	NS	0.19	NS

Since there was no available data on 3DE LVMD indices in our population, we evaluated them in 50 controls before studying HF patients. Our SDI readings were comparable to those reported for healthy subjects from other geographical areas of the world.[19]

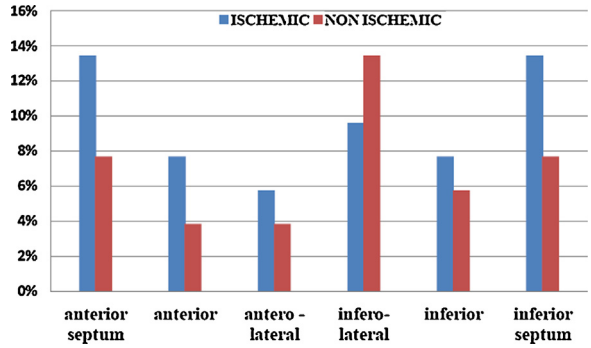

Fig. 2. Percent distribution of most asynchronous segments in various areas of left ventricle in heart failure with narrow QRS of ischemic or non-ischemic etiologies.

In terms of SDI, more than half (55.7%) of narrow QRS HF patients were found to have LVMD, as is also reported by other investigators using different imaging modalities.[17] We assessed global and inter segmental dyssynchrony separately using four LVMD parameters because in another study, tissue Doppler imaging based parameters of global LVMD (Yu index) as well as segmental LVMD (inter-segmental difference in systolic shortening time) correlated well with responsiveness to CRT.[22] In our study, all four LVMD indices indicated that, irrespective of QRS duration, the frequency and extent of dyssynchrony were significantly more in LV dysfunction patients compared to controls. There was no statistically significant difference in the severity of LVMD among narrow QRS and LBBB groups. Similar observations have been reported by investigators using dyssynchrony evaluation methods other than 3DE.[17,23]

4.2. Spatial patterns of dyssynchrony

There is emerging literature indicating superior benefit from CRT when LV is paced at the segment that is delayed the most in

Table 5
Reproducibility of dyssynchrony parameters (Intra-observer variability).

Parameter	Correlation coefficient[a]	Mean bias ± SD[b]
Tmsv	0.96[a]	−0.12 ± 0.34
Tmsv-%R–R	0.96[a]	−0.11 ± 0.34

[a] Pearson's correlation coefficients (all correlations are significant at the 0.001 level).
[b] Bland Altman analysis.

terms of achieving peak systolic contraction, making it important to map the most asynchronous segment.[24] Some studies have shown higher benefit from CRT when the lead placement is targeted by speckle-tracking assisted localization of most delayed LV segment.[15] This strategy has been proven useful in HF with LBBB.[15,16,18] Since HF patients with narrow QRS don't have fixed sequence vectors of myocardial depolarization determined by specific bundle branch blocks, they are expected to have more scattered distribution of most asynchronous or delayed contracting LV segments (i.e. they can be present in any part of LV). Localization of these areas is likely to be more relevant in patients with narrow QRS. On evaluation of spatial patterns of LVMD in narrow QRS group using 3DE, we observed that the most asynchronous segments were scattered in all the areas of LV. This observation was strongly in contrast to what has been reported in LBBB patients in whom asynchronous LV segments were distributed heterogeneously and were seen located predominantly in anterolateral, inferolateral and inferior areas.[3] This suggests that CRT may not achieve synchronized LV function in narrow QRS patients if the LV lead is stationed at one of the traditionally targeted sites i.e. anterolateral or inferolateral segments. Similar observations were reported in wide QRS patients by other investigators.[18] Our study revealed that in narrow QRS group, 47.16% patients had their most delayed segment lying in one of anterolateral, inferolateral or inferior LV segments (example: Fig. 2A) but at the same time, a substantial proportion of patients (33.96%) had their earliest and not the last contracting segments lying in either of these segments (example: Fig. 2B). Unless such cases are recognized, so that earliest contracting segments are not inadvertently paced, there is a chance that CRT may worsen the LV synchronicity. This observation may explain clinical worsening after CRT in some cases; however, it needs to be confirmed further in larger number of patients.

3DE may also prove beneficial in guiding post CRT device optimization by adjusting parameters such as AV delay to achieve maximum intra-ventricular synchronization. Currently, the data supports setting the AV delay at about 70% of intrinsic AV delay to achieve best hemodynamic results.[25] However, this may not be applicable to narrow QRS patients as it has been shown that AV delay programmed closer to the intrinsic AV delay results in more benefit in moderately (less) narrow QRS patients.[26]

5. Conclusions

3DE assessment confirms that LVMD is as severe and as prevalent in HF patients with narrow QRS as in those with LBBB. When evaluated for regional indices, dyssynchrony is more prevalent in both the groups but these indices need to be clinically validated for CRT responsiveness. 3D distribution patterns of asynchronous segments provide insights suggesting left ventricular mechanics related to lack of CRT responsiveness, and after appropriate validation, may lead to modifications in implantation technique that can convert such patients to responders; however, at this stage, these findings may be considered as hypothesis generating observations.

For any treatment to become successful, it is important to: a. select most eligible patients; b. recognize patients who are unlikely to respond due to scientifically proven reasons; and c. effectively administer the treatment. 3DE, by its virtue of ability to interrogate whole volume of LV directly and simultaneously, has strong potential in guiding CRT in terms of selection of most eligible patients (with higher magnitude of LVMD), targeting most appropriate LV segment for lead placement and post procedure device optimization. Although, LVMD can also be directly assessed in 3 dimensions by magnetic resonance imaging,[8] or radionuclide ventriculography,[27] RT3DE may be more useful being more easily available, and cost effective.

Conflict of interest

None.

References

1. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. *N Engl J Med*. 2002;346:1845–1853.
2. Linde C, Braunschweig F, Gadler F, et al. Long-term improvements in quality of life by biventricular pacing in patients with chronic heart failure: results from the Multisite Stimulation in Cardiomyopathy Study (MUSTIC). *Am J Cardiol*. 2003;91:1090–1095.
3. Bradley DJ, Bradley EA, Baughman KL, et al. Cardiac resynchronization and death from progressive heart failure: a meta-analysis of randomized controlled trials. *JAMA*. 2003;289:730 7–40.
4. Ghio S, Constantin C, Klersy C, et al. Interventricular and intraventricular dyssynchrony are common in heart failure patients, regardless of QRS duration. *Eur Heart J*. 2004;25:571–578.
5. Bleeker GB, Holman ER, Steendijk P, et al. Cardiac resynchronization therapy in patients with a narrow QRS complex. *J Am Coll Cardiol*. 2006;48:2243–2250.
6. Gasparini M, Regoli F, Galimberti P, et al. Three years of cardiac resynchronization therapy: could superior benefits be obtained in patients with heart failure and narrow QRS? *Pacing Clin Electrophysiol*. 2007;30(Suppl. 1):S34–S39.
7. Alonso C, Leclercq C, Victor F, et al. Electrocardiographic predictive factors of long-term clinical improvement with multisite biventricular pacing in advanced heart failure. *Am J Cardiol*. 1999;84:1417–1421.
8. Nelson GS, Curry CW, Wyman BT, et al. Predictors of systolic augmentation from left ventricular preexcitation in patients with dilated cardiomyopathy and intraventricular conduction delay. *Circulation*. 2000;101:2703–2709.
9. Ansalone G, Giannantoni P, Ricci R, et al. Doppler myocardial imaging in patients with heart failure receiving biventricular pacing treatment. *Am Heart J*. 2001;142:881–896.
10. Dai H, Guang X, Xiao Z. Letter by Dai et al. regarding article, cardiac resynchronization therapy in patients with heart failure and a QRS complex <120 milliseconds: the Evaluation of Resynchronization Therapy for Heart Failure (LESSER-EARTH) trial. *Circulation*. 2013;128(14)e217 (letter).
11. Beshai JF, Grimm RA, Nagueh SF, et al. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. *N Engl J Med*. 2007;357:2461–2471.
12. Thibault B, Harel F, Ducharme A, et al. Cardiac resynchronization therapy in patients with heart failure and a QRS complex <120 milliseconds: the Evaluation of Resynchronization Therapy for Heart Failure (LESSER-EARTH) trial. *Circulation*. 2013;127:873–881.
13. Ruschitzka F, Abraham WT, Singh JP, et al. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. *EchoCRT Study Group. N Engl J Med*. 2013;369(15):1395–1405.
14. Banker J, Rosenheck S, Gotsman I. Letter by Banker et al. regarding article, cardiac resynchronization therapy in patients with heart failure and a QRS complex <120 milliseconds: the Evaluation of Resynchronization Therapy for Heart Failure (LESSER-EARTH) trial. *Circulation*. 2013;128(14)e216 (letter).
15. Khan FZ, Virdee MS, Palmer CR, et al. Targeted left ventricular lead placement to guide cardiac resynchronization therapy: the TARGET study: a randomized, controlled trial. *J Am Coll Cardiol*. 2012;59(17):1509–1518.
16. Saba S, Marek J, Schwartzman D, et al. Echocardiography-guided left ventricular lead placement for cardiac resynchronization therapy: results of the Speckle Tracking Assisted Resynchronization Therapy for Electrode Region trial. *Circ Heart Fail*. 2013;6(3):427–434.
17. Yu CM, Lin H, Zhang Q, et al. High prevalence of left ventricular systolic and diastolic asynchrony in patients with congestive heart failure and normal QRS duration. *Heart*. 2003;89(1):54–60.
18. Derval N, Steendijk P, Gula LJ, et al. Optimizing hemodynamics in heart failure patients by systematic screening of left ventricular pacing sites: the lateral left ventricular wall and the coronary sinus are rarely the best sites. *J Am Coll Cardiol*. 2010;55(6):566–575.
19. Kapetanakis S, Kearney MT, Siva A, et al. Real-time three-dimensional echocardiography: a novel technique to quantify global left ventricular mechanical dyssynchrony. *Circulation*. 2005;112(7):992–1000.

20. Suffoletto MS, Dohi K, Cannesson M, et al. Novel speckle-tracking radial strain from routine black-and-white echocardiographic images to quantify dyssynchrony and predict response to cardiac resynchronization therapy. *Circulation*. 2006;113(7):960–968.
21. Iuliano S, Fisher SG, Karasik PE, et al. QRS duration and mortality in patients with congestive heart failure. *Am Heart J*. 2002;143:1085–1091.
22. Yu CM, Chau E, Sanderson JE, et al. Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. *Circulation*. 2002;105:438–445.
23. van Bommel RJ, Ypenburg C, Mollema SA, et al. Site of latest activation in patients eligible for cardiac resynchronization therapy: patterns of dyssynchrony among different QRS configurations and impact of heart failure etiology. *Am Heart J*. 2011;161(6):1060–1066.
24. Becker M, Hoffmann R, Schmitz F, et al. Relation of optimal lead positioning as defined by three-dimensional echocardiography to long-term benefit of cardiac resynchronization. *Am J Cardiol*. 2007;100(11):1671–1676.
25. Donahue T, Niazi I, Leon A, et al. Acute and chronic response to CRT in narrow QRS patients. *J Cardiovasc Transl Res*. 2012;5(2):232–241.
26. Auricchio A, Stellbrink C, Block M, et al. Effect of pacing chamber and atrioventricular delay on acute systolic function of paced patients with congestive heart failure. The Pacing Therapies for Congestive Heart Failure Study Group. The Guidant Congestive Heart Failure Research Group. *Circulation*. 1999;99(23):2993–3001.
27. Perrone-Filardi P, Bacharach SL, Dilsizian V, et al. Effects of regional systolic asynchrony on left ventricular global diastolic function in patients with coronary artery disease. *J Am Coll Cardiol*. 1992;19(4):739–744.