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A different cardiac resynchronization therapy technique might be needed in some patients with nonspecific intraventricular conduction disturbance pattern

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ABSTRACT

BACKGROUND Current cardiac resynchronization therapy (CRT), devised to eliminate dyssynchrony in left bundle branch block (LBBB), works by pacing the latest activated left ventricular site (LALVS). We hypothesized that patients with nonspecific intraventricular conduction disturbance (NICD) pattern respond less favorably to CRT, because their LALVS is far away from that in LBBB.

METHODS By measuring the amplitude and polarity of secondary ST-segment alterations in two optional frontal and horizontal surface electrocardiogram (ECG) leads and using a software, we determined the resultant 3D spatial secondary ST vector, which is directed 180° away from the LALVS, in 110 patients with LBBB pattern and 77 patients with NICD pattern and heart failure. To validate the ECG method, we also estimated the LALVS by echocardiography using 3D parametric imaging and 2D speckle tracking in 22 LBBB patients and 20 NICD patients. Patients with NICD pattern were subdivided according to their non-overlapping frontal plane resultant secondary ST vector ranges to the NICD-1 subgroup (n = 44) and the NICD-2 subgroup (n = 33).

RESULTS Based on the software determined coordinates of the resultant 3D spatial secondary ST vector directed 180° away from the LALVS, the LALVSs were located leftward, posterosuperior in the LBBB group, slightly left, superior in the NICD-1 subgroup, and slightly left, posteroinferior in the NICD-2 subgroup. The LALVS determined by ECG and echocardiography matched in all patients, except two.

CONCLUSIONS In the NICD-2 subgroup, a remote LALVS was found from that in LBBB pattern, which might explain the high non-response rate of the NICD pattern to the current CRT technique.

Most recently published large randomized studies demonstrated benefits of cardiac resynchronization therapy (CRT) only in patients with left bundle branch block (LBBB) pattern or with QRS duration ≥ 150 ms. CRT did not decrease the total mortality and/or non-fatal heart failure (HF) events in patients with non-LBBB pattern and a QRS duration of 120−149 ms and may be harmful in patients with a QRS duration < 130 ms.[1–9] Therefore, the indication of CRT in patients with non-LBBB pattern and a QRS duration of 130−149 ms is questionable according to the current guidelines.[10] However, the worse outcome of CRT in patients with non-LBBB pattern might not be determined by the QRS morphology itself, but may rather be due to unfavorable patient characteristics for CRT, such as more ischemic etiology and predominance of male patients, less dyssynchrony and the inability of the current CRT technique to eliminate dyssynchrony in these patients.[7,8] In fact, a recent meta-analysis has shown that QRS duration (and not QRS morphology) was the only inde-

pendent predictor of CRT effect on all-cause mortality and HF hospitalizations.[11] The current CRT technique was devised to eliminate dyssynchrony caused by LBBB pattern, but it is inappropriate in patients with pure, typical right bundle branch block (RBBB) pattern [without associated left hemiblock or without being an atypical RBBB, defined as the absence of characteristic S waves (S wave of greater duration than R wave or > 40 ms) in leads I and aVL] and may be inappropriate in patients with nonspecific intraventricular conduction disturbance (NICD) pattern to eliminate dyssynchrony.[7,8,12,13] There are very scarce data about the ventricular activation sequence in patients with NICD pattern from three studies investigating only a small number of patients.[14–16] In the first study conducted in 15 patients, the ventricular activation sequence was highly variable, heterogeneous, and characteristic activation pattern(s) could not be identified. The only consistent finding was the presence of fewer and smaller lines of slow conduction in the left ventricle (LV) compared with LBBB pattern, which was responsible for the less dyssynchrony and shorter QRS duration.[14] In the second study,[15] 23 patients with NICD pattern were investigated and the authors found that the direction of ventricular activation delay was similar in patients with NICD pattern and LBBB pattern, but the degree of ventricular activation delay was greater in patients with LBBB pattern. In the third study,[16] 23 consecutive patients with NICD pattern and a QRS duration ≥ 120 ms referred for CRT were examined by coronary venous 3D electroanatomical mapping. A delayed LV lateral wall activation defined as maximal activation time measured at the LV lateral wall exceeding 75% of the total QRS duration, was found in 52% (12/23) of these patients, indicating that a significant percentage of patients with NICD pattern are potential CRT responders. In patients with delayed LV lateral wall activation, the most delayed lateral region was usually confined to the basal lateral wall.

The main determinant of favorable response to CRT may not be the QRS morphology, but the presence of significant ventricular dyssynchrony and the ability of the CRT technique to eliminate it. Ventricular dyssynchrony can be successfully eliminated when the LV electrode is placed to the latest activated or adjacent LV region during CRT. Recent studies partly supported this hypothesis. When interventricular or LV intraventricular dyssynchrony was revealed by speckle tracking echocardiography or when the LV electrode was placed at the latest activated or adjacent LV regions, the outcome of CRT evaluated with hard primary clinical end points was as beneficial in patients with non-LBBB (either NICD or RBBB) pattern as in patients with LBBB pattern and/or ≥ 150 ms QRS width.[17–20] The finding that QRS duration was the only independent predictor of CRT outcome is also consistent with our hypothesis, as QRS duration is a rough measure of dyssynchrony.[7,11] We hypothesized that an important cause of less favorable response to CRT of patients with NICD pattern (the second greatest patient group among potential CRT candidates) might be that the latest activated LV site (LALVS) in many patients with NICD pattern might be far away from that in patients with LBBB pattern, and therefore the current CRT technique, devised to eliminate dyssynchrony caused by LBBB pattern, is ineffective.

METHODS

To test our hypothesis, we devised a surface electrocardiogram (ECG) method for the approximate localization of the LALVS, the principle of which is that the resultant secondary ST-segment vector associated with wide QRS complexes points away from the LALVS. To this end, we determined the resultant 3D spatial secondary ST vector and the LALVS located 180° away from the resultant 3D spatial ST vector in 110 patients with LBBB pattern and 77 patients with NICD pattern with HF. Initially, the ECGs of 119 patients with LBBB pattern and 99 patients with NICD pattern were analyzed, but 8% (9/119) of the ECGs with LBBB pattern and 22% (22/99) of the ECGs with NICD pattern were excluded from the analysis either because the ST deviations were not secondary but primary or because there were no discernible ST deviations (the STs were isoelectric). Intraventricular conduction disturbances were defined according to the 2009 AHA/ACCF/HRS recommendations[21] with some modifications concerning the definition of LBBB proposed by Strauss, *et al*.[22] NICD was diagnosed when the QRS duration was > 110 ms without cri-

teria for RBBB or LBBB. All experiments were carried out in accordance with relevant named guidelines and regulations. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Scientific and Research Ethics Committee of the Hungarian Medical Research Council, Budapest, Hungary (ETT-TUKEB IV/1370-2/2020/EKU). This was a retrospective cohort study in which we enrolled patients with HF associated with LBBB pattern or NICD pattern, who were treated at Department of Medicine and Hematology, Semmelweis University, Budapest, Hungary. In some of these patients, we routinely perform 3D echocardiographic examination and 2D speckle tracking strain analysis in order to better determine the etiology and severity of HF, these patients were enrolled to the echocardiographic validation study retrospectively. Due to the retrospective nature of the analysis, the Scientific and Research Ethics Committee of the Hungarian Medical Research Council, Budapest, Hungary approved an informed consent exemption for this study (ETT-TUKEB IV/1370-2/2020/EKU).

The Rationale Behind the Surface ECG Method Devised for the Estimation of LALVS

The mechanism of secondary ST-segment and T-wave changes is based on the potential differences between action potentials of the earliest and latest activated ventricular regions. The time difference between the phase 0 depolarizations of the action potentials of the earliest and latest activated ventricular regions corresponds to the QRS width. Figure 1A shows that under normal conditions, the time difference between the phase 0 depolarizations of the action potentials of the earliest activated endocardial and the latest activated epicardial regions is small, giving rise to a narrow QRS complex. The direction and magnitude of the potential difference between the plateaus of the above action potentials determines the ST-segment polarity and the magnitude of its deviation. Normally, there is no potential difference between the plateaus of the earliest activated endocardial site action potential and the latest activated epicardial site action potential, because the former ends later than the latter due to the shorter duration of the epicardial action potential,[23] therefore, the ST-segment will be isoelectric. In the case of a wide QRS complex, the phase 0 depolarizations of the action potential of the latest activated epicardial site is so significantly delayed compared with that of the earliest activated endocardial site, that despite the shorter duration of the epicardial action potential, the epicardial action potential ends after the endocardial action potential, therefore, its plateau is higher than that of the endocardial action potential (Figure 1B). Thus, the ST vector, which points from the greater to the smaller potential is directed from the latest activated epicardial towards the earliest activated endocardial region, i.e., away from the latest activated ventricular region. Thus, by analyzing the 12-lead ECG, we can determine the resultant secondary ST vectors in the frontal plane and horizontal plane and from these a resultant 3D spatial ST vector directed away from the LALVS can be constructed by vector summation. We devised a software tool (Figure 2), which automatically and more accurately calculated the resultant ST vectors than the traditional electrocardiographic method, providing not only their direction, but both their

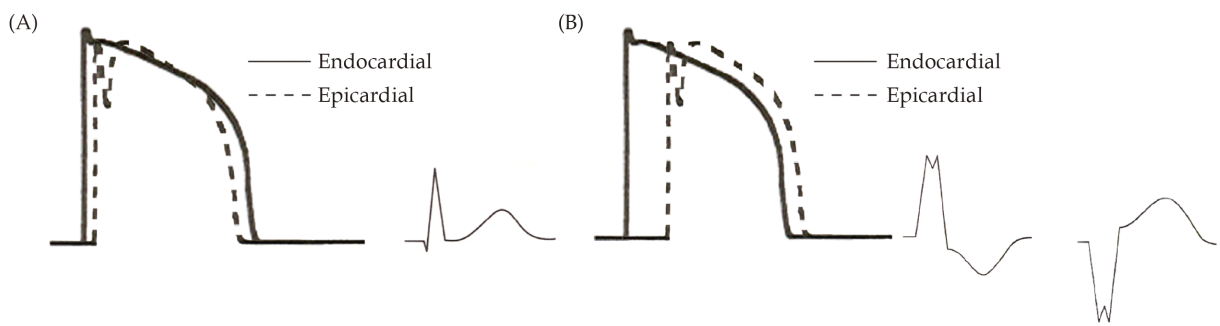

Figure 1 The rationale behind the electrocardiogram method devised for the estimation of the latest activated left ventricle region. (A): Illustration for the explanation of normal QRS complex with normal QRS width and ST segment; and (B): illustration for the explanation of wide QRS complex, with secondary ST segment changes. For further explanation see text.

direction and magnitude. After measuring manually the polarity and amplitude of the ST vectors in any optional two leads in the frontal plane and horizontal plane and entering the data to the software tool, the software tool calculated the individual resultant and the patient group mean resultant frontal plane secondary ST vectors respectively accurately and the individual resultant and patient group mean resultant horizontal plane secondary ST vectors respectively approximately. Then the 3D spatial secondary ST vector of each individual patient and each patient group was calculated from these by vector summation. We assumed that the precordial leads are located approximately at the following sites in the horizontal plane: lead V1 at 115°, V2 at 95°, V3 at 75°, V4 at 60°, V5 at 30°, and V6 at 0°.[23,24]

Echocardiographic Studies

The purpose of the echocardiographic examinations was to determine the approximate location of the LALVS and to check whether there is a matching in the location of the LALVS estimated by the electrocardiographic method and echocardiographic method. Thus, we intended to validate the ability of our electrocardiographic method to estimate the LALVS by using echocardiography. Echocardiography was carried out using the Philips Epiq 7c system (Philips Ultrasound, Bothell, WA, USA) equipped with the X5-1 xMATRIX array transducer (frequency range: 5–1 MHz) in 42 patients (22 patients with LBBB pattern, 20 patients with NICD patterns). Each patient underwent a routine echocardiographic examination and then we made online recordings for later offline analysis using the QLAB 11 software (Philips Andover, MA, USA) for 3D parametric imaging study and 2D speckle tracking echocardiography study.

We performed online 3D full volume recordings composed of 4–6 subvolumes in the apical four-chamber view and analyzed them offline using the 3D parametric imaging application of the QLAB 11 software for the assessment of regional myocardial function. Parametric imaging uses more than 800 endocardial data points to develop a polar map of the endocardial surface of the LV. Parametric imaging displays endocardial motion as shades of blue (for normal or hypokinetic segments), black (for akinetic segments), red (for dyskinetic segments) and timing of regional endocardial motion (time to maximal end-systolic excursion) in green (average time),

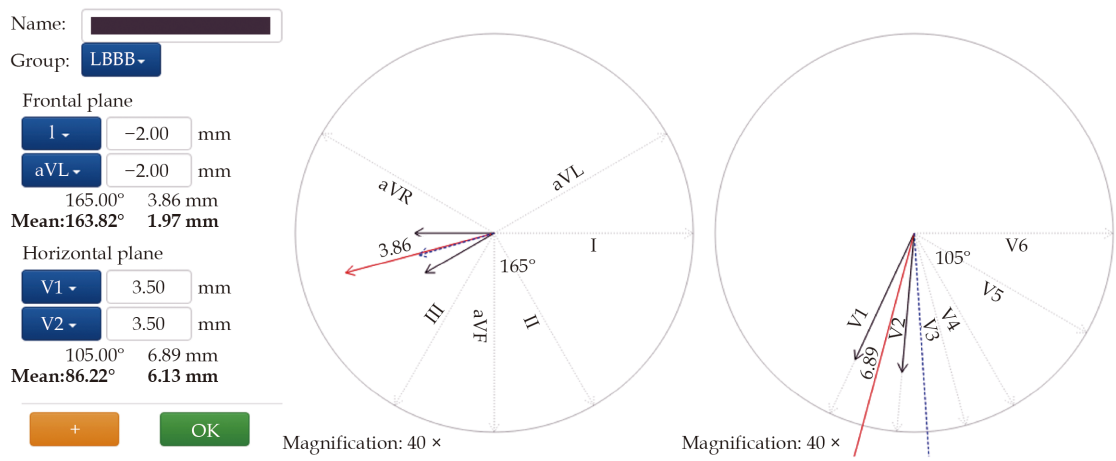

Figure 2 The demonstration of our software tool. The left figure panel shows the frontal plane, the right figure panel shows the horizontal plane. We manually measured from each electrocardiogram the polarity and magnitude of secondary ST vectors in two optional frontal and horizontal leads (denoted by black arrows in the figure panels) and entered the magnitude and polarity data of these ST vectors to the software (shown on the left side of the figure). Red arrows show the resultant frontal and horizontal plane secondary ST vectors calculated by the software tool from the entered data for this individual patient. The magnitude and polarity data for these vectors are shown by normal letters on the left side of the figure right below the entered manually measured data. Blue dashed line arrows show the mean resultant frontal and horizontal plane secondary ST vectors of the whole group the patient belongs to (in this case the LBBB group). The magnitude and polarity data of these vectors are denoted by bold letters on the left side of the figure. Then the software calculated the 3D spatial resultant secondary ST vectors of each individual patient and each patient group from the individual resultant and patient group mean resultant frontal and horizontal plane secondary ST vectors by vector summation (not shown in this figure). LBBB: left bundle branch block.

in blue (events happening before average motion) and red (events happening after average motion showing the latest activated LV segments). A polar map is created from the fine-tuned regional myocardial motion information and superimposed on the American Heart Association defined 17-segment model, which is displayed in a bull's eye plot.[25] We determined the longest time to minimal volume in the 17-segment LV model as well using the 3D parametric imaging application, which also identifies the latest activated LV segment.

Myocardial deformation was measured using 2D speckle tracking imaging. To optimize speckle tracking imaging, two-dimensional grayscale images were acquired at a frame rate of 60–80 Hz in the apical four-chamber view, two-chamber view, and three-chamber view and in the parasternal short-axis basal, mid papillary and apical views and three cardiac cycles were recorded. The grayscale image recordings were analyzed offline using the QLAB 11 software. The LV wall was divided into 17 segments and each segment was individually analyzed. From the three apical views, the time to peak longitudinal strain and from the parasternal short-axis views the time to peak circumferential strain of each segment was calculated and displayed in a bull's eye plot and the longest time identified the latest activated LV segment.

Testing Whether There is Matching in the Location of the Latest Activated LV Region Determined by Echocardiography and Electrocardiography

The estimated LALVSs in the patient groups determined by the ECG method were located at the crossing points where the retrograde elongation of the resultant 3D spatial secondary ST vectors reached a schematic heart figure, as the 3D spatial ST vectors are directed 180° away from the LALVS. The location of the LALVS determined by echocardiography was displayed on a very similar schematic heart figure displaying the segmental analysis of LV walls based on schematic views taken from the recommendations for chamber quantification by the American Society of Echocardiography Guidelines.[26] We compared the location of the LALVS determined by both methods and matching (complete or approximate) was diagnosed when identical or adjacent LV segments were determined by both methods.

Statistical Analysis

Differences in baseline characteristics between the LBBB patient group and NICD patient group were calculated using the Student's unpaired *t*-test for continuous variables and the Mann-Whitney *U* test for discrete variables. Gender distribution and aetiology in the two patient groups were compared by the Pearson's chi-squared test. For mean frontal and horizontal resultant secondary ST vector data analysis, the Kruskal-Wallis *H* test followed by the Dunn's multiple comparisons test were used for between-groups comparisons. A P-value < 0.05 value was considered statistically significant. All continuous variables are presented as mean ± SD unless otherwise stated. Statistical analysis was performed using GraphPad Prism 6.0 (GraphPad Software Inc., San Diego, CA, USA).

RESULTS

Table 1 shows the most important patient group characteristics. Compared with the LBBB group patients in the NICD group were slightly younger, their QRS duration was shorter, and their baseline rhythm was more frequently atrial fibrillation and less frequently sinus rhythm. In other characteristics (female/male ratio, HF etiology, LV ejection fraction), there were no significant between-groups differences.

Patients with NICD pattern were further subdivided according to their non-overlapping frontal plane resultant secondary ST vector ranges to two subgroups: (1) the NICD-1 subgroup (n = 44) with a frontal plane resultant secondary ST vector range of 60°–160°; and (2) the NICD-2 subgroup (n = 33) with a frontal plane resultant secondary ST vector range of −30°––175°. This subdivision of NICD group to NICD-1 subgroup and NICD-2 subgroup was justified by the significant difference (P < 0.001) in mean frontal plane resultant secondary ST vector positions (111.11° ± 3.79° for the NICD-1 subgroup *vs.* −118.7° ± 8.12° for the NICD-2 subgroup) (Table 2). The mean frontal plane resultant secondary ST vector position of the LBBB group also significantly differed from that of the NICD-2 subgroup (165.69° ± 4.26° *vs.* −118.7° ± 8.17°, P < 0.001) and that of the NICD-1 subgroup (165.69° ± 4.26° *vs.* 111.11° ± 3.79°, P < 0.001) as well (Table 2). The mean horizontal plane resultant secondary ST vector position of the LBBB group significantly differed from that of the

Table 1 Most important patient characteristics.

Characteristics	LBBB group (n = 110)	NICD group (n = 77)
Age, yrs	71.29 ± 10.74	66.35 ± 12.70**
Gender		
Female	46 (41.8%)	27 (35.1%)
Male	64 (58.2%)	50 (64.9%)
Etiology		
Ischemic cardiomyopathy	70 (63.6%)	49 (63.6%)
Nonischemic cardiomyopathy	40 (36.4%)	28 (36.4%)
QRS duration, ms	161.6 ± 22.6	140.5 ± 23.8***
Left ventricle ejection fraction, %	37.47 ± 13.50	34.3 ± 14.3
Baseline rhythm		
Sinus rhythm	97 (88%)	58 (75%)*
Atrial fibrillation	12 (11%)	18 (23%)*
Atrial tachycardia	1 (0.9%)	1 (1.3%)

Data are presented as means ± SD or n (%). *Presented as $P < 0.05$ (NICD group *vs.* LBBB group). **Presented as $P < 0.01$ (NICD group *vs.* LBBB group). ***Presented as $P < 0.001$ (NICD group *vs.* LBBB group). LBBB: left bundle branch block; NICD: nonspecific intraventricular conduction disturbance.

NICD-2 subgroup (90.4° ± 1.31° *vs.* 112.16° ± 9.45°, $P < 0.05$) (Table 2).

In the LBBB group, the resultant 3D spatial ST vector pointed to the right, anterior, and slightly downward direction; in the NICD-1 subgroup, to the right, slightly anterior, and downward; and in the NICD-2 subgroup, to the slightly right, anterior, upward direction (Figure 3, Table 2). Therefore, the LALVS was at the expected left superior posterolateral position in the LBBB group; while it was located at a close slightly left, slightly posterior, and superior LV region in the NICD-1 subgroup; and at a slightly left, posteroinferior LV region in the NICD-2 subgroup. In the NICD-2 subgroup, the LALVS was remote from that in the LBBB group, but the LALVS in the NICD-1 subgroup was quite close to that in the LBBB group (Figure 4).

The LALVS determined by ECG and echocardiography matched (complete or approximate matching) in all patients, except two. Figure 5 demonstrates in a representative case how the location of LALVS was determined in practice by electrocardi-

Table 2 Coordinates of the frontal plane, horizontal plane and 3D spatial resultant secondary ST vectors in the different patient groups.

Characteristics	LBBB group (n = 110)	NICD group (n = 77)	
		NICD-1 subgroup (n = 44)	NICD-2 subgroup (n = 33)
Mean frontal plane resultant secondary ST vector			
Position, °	165.69 ± 4.26*	111.11 ± 3.79*	−118.7 ± 8.12*
Amplitude, mV	0.232 ± 0.015	0.19 ± 0.019	0.155 ± 0.018
Mean horizontal plane resultant secondary ST vector			
Position, °	90.4 ± 1.31**	102.29 ± 9.91	112.16 ± 9.45
Amplitude, mV	0.576 ± 0.044	0.414 ± 0.07	0.379 ± 0.065
3D spatial resultant secondary ST vector coordinates			
x axis, mV	−0.229	−0.157	−0.2174
y axis, mV	−0.057	−0.177	0.136
z axis, mV	0.576	0.405	0.351

Data are presented as mean ± SE or n. *Presented as $P < 0.001$ *vs.* the other two groups. **Presented as $P < 0.05$ *vs.* the NICD-2 subgroup. LBBB: left bundle branch block; NICD: nonspecific intraventricular conduction disturbance.

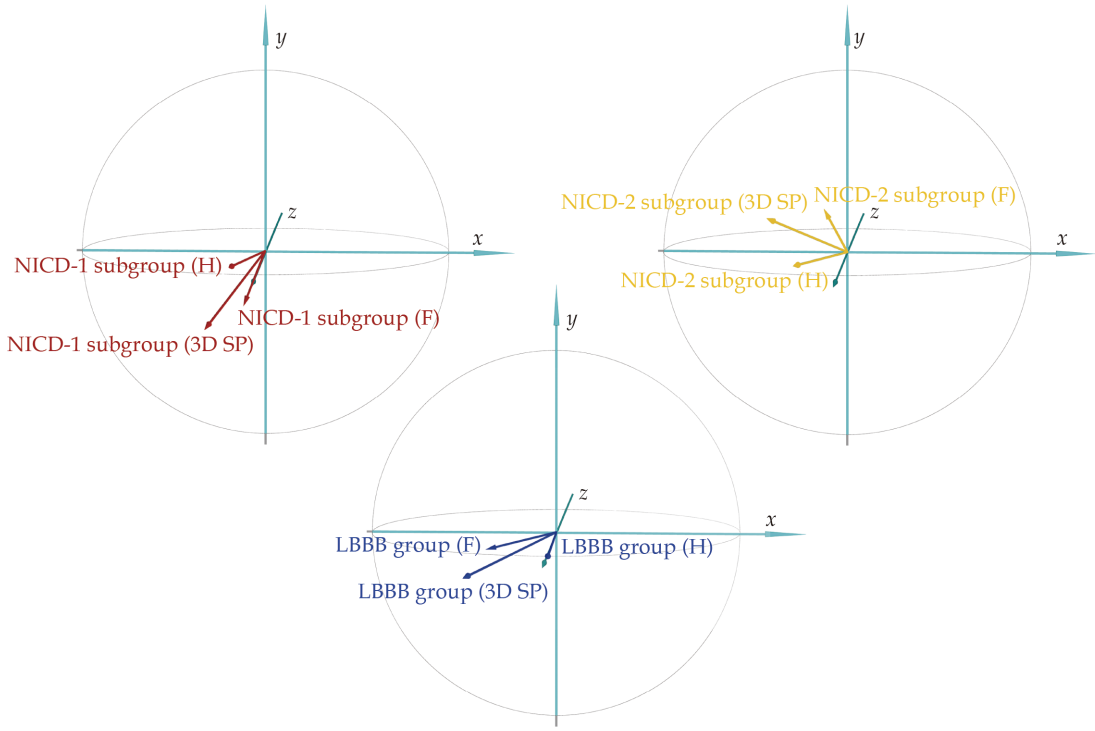

Figure 3 The mean resultant F plane, H plane and resultant 3D SP secondary ST vectors in each patient group. The vector coordinates are shown in Table 2. F: frontal; H: horizontal; LBBB: left bundle branch block; NICD: nonspecific intraventricular conduction disturbance; 3D SP: 3D spatial.

ography and echocardiography, and how matching in the LALVS determined by the two methods was assessed.

When the LBBB group and NICD group were separated to patients with ≥ 150 ms and < 150 ms QRS duration subgroups, the LALVSs of the > 150 ms subgroup were almost exclusively in the anterolateral (anterior) or inferolateral areas and those of the < 150 ms subgroup were in the above mentioned areas or elsewhere, sometimes far away from these areas (Figure 6).

DISCUSSION

The main finding of this study is that the inadequacy of the current CRT technique, devised to eliminate LV intraventricular dyssynchrony caused by LBBB pattern by placing the LV electrode to the lateral or posterolateral LV wall, a remote site from the estimated LALVS in many patients with NICD pattern, might be an important cause, besides less dyssynchrony (indicated by the shorter QRS duration in the NICD group), for the relatively high nonresponse rate to CRT in patients with NICD pattern. Patients, whose LALVS is adjacent or not far away

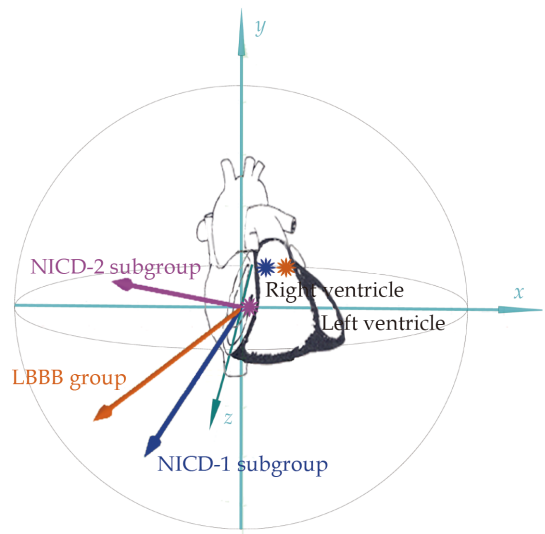

Figure 4 The approximate location of the latest activated left ventricle regions marked by stars of different colors in each patient group. Dark yellow, blue and pink stars are the latest activated left ventricle regions in the LBBB group, NICD-1 subgroup, and NICD-2 subgroup, respectively. LBBB, NICD-1, NICD-2: resultant 3D spatial ST vectors in the LBBB group, NICD-1 subgroup, and NICD-2 subgroup, respectively. Axes marked by green are x axis, y axis, z axis 3D coordinate system axes. LBBB: left bundle branch block; NICD: nonspecific intraventricular conduction disturbance.

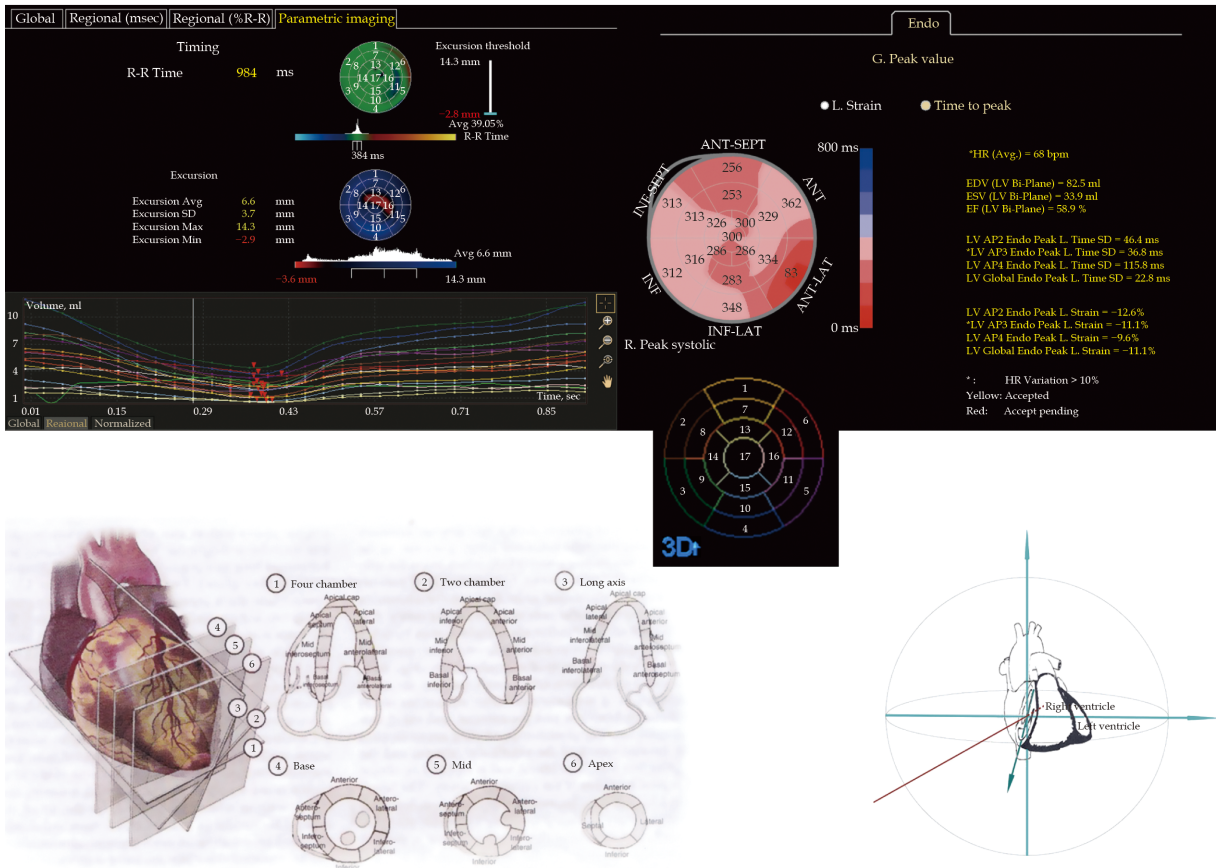

Figure 5 The determination of the LALVS in a patient with left bundle branch block pattern using the electrocardiogram method and echocardiographic method. The parametric imaging results are displayed in the left sided figure of the upper panel of the figure, where red shade in the upper bull's eye plot demonstrates that the LALVS is segment 6 (basal anterolateral). The latest red arrowhead in the time to minimal volume curves in the lower part of the upper left sided figure also belongs to segment 6 (longest time to minimal volume: 418 ms). The small bull's eye plot right below the right sided figure in the upper panel shows by color code, which time to minimal volume curve belongs to which segment. The right sided figure in the upper panel showing the bull's eye plot of the time to peak longitudinal strain, shows the longest time in segment 6 (362 ms). Thus, by echocardiography segment 6 is the LALVS. The right lower figure shows the 3D resultant spatial secondary ST vector (red continuous line) of the patient determined by the electrocardiogram method using the software tool, which when elongated backwards (dashed red line), its crossing point with the schematic heart figure (end of the red dashed line marked by X) determines the LALVS. This LALVS corresponds also approximately to segment 6 (basal anterolateral) according to the lower left sided figure demonstrating the location of LV segments of the 17-segment model recommended by the American Society of Echocardiography in a schematic figure (see plane 1 crossing the schematic heart figure). Thus, there is a complete matching in LALVS determined by the electrocardiographic and echocardiographic methods. LALVS: latest activated left ventricular site.

from the tip of the LV electrode, may respond to CRT. The LALVS in the NICD-2 subgroup was far away, but in the NICD-1 subgroup was not far away from that in patients with LBBB pattern; therefore, the NICD-1 subgroup patients might still be responders, while there is a high likelihood that the NICD-2 subgroup patients will be non-responders. The proportion of the NICD-2 subgroup patients among the NICD patients [43% (33/77)] approximately corresponded to the proportion (48%) without delayed LV lateral wall activation and the greater 30%–40% non-response rate of patients with NICD pattern.[16,17] Thus, it is conceivable that the application of a different CRT technique with placement of the LV electrode at or near the LALVS might improve the CRT outcome in some patients with NICD pattern. It is very likely that regarding the ventricular activation sequence patients with NICD pattern comprise a heterogeneous group. Therefore, further studies (e.g., invasive electroanatomic or noninvasive electrocardiographic imaging mapping) are needed, which can more accurately elu-

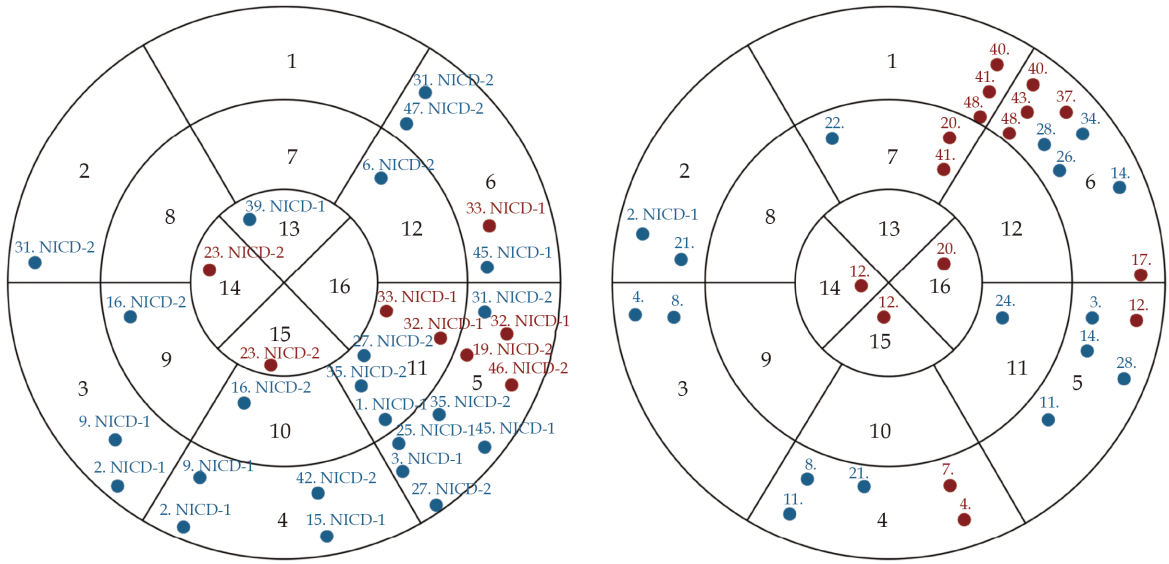

Figure 6 The location of the LALVS determined by echocardiography displayed in a 16-segment bull's eye plot in the NICD group (left plot) and LBBB group (right plot) separated to two subgroups: patients with ≥ 150 ms (red dots) and < 150 ms (blue dots) QRS durations. Numbers above dots indicate a given patient, one patient may had more than one LALVSs. Septal segments: 2, 3, 8, 9, 14, lateral segments: 5, 6, 11, 12, 16. LALVS: latest activated left ventricular site; LBBB: left bundle branch block; NICD: nonspecific intraventricular conduction disturbance.

cidate the characteristics of ventricular activation sequence and may identify characteristic subgroups based on ventricular activation patterns in patients with NICD pattern.

The initial ventricular activation in a supraventricular rhythm with wide QRS complexes is unaltered and therefore septal, the wider the QRS complex, the LALVS should be located at a more distant site from the septum, as the QRS duration is determined by the time needed for propagation of the electrical impulse from the initial to the latest ventricular activation sites. The most distant sites from the septum are the anterolateral (anterior) or inferolateral sites. That's why the current CRT technique, which applies anterolateral or inferolateral LV electrode positions, is effective in patients with wide (≥ 150 ms) QRS complexes and can be ineffective in some patients with less wide (< 150 ms) QRS complexes whose LALVS can be far away from the anterolateral or inferolateral positions (Figure 6).

Our novel surface ECG method can at best roughly estimate the location of the LALVS. Although our echocardiographic studies supported the suitability of our novel surface ECG method for the approximate localization of LALVS, its applicability for this purpose should be verified by more accurate mapping methods. If this will be the case, it can be used in the future to select those patients with NICD pattern, for whom a different CRT technique from the current one should be used to achieve a beneficial response.

LIMITATIONS

The small number of patients and our observation that the ECG method used for the determination of the resultant ST vectors could not be applied in 14% (31/218) of all ECGs, especially in ECGs recorded in patients with NICD pattern [22% (22/99)], because either ST deviations were not secondary but primary, or the ST-segments were isoelectric are limitations of this study. Therefore, in the future of clinical practice, we would like to apply the ST vector ECG method together with our novel ECG dyssynchrony criteria[8] (the latter method can be applied in all patients) in order to improve patient selection for CRT. Another important limitation is the extrapolation of the location of the LALVS to the crossing point at which the retrograde elongation of the calculated 3D spatial resultant secondary ST vector reaches a schematic heart figure instead of a real heart. Although our echocardiographic studies supported the ability of our ECG method for the approximate localization of the LALVS, the suitability

of our ECG method for this purpose needs further confirmation by more accurate mapping methods (invasive electroanatomical mapping, ECG imaging) and by other independent investigators.

CONCLUSIONS

In conclusion, our results suggest that the greater non-response rate of patients with NICD pattern than with LBBB pattern to CRT might be due, besides less dyssynchrony, to the inability of the current CRT technique, devised to eliminate dyssynchrony caused by LBBB pattern, to eliminate dyssynchrony in some of these patients. This may be due to the remote location of the LALVS in many patients with NICD pattern (NICD-2 subgroup) from that in patients with LBBB pattern. If these results of our hypothesis-generating article will be confirmed by other independent investigators, it might lead to the development of a different CRT technique for some patients with NICD pattern in the future.

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