



## The role of electrocardiography in the elaboration of a new paradigm in cardiac resynchronization therapy for patients with nonspecific intraventricular conduction disturbance

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### Abstract

Cardiac resynchronization therapy (CRT) is associated with a favorable outcome only in patients with left bundle branch block (LBBB) pattern and in patients with a QRS duration > 150 ms, in patients with non-LBBB pattern with a QRS duration of 120–150 ms usually is not beneficial. After adjusting for QRS duration, QRS morphology was no longer a determinant of the clinical response to CRT. In contrast to the mainstream view, we hypothesized that the unfavorable CRT outcome in patients with non-LBBB and a QRS duration of 120–150 ms is not due to the QRS morphology itself, but to less dyssynchrony and unfavorable patient characteristics in this subgroup, such as more ischemic etiology and greater prevalence of male patients compared with patients with LBBB pattern. Further, the current CRT technique is devised to eliminate the dyssynchrony present in patients with LBBB pattern and inappropriate to eliminate the dyssynchrony in patients with non-LBBB pattern. We also hypothesized that electrocardiography may also provide information about the presence of interventricular and left intraventricular dyssynchrony and the approximate location of the latest activated left ventricular (LV) region. To this end, we devised new ECG criteria to estimate interventricular and LV intraventricular dyssynchrony and the approximate location of the latest activated LV region. Our preliminary data demonstrated that the latest activated LV region in patients with nonspecific intraventricular conduction disturbance (NICD) pattern might be at a remote site from that present in patients with LBBB pattern, which might necessitate the invention of a novel CRT technique for patients with NICD pattern. The application of the new interventricular and LV intraventricular dyssynchrony ECG criteria and a potential novel CRT technique might decrease the currently high nonresponder rate in patients with NICD pattern.

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### 1 Introduction

Most recently published large randomized studies demonstrated favorable outcome after cardiac resynchronization therapy (CRT) only in patients with left bundle branch block (LBBB) pattern, and CRT did not decrease the total mortality and/or nonfatal heart failure events in patients with non-LBBB pattern.<sup>[1–6]</sup> A recent meta-analysis of randomized CRT trials using individual instead of aggregate patient data has shown that only QRS duration was an independent predictor of the CRT effect on all cause mortality

and heart failure hospitalizations.<sup>[7]</sup> Especially, QRS duration > 140 ms indicated a high probability of benefit from CRT. After adjusting for QRS duration in their analysis, QRS morphology was no longer a determinant of the clinical response to CRT. Moreover, in contrast to other studies, this meta-analysis revealed that other patient characteristics, such as male gender, ischemic etiology and older age, that are considered to unfavorably influence the CRT outcome, did not prove to be independent predictors of CRT outcome.<sup>[7,8]</sup>

The worse outcome of CRT in patients with non-LBBB pattern might be due to less dyssynchrony and unfavorable patient characteristics, such as more ischemic etiology and greater prevalence of male patients compared with patients with LBBB pattern.<sup>[1,9,10]</sup> The less dyssynchrony manifested in a shorter QRS duration in patients with nonspecific intraventricular conduction disturbance (NICD) and right bundle branch block (RBBB) patterns compared with LBBB pattern.<sup>[1]</sup>

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However, in contrast to the mainstream view, some smaller recently published randomized studies and a retrospective study conducted in patients with non-LBBB pattern demonstrated that when intraventricular or interventricular dyssynchrony was revealed by speckle tracking echocardiography or the left ventricular (LV) electrode was placed right at the latest activated or adjacent LV regions, the outcome of CRT evaluated with hard primary 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.<sup>[9,11–14]</sup> In summary, these data demonstrate that the most important independent predictor of CRT outcome is the presence of intra- and interventricular dyssynchrony.

In prospective trials, which enrolled consecutive patients who underwent CRT, the most common ECG morphology was LBBB (approx. 50%–70%), NICD morphology was the second most prevalent (approx. 10%–35%) and RBBB morphology was the least prevalent (approx. 5%–18%).<sup>[1,2,4,9]</sup> The still significant non-responder rate of approximately 30% can be mostly improved by better selection or using different CRT implantation techniques in patients with non-LBBB morphology, because the number of non-responders are high in this subgroup. It is difficult to decrease further the already low ( $\leq 20\%$ ) non-responder rate in patients with LBBB pattern, because their CRT outcome is very good using the traditional patient selection and CRT technique. Therefore, we are interested in the second largest group of CRT candidates: patients with NICD pattern.

## 2 Hypothesis

The outcome of CRT is not related to ECG morphology in itself, but to the degree of dyssynchrony and the appropriateness of the current CRT technique to eliminate or diminish dyssynchrony related to a certain ECG morphology. We hypothesized that the 12 lead surface ECG, which was used so far in patients selected for CRT only to measure QRS duration and QRS morphology assessment, may provide additional important information necessary for better patient selection for CRT and for optimal LV electrode placement, such as estimation of interventricular and LV intraventricular dyssynchrony and the approximate determination of the latest activated LV region. Because dyssynchrony is a primarily electrically determined alteration with secondary mechanical consequences, it seems logical that ECG might have a greater role or at least as important role as imaging modalities in the detection of dyssynchrony. We also hypothesized that the approximate determination of the latest activated LV region might help to devise a new and improved CRT technique for patients

with NICD pattern, which will improve the CRT response rate in this subgroup.

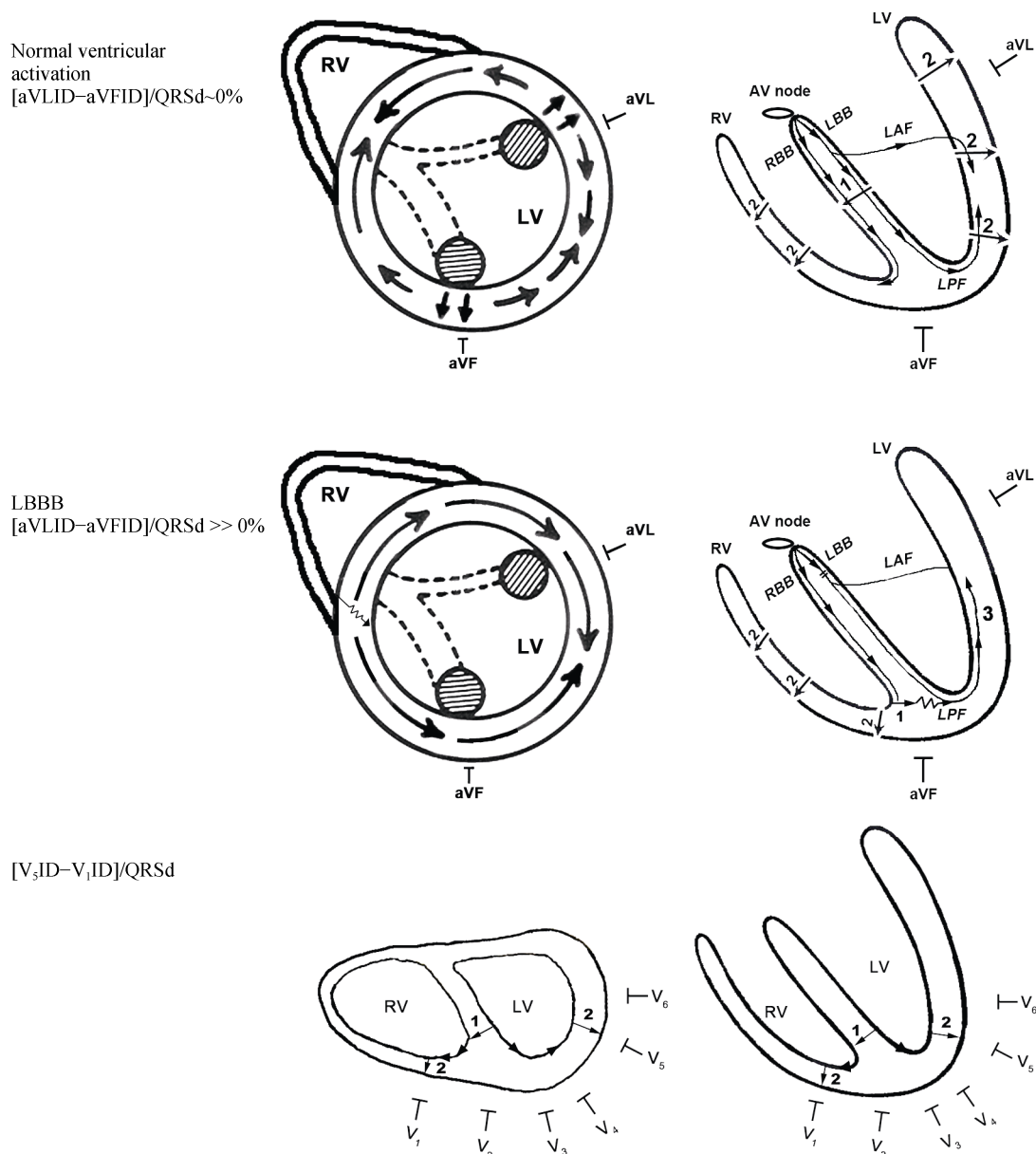
### 2.1 New ECG criteria serving as surrogate markers of interventricular and LV intraventricular dyssynchrony

We devised new electrocardiographic criteria using the standard 12 lead ECG to estimate interventricular and LV intraventricular dyssynchrony and predict the approximate latest activated LV region for better selection of patients with NICD pattern for CRT and invention of a more appropriate CRT technique for these patients.

We used the following assumptions for devising the LV intraventricular dyssynchrony ECG criterion: (1) LV intraventricular dyssynchrony means that the activation of at least one region in the LV is delayed compared with the normal LV activation sequence; (2) During normal ventricular activation the two ventricles, and within the LV the two papillary muscles are activated approximately simultaneously; (3) the unipolar leads aVL and aVF are located approximately over the anterior and posterior papillary muscles respectively (see Figure 1 upper panel); and (4) the time to the onset of the intrinsicoid deflection (ID), which in the further discussion will be simply mentioned as ID, in a unipolar lead reflects the time interval that elapsed from the onset of ventricular electrical activation until the electrical impulse reached the ventricular myocardium lying below the exploring unipolar electrode.

During normal ventricular activation, the two papillary muscles are activated synchronously via the left anterior and posterior fascicles and the aVL and aVF unipolar leads are located approximately above the anterior and posterior papillary muscles respectively. Thus, during physiological conditions, the IDs in leads aVL and aVF (aVLID and aVFID) should be approximately equal, therefore their difference is zero or close to zero. In the presence of LV intraventricular dyssynchrony associated with altered LV activation either the anterior or the posterior papillary muscle will be activated earlier (Figure 1 mid panel). Consequently, the aVLID and aVFID will be unequal and therefore the absolute value of the difference between aVLID and aVFID will increase and will be significantly  $> 0$ . Based on these premises, we devised a new ECG criterion to serve as a surrogate marker of LV intraventricular dyssynchrony in 2010,<sup>[15]</sup> which was calculated as the absolute value of the difference between aVLID and aVFID indexed to QRS duration (QRSd):  $[aVLID - aVFID]/QRSd(\%)$ .

To assess the degree of interventricular dyssynchrony, we applied the IDs in unipolar leads  $V_5$  and  $V_1$  reflecting the approximate left and right ventricular activation times respectively (see Figure 1 lower panel). The absolute difference



**Figure 1. The rationale behind the interventricular and left intraventricular dyssynchrony ECG criteria.** The upper and mid panel shows the rationale behind the left intraventricular dyssynchrony criterion demonstrating its behavior during normal ventricular activation and abnormal ventricular activation pattern due to LBBB. The left upper panel shows a schematic section of the heart similar to the parasternal short axis view obtained by echocardiography at the mid papillary muscle level. The striped circles represent the anterior and posterior papillary muscles activated via the left anterior and posterior fascicles denoted by dashed lines. The mid panel demonstrates that during LBBB the left ventricle (LV) is activated from the right ventricle via transeptal conduction. The conduction velocity in the right side of the interventricular septum is normal, in the left side is slowed denoted by the arrow in the interventricular septum, the first part of which is a straight line representing normal conduction velocity, the second part of which is a serrated line indicating slow conduction. Please, note that after the transeptal activation of the LV the electrical impulse reaches the myocardium lying below lead aVF much earlier than that lying below lead aVL, thus aVLID will be much longer than aVFID, as a consequence the value of the LV intraventricular ECG criterion will be much greater than zero. The schematic transverse and longitudinal sections of the heart in the lower panel show the rationale behind the interventricular dyssynchrony ECG criterion. For further explanation see text. LAF: left anterior fascicle; LBB: left bundle branch; LBBB: left bundle branch block; LPF: left posterior fascicle; LV: left ventricle; RBB: right bundle branch; RV: right ventricle.

between the IDs of leads  $V_5$  and  $V_1$  was indexed to QRSd using the following formula:  $[V_5ID - V_1ID] / QRSd (\%)$ . Dur-

ing normal ventricular activation, the difference between  $V_5ID$  and  $V_1ID$  is quite small, approximately 20 ms, be-

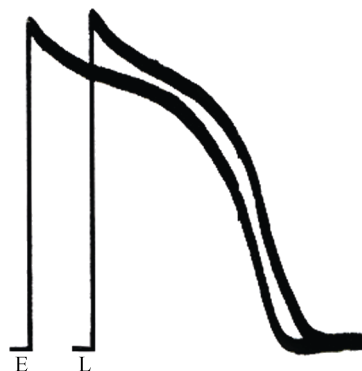
cause the normal ID is  $\leq 30$  ms in leads  $V_1$  or  $V_2$  and  $\leq 50$  ms in leads  $V_5$  or  $V_6$ .<sup>[16]</sup> Therefore, the interventricular ECG criterion should have a low value ( $\leq 25\%$ ) during normal ventricular activation in the absence of interventricular dyssynchrony.

When the value of either of these two new criteria determined in ECGs recorded prior to biventricular pacemaker implantation in patients selected for CRT based on the current criteria arbitrarily is  $> 25\%$ , the patient is considered an expected responder (R), if their value  $\leq 25\%$ , the patient is considered an expected non-responder (NR) by the criterion applied. Applying the two criteria together, when at least one of the two criteria suggests R diagnosis, the final R diagnosis is made, when both criteria suggest NR diagnosis, the final NR diagnosis is made.

## 2.2 New ECG method to determine the approximate location of the latest activated LV region

Patients selected for CRT using the current guidelines have wide QRS complexes, which are almost always (according to our experience in approx. 90% of cases) associated with secondary ST-T changes (with the exception of cases associated with primary ST-T changes). Secondary ST-T changes are defined as ST segments and T waves having opposite polarity compared to that of the terminal part of the QRS complex they are belonging to.

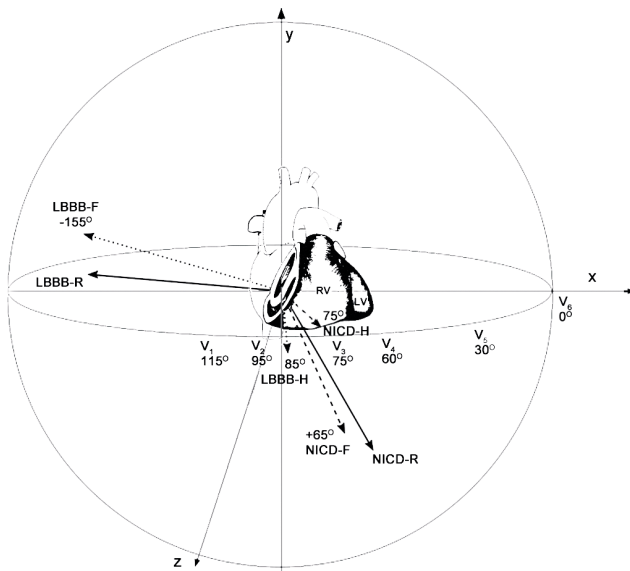
The mechanism of secondary ST-T changes is based on the potential difference between action potentials of the earliest and latest activated ventricular regions. The action potential of the latest activated ventricular region is delayed compared with that of the earliest activated ventricular region (the time difference between the phase 0 depolarizations of the two action potentials corresponds to the QRS width) and reaches a higher plateau (see Figure 2). Therefore, the potential difference gives rise to a resultant secondary ST vector directed away from the latest activated ventricular region and pointing towards the earliest activated ventricular region. Thus, we can determine the resultant secondary ST vector both in the frontal and horizontal planes, which is possible in approximately 90% of cases using the standard 12 lead ECG. From the resultant secondary ST vectors in the frontal and horizontal planes one can construct a resultant 3D space secondary ST vector, which is directed  $180^\circ$  away from the latest activated ventricular region, thus by determining the resultant secondary 3D space secondary ST vector, we can identify the approximate location of the latest activated ventricular region. The depolarization proceed from the earliest to the latest activated region therefore the QRS vector points away from the earliest and towards the latest activated ventricular region, giving



**Figure 2.** Action potentials of the earliest (E) and latest (L) activated ventricular regions.

rise to a QRS complex of opposite polarity to the secondary ST-T changes.

With this simple method we might be able to estimate the approximate location of the latest activated LV region in patients with NICD pattern, which is the ideal site for LV lead placement. To this end, we analyzed the 12 lead ECGs recorded prior to the CRT in patients with heart failure with NICD ( $n = 37$ ) or LBBB ( $n = 38$ ) patterns. The resultant ST vectors in the frontal and horizontal planes were determined, from which we constructed the 3D space resultant ST vectors (Figure 3). In patients with LBBB pattern, the resultant horizontal plane ST vectors were between leads  $V_2$  and  $V_3$  giving rise to a mean horizontal plane resultant ST vector of approx.  $85^\circ$ ; in the frontal plane the resultant ST vectors were between  $-60$  and  $(+)110^\circ$  giving rise to a mean resultant frontal plane ST vector of  $-155^\circ$ . Thus, the resultant 3D space ST vector pointed toward a right, anterior and slightly upward direction. As a consequence, as expected the latest activated LV region in LBBB is located at an opposite left, posterior and slightly downward site (left infero- and posterolateral region). Interestingly in patients with NICD pattern the resultant ST vectors in the horizontal plane were between  $V_2$  and  $V_4$  giving rise to a mean vector pointing toward  $V_3$  (approx.  $75^\circ$ ); in the frontal plane the resultant frontal ST vectors were between  $0^\circ$  and  $(+)130^\circ$ , giving rise to a mean resultant frontal plane ST vector of  $+65^\circ$ . Thus, the resultant 3D space ST vector in patients with NICD pattern pointed to the left, anterior and downward direction, determining the site of latest LV activation in the opposite right posterior and superior location in these patients. This means that according to our preliminary data the right, posterior and superior site of latest LV activation in patients with NICD pattern is almost opposite to the left, inferolateral, posterior location of latest LV activation site in patients with LBBB pattern. Therefore, the current technique of CRT devised for patients with LBBB pattern, when



**Figure 3. The resultant secondary ST vectors in the frontal and horizontal planes and the resultant 3D space secondary ST vectors in patients with LBBB and NICD patterns.** LBBB: left bundle branch block; LBBB-F: resultant frontal plane ST vector in patients with LBBB pattern; LBBB-H: resultant horizontal plane ST vector in patients with LBBB pattern; LBBB-R: resultant 3D space ST vector in patients with LBBB pattern; LV: left ventricle; NICD: nonspecific intraventricular conduction disturbance; NICD-F, NICD-H, NICD-R: the same kind of ST vectors as described above in patients with NICD pattern; RV: right ventricle.

the LV electrode is placed to the inferolateral LV wall a remote site from the potential latest activated LV region in patients with NICD pattern might be one important reason, besides the less dyssynchrony, why less patients are responders with NICD pattern than with LBBB pattern.

### 3 Arguments to support the hypothesis

#### 3.1 The currently applied CRT technique is appropriate only for patients with LBBB pattern

The QRS morphology subgroup analyses of all large randomized CRT trials are significantly biased, because these are based on the unfair comparison of the outcome of CRT devised to correct the dyssynchrony present in LBBB, which may not be appropriate to correct the dyssynchrony present in patients with NICD and RBBB patterns. Thus, the less dyssynchrony, the inappropriate CRT technique and the unfavorable patient characteristics, such as high prevalence of ischemic cardiomyopathy and male gender that adversely affect the CRT response, and not the ECG morphology in itself, are responsible for the worse CRT outcome of patients with non-LBBB pattern.

The ventricular activation patterns were studied quite extensively in patients with LBBB pattern and were also investigated in patients with RBBB pattern.<sup>[17]</sup> However, we know almost nothing about the characteristic ventricular activation pattern(s) in patients with NICD pattern. To the best of our knowledge, there is only one recent study in which the ventricular activation pattern of patients with NICD pattern was investigated in a small patient group ( $n = 15$ ) using electrocardiographic activation mapping.<sup>[18]</sup> The ventricular activation sequence was highly variable, heterogeneous, characteristic activation pattern(s) could not be identified in these patients. The only consistent finding was the presence of fewer and smaller lines of slow conduction in the LV compared with LBBB pattern, which is responsible for less dyssynchrony and shorter QRS duration.<sup>[18]</sup> If we can find characteristic ventricular activation patterns in these patients with the identification of latest activated LV regions, we could devise a more effective CRT technique for this patient subgroup by placing the LV electrode to the latest activated LV region. Thus, selecting patients with non-LBBB pattern only with proven inter- and intraventricular dyssynchrony for CRT and identifying the latest activated LV region in order to place there the LV electrode may improve the outcome of CRT in these patients.

So far complicated and expensive imaging techniques were used to achieve the above goals, such as 3D echocardiography, 2D and 3D speckle tracking echocardiography, cardiac MRI and the novel electrocardiographic activation mapping technique. It was assumed that the standard 12 lead surface ECG other than providing the QRS duration, a rough measure of dyssynchrony, is not able to provide further useful information about the presence or absence of inter- and intraventricular dyssynchrony and the location of the latest activated LV region. There is still no unequivocal evidence that detection of dyssynchrony by imaging techniques is useful in the selection of patients for CRT. The multicenter PROSPECT trial with a 6-month follow up suggested that echocardiographic dyssynchrony indices had an inadequate predictive value to alter the current selection criteria for CRT.<sup>[19]</sup> More recent single center randomized studies however demonstrated that dyssynchrony estimated by speckle tracking echocardiography radial strain, which was not studied in the PROSPECT trial, could predict CRT outcome defined by hard clinical endpoints, and may be useful for patient selection for CRT.<sup>[9,11]</sup> However, it needs to be confirmed in large multicenter randomized studies whether this speckle tracking echocardiography method will be able to predict CRT responder non-LBBB patient with a QRS duration of 120–150 ms.

Although QRS duration is a robust and independent

marker of mortality and morbidity and CRT response irrespective of QRS morphology in heart failure patients,<sup>[7,20]</sup> QRS duration is only a rough measure of dyssynchrony.

## 4 Schedule for testing the hypothesis

### 4.1 Retrospective study

We would like to analyze the characteristic features of ventricular activation patterns retrospectively in 30 patients with heart failure and NICD pattern who underwent an electrophysiological (EP) study, during which electroanatomical mapping was performed. Although heart failure patients with NICD pattern are probably a heterogeneous group in regard to ventricular activation, we might be able to discern a few characteristic ventricular activation patterns and latest activated ventricular region(s). Then we would like to check whether the approximate location of the latest activated ventricular region determined by electroanatomical mapping as a gold standard method can be predicted by the determination of the resultant 3D space secondary ST vector in the 12 lead ECG. If there is a reasonable match between the latest activated ventricular site determined by the two methods, the 3D space resultant ST vector might be used to guide the placement of the LV electrode in these patients.

### 4.2 Prospective study

#### 4.2.1 First phase

We schedule to enroll consecutive patients with heart failure (EF < 40%) and with NICD pattern who will undergo EP evaluation with electroanatomical mapping for some reason (e.g., patients with nonischemic or ischemic cardiomyopathy with ventricular tachycardia) in the prospective study. Post-infarction patients with extensive myocardial scarring, that may significantly alter the sequence of ventricular activation will be excluded. Prior to the EP study a 12 lead ECG is recorded and detailed echocardiography is performed.

##### 4.2.1.1 12 lead ECG

In the 12 lead ECG, we will determine the new ECG criteria serving as surrogate markers of interventricular and LV intraventricular dyssynchrony and the resultant ST vectors in the horizontal and frontal planes and from these latter ST vectors the 3D space resultant ST vector. From the 3D space resultant ST vector, we try to determine the approximate location of the latest activated ventricular region.

##### 4.2.1.2 Echocardiography

During echocardiography in addition to a detailed as-

essment of systolic and diastolic LV function, we estimate the presence of interventricular and LV intraventricular dyssynchrony and determine the latest activated LV region.

To estimate interventricular dyssynchrony, we measure the difference between the QRS onset-LV outflow tract velocity interval and the QRS onset-right ventricular outflow tract velocity interval. If the absolute value of this difference is > 40 ms, it suggests interventricular dyssynchrony. To estimate LV intraventricular dyssynchrony, we determine radial dyssynchrony in the mid parasternal short axis view (at the papillary muscle level) using speckle tracking echocardiography, by measuring the time difference between the maximal radial strain values of the anterior septal and LV posterior wall segments. If this value is > 130 ms, it indicates significant radial (and at the same time LV intraventricular) dyssynchrony.

We also determine the latest activated LV region using speckle tracking imaging. In the basal (at mitral valve level) and mid (at papillary muscle level) parasternal short axis views we evaluate 6–6 segments and in the apical 4 chamber, 2 chamber and 3 chamber (longitudinal) views we evaluate a total of 17 ventricular myocardial segments. In these segments we measure the time intervals from the QRS onset to the maximal circumferential and longitudinal strain values. The segment, which has the longest time interval will be the latest activated segment, which is also well displayed on the color coded bull's eye plot.

##### 4.2.1.3 Comparison of the results obtained by ECG, echocardiography and EP study

We compare the location of the latest activated ventricular region detected by electroanatomical mapping with that estimated by the determination of 3D space resultant ST vector in the ECG and determined by speckle tracking echocardiography. We also compare the sequence of ventricular activation, ventricular activation times and isochrones detected by electroanatomical mapping with the estimation of interventricular and LV intraventricular dyssynchrony by ECG and echocardiography. Ultimately, we will see how accurately the non-invasive methods are able to determine the presence or absence of dyssynchrony and the approximate location of the latest activated LV region. We try to identify characteristic ventricular activation patterns, slow conduction areas and earliest and latest activated ventricular regions by electroanatomical mapping to be able to devise a more effective CRT technique for patients with NICD pattern. If the non-invasive methods prove to be sufficiently accurate to estimate dyssynchrony and the approximate location of the latest activated ventricular region a 2<sup>nd</sup> phase prospective study will be conducted.

### 4.2.2 Second phase

In this phase of the prospective study we plan to enroll heart failure patients with LBBB and NICD patterns selected according to the current guidelines for CRT (patients with heart failure refractory to optimal medical treatment, if no improvement can be expected from other interventions such as coronary revascularization or heart valve surgery, in NYHA functional stage II, III and ambulatory IV, with LVEF  $\leq$  35 %, QRS duration  $\geq$ 120 ms).

In patients with NICD pattern and a QRS duration of 120–150 ms, CRT will be advocated only if the ECG criteria and/or the echocardiographic assessments indicating the presence of either interventricular or LV intraventricular dyssynchrony. The patient is considered an expected R if either ECG criterion indicates a R diagnosis and/or speckle tracking imaging verifies interventricular and/or LV intraventricular dyssynchrony. The patient is considered an expected NR if both ECG criteria indicate a NR diagnosis and/or speckle tracking imaging cannot verify interventricular or LV intraventricular dyssynchrony. In the latter case, CRT will not be performed in patients with NICD morphology and a QRS duration of 120–150 ms. We will assess whether the ECG and echocardiography guided CRT selection of patients with NICD pattern will decrease or not the nonresponder rate in this patient subgroup.

In patients with LBBB pattern we will also investigate how accurately the noninvasive methods can predict the CRT outcome. If the NR diagnosis by the ECG criteria and the absence of dyssynchrony by speckle tracking imaging reliably identify nonresponders, these noninvasive methods might be used in the future to deny CRT for patients with LBBB pattern predicted as NRs by both noninvasive methods. Finally, the comparison of electroanatomical mapping, ECG and echocardiography results in patients with NICD pattern might render possible to devise an innovative CRT technique for these patients and guidance of placement of the LV electrode to the latest activated or adjacent LV region by noninvasive methods.

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