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Response to cardiac resynchronization therapy is determined by intrinsic electrical substrate rather than by its modification☆

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ABSTRACT

Background: Electrocardiographic mapping (ECM) expresses electrical substrate through magnitude and direction of the activation delay vector (ADV). We investigated to what extent the response to cardiac resynchronization therapy (CRT) is determined by baseline ADV and by ADV modification through CRT and optimization of left ventricular (LV) pacing site.
Methods: ECM was performed in 79 heart failure patients (4 RBBB, 12 QRS < 120 ms, 23 non-specific conduction delay [NICD] and 40 left bundle branch block [LBBB]). 67 patients (QRS ≥ 120 ms) underwent CRT implantation and in 26 patients multiple LV pacing site optimization was performed. ADV was calculated from locations/depolarization times of 2000 virtual epicardial electrodes derived from ECM. Acute response was defined as ≥10% LVdP/dt_{max} increase, chronic response by composite clinical score at 6 months.
Results: During intrinsic conduction, ADV direction was similar in patients with QRS < 120 ms, NICD and LBBB, pointing towards the LV free wall, while ADV magnitude was larger in LBBB (117 ± 25 ms) than in NICD (70 ± 29 ms, $P < 0.05$) and QRS < 120 ms (52 ± 14 ms, $P < 0.05$). Intrinsic ADV accurately predicted the acute (AUC = 0.93) and chronic (AUC = 0.90) response to CRT. ADV change by CRT only moderately predicted response (highest AUC = 0.76). LV pacing site optimization had limited effects: +3 ± 4% LVdP/dt_{max} when compared to conventional basolateral LV pacing.
Conclusion: The baseline electrical substrate, adequately measured by ADV amplitude, strongly determines acute and chronic CRT response, while the extent of its modification by conventional CRT or by varying LV pacing sites has limited effects.

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1. Introduction

Cardiac resynchronization therapy (CRT) is now mainstream therapy for the management of symptomatic patients with heart failure with reduced ejection fraction (HF-REF) significant ventricular conduction disorder. Efforts to increase CRT efficacy focus primarily on identifying the correct electrical substrate. This is done by either improving patient selection, or by improving the treatment of the electrical substrate by CRT, mainly by targeting the optimal left ventricular (LV) pacing site [1]. The importance of the baseline electrical substrate has been shown while the added benefit of choosing the optimal LV pacing site is debated. Some studies show that pacing in a large part of the LV lateral wall results in similar CRT response [2] whereas others suggest that the optimal LV pacing site is heterogeneous among patients [3] and could be targeted [4].

Experiments in canine hearts showed that an activation delay vector (ADV) concisely expresses the pattern of electrical asynchrony since it combines the amount and direction of activation delay in 3D [5, 6] and therefore provides a more comprehensive description of the electrical substrate than QRS duration and a more quantitative expression than the qualification LBBB. Electrocardiographic mapping (ECM) is a non-

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invasive high-resolution mapping system with single-beat acquisition which gives comprehensive information of biventricular electrical activation in 3D [7].

The aim of the present study was to 1) derive the ADV from ECM recordings to adequately express the electrical substrate in CRT candidates and 2) investigate the contribution of the baseline electrical substrate and of its modification by CRT (conventional and optimization of LV pacing site) to the acute hemodynamic and chronic clinical response to CRT.

2. Methods

The execution of the study conformed to the principles outlined in the Declaration of Helsinki on research in human subjects. All patients gave written approval to participate in the study, which was approved by the Bordeaux CHU ethics committee.

2.1. Patient population and CRT response

We performed ECM in 79 patients with a wide range of QRS durations and morphologies; New York Heart Association (NYHA) functional class II, III or IV despite optimal medical therapy; and left ventricular (LV) ejection fraction ≤35% during sinus rhythm. A part of the study population was used for earlier work [7, 8]. Heart failure etiology was considered ischemic in the presence of significant coronary artery disease (≥50% stenosis in ≥1 of the major epicardial coronary arteries) and/or a history of myocardial infarction or revascularization. The mean age was 67 ± 10 years; 62 patients (78%) were male, 38 (48%) had an ischemic cardiomyopathy, median NYHA functional class was 3 (range 2 to 4). Mean LV ejection fraction was 29 ± 5%. By analysis of the 12 leads surface ECG, 12 patients had QRS width of <120 ms (narrow-QRS) 40 patients had a left bundle branch block (LBBB) according to AHA/ESC criteria [9], 23 patients a non-specific conduction delay (NICD) and 4 patients a right bundle branch block (RBBB). Patients with QRS complexes ≥120 ms ($n = 67$) underwent CRT device implantation. The right ventricular (RV) lead was systematically implanted at the RV apex while the final position of the LV lead was determined by coronary venous anatomy, good stability, acceptable pacing threshold, and absence of phrenic nerve capture. Biventricular (BIV) pacing was performed in VDD mode with a sensed AV delay of 80 ms and a VV delay of 0 ms. Acute CRT response was defined by a $LVdP/dt_{max}$ (Radi Medical Systems, Uppsala, Sweden) increase by at least 10% compared with baseline AAI pacing. To assess chronic CRT response, we used a clinical composite score that combines changes in clinical status (NYHA functional class) with the occurrence of major clinical events (hospitalization or death) [10]. Patients were considered as clinical responders if, during 6 months of follow-up, they remained alive, did not experience hospitalization for heart failure, and demonstrated an improvement of at least 1 NYHA functional class. This score was previously used in studies evaluating the efficacy of CRT [7, 11].

In a sub-group of 26 patients, the effects of varying LV pacing sites on ADV and acute hemodynamic effects were measured during stimulation of at least 3 LV pacing sites (in multiple coronary veins) during CRT implantation. For each LV pacing location, full LV capture was ensured with pacing output up to 10 V. During the maximal duration of one hour, up to seven LV pacing sites were tested.

2.2. Electrocardiographic mapping

Ventricular activation maps were acquired using a noninvasive high-resolution ECM system (CardioInsight Technologies Inc., Cleveland, OH). As previously described in detail, body surface potentials were recorded from ≈250 electrodes around the entire surface of the torso [7, 8]. A thoracic computed tomography scan was performed with the electrodes attached to the patient. The body surface potentials and computed tomography images were then combined and processed to reconstruct ≈2000 epicardial unipolar electrograms. Ventricular activation times were calculated from the onset of the QRS duration to the maximal negative slope of each unipolar electrogram. Multiple electrical asynchrony indexes were derived from acquired activation maps. The total activation time (TAT) was defined as the duration (in milliseconds) from the earliest to the latest site of ventricular activation. Ventricular electrical uncoupling (VEU) was calculated as the difference between the mean LV and RV activation times (in milliseconds); a positive value reflects LV pre-contraction, whereas a negative value reflects RV pre-contraction [7].

The activation delay vector (ADV) describes the imbalance of ventricular depolarization, or activation delay, in time (by its amplitude) and in space by its direction. ADV calculation was based on invasive mapping experiments in canine LBBB hearts [6]. The ADV was calculated in three steps. First, for every acquired heartbeat, the depolarization times and coordinates of over 2000 virtual electrodes were recorded and exported. Then, for every virtual electrode, the coordinates (X, Y and Z distances from the center of the heart in millimeters) were multiplied by their respective depolarization time (in milliseconds) to create over 2000 subvectors per acquired heartbeat. Finally, all subvectors were summed to create the resulting ADV. An example of the creation of the subvectors and the resulting net ADV is shown in a movie (Supplemental Video 1). The length of the ADV (in milliseconds) expresses biventricular depolarization imbalance in 3D and was used as a measure of electrical substrate. The angle of the ADV (in degrees) was calculated in the frontal plane and in the transversal plane; the center of the LV free wall was used as a reference (0°). A rightward pointing vector was considered as negative.

2.3. Statistical analysis

Categorical variables were expressed as absolute numbers (percentages) and continuous variables were expressed as mean ± SD or median (range). For comparison of baseline characteristics, one-way ANOVA was performed followed by post-hoc Tukey's honestly significant difference test. Comparisons between NICD and LBBB were made using either the Student *t*-test or the Mann-Whitney *U* test, as appropriate. For comparisons of angular parameters, circular statistics was used [12]. As a measure of the ability to predict a positive response by QRS duration, VEU and ADV, receiver-operating characteristic (ROC) curves were generated and areas under the curve (AUCs) were reported with optimal threshold, sensitivity and specificity. We used the nonparametric method for comparing AUCs based on the Mann-Whitney U-statistic for comparing distributions of values from two samples [13, 14]. Statistical analyses were performed using SPSS software, version 18.0 (SPSS Inc., Chicago, Illinois) and the Statistical Analysis of ROC Curves (StAR) tool [14]. Statistical significance was assumed at $P < 0.05$.

3. Results

3.1. Intrinsic conduction

Fig. 1A shows typical activation time maps of HF-REF patients with RBBB, narrow-QRS, NICD and LBBB conduction patterns on the ECG. The RBBB patient shows left-to-right activation while the other patients express right-to-left activation, with vectors similar in direction while significant progression in magnitude. In NICD and LBBB, early RV depolarization is followed by slow conduction over the anterior and posterior wall and delayed activation of the LV free wall. Baseline clinical and mapping characteristics of study participants are shown in Table 1. Compared with the narrow-QRS patients, NICD patients had a longer total activation time, a larger VEU and a larger ADV. LBBB patients had an even longer total activation time, a larger VEU and a larger ADV. While significant differences existed in magnitude of dyssynchrony between narrow-QRS, NICD and LBBB patients, the direction of dyssynchrony was comparable as ADV angles were similar in both the transversal and frontal planes (Table 1). This is further highlighted in Fig. 1B (see Online Supplemental Material for rotating movie) where the ADVs during intrinsic conduction are shown for all 79 patients (RBBB in blue, narrow-QRS in yellow, NICD in red and LBBB in black vectors) in a heart model in the frontal plane (left panel) and transversal plane (right panel). A high similarity in ADV angles in the transversal and frontal planes is shown between narrow-QRS, NICD and LBBB patients, mainly pointing towards the LV free wall.

3.2. Biventricular pacing and acute hemodynamic response

Fig. 2A shows activation time maps of a patient with LBBB during intrinsic conduction (left panel) and BIV-pacing at the RV apex and LV lateral base (right panel). During BIV-pacing, opposing wave fronts are seen from the RV and LV pacing locations, which fuse and resynchronize the ventricles, the resulting ADV points towards the base and towards the left. The effect of resynchronization is also shown by the shorter amplitude of the ADV; 66 ms as compared with 130 ms during LBBB.

In all patients, the global direction of ADV during BIV-pacing was towards the base and towards the left. ADV length and angle during BIV-pacing were not significantly different between NICD patients (69 ± 26 ms) and LBBB patients (71 ± 22 ms, P=NS), indicating that the electrical substrate at baseline does not determine electrical activation during CRT. While CRT was electrically similar, there were significant differences in CRT response. NICD patients had an average $LVdP/dt_{max}$ increase of 1 ± 12% while the LBBB patients expressed an average increase of 16 ± 9% ($P < 0.05$).

In the 57 CRT patients with invasive measurements, ADV magnitude during intrinsic conduction accurately predicted acute CRT response with area under the ROC curve (AUC) of 0.93, significantly better than QRS duration (AUC 0.76, $P < 0.05$, see also Supplemental Table 1). ADV magnitude (or any other electrical parameter) during BIV-pacing and its change from baseline did not predict acute clinical response (AUC

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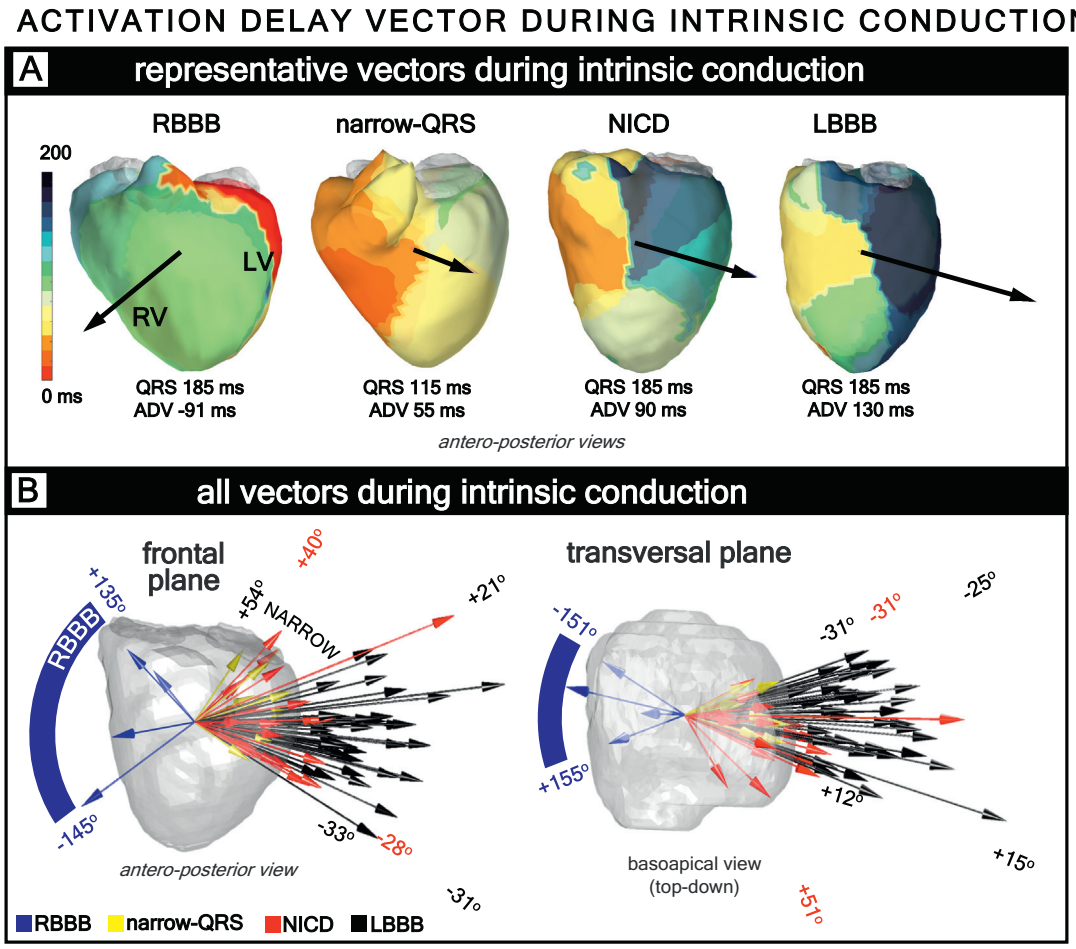


Fig. 1. A] Electrocardiographic activation time maps with activation delay vector (ADV) during intrinsic conduction in four systolic heart failure patients with right bundle branch block (RBBB), narrow-QRS complex, non-specific intraventricular conduction delay (NICD) and left bundle branch block (LBBB). B] Activation delay vectors during intrinsic conduction of all 79 patients plotted in a cardiac model (left panel: frontal plane with antero-posterior view, right panel: transversal plane with basoapical view). Blue vectors represent RBBB patients, yellow vectors narrow-QRS patients, red vectors NICD patients and black vectors represent LBBB patients. For each group, the range in vector angles is limited with large agreement between patients with narrow-QRS, NICD and LBBB. LV = left ventricle. RV = right ventricle. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

of 0.53 and 0.66, respectively). The ROC curves for the different diagnostic entities are also shown in Supplemental Fig. 1.

3.3. LV pacing site optimization

In Fig. 2B all 104 tested LV pacing sites from all 26 patients combined are represented on one epicardial biventricular surface (from the first patient). A median of 4 [2–6] LV pacing sites per patient were tested. LV pacing sites were more likely to be basal than apical. The lateral base was accessible from different veins.

Fig. 3 shows that the change in LV$dP/dt_{max}$ varied more *between* patients than *within* patients, indicating the dominant effect of patient selection. Average change in LV$dP/dt_{max}$ (during CRT as compared with baseline) *between* patients ranged from −16% to +35%. Patients with absence of scar, presence of LBBB, QRS ≥150 ms and/or ADV ≥95 ms were more likely to have higher improvements in LV$dP/dt_{max}$. The differences *within* patients, induced by changing the LV pacing site, were limited, with an average range of 11% per patient. The optimal LV pacing site added on average 3 ± 4% LV$dP/dt_{max}$ ($P < 0.01$) to the LV pacing site closest to the lateral base (conventional site). In only 6 out of 26 patients (23%), one or more alternative LV pacing sites resulted in a LV$dP/dt_{max}$ increase ≥10% while LV pacing at the lateral base resulted in a LV$dP/dt_{max}$ increase <10%. In line with these results, ECM during LV optimization was unable to predict the LV pacing site which resulted in optimal acute hemodynamic response. For instance, the LV pacing site which resulted in the shortest ADV (51 ± 17 ms; most effective electrical resynchronization) did not result in higher LV$dP/dt_{max}$ when compared to the conventional basolateral LV pacing site (average increase in LV$dP/dt_{max}$ + 10 ± 13% versus +11 ± 14% respectively, *P*=NS).

3.4. Prediction of 6-month clinical response

Six-month follow-up data was successfully acquired in 55 out of 67 CRT patients of which 36 (66%) patients were clinical responders. While 89% of LBBB patients responded to CRT, only 37% of NICD patients showed clinical response ($P < 0.05$). The presence of LBBB predicted clinical response with a sensitivity of 78% and a specificity of 79% (Supplemental Table 2). QRS duration had a lower specificity (68%, $P < 0.05$ versus LBBB morphology). Baseline ADV magnitude also outperformed QRS duration with AUC 0.90 ($P < 0.05$ versus QRS duration) with sensitivity 83% and specificity 90%. Using ADV only two out of 55 patients were incorrectly predicted to become responders. While ADV magnitude during intrinsic conduction performed well, delta ADV (% change from intrinsic to CRT) was moderately predictive (AUC 0.76, $P < 0.05$) and ADV magnitude during CRT was not predictive for response (AUC 0.53). ADV direction (tested separately in the transversal, frontal and sagittal planes) during intrinsic conduction, its change from intrinsic to CRT or its values during CRT were also not predictive for response (AUC below 0.60 for all angular parameters).

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Table 1
Baseline characteristics of study participants grouped per conduction abnormality (RBBB, narrow-QRS, NICD and LBBB) showing data for clinical and electrocardiographic mapping parameters.

	RBBB [$n = 4$]	Narrow-QRS [$n = 12$]	NICD [$n = 23$]	LBBB [$n = 40$]
Clinical parameters				
Age [years]	72 ± 12	64 ± 11	67 ± 10	67 ± 10
Male sex	4 (100%)	11 (92%)	16 (76%)	31 (78%)
Ischemic heart disease	4 (100%)	6 (50%)	14 (67%)	14 (35%)
LV ejection fraction [%]	33 ± 5	27 ± 5	27 ± 5	29 ± 5
New York Heart Association class	2.8 ± 0.5	2.7 ± 0.5	2.6 ± 0.6	2.5 ± 0.7
QRS width [ms]	168 ± 11	106 ± 13	140 ± 19*	165 ± 17*†
Electrocardiographic mapping				
Total activation time [ms]	111 ± 27	68 ± 17	99 ± 25*	137 ± 19*†
Ventricular electrical uncoupling [ms]	−36 ± 12	26 ± 12	34 ± 32*	76 ± 12*†
ADV length [ms]	−62 ± 19	52 ± 14	70 ± 29*	117 ± 25*†
ADV angle in transversal plane [°]	179 ± 22	−7 ± 14	4 ± 18	−6 ± 11
ADV angle in frontal plane [°]	168 ± 41	15 ± 25	3 ± 25	−5 ± 11

ADV = activation delay vector. Means ± SD are shown with either percentages or range.
* $P < 0.05$ compared with narrow QRS.
† $P < 0.05$ compared with NICD.

4. Discussion

In this largest electrocardiographic mapping study in heart failure patients to-date, we show that the ADV of patients with narrow-QRS, NICD and LBBB is very similar in direction while significant differences exist in its magnitude. The intrinsic ADV is an excellent predictor of both acute and chronic CRT response. ADV during intrinsic conduction was in fact the key component for CRT response while its modification by conventional CRT or by varying LV pacing sites plays a limited role.

4.1. Intrinsic electrical substrate is key component for CRT response

The electrical substrate of a CRT candidate is commonly described using surface-ECG parameters such as QRS duration and morphology. While we confirmed that the presence of LBBB is a strong predictor for CRT, cardiac mapping provides a more detailed description of the electrical substrate. We chose ECM since it is a non-invasive high-resolution mapping system with single-beat acquisition. Derived from ECM, the ADV provides a summary of the activation sequence of the electrical substrate in 3D. Non-contact mapping systems such as ECM, are associated with a degree of error in its ability to reproduce electrograms on the cardiac surface as compared to direct contact mapping. While the exact amount of error is not known for ECM, the slow conducting ventricular depolarization in our study patients combined with the design of the ADV which balances out much of the possible heterogeneous inadequacies leads us to believe that the ADV accurately describes electrical asynchrony. This assumption is strengthened by the high diagnostic potential of the ADV to predict acute and chronic response. We revealed that the direction of activation delay was similar between patients while significant differences existed in its magnitude. This combination signifies that it is in fact the extent of right-to-left activation delay which separate patients from each other and identifies responders. We established this observation with the excellent ability of the ADV magnitude during intrinsic conduction to predict acute and chronic CRT response. ADV had higher AUC as compared to QRS duration and tended to show higher specificity than QRS morphology. This may be explained by the fact that the ADV magnitude more carefully describes the spatial and temporal imbalance of electrical activation

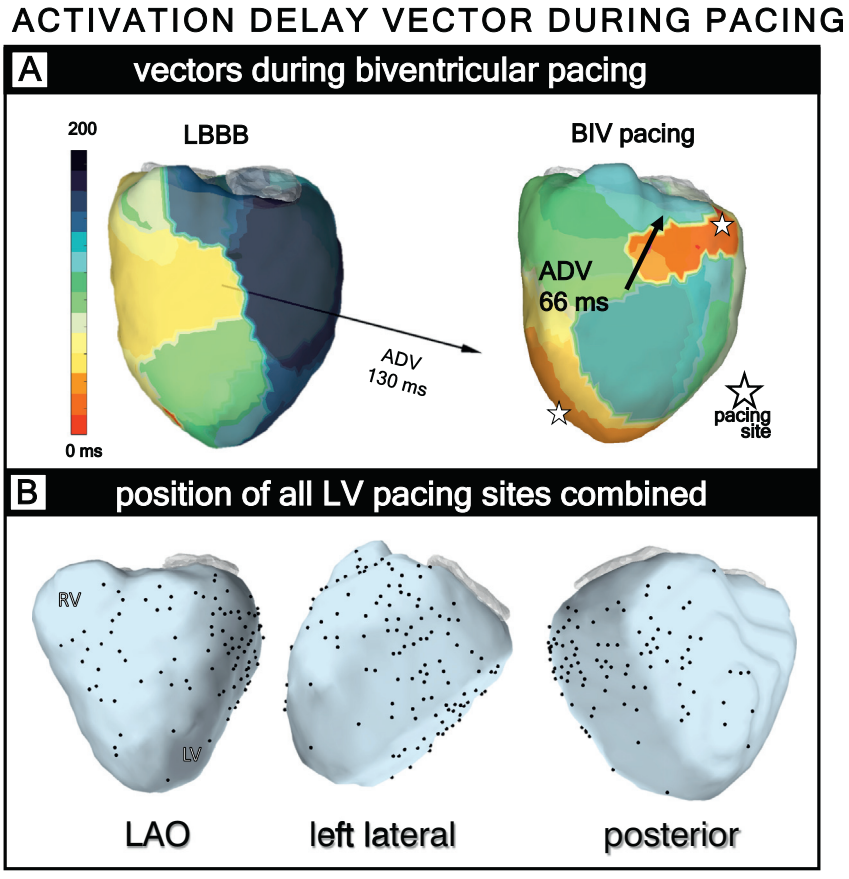


Fig. 2. A] Examples of activation time maps with activation delay vectors in a patient with LBBB during intrinsic conduction and BIV-pacing. B] Epicardial biventricular model which shows the position of all 104 LV pacing sites of all patients combined. LAO: left anterior oblique. LV: left ventricle. RV: right ventricle. Mitral valves are shown as transparent structures.

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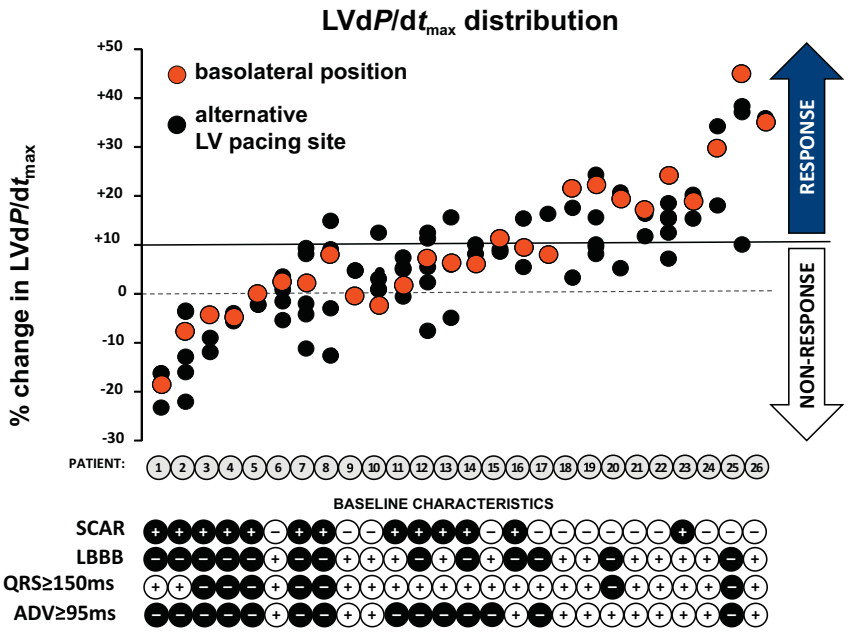


Fig. 3. Percent change in LVdP/dt_{max} is shown for every patient in which multiple LV pacing sites were tested with basolateral LV pacing site in red. Patients were sorted according to their average change in LVdP/dt_{max}. A selection of baseline characteristics is shown for every patient (presence of scar, LBBB, QRS ≥150 ms, ADV ≥95 ms). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

within the biventricular myocardium. As compared to QRS duration the ADV provides both the extent and direction of dyssynchrony. As compared to QRS morphology (e.g. LBBB vs. non-LBBB) ADV is less prone to subjectivity, more quantitative and provides a continuous value. It seems that it is the improved description of the right-to-left delay which renders the ADV superior to QRS duration to predict acute and chronic CRT response.

4.2. Varying LV pacing site plays a limited role

The ability of ECM to adequately identify CRT responders *before* pacing the heart already implies that the extend of modification of the electrical substrate, by conventional CRT and by varying LV pacing sites, can only play a limited role. Our results demonstrate that selecting patients with sufficient pre-existing right-to-left activation delay is key to CRT response and patients with LBBB best fit this criterion. While the notion that correct electrical substrate needs to exist for CRT to be successful is well established in the guidelines, the importance of optimizing CRT remains controversial [15]. In our study, ADV magnitude during CRT did not predict acute or chronic response and while the ADV decrease created by CRT is moderately predictive, it is dependent of the value during intrinsic conduction (a larger baseline value coincides with a larger change by CRT). A recent body-surface mapping study using an electrode belt postulated that the amount of decrease in electrical dyssynchrony by CRT is predictive of the optimal LV pacing site [4]. In that study, the LV pacing site which showed most reduction in standard deviation of biventricular activation times resulted in the largest increase in LVdP/dt_{max} or within 5% of this optimum in 35 of 40 patients (88%). This percentage was comparable in the present study-population (21 of 25 patients, 81%). However, the 3 ± 4% increase in LV dP/dt_{max} when moving from the custom implant site to the optimal one indicates the relatively small effect of pacing site, especially considering the variability in hemodynamic variables [16].

4.3. Clinical implications

Our results indicate that to reach highest CRT efficacy, the intrinsic electrical substrate needs to be correctly identified. This can be done using surface-ECG parameters such as QRS duration or the existence of LBBB morphology, but higher accuracy is acquired using electrocardiographic mapping (specifically the extent of right-to-left delay). Even when only "intermediate" patients were analyzed (patients who do not receive class IA recommendation for CRT implantation which are NICD patients and LBBB patients with QRS <150 ms), diagnostic accuracy remains high (specificity 82%, sensitivity 78%). Our results give rise to the reassuring notion that since intrinsic electrical substrate defines CRT response, a conventional pacing strategy targeting the LV basolateral wall is justified. We do not advocate that CRT optimization should not be attempted, but when the majority of response is determined before implantation, the effects of optimization are expected to be relatively small and therefore difficult to demonstrate.

4.4. Study limitations

The number of patients included in this study is modest. However, this is the largest study to date of detailed mapping of electrical activation abnormalities in heart failure patients. Our results apply to conventional CRT using LV pacing electrode in an epicardial LV vein while novel approaches such as endocardial [5, 17], transseptal [18, 19], multi-site [20, 21] or multipoint [22] LV pacing may influence the relation between importance of the electrical substrate and its modification by CRT. Also, LV pacing site optimization was only assessed by hemodynamical parameters which are not necessarily translatable to clinical outcome. We were not able to investigate the role of presence and location of myocardial infarction on LV pacing site since we possessed insufficient cardiac magnetic resonance imaging data.

5. Conclusion

In HF-REF patients, the activation delay vector is similar in direction though its magnitude varies greatly while greatest in LBBB patients. The intrinsic right-to-left activation delay determines response to CRT while the extent of its modification by conventional CRT or by varying LV pacing site plays a minor role on acute hemodynamic response.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.06.005.

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Conflict of interest

The authors report no conflicts of interest.

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