Cardiac electrical dyssynchrony is accurately detected by noninvasive electrocardiographic imaging

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BACKGROUND Poor identification of electrical dyssynchrony is postulated to be a major factor contributing to the low success rate for cardiac resynchronization therapy. OBJECTIVE The purpose of this study was to evaluate the sensitivity of body surface mapping and electrocardiographic imaging (ECGi) to detect electrical dyssynchrony noninvasively. METHODS Langendorff-perfused pig hearts (n = 11) were suspended in a human torso-shaped tank, with left bundle branch block (LBBB) induced through ablation. Recordings were taken simultaneously from a 108-electrode epicardial sock and 128 electrodes embedded in the tank surface during sinus rhythm and ventricular pacing. Computed tomography provided electrode and heart positions in the tank. Epicardial unipolar electrograms were reconstructed from torso potentials using ECGi. Dyssynchrony markers from torso potentials (eg, QRS duration) or ECGi (total activation time, interventricular delay [D-LR], and intraventricular markers) were correlated with those recorded from the sock. RESULTS LBBB was induced (n = 8), and sock-derived activation maps demonstrated interventricular dyssynchrony (D-LR and total activation time) in all cases (P < .05) and intraventricular dyssynchrony for complete LBBB (P < .05) compared to normal sinus rhythm. Only D-LR returned to normal with biventricular pacing (P = .1). Torso markers increased with large degrees of dyssynchrony, and no reduction was seen during biventricular pacing (P > .05). Although ECGi-derived markers were significantly lower than recorded (P < .05), there was a significant strong linear relationship between ECGi and recorded values. ECGi correctly diagnosed electrical dyssynchrony and interventricular resynchronization in all cases. The latest site of activation was identified to 9.1 ± 0.6 mm by ECGi.

CONCLUSION ECGi reliably and accurately detects electrical dyssynchrony, resynchronization by biventricular pacing, and the site of latest activation, providing more information than do body surface potentials.

KEYWORDS CRT; Electrocardiography; ECGi; LBBB; Noninvasive electrocardiographic imaging

Introduction

Cardiac resynchronization therapy (CRT) is as an established treatment in patients with heart failure with severely impaired ejection fraction and conduction abnormalities, significantly reducing mortality and morbidity.1,2 The recommended selection criteria are currently based on the 12-lead electrocardiogram (ECG): prolonged QRS duration (QRSd) and/or left bundle branch block (LBBB) morphology.3 However, approximately one-third of patients show no response to CRT,2 likely owing to insufficient electrical dyssynchrony before CRT or persistent electrical dyssynchrony afterward.4 This points to an inadequate ability to detect and quantify electrical dyssynchrony using QRSd and QRS morphology.

Noninvasive electrocardiographic imaging (ECGi) has been developed to provide high-resolution imaging of epicardial activation.5 ECGi has been used previously to characterize conduction abnormalities in patients amenable to CRT and to optimize biventricular (BiV) pacing.4,6–11 From these studies, intraventricular electrical dyssynchrony, defined as inhomogeneous left ventricular (LV) activation, and interventricular electrical dyssynchrony, defined as activation delay between the LV and the right ventricle...
(RV), were considered predictors for CRT response. Markers have been developed to quantify intraventricular and interventricular electrical dyssynchrony, and the initial results suggest that they are better predictors than traditionally used QRSd and QRS morphology.\textsuperscript{6–11} ECGi has been assumed to provide accurate detection of electrical dyssynchrony according to previous validation studies in healthy hearts during pacing.\textsuperscript{12,13} However, the reconstruction of activation maps in the presence of electrical dyssynchrony and the accuracy of electrical

**Figure 1** Experimental and postprocessing workflow. **A:** Torso-tank experimental setup with Langendorff perfused pig heart. **B:** Representative ablation lesions. **C:** Three-dimensional fluoroscopy scan of (left) full torso and (right) segmented tank (red) and sock (yellow) electrodes. **D:** Epicardial potentials were reconstructed using ECGi. Derived ATs and electrical dyssynchrony markers were compared to sock recordings. AT = activation time; ECGi = electrocardiographic imaging; LV = left ventricle; RV = right ventricle.
dysynchrony markers have not been evaluated experimentally. Furthermore, it is not clear whether the level of precision provided by ECGi is required or whether electrical dysynchrony can be accurately detected directly from body surface potentials.\textsuperscript{14,15}

The objective of this study was to evaluate the sensitivity of body surface mapping or ECGi to detect electrical dysynchrony of various degrees.

**Methods**

Detailed methods are available in the Supplement.

**Ex vivo experimental data**

Hearts were excised from pigs (n = 11; 30–40 kg) as approved by Directive 2010/63/EU of the European Parliament on the protection of animals used for scientific purposes and the local ethics committee. Hearts were perfused in Langendorff mode with a 1:9 mixture of blood and Tyrode’s solution oxygenated with 95%/5% O\textsubscript{2}/CO\textsubscript{2} (pH 7.4, 37°C). An epicardial electrode sock (108 electrodes) was attached to the ventricles and bipolar pacing leads to the RV apex and posterolateral LV epicardial free wall. An ablation catheter tip was placed in the LV and stitched over the bundle of His to allow some maneuverability.

After instrumentation, perfusion was changed to 100% Tyrode’s solution and the heart was transferred to a human-shaped torso tank (Figure 1A). LBBB was induced by 2–5 local radiofrequency ablation procedures (25–30 W; 30–60 seconds) (Figure 1B). Tank (128 electrodes) and sock potentials were recorded simultaneously (BioSemi, The Netherlands) during sinus rhythm (SR) after ablation and during LV, RV, and BiV pacing in VOO mode. Afterward, computed tomography (Artis, Siemens, Germany) was used to obtain the positions of the epicardium and electrodes with respect to the tank (Figure 1C).

** Definitions and markers for electrical dyssynchrony**

LBBB was defined when SR-recorded activation maps showed (1) epicardial breakthrough on the RV with rapid RV activation, (2) no LV breakthrough, and (3) late activation of the LV from the septum. These activation patterns are consistent with previous LBBB epicardial mapping studies in humans.\textsuperscript{7,16,17} The degree of LBBB was considered mild or incomplete if QRS\textsubscript{d} increase was <40%.

Epicardial activation times (ATs) were derived from recorded electrograms at the moment of the minimum derivative (dV/dt) and from ECGi-derived signals by fitting a global activation field to activation delays between electrograms.\textsuperscript{15} *Time to RS downslope* was defined as the time from QRS onset to the minimum dV/dt.\textsuperscript{15} Electrical dyssynchrony markers were derived from epicardial electrograms (recorded or ECGi-derived) and tank potentials (defined in Table 1). In addition, the recorded and ECGi-derived sites of latest activation were compared.

**ECGi reconstruction and comparison**

Electrograms were reconstructed from tank potentials to experiment-specific epicardial surfaces derived from computed tomography (Figure 1D) using ECGi methods used clinically.\textsuperscript{21,22} Electrical dyssynchrony markers and ATs derived from ECGi were compared with those recorded with the sock using root mean square error (RMSE), the RMSE of the linear regression residuals (S\textsubscript{Res}), and Pearson correlation coefficient (R). *Localization error of the site of latest activation* was defined as the Euclidean distance between sock electrodes demonstrating the latest AT in recorded and ECGi-derived signals.

Statistical analysis was conducted using SAS University Edition Studio 4.3. Normality was tested using the Shapiro-Wilk test. For each metric, the significance of differences between sequence types was tested using a 1-way analysis of variance. A repeated-measures analysis of variance was used to determine differences between recorded and ECGi-derived metrics, accounting for possible interaction with sequence type. For $P < .05$, the source of the difference was sought using a matrix of mutually orthogonal contrast vectors. Data are expressed as mean ± SD.

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**Table 1** Electrical dyssynchrony markers derived from sock and torso potentials

<table>
<thead>
<tr>
<th>Sock markers\textsuperscript{7–11,19} (recorded and ECGi-derived markers were compared)</th>
<th>D-LR</th>
<th>Difference in mean activation between the LV and RV free wall (positive value reflects LV delay relative to RV delay)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAT</td>
<td>Difference between maximum and minimum epicardial ATs</td>
<td></td>
</tr>
<tr>
<td>LVTAT</td>
<td>Difference between maximum and minimum ATs of the LV epicardium</td>
<td></td>
</tr>
<tr>
<td>SD-LVAT</td>
<td>Standard deviation of ATs on the LV epicardium</td>
<td></td>
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<tr>
<td>QRS\textsubscript{d}</td>
<td>QRS duration estimated manually with calipers from the 3 limb leads as recommended by the guidelines\textsuperscript{15}</td>
<td></td>
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<tr>
<td>LV-RS\textsuperscript{14,15}</td>
<td>Average time from QRS onset to RS downslope for torso electrodes closer to the LV than the RV (defined by the Euclidean distance) (as a measure of late LV activation)</td>
<td></td>
</tr>
<tr>
<td>SD-RS\textsuperscript{15}</td>
<td>Standard deviation of the time to RS downslope for all torso electrodes (as a measure of interventricular electrical dyssynchrony)</td>
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</tr>
</tbody>
</table>

\textsuperscript{AT} = activation time; D-LR = interventricular delay; ECGi = electrocardiographic imaging; LV = left ventricle/ventricular; RV = right ventricle/ventricular; TAT = total activation time.
Results
Of the 11 experiments, normal SR was recorded before ablation in 4 hearts (defined as control). LBBB was induced in 8 hearts (1 heart had both control and LBBB states). For 5 of the 8 LBBB hearts, electrical dyssynchrony was substantially augmented through further ablation and a second SR recording was analyzed. Pacing sequences were analyzed for final state LBBB hearts.

Markers for dyssynchrony derived from recordings
Figure 2A presents representative recorded SR activation maps in control (left) and with increasing degrees of LBBB (middle and right). In control, multiple epicardial exit sites are seen with the majority of the subepicardial myocardium activating simultaneously (short total activation time [TAT]) (Figure 2B). In mild LBBB (middle), the activation map shows early breakthrough on the RV and late activation over the LV or interventricular electrical dyssynchrony (Figure 2B). Despite the increase in TAT, no intraventricular electrical dyssynchrony was present, with LVTAT similar to control (cf Figure 2B, left to middle). With an increased degree of LBBB (right), the TAT, interventricular delay [D-LR], and LVTAT increased.

In Figure 2C, histogram of time to RS derived from torso electrodes are presented with the corresponding lead I. Mild LBBB (middle) did not cause increased QRSD or LV-RS compared to control (left), although both are increased with complete LBBB (right). The interventricular dissociation of ATs seen in mild LBBB was not replicated by time to RS between the left and right torso (Figure 2B vs Figure 2C, middle).

Figure 3A presents recorded activation maps from the complete LBBB heart (Figure 2, right) during RV (left), LV (middle), and BiV (right) pacing. In RV pacing, propagation was similar to complete LBBB-SR with a large interventricular dissociation of activation (Figure 3B), although spread across the RV and LV free wall was slower. LV
pacing reversed the interventricular dyssynchrony with early activation on the LV, terminating on the RV. During BiV pacing, activation spread from both pacing sites, with latest activation over the epicardial aspect of the septum. While there was no interventricular AT dissociation (see overlapping red and green bars in Figure 3B), activation spread was slow compared to control-SR (Figure 2C). The dispersion of time to RS recorded from the body surface was similar to complete LBBB-SR during RV pacing (Figure 3C, left), while for LV and BiV pacing (Figure 3C, middle and right), the time to RS was now later on the right torso.

Figure 4 presents box plots of torso and epicardially derived electrical dyssynchrony markers during control-SR, LBBB-SR, and LBBB-BiV pacing. Supplemental Table 1 summarizes these markers for all sequence types. Torso-derived markers (Figures 4A–4C) were significantly increased with LBBB-SR compared to control-SR ($P < .04$), with no difference compared to LBBB-SR values ($P > .39$). Intraventricular electrical dyssynchrony markers (LVTAT and SD-LVTAT) (Figures 4F and 4G) did not increase in LBBB-SR except with larger levels of interventricular dyssynchrony (D-LR > 25 ms and TAT > 65 ms).

During LBBB-BiV pacing, QRSd, LV-RS, and SD-RS were significantly larger than control-SR ($P < .04$), with no difference compared to LBBB-SR values ($P > .39$). Interventricular electrical dyssynchrony present in LBBB-SR was rectified with BiV pacing ($P > .0001$), indicated by $|\text{D-LR}| < 20$ ms and no difference compared to control values ($P = .89$). TAT showed no change ($P = .39$), while LVTAT and SD-LVAT increased with BiV pacing ($P < .02$). All 3 markers were longer than control values ($P < .02$).

**ECGi activation maps**

Figure 5A shows recorded (left) and ECGi-derived (right) activation maps for 2 LBBB hearts in SR. In both hearts,
recorded maps showed typical LBBB patterns with early rapid activation of the RV and late-activated LV. ECGi correctly reproduced this here and in all other cases of mild and severe LBBB. ECGi in heart 2 (but not in heart 1) presented U-shaped activation around a line of block (very dense isochrones) on the anterior epicardial aspect of the septum that was not recorded. This septal crowding of isochrones was observed in 5 of 13 cases.

Overall, the site of latest activation was identified to $9.1 \pm 0.6$ mm (Figure 5B), that is, to the correct electrode in 2 hearts (0 mm), within 1 electrode spacing in 7 hearts (5–14 mm), and within 2 electrodes for the rest (14–17.8 mm).
Figure 6 shows the comparison between ECGi-derived and recorded ATs under various conditions. Overall, the overall correlation was high and residuals were low ($R^2 = 0.68 \pm 0.25$; RMSE $= 13.4 \pm 5.3$ ms; $S_{Res} = 11.4 \pm 3.7$ ms). $R$ was lower in control-SR and BiV pacing than in other sequences ($P < .001$). $S_{Res}$ was lower in SR than in any pacing modality ($P < .001$). There was no difference in RMSE between any sequence type ($P = .3$).

Figure 5  

A: (Left) Recorded and (right) ECGi-derived activation maps for 2 LBBB-SR hearts. B: Scatter and box plot for localization error of the site of latest activation (n = 13; LBBB-SR). AT = activation time; ECGi = electrocardiographic imaging; LBBB = left bundle branch block; LV = left ventricle; RV = right ventricle; SR = sinus rhythm.

**ECGi-derived markers for dyssynchrony**

Figures 4D–4F show that as with recorded values, ECGi showed a significant increase in TAT and D-LR with LBBB-SR compared to control-SR ($P < .03$). Recorded LVTAT and SD-LVAT showed an increase in 60% and 80% of all LBBB-SR cases. ECGi captured this increase with a sensitivity of 83% and 100% and a specificity of 56% and 33%, respectively.
As with recorded values, ECGi-derived TAT during BiV pacing was not significantly different to in LBBB-SR ($P = .72$). ECGi-derived D-LR was significantly reduced ($P < .0001$) and, like recorded values, showed effective electrical interventricular resynchronization, with no significant difference compared to control ($P = .10$). ECGi replicated the difference in LVTAT and SD-LVAT between control-SR and BiV pacing seen with recorded values.
though, unlike recorded data, no significant difference was seen compared to equivalent LBBB-SR values ($P = .09$).

Bland-Altman plots of recorded and ECGi-derived markers are presented in Figure 7. ECGi-derived TAT and SD-LVAT showed high RMSE (21 and 4.2 ms, respectively), although there was a strong correlation and low regression error ($S_{Res}$) compared to recorded values. Overall, ECGi underestimated TAT and SD-LVAT ($P < .04$), as seen with the positive mean difference line (Figures 7A and 7D). For D-LR, there was a significant interaction with sequence type ($P < .0001$), with ECGi underestimating D-L-R more the greater the dyssynchrony. This was seen with the positive trend in error between ECGi-derived and recorded values (Figure 7B). Furthermore, the relationship between ECGi-derived and recorded values was strong ($R = 0.95$) with low $S_{Res}$. Although the ECGi-derived LVTAT was neither significantly longer nor shorter than the recorded value ($P = .56$), the relationship was the weakest ($R = 0.66$) and $S_{Res}$ similar to TAT.

**Discussion**

Several markers have been developed to quantify electrical dyssynchrony between the ventricles (interventricular) or within the LV (intraventricular) using either body surface potentials\textsuperscript{14,15} or ECGi.\textsuperscript{6–11} It has largely been assumed that each of these metrics can accurately detect both small and large degrees of electrical dyssynchrony. ECGi is further assumed to provide accurate reconstruction of activation
patterns in the presence of electrical dyssynchrony,\textsuperscript{4,6,7,9–11} partially justified by previous studies evaluating the performance of ECGi to detect activation and stimulus sites from healthy hearts during pacing.\textsuperscript{12,13} In addition, the accuracy of the detection of late (as opposed to early) activated sites with ECGi has never been evaluated.

Our study has evaluated the accuracy of body surface potentials and ECGi-derived markers to detect electrical dyssynchrony with varying degrees of LBBB. The main results from our study are summarized as follows. Body surface markers (LV-RS and SD-RS) provide no higher sensitivity to the degree of dyssynchrony than does QRSd in LBBB. Epicardial markers are sensitive to electrical dyssynchrony, and the combination of interventricular and intraventricular markers provide important information about electrical activation not provided by QRSd. ECGi can be applied to reliably and noninvasively provide these markers, activation patterns, and the site of latest activation.

Detection of electrical dyssynchrony from body surface potentials

Recent studies have suggested that by expanding the 12-lead ECG to 53-electrode body surface mapping, electrical dyssynchrony can be better diagnosed by LV-RS and SD-RS without the need for complex ECGi.\textsuperscript{14,15} Our study shows that LV-RS, SD-RS, and QRSd were less sensitive than ECGi-derived markers. Specifically, ECGi-derived D-LR showed an increase for all LBBB cases, while QRSd, SD-RS, and LV-RS were within the control range for several mild LBBB cases. None of the body surface–derived markers showed an improvement with BiV pacing to give indication of resynchronization. Thus, ECGi adds significantly to the diagnostic and therapeutic potential in cases of LBBB, although the technique is more time-consuming and requires cardiothoracic imaging and segmentation.

The added value of LV-RS and SD-RS is explained by the fact that each torso lead contains information of the entire heart, weighted heavily toward the closest ventricle. As expected, the time to RS on the left and right torso gave a blurred reflection of their respective ventricular ATs (Figures 2 and 3). This means the time to RS can give some indication of the directionality of electrical dyssynchrony, but ECGi would still provide a more precise image of the mechanisms involved.

A theoretical limitation of LV-RS and SD-RS is ambiguity in marker placement on the steepest RS downslope (according to previous studies\textsuperscript{14,15}) in LBBB and during BiV pacing because of the tendency of ECGs to have slurred, notched, or irregular RS slopes (Figure 1D).

Epicardial electrical dyssynchrony markers

Our results have shown that epicardial electrical dyssynchrony markers can not only identify minor interventricular electrical dyssynchrony (D-LR as low as 15 ms) but also provide important information that is not provided by QRSd. With mild LBBB, LV activation was rapid (LVTAT and SD-LVT similar to control), though delayed with respect to the RV (increase in D-LR and TAT). This is likely due to partially blocked conduction through the main fascicles of the left bundle branches (possibly equivalent to incomplete LBBB or intraventricular conduction delays in humans). LV activation was more slowed with an increased degree of LBBB (increased LVTAT and SD-LVTAT), attributed to failed conduction via all the left Purkinje branches (complete LBBB). Thus, the application of multiple epicardial electrical dyssynchrony markers helps to delineate the various degrees of both inter- and intraventricular electrical dyssynchrony.

While the heart was electrically resynchronized with BiV pacing (D-LR substantially reduced), myocardial activation was slow compared to control-SR, as shown by TAT, LVAT, and SD-LVAT remaining similar to their corresponding values in LBBB-SR. These markers paradoxically increased in some cases. Our observations suggest that in the absence of complete Purkinje activation after pacing, the myocardial conduction velocity is insufficient to provide normalization of synchronization, even in the presence of BiV pacing. This supports the idea that CRT is effective only when considerable electrical dyssynchrony is present during intrinsic activation.\textsuperscript{4} Previous studies have demonstrated a hemodynamic CRT response with both reduction\textsuperscript{8} and increase\textsuperscript{10} in ECGi-derived dyssynchrony markers. Potential thus exists to further improve resynchronization therapy if methods can be developed to ensure resynchronization. Multisite and/or endocardial pacing may further improve not only interventricular but also intraventricular resynchronization, although the additional benefit on hemodynamic function remains questionable.\textsuperscript{23}

Accuracy of ECGi for describing electrical dyssynchrony

With direct comparison of ECGi and recorded electrical dysynchrony markers (Figure 7), we demonstrated that ECGi successfully reconstructed the presence of electrical dyssynchrony and resynchronization through pacing. Of all the electrical dyssynchrony markers, D-LR was most accurately reconstructed. The variability seen in the correspondence of ECGi-derived to recorded markers is likely the result of 2 known shortcomings of ECGi. First, ECGi tends to reduce the overall AT dispersion.\textsuperscript{24} This is seen directly with TAT results and has likely influenced the accuracy of LVTAT. Second, a heterogeneous spatial mismatch often exists between ECGi and recorded electrograms and thus ATs.\textsuperscript{25} This spatial shift is generally small but important for LVTAT, SD-LVAT, and D-LR, which are derived from ATs within specific regions of the heart.

Inaccuracy of ECGi-derived ATs is not always a cause for electrical dyssynchrony marker inaccuracy. Although ECGi-derived activation patterns correlated poorly with those recorded during control-SR in this study ($R = 0.17 \pm 0.37$), ECGi reproduced the relatively simultaneous activation over both ventricles, and short activation dispersion, resulting in accurate electrical dyssynchrony markers. There is
Comparison with previous clinical studies of ECGi and LBBB

This study corroborates the results of several previous clinical studies using ECGi in CRT candidates. For example, in agreement with a study investigating 11 patients with LBBB, we found in both ECGi and contact measurements that LV free wall activation was slower during RV pacing compared to intrinsic rhythm. In contrast, these studies also frequently report the presence of functional U-shaped activation and/or line of block in patients with LBBB. In this study, U-shaped activation was present in some (but not all) ECGi-derived activation maps (Figure 5) but not in any direct recordings. This supports the notion that this is an artifact produced by ECGi. We speculate that in regions of change in electrogram morphology or conduction velocity, such as the epicardial region over the septum in LBBB, or near the LV morphology or conduction velocity, such as the epicardial reports the notion that this is an artifact produced by ECGi. An artifactual apparent propagation of electrical activity from the heart to the body neurous. Although the inclusion of other organs may alter propagation of electrical activity from the heart to the body surface, previous studies have demonstrated that the inclusion of inhomogeneous structures produces no systematic improvement in ECGi-derived potentials.

No endocardial recordings were made to assess transspatial conduction, and the electrode sock did not entirely cover the posterior surface, meaning epicardial markers may have been slightly underestimated; that is, TAT appears to be 10%–20% shorter than QRSd (Figure 4). Despite this missing information, epicardial markers still showed a higher sensitivity to dyssynchrony than do body surface markers.

As the ECGi methods used cannot assess endocardial or septal information, electrical activity and dyssynchrony was assessed only at the epicardial surface. Because endocardial activation differences may play an important role in both CRT patient selection and therapy delivery, further investigation and development of methods are required.

Electrical dyssynchrony markers were assessed using acute models of LBBB, without cardiomyopathy or infarction, in order to demonstrate their sensitivity to small degrees of electrical dyssynchrony. While we expect that these results are translatable to the large population of patients without structural abnormalities, the incorporation of scar tissue into the model will be investigated in future studies.

Conclusion

We have demonstrated that ECGi is highly applicable in detecting mild to severe electrical dyssynchrony and its synchronization during BiV pacing. ECGi provides more information than is available from the 12-lead ECG or body surface mapping, particularly concerning quantitative measures of the spread of epicardial activation and accurate detection of the latest site of activation. This noninvasive approach may improve response rates to CRT by improving patient selection, optimization of treatment delivery, and patient safety by reducing fluoroscopy times.

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Appendix

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrtm.2018.02.024.

References


