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Cardiology Research and Practice

Comparison of Echocardiographic and Electrocardiographic Mapping for Cardiac Resynchronisation Therapy Optimisation

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20 **ABSTRACT**

Study hypothesis:

We sought to investigate the association between echocardiographic optimisation and ventricular activation time in cardiac resynchronization therapy (CRT) patients, obtained
25 through the use of electrocardiographic mapping (ECM). We hypothesised that echocardiographic optimisation of the pacing delay between the atrial and ventricular leads - atrio-ventricular delay (AVD) and the delay between ventricular leads - inter-ventricular pacing interval (VVD) would correlate with reductions in ventricular activation time.

Background: Optimisation of AVD and VVD may improve CRT patient outcome. Optimal
30 delays are currently set based on echocardiographic indices; however, acute studies have found that reductions in bulk ventricular activation time correlate with improvements in acute haemodynamic performance.

Materials and methods: Twenty-one patients with established CRT criteria were recruited. After implantation, patients underwent echo-guided optimisation of the AVD and VVD.
35 During this procedure, the participants also underwent non-invasive ECM. ECM maps were constructed for each AVD and VVD. ECM maps were analysed offline. Total ventricular activation time (TVaT) and a ventricular activation time index (VaT₁₀₋₉₀) were calculated to identify the optimal AVD and VVD timings that gave the minimal TVaT and VaT₁₀₋₉₀ values. We correlated cardiac output with these electrical timings.

40 Results: Echocardiographic programming optimisation was not associated with the greatest reductions in biventricular activation time (VaT₁₀₋₉₀ and TVaT). Instead, bulk activation times were reduced by a further 20% when optimised with ECM. A significant inverse correlation was identified between reductions in bulk ventricular activation time and improvements in

LVOT VTI ($p < 0.001$), suggesting that improved ventricular hemodynamics are a sequelae of
45 more rapid ventricular activation.

Conclusions:

EAM guided programming optimisation may achieve superior fusion of activation wave
fronts leading to improvements in CRT response.

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Introduction

Cardiac Resynchronisation Therapy (CRT) is recommended for patients with systolic heart
failure, prolonged QRS duration, and left bundle branch block (Cleland et al. 2001; Yancy et
55 al. 2017). Despite the fact that CRT has been available for more than 20 years, up to 30% of
patients fail to respond to this therapy (Auricchio and Prinzen 2011). Left ventricular (LV)
pacing alone has been proposed as an alternative to biventricular pacing, allowing for
simpler systems that avoid the complication of right ventricular pacing (Thibault et al. 2011).
However, some features of cardiac remodelling respond better to biventricular pacing
60 compared with LV pacing, suggesting that optimisation of biventricular pacing should be
pursued in CRT (Faghfourian et al. 2017; Skaf et al. 2017). One approach designed to
improve CRT response is optimisation of the pacing delay between the atrial and ventricular
leads (atrio-ventricular delay or AVD) and the delay between the ventricular leads (inter-
ventricular pacing interval or VVD) for each individual patient (Brabham and Gold, 2013).
65 While there are multiple strategies for AVD and VVD optimisation, there is no clear “gold
standard” and existing guidelines do not provide recommendations (Brabham and Gold

2013a). As a consequence, different protocols are used that either consider echocardiographic parameters or use electrograms to determine the optimal device timings (Raphael et al. 2013).

70 CRT aims to eliminate the dyssynchrony, which results from bundle branch block activation, by reducing the left ventricular activation time (LVaT) and restoring the mechano-energetic efficiency of the heart. Rapid LV activation is preferred and is associated with improvements in functional class and symptoms (Van Gelder and Bracke 2015; Duckett et al. 2011). Sohal et al. (2015) reported a difference in LVaT between responders and non-responders to CRT; 75 with responders exhibiting greater activation homogeneity, measured using the delay between the 10th and 90th percentiles of LVaT (LVaT₁₀₋₉₀ Index). The cumulative rate of LV activation appears critical, a finding consistent with previous modelling studies (Niederer et al. 2012; Sohal et al. 2015).

CRT programming aims to resynchronise the electrical activity to ensure the optimal fusion 80 of all activation wave fronts: intrinsic right ventricular depolarisation, RV paced activation, and LV depolarisation (Vatasescu et al. 2009). Patients with partial fusion of their intrinsic depolarisation with LV pacing have been found to have greater LV reverse remodelling and haemodynamic response (Van Gelder et al. 2005). Furthermore, the use of electrocardiographic indices to optimise AVD to achieve optimal activation wave front 85 fusion is associated with significant improvements in acute haemodynamic response (AHR) (Engels et al. 2017). Another development capable of improving AHR is Multipolar Pacing (MPP), where stimulation is delivered from multiple poles along the LV lead, allowing the avoidance of pacing in and around scar. This technique has been associated with improvements in CRT response (Sardu, Barbieri, et al. 2017).

90 The close relationship between activation wave fusion and AHR suggests that the use of electrical indices for CRT optimisation would be beneficial. The recent availability of non-invasive electrocardiographic mapping (ECM) means detailed, patient specific biventricular activation can now be calculated non-invasively (Ramanathan et al. 2017; Ploux et al. 2013).

95 **Hypothesis and study aim**

We sought to investigate the association between echocardiographic optimisation and ventricular activation time, obtained through the use of ECM. We hypothesised that echocardiographic optimisation of AVD and VVD would correlate with reductions ventricular activation time.

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Materials and Methods

We undertook a prospective study recruiting consecutive heart failure (HF) patients indicated for CRT-Pacemaker (CRT-P) or CRT-Defibrillator (CRT-D) at St Thomas' Hospital, London. The study conformed to the principles outlined in the Declaration of Helsinki on
105 research in human subjects. All patients gave written informed consent to participate in the study, which was approved by the Research Ethics Committee (**ClinicalTrials.gov Identifier:** NCT01831518). We aimed to recruit 20 patients within 18 months, the first patient was recruited in September 2014 and the last patient in November 2015. In total, 21 patients were selected on the basis of fulfilling the criteria for CRT implantation: NYHA Class II-IV;
110 echocardiographic Left Ventricular Ejection Fraction (LVEF) < 35%, QRS duration > 120 ms (independently of the QRS morphology) and optimal medical therapy (OMT) for heart failure. The aetiology of heart failure was classified as ischemic if there was substantial

coronary artery disease or history of myocardial infarction or revascularisation, and as non-
ischaemic if none of these were present. Intraventricular conduction disturbances were
115 defined according to AHA/ACCF/HRS Recommendations for the Standardisation and
Interpretation of the Electrocardiogram (Surawicz et al. 2009). 12-lead ECGs were acquired
with a GE Mac 5000 ECG system (General Electric-Vingmed, Milwaukee, WI) using standard
American Heart Association (AHA)-recommended filter settings at a sweep rate of 25 mm/s
and a gain of 10 mm/mV. Echocardiography was performed using an IE33 or EPIC model
120 scanner (Philips Healthcare, Best, The Netherlands).

CRT implantation

Implantation was performed via the cephalic, axillary or subclavian veins. The RV lead was
implanted at the RV apex or high septum at the discretion of the implanting physician, and
125 the right atrial lead was placed at the right atrial appendage. The LV lead was preferentially
placed in the lateral or postero-lateral vein tributary of the coronary sinus. In case of
technical difficulties, unacceptable pacing thresholds or phrenic nerve stimulation, an
alternative location was chosen in the antero-lateral, posterior, or anterior regions.

130 Echocardiographic optimisation

Echocardiographic optimisation of the AVD and VVD was performed the day after
implantation, with the exception of patients with atrial fibrillation who had only their VVD
but not their AVD echocardiographically optimised. Varying AV intervals were progressively
applied (from 60 ms to 200 ms in 20 ms increments) and the echocardiographic optimal AVD
135 was calculated using an iterative method based on the maximal separation of E and A waves
recorded by Pulsed-wave Doppler of diastolic mitral inflow and the maximal mitral velocity-

time integral (VTI), as previously described (Brabham and Gold 2013b; Gorcsan et al. 2008). The AVD with distinct E- and A-waves, yielding the maximal atrial contribution to ventricular filling and minimal mitral regurgitation, was considered the optimal AVD. VVD optimisation was performed following AVD optimisation, starting with simultaneous RV and LV pacing. Varying VVD was applied by progressively increasing LV pre-excitation in increments of 15, 20, 30, and 40 ms, and then increasing RV pre-excitation in increments of 20 and 40 ms. The optimal VVD was defined as the delay producing the maximal LVOT VTI, which represents the maximal LV stroke volume (a reproducible measure of global LV function that has proven to be useful for improving the response to CRT) (Houthuizen, Bracke, and Van Gelder 2011). The effects of each applied AVD and VVD setting on mitral and LVOT VTI were assessed after 10 consecutive beats in order to minimise the effects of beat-to-beat variability in optimisation measures, which have been shown to be substantial and potentially limiting in research settings (Sohaib et al. 2013). It should be noted that the LVOT VTI method was preferred to other haemodynamic outcome measures (e.g. dp/dtmax) as this is a feasible, non-invasive, reproducible and direct measure of global LV function, comparable to other measures (Thomas et al. 2009).

Electrocardiographic mapping

During AVD and VVD optimisation, patients underwent ECM using a CardioInsight ECSYNC system (CardioInsight Technologies Inc., Cleveland, OH, USA) to non-invasively record biventricular epicardial ventricular electrograms and construct 3D isochrone and isopotential activation maps. The key component of the ECM system is a vest embedded with 252 electrodes that is fitted to the patient's torso. ECM maps were constructed on a beat-by-beat basis for the different AVD and VVD tested. After optimisation and acquisition

of vest electrograms under each configuration, the participants, with the vest still in position, underwent a thoracic computed tomographic (CT) scan to determine the precise anatomic relation between the cardiac geometry and the torso electrodes, which was used to reconstruct approximately 1500 unipolar electrograms on the epicardial surface of the heart. Based on each data set obtained with the ECSYNC, an activation map of both ventricles was generated offline by animating the activation waveform on the patient-specific CT-derived epicardial surface. Ventricular activation times were calculated from the onset of the QRS to the maximal negative slope of each electrogram, and combined for the construction of 3D epicardial isochrone maps. The propagation of depolarisation was evident from the 3D epicardial isochrone maps. (Figure 1) Subsequently, extraction of specific raw data from epicardial maps obtained at baseline and in each AVD and VVD assessed permitted the calculation of total ventricular activation time (TVaT) and ventricular activation time₁₀₋₉₀ index (VaT₁₀₋₉₀) with custom-developed MATLAB code (MathWorks, Natick, MA, USA) as previously described by Pereira et al. (Pereira et al. 2018). TVaT is a measure of the total time required for both ventricles to activate and VaT₁₀₋₉₀ is the time delay between the 10th and 90th percentiles of activation.

Statistical analysis

Statistical analyses were performed using PASW Statistics 21 (SPSS Inc., Chicago, IL). Changes in ventricular activation times were compared using the Mann–Whitney U test, ANOVA and the Kruskal–Wallis Test. Post hoc comparisons were performed using Tukey’s HSD. Correlations were assessed by the Pearson correlation test. P values less than 0.05 were deemed statistically significant.

185 Results and Discussion

The characteristics of the 21 patients are shown in Table 1. The mean age was 69 ± 12 years. Patients were predominantly male, and most had an ischemic aetiology (62%). The mean LVEF was $27 \pm 10\%$ and the mean QRS duration was 162 ± 21 ms. Fifteen patients (71%) had QRS >150 ms and 15 (71%) had left bundle branch block. Baseline values are shown in Table

190 2.

AV optimisation and electrical timing

The effects of varying AVD on ventricular activation time is shown in Table 3. There was no significant difference in TVaT ($p=0.98$) or VaT_{10-90} index ($p=0.701$) between the different AVD values tested across the cohort, suggesting that no single AVD was optimal for electrically synchronizing all patients. The shortest VaT_{10-90} index was seen with AVD 100 ms (62 ± 20 ms) and longer VaT_{10-90} index values were observed with longer AVDs, especially with AVD 200 ms (VaT_{10-90} index 81 ± 21 ms). In contrast, the shortest AVD tested (AVD 60 ms) gave the longest TVaT (147 ± 26). The optimal AVD found with echocardiographic optimisation did not correspond to the shortest ventricular times observed. The average VaT_{10-90} and TVaT values were 21% and 20% lower, respectively, than the optimal AVD found through the iterative method, see Figure 2. Whilst these findings failed to achieve statistical significance ($p = 0.368$), this is in part explained by the potential for large variability in beat-to-beat and test-retest measurement of LVOT VTI (Sohaib et al. 2013).

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Echocardiographic CRT optimisation consistently failed to achieve the greatest reduction in ventricular activation, see Figure 3. Two groups of patients were identified; those with clear

optimal value that well-distinguished within the evaluated AVD's range (60%), and those in which AVD settings had very limited effect on TVaT or VaT₁₀₋₉₀ index (40%) (Figure 4).

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VVD optimisation and electrical timings

The effects of each applied VVD on ventricular activation times and LVOT VTI are shown in Table 4. LVOT VTI values were higher when LV was programmed to be paced before RV, by either 15 ms or 30 ms (LV15 and LV30), and were associated with the shortest values for the VaT₁₀₋₉₀ index. LV15 appeared to offer the highest LVOT VTI and the shortest VaT₁₀₋₉₀ index and TVaT. No single VVD achieved significant reductions in ventricular activation time when plotted for each patient (Figure 5). A negative correlation between LVOT VTI and VaT₁₀₋₉₀ index ($r = -0.31$; $p < 0.001$), and between LVOT VTI and TVaT ($r = -0.44$; $p < 0.001$) (Figure 6) was observed.

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Findings and comparison with previous studies

We assessed if the optimal parameters obtained through echocardiographic CRT optimisation rendered similar AVD and VVD timings as assessed by ECM. The main findings of this study were as follows:

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- 1) Echocardiographic programming optimisation was not associated with the greatest reductions in biventricular activation time (VaT₁₀₋₉₀ and TVaT). Instead, bulk activation times were reduced by a further 20% when optimised with ECM.
- 2) A significant inverse correlation was identified between reductions in bulk ventricular activation time and improvements in LVOT VTI ($p < 0.001$), suggesting that

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improved ventricular hemodynamics are a sequelae of more rapid ventricular activation.

235 In keeping with previous studies, we identified that echocardiographic optimisation and ECM optimisation were patient-specific. However, ventricular activation was consistently more rapid when optimised via ECM than when echocardiographic optimisation was performed. These findings appear to suggest that programming changes which improve mitral inflow and left ventricular filling do not necessarily achieve a reduction in total ventricular activation time raising the question as to whether AVD should be set to achieve
240 optimal filling, optimal electrical synchrony or potentially a combination of the two.

LVOT VTI is widely accepted as an echocardiographic parameter positively correlated with both stroke volume and cardiac output (Kamdar et al. 2010). Previous work has highlighted the haemodynamic benefits of minimising ventricular activation time (Vatasescu et al. 245 (Vatasescu et al. 2009). Our finding of a significant inverse correlation between increasing LVOT VTI and decreases in ventricular activation time, measuring using non-invasive ECM, suggests a future role for electrical optimisation using this approach, when looking to maximise cardiac output.

250 **Clinical relevance**

Our findings suggest that when looking to optimise CRT programming, a strategy of aiming to minimise ventricular activation is associated with significant improvements in LVOT VTI. In addition, this approach is associated with a greater degree of electrical resynchronisation

than is typically achieved using echo guided programming optimisation. Our results also
255 indicate that optimal electrical resynchronisation is associated with the best cardiac output.

Limitations

The main limitation of our study is the relatively small cohort of patients included at a single
260 centre. Risk factors and multifactorial diseases affect clinical response to CRT (Sardu,
Santamaria, et al. 2017; Sardu, Marfella, and Santulli 2014) and these have not been
characterised within our cohort. Long term response to CRT is a critical outcome measure
when evaluating this population; however, this study was designed to assess acute changes
in ventricular performance following programming optimisation.

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Whilst improvements in AHR, measured using Dp/Dt_{max} , have previously been correlated
with enhanced long term response (Duckett et al. 2011) this measurement technique relies
upon the use of invasive haemodynamic data which did not form part of this study protocol.
As such, our findings would need to be corroborated in a larger, randomised analysis before
270 altering practice. A further limitation was the fact that this study did not address the posi-
tion of the implanted LV lead used to provide LV stimulation.

No significant difference was observed in TVaT and VaT₁₀₋₉₀ activation times amongst both
echocardiographically and electrically optimised patients. One explanation could be the
275 degree of scar or fibrosis present in our cohort. Since these patients did not have late
enhancement CMR, the level of scarring and myocardial fibrosis is unknown. Additionally,
the sensitivity of ECM, which measures epicardial activation times, to identify small,

potentially intramural, late activating regions may be much less than invasive electro-anatomical mapping studies. Finally, it is not possible to analyse septal depolarisation as this
280 is not observed during epicardial mapping.

The study only considered a single acute measure, either ECM or echocardiogram to optimise device timings. Novel blood biomarkers are potential diagnostic and prognostic markers in an acute heart failure setting (Ky et al. 2011; Lellouche et al. 2007; Sardu, Paolisso, et al. 2018). Extending our study beyond electrical and mechanical measures of
285 cardiac function to include blood biomarkers (Skali et al. 2016; Sardu, Marfella, et al. 2018; Gruson et al. 2014; Pascual-Figal and Januzzi 2015; Anand et al. 2014; Petretta et al. 2007) may further improve device setting optimisation. However, how best to integrate real time feedback from ECM and echocardiogram markers with the inherent delay in blood biomarker readings will need to be addressed.

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Conclusions

Echocardiographic programming optimisation does not result in the fastest possible
295 biventricular activation. Instead, activation was consistently more rapid when optimised via ECM than with echocardiographic optimisation. ECM guided programming optimisation may achieve superior fusion of activation wave fronts leading to improvements in CRT response.

Data Availability

The data used to support the findings of this study are included within the article.

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