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Comparison of Echocardiographic and Electrocardiographic Mapping for Cardiac Resynchronisation Therapy Optimisation

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ABSTRACT

Study hypothesis:

We sought to investigate the association between echocardiographic optimisation and ventricular activation time in cardiac resynchronization therapy (CRT) patients, obtained 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 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. 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 (VaT_{10-90}) were calculated to identify the optimal AVD and VVD timings that gave the minimal TVaT and VaT_{10-90} values. We correlated cardiac output with these electrical timings.

Results: Echocardiographic programming optimisation was not associated with the greatest reductions in biventricular activation time (VaT_{10-90} 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 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 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 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). 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).

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; with responders exhibiting greater activation homogeneity, measured using the delay between the 10th and 90th percentiles of LVaT ($LVaT_{10-90}$ 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 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 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).

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).

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.

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 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; 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 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 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 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.

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 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 VaT_{10-90} 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.

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±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 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 $VaT_{10\text{-}90}$ 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 $VaT_{10\text{-}90}$ index was seen with AVD 100 ms (62 ± 20 ms) and longer $VaT_{10\text{-}90}$ index values were observed with longer AVDs, especially with AVD 200 ms ($VaT_{10\text{-}90}$ 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 $VaT_{10\text{-}90}$ 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).

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 VaT_{10-90} index (40%) (Figure 4).

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 VaT_{10-90} index. LV15 appeared to offer the highest LVOT VTI and the shortest VaT_{10-90} 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 VaT_{10-90} index ($r= -0.31$; $p<0.001$), and between LVOT VTI and TVaT ($r= -0.44$; $p<0.001$) (Figure 6) was observed.

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:

1) Echocardiographic programming optimisation was not associated with the greatest reductions in biventricular activation time (VaT_{10-90} 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

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

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 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. (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.

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 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 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.

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 altering practice. A further limitation was the fact that this study did not address the position of the implanted LV lead used to provide LV stimulation.

No significant difference was observed in TVaT and VaT_{10-90} activation times amongst both echocardiographically and electrically optimised patients. One explanation could be the 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 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 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.

Conclusions

Echocardiographic programming optimisation does not result in the fastest possible 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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References

Anand, Inder S, Thomas S Rector, Michael Kuskowski, James Snider, and Jay N Cohn. 2014. "Prognostic Value of Soluble ST2 in the Valsartan Heart Failure Trial." *Circulation. Heart Failure* 7 (3): 418–26. doi:10.1161/CIRCHEARTFAILURE.113.001036.

Auricchio, Angelo, and Frits W. Prinzen. 2011. "Non-Responders to Cardiac Resynchronization Therapy." *Circulation Journal* 75 (3). The Japanese Circulation Society: 521–27. doi:10.1253/circj.CJ-10-1268.

Brabham, William W., and Michael R. Gold. 2013a. "The Role of AV and VV Optimization for CRT." *Journal of Arrhythmia* 29 (3). Elsevier: 153–61. doi:10.1016/j.joa.2013.02.001.

———. 2013b. "The Role of AV and VV Optimization for CRT." *Journal of Arrhythmia* 29 (3). No longer published by Elsevier: 153–61. doi:10.1016/J.JOA.2013.02.001.

Duckett, Simon G, Matthew Ginks, Anoop K Shetty, Julian Bostock, Jaswinder S Gill, Shoaib Hamid, Stam Kapetanakis, et al. 2011. "Invasive Acute Hemodynamic Response to Guide Left Ventricular Lead Implantation Predicts Chronic Remodeling in Patients Undergoing Cardiac Resynchronization Therapy." *JAC* 58: 1128–36. doi:10.1016/j.jacc.2011.04.042.

Engels, Elien B., Masih Mafi-Rad, Ben J.M. Hermans, Alfonso Aranda, Antonius M.W. van Stipdonk, Michiel Rienstra, Coert O.S. Scheerder, Alexander H. Maass, Frits W. Prinzen, and Kevin Vernooy. 2017. "Tailoring Device Settings in Cardiac Resynchronization Therapy Using Electrograms from Pacing Electrodes." *Europace*, no. October: 1–8. doi:10.1093/europace/eux208.

Gelder, Berry M. Van, and Frank A. Bracke. 2015. "Acute Hemodynamic Effects of Single- and Dual-

Site Left Ventricular Pacing Employing a Dual Cathodal Coronary Sinus Lead." *PACE - Pacing and Clinical Electrophysiology* 38 (5): 558–64. doi:10.1111/pace.12606.

Gelder, Berry M. Van, Frank A. Bracke, Albert Meijer, and N. H J Pijls. 2005. "The Hemodynamic Effect of Intrinsic Conduction during Left Ventricular Pacing as Compared to Biventricular Pacing." *Journal of the American College of Cardiology* 46 (12). Elsevier Masson SAS: 2305–10. doi:10.1016/j.jacc.2005.02.098.

Gorcsan, John, Theodore Abraham, Deborah A. Agler, Jeroen J. Bax, Genevieve Derumeaux, Richard A. Grimm, Randy Martin, et al. 2008. "Echocardiography for Cardiac Resynchronization Therapy: Recommendations for Performance and Reporting–A Report from the American Society of Echocardiography Dyssynchrony Writing Group Endorsed by the Heart Rhythm Society." *Journal of the American Society of Echocardiography* 21 (3): 191–213. doi:10.1016/j.echo.2008.01.003.

Gruson, Damien, Thibault Lepoutre, Sylvie A. Ahn, and Michel F. Rousseau. 2014. "Increased Soluble ST2 Is a Stronger Predictor of Long-Term Cardiovascular Death than Natriuretic Peptides in Heart Failure Patients with Reduced Ejection Fraction." *International Journal of Cardiology* 172 (1): e250–52. doi:10.1016/j.ijcard.2013.12.101.

Houthuizen, Patrick, Frank A L E Bracke, and Berry M. Van Gelder. 2011. "Atrioventricular and Interventricular Delay Optimization in Cardiac Resynchronization Therapy: Physiological Principles and Overview of Available Methods." *Heart Failure Reviews* 16 (3): 263–76. doi:10.1007/s10741-010-9215-1.

Kamdar, R., E. Frain, F. Warburton, L. Richmond, V. Mullan, T. Berriman, G. Thomas, et al. 2010. "A Prospective Comparison of Echocardiography and Device Algorithms for Atrioventricular and Interventricular Interval Optimization in Cardiac Resynchronization Therapy." *Europace* 12 (1). Oxford University Press: 84–91. doi:10.1093/europace/eup337.

Ky, Bonnie, Benjamin French, Kristin McCloskey, J. Eduardo Rame, Erin McIntosh, Puja Shahi, Daniel L. Dries, et al. 2011. "High-Sensitivity ST2 for Prediction of Adverse Outcomes in Chronic Heart

Failure." *Circulation: Heart Failure* 4 (2): 180–87. doi:10.1161/CIRCHEARTFAILURE.110.958223.

Lellouche, Nicolas, Carlos De Diego, David A. Cesario, Marmar Vaseghi, Barbara Natterson Horowitz, Aman Mahajan, Isaac Wiener, Noel G. Boyle, Gregg C. Fonarow, and Kalyanam Shivkumar. 2007. "Usefulness of Preimplantation B-Type Natriuretic Peptide Level for Predicting Response to Cardiac Resynchronization Therapy." *The American Journal of Cardiology* 99 (2): 242–46. doi:10.1016/j.amjcard.2006.08.018.

Pascual-Figal, Domingo A., and James L. Januzzi. 2015. "The Biology of ST2: The International ST2 Consensus Panel." *The American Journal of Cardiology* 115 (7): 3B–7B. doi:10.1016/j.amjcard.2015.01.034.

Pereira, H., T.A. Jackson, B. Sieniewicz, J. Gould, C. Yao, S. Niederer, and C.A. Rinaldi. 2018. "Non-Invasive Electrophysiological Assessment of the Optimal Configuration of Quadripolar Lead Vectors on Ventricular Activation Times." *Journal of Electrocardiology* 51 (4). doi:10.1016/j.jelectrocard.2018.05.006.

Petretta, Mario, Annamaria Colao, Celestino Sardu, Franco Scopacasa, Paolo Marzullo, Rosario Pivonello, Luca Fontanella, Maurizio de Caterina, Adriano de Simone, and Domenico Bonaduce. 2007. "NT-ProBNP, IGF-I and Survival in Patients with Chronic Heart Failure." *Growth Hormone & IGF Research* 17 (4): 288–96. doi:10.1016/j.ghir.2007.01.020.

Ploux, Sylvain, Joost Lumens, Zachary Whinnett, Michel Montaudon, Maria Strom, Charu Ramanathan, Nicolas Derval, et al. 2013. "Noninvasive Electrocardiographic Mapping to Improve Patient Selection for Cardiac Resynchronization Therapy Beyond QRS Duration and Left Bundle Branch Block Morphology." *Journal of the American College of Cardiology* 61: 2435–43. doi:10.1016/j.jacc.2013.01.093.

Ramanathan, Charulatha, Ping Jia, Raja Ghanem, Kyungmoo Ryu, and Yoram Rudy. 2017. "Activation and Repolarization of the Normal Human Heart under Complete Physiological Conditions." Accessed June 11. http://www.pnas.org/content/103/16/6309.full.pdf.

Raphael, Claire E., Andreas Kyriacou, Siana Jones, Punam Pabari, Graham Cole, Resham Baruah, Alun

D. Hughes, and Darrel P. Francis. 2013. “Multinational Evaluation of the Interpretability of the Iterative Method of Optimisation of AV Delay for CRT.” *International Journal of Cardiology* 168 (1). Elsevier Ireland Ltd: 407–13. doi:10.1016/j.ijcard.2012.09.097.

Sardu, Celestino, Michelangela Barbieri, Matteo Santamaria, Valerio Giordano, Cosimo Sacra, Pasquale Paolisso, Alessandro Spirito, Raffaele Marfella, Giuseppe Paolisso, and Maria Rosaria Rizzo. 2017. “Multipolar Pacing by Cardiac Resynchronization Therapy with a Defibrillators Treatment in Type 2 Diabetes Mellitus Failing Heart Patients: Impact on Responders Rate, and Clinical Outcomes.” *Cardiovascular Diabetology* 16 (1): 75. doi:10.1186/s12933-017-0554-2.

Sardu, Celestino, Raffaele Marfella, Matteo Santamaria, Stefano Papini, Quintino Parisi, Cosimo Sacra, Daniele Colaprete, Giuseppe Paolisso, Maria R. Rizzo, and Michelangela Barbieri. 2018. “Stretch, Injury and Inflammation Markers Evaluation to Predict Clinical Outcomes After Implantable Cardioverter Defibrillator Therapy in Heart Failure Patients With Metabolic Syndrome.” *Frontiers in Physiology* 9 (June). Frontiers: 758. doi:10.3389/fphys.2018.00758.

Sardu, Celestino, Raffaele Marfella, and Gaetano Santulli. 2014. “Impact of Diabetes Mellitus on the Clinical Response to Cardiac Resynchronization Therapy in Elderly People.” *Journal of Cardiovascular Translational Research* 7 (3): 362–68. doi:10.1007/s12265-014-9545-9.

Sardu, Celestino, Pasquale Paolisso, Cosimo Sacra, Matteo Santamaria, Claudio de Lucia, Antonio Ruocco, Ciro Mauro, et al. 2018. “Cardiac Resynchronization Therapy with a Defibrillator (CRTd) in Failing Heart Patients with Type 2 Diabetes Mellitus and Treated by Glucagon-like Peptide 1 Receptor Agonists (GLP-1 RA) Therapy vs. Conventional Hypoglycemic Drugs: Arrhythmic Burden, Hospitalizations for Heart Failure, and CRTd Responders Rate.” *Cardiovascular Diabetology* 17 (1): 137. doi:10.1186/s12933-018-0778-9.

Sardu, Celestino, Matteo Santamaria, Stefania Funaro, Cosimo Sacra, Michelangela Barbieri, Pasquale Paolisso, Raffaele Marfella, Giuseppe Paolisso, and Maria Rosaria Rizzo. 2017. “Cardiac Electrophysiological Alterations and Clinical Response in Cardiac Resynchronization Therapy with a Defibrillator Treated Patients Affected by Metabolic Syndrome.” *Medicine* 96

(14): e6558. doi:10.1097/MD.0000000000006558.

Skali, Hicham, Robert Gerwien, Timothy E. Meyer, James V Snider, Scott D. Solomon, and Craig M. Stolen. 2016. “Soluble ST2 and Risk of Arrhythmias, Heart Failure, or Death in Patients with Mildly Symptomatic Heart Failure: Results from MADIT-CRT.” *Journal of Cardiovascular Translational Research* 9 (5–6): 421–28. doi:10.1007/s12265-016-9713-1.

Surawicz, Borys, Rory Childers, Barbara J. Deal, and Leonard S. Gettes. 2009. “AHA/ACCF/HRS Recommendations for the Standardization and Interpretation of the Electrocardiogram. Part III: Intraventricular Conduction Disturbances A Scientific Statement From the American Heart Association Electrocardiography and Arrhythmias Committee, .” *Journal of the American College of Cardiology* 53 (11): 976–81. doi:10.1016/j.jacc.2008.12.013.

Vatasescu, Radu, Antonio Berruezo, Lluis Mont, David Tamborero, Marta Sitges, Etel Silva, Jose María Tolosana, Bárbara Vidal, David Andreu, and Josep Brugada. 2009. “Midterm ‘super-Response’ to Cardiac Resynchronization Therapy by Biventricular Pacing with Fusion: Insights from Electro-Anatomical Mapping.” *Europace* 11 (12): 1675–82. doi:10.1093/europace/eup333.

Yancy, Clyde W., Mariell Jessup, Biykem Bozkurt, Javed Butler, Donald E. Casey, Monica M. Colvin, Mark H. Drazner et al. 2017. "2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America." *Journal of the American College of Cardiology* 70 (6): 776-803. doi: 10.1016/j.jacc.2017.04.025