Is individualised Cardiac Resynchronisation Therapy (CRT) programming superior to conventional programming with respect to QRS narrowing?

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DClinSci 2021

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This thesis is submitted in partial fulfilment of the requirements of Manchester Metropolitan University for the award of Doctorate in Clinical Science (DClinSci)

Department of Physiological Sciences Manchester Metropolitan University, in collaboration with Rotherham NHS Foundation Trust

2021

Abstract

Introduction

QRS narrowing is emerging as a key marker of successful Cardiac Resynchronisation Therapy (CRT) (Cleland et al, 2013; Jastrzebski et al, 2018). Individualised CRT programming, via fusion pacing, such as SyncAV) or multipoint pacing (MPP), has been shown to narrow QRS and give acute benefit (Varma et al, 2018; Forleo et al, 2017). Combining technologies may augment the benefit but there is little evidence to support this (O'Donnell et al, 2016). Accurate measurement of QRS duration (QRSd) is critical in CRT, but different methods are used in clinical practice. This study aims to establish whether individualised CRT programming is superior to conventional programming with respect to QRS narrowing. A secondary aim is to determine whether abbreviated global QRS methodology is comparable to single lead measurement for assessing QRS duration.

Method

This observational study (n=28) compared five CRT programming strategies [Mode 1=Best single point pacing, Mode 2=Nominal SyncAV, Mode 3=Individualised SyncAV, Mode 4=MPP, Mode 5=Individualised Sync AV +MPP]. Optimal CRT was considered as narrowest QRSd (ms). QRSd was assessed by both individual ECG lead measurement and abbreviated global QRS methodology (QRS_aGlobal) over 5 leads. Patient response to CRT was assessed after a five-month follow-up period, using clinical and functional measures.

Results

All CRT modes reduced QRSd compared to baseline ($p<0.0001$). Largest mean QRSd reductions were obtained with individualised programming modes. Mode 3 showed greater reduction in QRS when compared to Mode 1 ($p=0.0036$) and Mode 2 ($p=0.0001$). Mode 5 also reduced QRSd when compared to Mode 1 ($p=0.0146$), 2 ($p=0.0301$) and 4 ($p=0.0049$). QRSd measurements varied within the individual leads of the 12 Lead ECG;

maximum standard deviation (SD) 21.6 ms, minimum SD 3.98 ms. Comparison of QRS_aGlobal and individual lead methodologies showed mean differences in QRSd ranging from 5.9 ms (V2) to 14.2 ms (Lead I) with broader limits of agreement 27.1 ms (QRS_Mean) to 37.5 ms (Lead II). QRS_aGlobal methodology demonstrated intra-operator variability of 4.8 ms ± 9.5 ms and inter-operator variability of 7.9 ms ± 15.5 ms. Assessment of response was limited by COVID19.

Conclusion

This study supports the view that individualised CRT programming can produce maximal QRS narrowing. SyncAV appeared to have the greatest contribution to QRS narrowing. Further research is required as to whether individualised programming can influence patient outcomes. This study recommends standardisation of the methodology for measuring QRSd; different methods should not be used interchangeably. Abbreviated global QRSd is a pragmatic alternative to individual lead QRSd measurement using the Abbott programmer.

Acknowledgements

I would like to give special thanks to Dr Mike Smith, Consultant Physicist (now retired) for his continual encouragement and guidance with the statistical analysis of this thesis. In addition, I am very grateful to the ongoing support and professional guidance offered by Dr Simon Smith, Lead Cardiologist. I would also like to acknowledge Dr Duncan White, Consultant Physicist, for his ongoing support and patience. I would like to praise my university supervisor for his advice and academic input. My colleagues and friends in the Cardiology Department must be specially commended for their contributions and laughter during the development of this thesis. Finally, I would like to thank my family for their unwavering support and love.

Declaration

No portion of this thesis has been submitted in support of an application for another qualification in any other university or institution of learning.

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Abbreviations

Abbreviation	Full Meaning
AF	Atrial Fibrillation
AHA	American Heart Association
ATS	American Thoracic Society
AV	Atrioventricular
AVB	Atrioventricular Block
AVD	Atrioventricular Delay
BHRS	British Heart Rhythm Society
BSE	British Society of Echocardiography
BiV	Biventricular Pacing
CCS	Clinical Composite Score
CI	Confidence Intervals
CMR	Cardiac Magnetic Resonance
COVID-19	Disease caused by a new strain of coronavirus
CPET	Cardiopulmonary Exercise Testing
CRT	Cardiac Resynchronisation Therapy
CRT-P	Cardiac Resynchronisation Therapy Pacemaker
CRT-D	Cardiac Resynchronisation Therapy Defibrillator
DNA	Did Not Attend
ECG	Electrogram
EP	Electrophysiology
ESC	European Society of Cardiology
GCP	Good Clinical Practice
HF	Heart Failure
HFH	Heart Failure Hospitalisation
HRA	Health Research Authority
HRC	Heart Rhythm Congress
HRQL	Health Related Quality of Life Questionnaire
HSST	Higher Specialist Scientist Training programme
ICD	Implantable Cardioverter Defibrillator

LA	Left Atrium
LBBB	Left Bundle Branch Block
LV	Left Ventricle
LVEDV	Left Ventricular End Diastolic Volume
LVEF	Left Ventricular Ejection Fraction
LVESV	Left Ventricular End Systolic Volume
LoA	Limits of Agreement
MLHFQ	Minnesota Living with Heart Failure Questionnaire
Baseline_QRS	Abbreviated Global QRSd measured at baseline
Mode1_QRS	Abbreviated Global QRSd measured by Programmed Mode 1
Mode2_QRS	Abbreviated Global QRSd measured by Programmed Mode 2
Mode3_QRS	Abbreviated Global QRSd measured by Programmed Mode 3
Mode4_QRS	Abbreviated Global QRSd measured by Programmed Mode 4
Mode5_QRS	Abbreviated Global QRSd measured by Programmed Mode 5
MR	Mitral Regurgitation
MR-Conditional	Magnetic Resonance Conditional
MPP	Multipoint Pacing
Ms	Milliseconds
NHS	National Health Service
NICE	National Institute for Health & Care Excellence
NICOR	National Institute of Cardiovascular Research Outcomes
NYHA	New York Heart Association
PAC	Pre-Assessment Clinic
PIL	Patient Information Leaflet
pVO2	Peak Oxygen Uptake

QLV	Electrical interval defined from the onset of the QRS on the surface ECG to the first large positive or negative peak of the LV electrogram
QRS	Electrical interval defined from the first positive or negative deflection from the isoelectric line to the J point on the ECG
QRSd	QRS Duration (ms)
QRS_aGlobal	Abbreviated Global QRS Duration
QRS_Global	Global QRS (over 12 Leads) Duration
QRS_Max	Maximum QRS duration measured from all 12 ECG Leads
QRS_Mean	Mean QRS Duration measured from all 12 ECG leads
QRS_individual lead (e.g. QRS_LeadI, QRS_aVR)	QRS Duration measured in any of the individual ECG leads e.g. Lead I, aVR
RA	Right Atrium
RBBB	Right Bundle Branch Block
RCT	Randomised Controlled Trial
R&D	Research and Development
REC	Research Ethics Committee
RV	Right Ventricle
SCST	Society of Cardiological Science and Technology
SD	Standard Deviation
STP	Scientist Training Programme
SyncAV	Automated & Dynamic fusion algorithm on Abbott CRT Devices
UK	United Kingdom
VV	Interventricular timing intervals
6MWD	Six Minute Walk Distance
6MWT	Six Minute Walk Test

1.0 Introduction

Heart failure (HF) describes a clinical syndrome characterised by impaired cardiac output or elevated intracardiac pressures (Sieniewicz et al, 2019). There are distinct categories of heart failure depending on the measurement of left ventricular ejection fraction (LVEF): heart failure with reduced LVEF ≤40% (HFrEF), heart failure with mildly reduced LVEF 41-49% (HFmrEF) and heart failure with preserved LVEF ≥50% (HFpEF) (McDonagh et al, 2021). For those with HFrEF, progressive compensatory changes cause the heart to become dilated and more globular in shape as contractile function deteriorates (Sieniewicz et al, 2019). This process is known as remodelling and may result in delayed electrical activation of the left ventricle, dyssynchronous contraction and the typical broad QRS complex with left bundle branch block (LBBB) morphology on the electrogram (ECG). Common symptoms include breathlessness, ankle swelling and fatigue (Ponikowski et al, 2016). The prevalence of heart failure is 1-2% of adults in developed countries, rising to greater than 10% of the older population (Ponikowski et al, 2016). 12 month mortality rates range between 7-17% and the rate of hospitalisation within 12 months ranges from 32-44% (Ponikowski et al, 2016).

Cardiac Resynchronisation Therapy (CRT) has been shown to improve cardiac performance and quality of life in specific patients with HFrEF (Cleland et al, 2013; Moss et al, 2009). CRT is an implantable device therapy also known as biventricular (BiV) cardiac pacing. During CRT, both the left and right ventricles are stimulated to coordinate electrical activation of the heart and give rise to a more efficient contraction. Several large randomised controlled trials have established the efficacy of CRT therapy, notably a reduction in heart failure hospitalisations (HFH) and death, as shown in Table 1 (Sieniewicz et al, 2019; Cleland et al, 2013; Cleland et al, 2005; Bristow et al, 2004). Moss et al (2009) showed that the morbidity and mortality benefit even extends to those with only minimal HF symptoms by reversing the remodelling mechanism within the left ventricle.

Table 1. Endpoints, design and main findings of randomized clinical trials evaluating CRT in heart failure. Reproduced from Linde et al (2012). Accessed by: https://www.heartrhythmjournal.com/article/S1547-5271(12)00414-6/pdf

Study	Endpoints	Design	Main findings
MUSTIC-SR[8]	6MWT, QOL, pVO_2, Hosp	Single-blinded, controlled, crossover, 6 months	CRT-P improved: 6MWT, QOL, pVO_2; reduced Hosp
MIRACLE[9]	NYHA class, QOL, pVO_2	Double-blinded, controlled, 6 months	CRT-P improved: NYHA, pVO_2, 6MWT
MUSTIC AF[10]	6MWT, QOL, pVO_2, Hosp	Single-blinded, controlled, crossover, 6 months	CRT-P (high dropout rate): improved all; reduced Hosp
PATH CHF[11]	6MWT, pVO_2	Single-blinded, controlled, crossover, 12 months	CRT-P improved: 6MWT, pVO_2
MIRACLE ICD[12]	6MWT, QOL, Hosp	Double-blinded, ICD vs CRT-D 6 months	CRT-D improved all from baseline (not ICD)
CONTAK CD[13]	Mortality + Hosp HF + VA, pVO_2, 6MWT, NYHA class, QOL, LVEDD + LVEF	Double-blinded, ICD vs CRT-D 6 months	CRT-D improved: pVO_2, 6MWT; reduced LVEDD; increased LVEF
MIRACLE ICD II[14]	VE/CO_2, pVO_2, NYHA, QOL, 6MWT, LV volumes/ LVEF	Double-blinded, ICD vs CRT-D 6 months	CRT-D improved: NYHA, VE/CO_2, volumes, LVEF
COMPANION[16]	(1) All-cause death or Hosp	Double-blinded, controlled, OPT, CRT-D, CRT-P, about 15 months	CRT-P/CRT-D: reduced (1)
CARE-HF[17]	(1) All-cause death or Hosp for major CV event (2) Death from any cause	Double-blinded, controlled, OPT, CRT-P, 29 months	CRT-P reduced (1) and (2)
REVERSE[19]	(1) Percent worsened by clinical composite endpoint (2) LVESVi (3) Hosp for HF (4) Mortality	Double-blinded, controlled, OPT, CRT-P ± ICD, 12 months	Primary endpoint NS CRT-P/CRT-D reduced (2) and (3) but not (4)
MADIT-CRT[20]	(1) HF events or death (2) Mortality (3) LVESVi	Controlled, CRT-P, CRT-D, 2.4 years	CRT-D reduced (1) and (3) but not (2)
RAFT[21]	(1) Death from any cause or Hosp for HF (2) Death from any cause (3) Death from CV cause (4) Hosp for HF	Controlled, CRT-P vs CRT-D 40 months	CRT reduced (4)

6MWT = 6-minute walk test; CRT = cardiac resynchronization therapy; CRT-D = biventricular pacer with a defibrillator; CRT-P = biventricular pacemaker; CV = cardiovascular; HF = heart failure; Hosp = hospitalizations; ICD = implantable cardioverter-defibrillator; LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESVi = left ventricular end-systolic volume index; NS = not significant; NYHA = New York Heart Association; OPT = optimal medical therapy; pVO_2 = peak oxygen consumption; QOL = quality of life; VE/CO_2 = ventilation/carbon dioxide ratio.

1.1 Cardiac Resynchronisation Therapy

CRT is one of the most significant therapies for symptomatic HFrEF to be developed within the last 25 years (Daubert et al, 2012). In conventional CRT, transvenous pacing leads are implanted in the right ventricle and within the left ventricular free wall (Rinaldi et al, 2013). A right atrial (RA) lead is often implanted in the absence of atrial fibrillation. The right ventricular (RV)

lead is implanted either at the RV apex or a septal position. The left ventricle (LV) is stimulated through the myocardial wall, by passing the lead down the coronary sinus to the target vein, typically in a lateral or posterolateral position of the left ventricle (Brignole et al, 2013). Figure 1 shows the position of the 3 leads in a conventional CRT. Optimal LV lead placement differs between individuals as venous anatomy and the electrical activation sequence is patient specific (Daubert et al, 2017). The pulse generator is usually positioned in the left pectoral region underneath the collar-bone. A standard CRT pacemaker is called a CRT-P; if combined with an implantable cardioverter defibrillator, it is known as CRT-D. The battery life of a CRT is typically 5-8 years, after which time the patient may undergo a battery replacement.

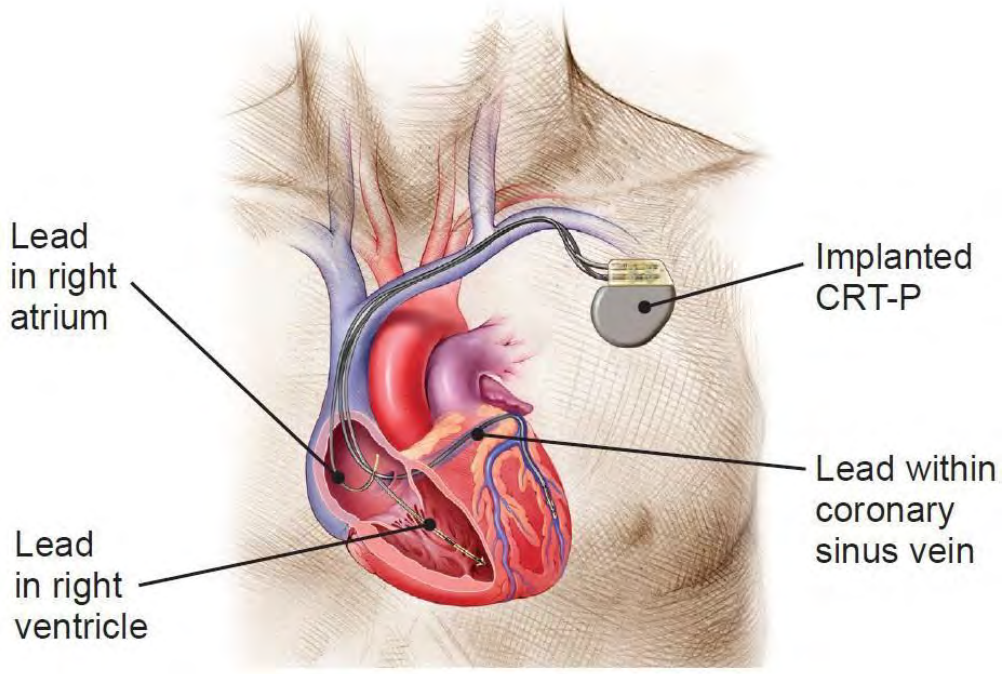


Figure 1: **Conventional CRT.** This image shows the common position of the RA, RV and LV leads within the heart, inserted by a transvenous approach. In this example, the pulse generator is implanted in the left pectoral region. Accessed by: https://www.bostonscientific.com/en-US/patients/about-your-device/crt-devices/how-crts-work/_jcr_content/maincontent-par/image.img.patients_crt-p_device_placement.jpg

The position of the RV lead has been closely studied as it was previously believed that a septal position may give haemodynamic benefit over RV apical pacing. However, despite being the focus of several trials, the evidence of long-term survival benefit is less compelling. One study demonstrated improvement in LVEF after 12 months of follow-up in pacemaker dependant patients (Molina et al, 2014). Bai et al (2016) found no significant clinical benefits of septal pacing after 12 months of follow-up, although there was a trend towards reduced dysynchrony and improved LVEF using septal pacing over apical positions. A meta-analysis of 14 randomised controlled trials (RCTs) by Shimony at el (2012) concluded that non-apical pacing was associated with better LVEF in patients with reduced ejection fraction at baseline, but there was no difference in those with preserved LVEF at baseline after 1 year of follow-up. Zhuang et al (2018) conducted a meta-analysis of 16 RCTs comparing RV apical pacing against septal or HIS bundle pacing; and whilst RV septal pacing was associated with higher LVEF, further RCTs were recommended to assess the safety and efficacy of this approach. Consequently, there remains no consensus and RV lead positioning is frequently based on operator preference.

In a healthy heart, mechanical contraction of the myocardium is coordinated by the heart's natural conduction system; formed of specialised cardiac cells which generate and facilitate rapid transmission electrical impulses across the heart. The specialised cardiac conduction system and normal electrogram (ECG) is shown in Figure 2. Initiation of a cardiac cycle begins at the sino-atrial node (SAN), which is located within the right atrium. The SAN initiates a wave of electrical excitation which depolarises across both atria and subsequently results in mechanical contraction. The depolarisation is stalled momentarily at the atrioventricular node (AVN) to enable the ventricles to fill completely with blood before they are depolarised (Padala et al, 2021). From the AVN, the wave of depolarisation travels across the Bundle of His and down both the left and right bundle branches before being disseminated across the ventricles via the purkinjee system (Padala et al, 2021). This stimulates contraction of the ventricles to pump blood to the lungs

and around the body. The electrical wavefront for a single cardiac cycle is represented on the electrogram (ECG) by the PQRST complex. The time taken for depolarisation of the ventricles corresponds to the duration of the QRS complex, measured in milliseconds (ms).

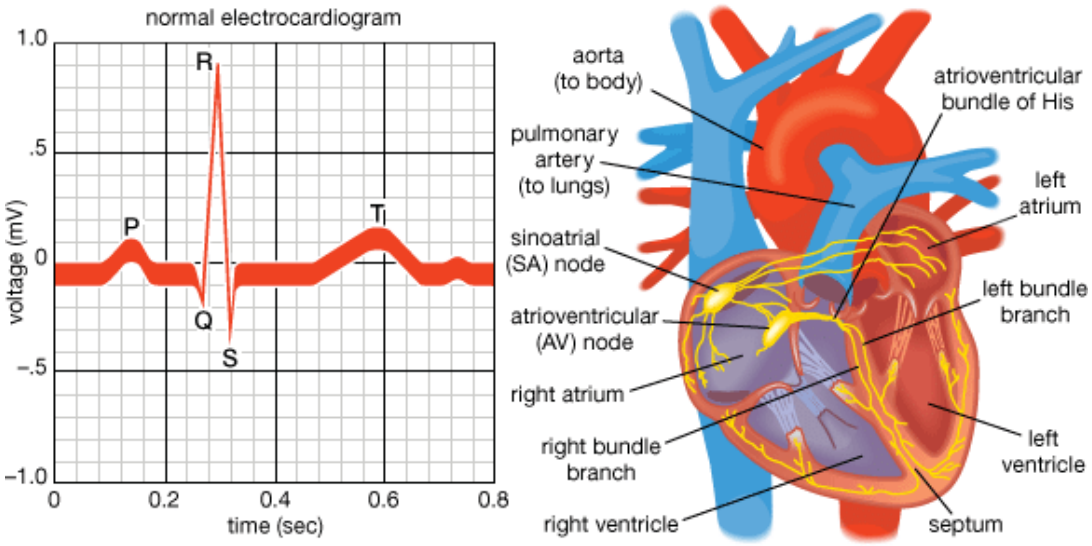


Figure 2: Cardiac Conduction System and Normal ECG. This diagram shows the main structures of the heart and components of the specialised conducting tissues. A normal healthy heartbeat is initiated by the SA node and spreads across the atria to the AV node. The electrical impulse travels down both left and right bundle branches at the same speed and the ventricles are simultaneously depolarised. An electrocardiogram (ECG) is a visual display of how electrical activity flows across the heart to stimulate mechanical contraction of the heart chambers. The PQRST waveform represents a single cardiac cycle; the P wave corresponds to depolarisation of the atria, the QRS complex represents depolarisation of the ventricles and the T wave represents repolarisation of the ventricles. The normal duration of the QRS is <0.12 seconds. Accessed by: https://www.researchgate.net/profile/Leah_Cannon/publication/267232530/figure/fig5/AS:669384368480264@1536605078618/Diagram-of-a-normal-ECG-and-the-cardiac-conduction-system.ppm

In systolic heart failure, LV remodelling and fibrogenic damage to conducting tissues can result in the development of left bundle branch block (LBBB); where the left bundle branch is no longer able to transmit electrical depolarisation across the left ventricle (Sieniewicz et al, 2018). The electrical wavefront must travel cell to cell across non-specialised myocardial tissues to stimulate the left ventricle. Electrical depolarisation of the ventricles is

subsequently slowed, leading to a broader QRS complex and longer QRS duration; the characteristic features of LBBB on the ECG are shown in Figure 3. The goal of CRT is to coordinate electrical activation sequence of the heart for more efficient mechanical contraction, which in turn may increase cardiac output (Sieniewicz et al, 2018; Brignole et al, 2013). In many cases, the left ventricle is stimulated a little earlier than the right ventricle to overcome the electrical delay caused by LBBB; ideally, the LV lead should be positioned at the site of latest activation (Daubert et al, 2017). However, the timing intervals between the ventricles is programmable and the optimal intervals vary between individuals (Varma et al, 2018). Patients are thought to obtain greatest benefit when the ventricles are paced 100% of the time (Daubert et al, 2017). CRT is a dynamic process and a useful animation is shown in Appendix 1.

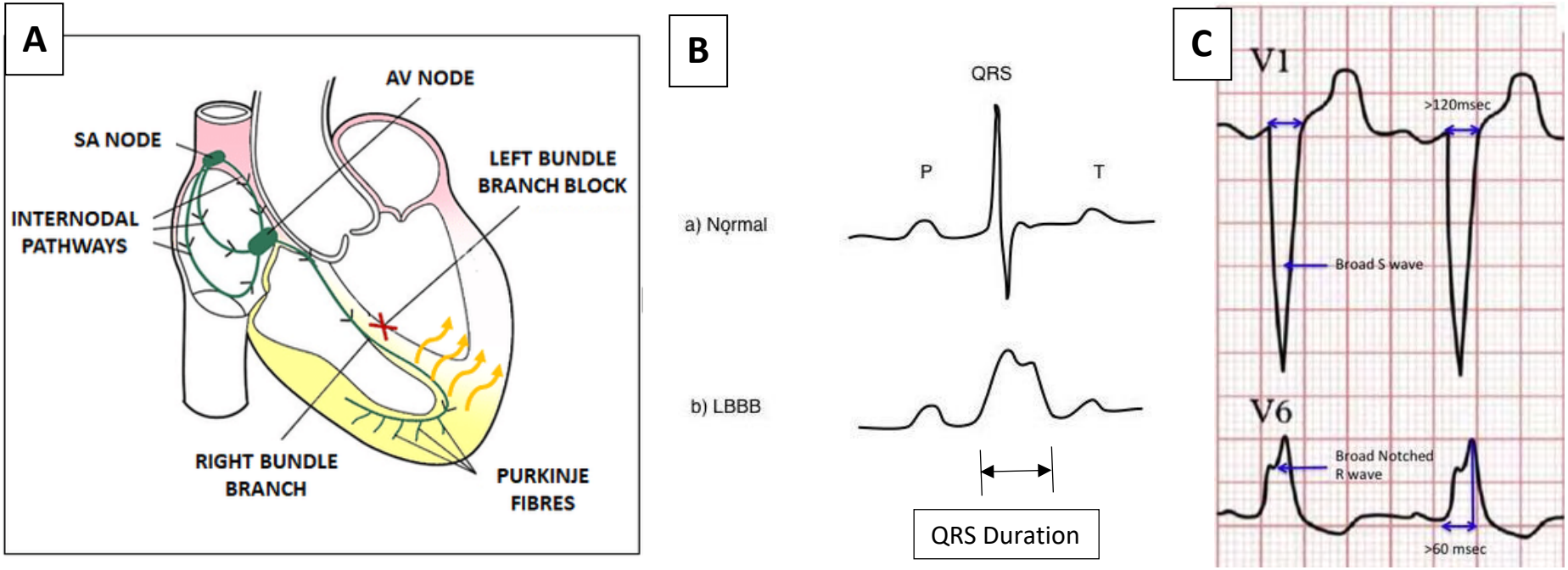


Figure 3: LBBB Characteristics.
[A] shows how block in the LBB results in slow cell-to-cell transmission of the electrical waveform across the LV (yellow arrows). [B] shows how the resulting QRS waveform becomes broad and the QRS duration is longer in LBBB. [C] shows characteristic QRS morphology of LBBB in leads V1 and V6 of the 12 Lead ECG with QRS duration >0.12 ms.

Images adapted from: https://www.researchgate.net/figure/Left-Bundle-Branch-Block-LBBB-and-the-four-coupled-oscillators-model_fig5_335620523 and https://www.google.com/url?sa=i&url=https%3A%2F%2Fwww.wikidoc.org%2Findex.php%2FFile%3ALeft_bundle_branch_block_ECG_characteristics.png&psig=AOvVaw3wzWW9OHbv-2r28KS0phmX&ust=1612790881925000&source=images&cd=vfe&ved=0CAIQjRxqFwoTCKjY567w1-4CFQAAAAAdAAAAABAJ

The 12 lead ECG can be used to observe the characteristics of cardiac pacing. QRS morphology can be a useful indicator of the presence and site of right ventricular (RV), left ventricular (LV) and biventricular capture (BiV) (Daubert et al, 2012). In summary, pacing from the RV apex typically produces a broad QRS with a negative component in lead V1, with left axis deviation. Pacing from the LV usually produces a broad complex with a positive QRS in lead V1 and right axis deviation. Conventional biventricular pacing is a combination of RV and LV pacing and typically produces a dominant positive component (R wave) in V1 and S wave in lead I, which is widely considered to be an indicator of successful biventricular pacing (Daubert et al, 2012). Figure 4 shows the 12 Lead ECG characteristics of pacing from different sites within the heart.

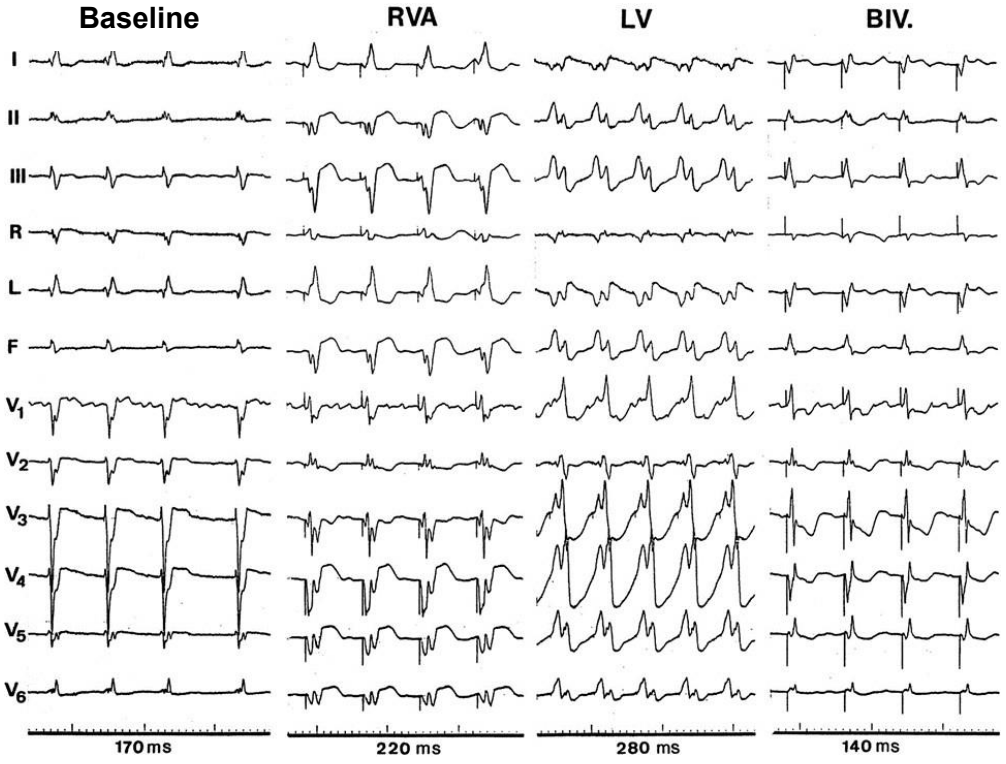


Figure 4 ECG characteristics of cardiac pacing.
Changes in QRS morphology and duration during RV apical pacing (RVA), LV lateral pacing (LV) and biventricular (BiV) pacing. Baseline ECG shows underlying atrial fibrillation and LBBB. Image from Daubert et al (2012).

1.2 CRT Response

Not all patients respond favourably to CRT (Ponikowski et al, 2016; Tomassoni, 2016a). It is widely considered that up to 30% of patients are thought to be clinical non-responders and up to 50% do not achieve reverse remodelling (Trucco et al, 2018; Tomassoni, 2016a). Daubert et al (2012) pooled data from multiple CRT trials which highlighted the great variation in CRT non-responder rates at between 15-45%. This constitutes poor value for money for a relatively expensive and invasive therapy (Molhoek et al, 2004). Notably non-responders have worse outcomes due to lesser degree of ventricular remodelling but so-called super responders do extremely well (Ponikowski et al, 2016; Moss et al, 2009). The absence of deterioration may also be considered as a positive response to CRT in such a progressive condition (Tomassoni, 2016a; Bax and Gorcsan, 2009). For example, in two large CRT trials, an *unchanged* category was included, in addition to improved and worsened (Forleo et al, 2017, Niazi et al, 2017).

The cause of CRT non-response is not well understood (Leclercq et al, 2019). Multiple factors are thought to influence response to CRT, as shown in Figure 5. These can be broadly classified into patient selection, technical limitations during implantation and programming post implant (Mullens et al, 2009; Sieniewicz et al, 2019). Suboptimal lead placement is considered one of main factors, but in many cases this is unavoidable due to patient anatomy (Leclercq et al, 2019). High pacing threshold and phrenic nerve stimulation can also be difficult to overcome (Zanon et al, 2015). Figure 5 does not reference other causes of patient symptoms, such as Chronic Obstructive Pulmonary Disease (COPD). HF patients often have multiple comorbidities, which may influence their response to CRT (Daubert et al, 2012). These patients are usually excluded from clinical trials, hence CRT is not well understood in these cohorts.

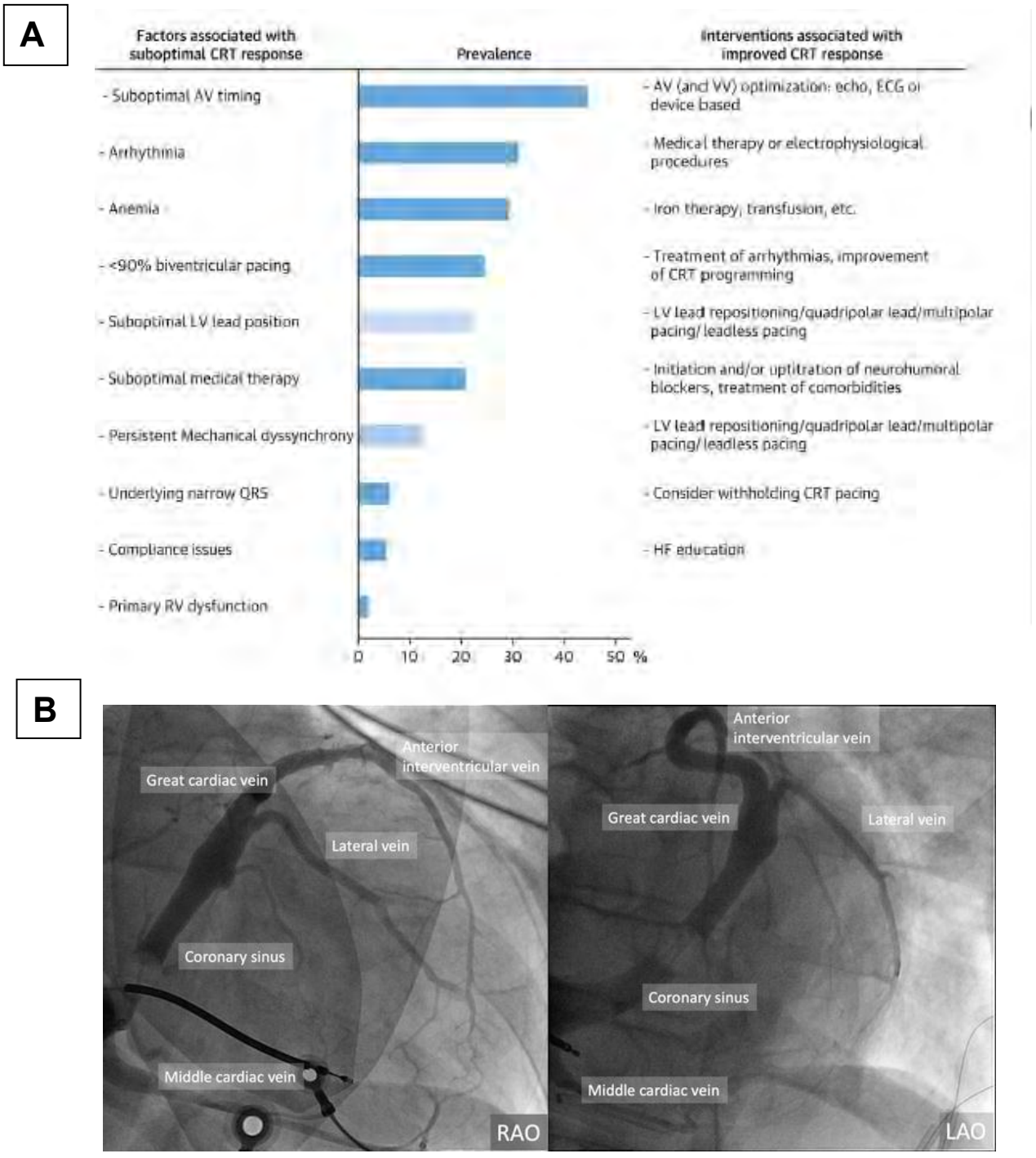


Figure 5 Factors associated with sub-optimal CRT response. [A] shows the main factors of suboptimal CRT response & frequency. Adapted from Mullens et al (2009) and reproduced from Sieniewicz et al (2019). [B] shows fluoroscopy of the coronary sinus in RAO and LAO views. The ideal lead position is a lateral branch with the ability to pace from a basal position. Accessed by: https://api.intechopen.com/media/chapter/66474/media/F1.png

Landmark studies have defined the patient populations most likely to benefit, culminating in the current consensus criteria for CRT implantation: symptomatic heart failure, left ventricular ejection fraction (LVEF) <35%, broad QRS duration with complete left bundle branch block morphology, in sinus rhythm and on optimal medical therapy (Ponikowski et al,2016; Daubert et al, 2012; Brignole et al, 2013). Importantly, subgroup analysis has identified further categories of patients most likely to respond to CRT. This includes females, non-ischaemic cardiomyopathy, left bundle branch block morphology and wider QRS complexes (Brignole et al, 2013). The evidence of benefit in patients with non-LBBB is less convincing (Brignole et al, 2013, Daubert et al, 2012). The aetiology of HF can also influence response; ischaemic aetiology and greater scar burden can result in ineffective CRT and give rise to worse clinical outcomes (Daubert et al, 2012).

Importantly, QRS duration has been shown to be a strong predictor of CRT response based on morbidity and mortality and has shown increasing benefit with longer QRS durations, particularly >150 ms (Siphani et al, 2011; Cleland et al, 2013, Tomassoni, 2016a, De Pooter et al, 2017). Recent evidence suggests that CRT can even be harmful in patients without prolonged ventricular activation and QRS <130ms (De Pooter et al, 2017; Bernard et al, 2017). Conversely, it has been suggested that QRS duration does not correlate to mechanical desynchronisation, hence should not be used to predict responders (Mollo, et al, 2013). Nevertheless in clinical practice, QRS duration is the parameter of choice in patient selection (De Pooter et al, 2016).

Currently, there is no consensus on the universal definition of a CRT responder (Sieniewicz et al, 2019; Tomassoni, 2016a). Wide variation exists across research trials, with clinical assessments producing greater outcomes than functional assessments (Sieniewicz et al, 2019; Tomassoni, 2016a). One study compared definitions of CRT response for 26 of the most cited publications and found 17 different criteria for measuring response (Fornwalt

et al, 2010). 15 of these criteria were applied to the PROSPECT cohort of positive responders and showed poor agreement with response rates ranging from 32% to 91% (Fornwalt et al, 2010).

Moreover, there is no universally agreed timeframe to assess response to CRT (Sieniewicz et al, 2019; Tomassoni, 2016a). Variation in follow-up periods is observed in clinical trials (usually between 6 and 12 months), leading to disconnection between research and clinical practice (Tomassoni, 2016a). Disease progression in heart failure is often highly variable, adding weight to the view that distinct endpoints are less applicable in the real world (Tomassoni, 2016a). However, a follow-up period of 6 months has been described in the design of the more recent CRT studies and appears to be generally accepted (Leclercq et al, 2019, Forleo et al, 2017, Niazi et al, 2017; Daubert et al, 2017).

1.3 Measures of CRT Response

Several techniques have been utilised in the measurement of CRT Response (as shown in Table 2) and each method has limitations. Hard outcome measures (e.g. heart failure hospitalisation and death) tend to be the least biased but are less frequently used in clinical practice as they typically require a longer timescale and are less useful for current patients (Tommasoni, 2016a; Linde et al, 2012). Subjective assessments (such as New York Heart Association, NYHA) may give rise to the placebo effect and not correlate with reverse remodelling (Sieniewicz et al, 2019; Tommasoni, 2016a).

Some clinical trials now utilise a clinical composite score (CCS) across the different categories of measurement to account for these discrepancies (Linde et al, 2012; Tommasoni, 2016a; Bernard et al, 2017). However, there is even disparity in the composition of CCS; some utilising clinical and functional measures, others combining clinical measures with echocardiographic

parameters (Fornwalt et al, 2010). This lack of agreement may be a barrier to progression in this field (Fornwalt et al, 2010).

Table 2 Measures of CRT response.
The table below shows typical measures that have been used to measure CRT response in clinical trials. These can be separated into 3 main groups: clinical measures (including functional measures); assessment of LV reverse remodelling and hard outcome measures.

Clinical Measures
• New York Heart Association (NYHA) Class – improvement in one class • Minnesota Living with Heart Failure Questionnaire (MLHFQ) – reduction in symptom burden • Six minute walk test (6MWT) – 10% improvement in distance • Metabolic exercise testing (CPET)
Assessment of LV reverse remodelling
• Angiography: Cardiac Output; LVdP/dtmax • Echocardiography: 5% increase in LVEF, 15% reduction in LV end diastolic volume, reduction in mitral regurgitation (MR)
Hard Outcome Measures
• Reduction in Heart Failure Hospitalisation (HFH), morbidity and all-cause mortality

The use of echocardiography techniques for CRT response in clinical practice remains unproven and latest guidelines do not recommend echocardiography or indeed, any other imaging parameters when assessing response to CRT (Aalen et al, 2020; Ponikowski et al, 2016). There are inconsistencies in the evidence for echocardiographic parameters and concerns over poor correlation with long-term clinical response (Bernard et al, 2017; Tommasoni, 2016a; De Pooter et al, 2016). The PROSPECT trial (n=467) concluded that none of the 12 echocardiographic parameters assessed were able to predict

CRT responders from non-responders ‘to a degree that should affect clinical decision making’ (Chung et al, 2008). The MIRACLE study was one of the landmark trials for CRT-P (n=453), importantly this showed improvement in quality of life and functional measures with corresponding improvements in echocardiographic parameters (decreased left ventricular end diastolic dimension, increased LVEF and reduced mitral regurgitation) (Abraham et al, 2002). Fornwalt et al (2010) suggested that the relationship between LV End-diastolic volume and NYHA improvement was actually poor in MIRACLE (r=0.13), similarly for 6MWD and change in Left Ventricular Ejection Fraction (LVEF) (r=0.15). Interestingly, MIRACLE ICD showed similar improvements in clinical parameters in patients implanted with CRT-D, although improvements in the echocardiographic parameters were described as ‘less compelling’ (Young et al, 2003).

Furthermore, echocardiography is time consuming and requires access to specialist equipment and personnel (Gras et al, 2009). This is a particular challenge for the National Health Service in today’s climate, with a national shortage in trained Cardiac Scientists and Echocardiographers (BCS, 2015). Furthermore, in CRT responders, only modest improvements in imaging parameters are expected (5% increase in LVEF ± 15% decrease in LV end diastolic volume); this overlaps with inter-operator variability and is dependent on image resolution, which is often suboptimal in this patient group (Mollo et al, 2013). Importantly, high levels of intra-operator and inter-operator variability were noted in the PROSPECT trial (Chung et al, 2008). Missing data was noted in the REVERSE study which was due to image resolution (Sutton et al, 2015). Hence, routine echocardiography assessment of LV remodelling is not standard in the everyday setting.

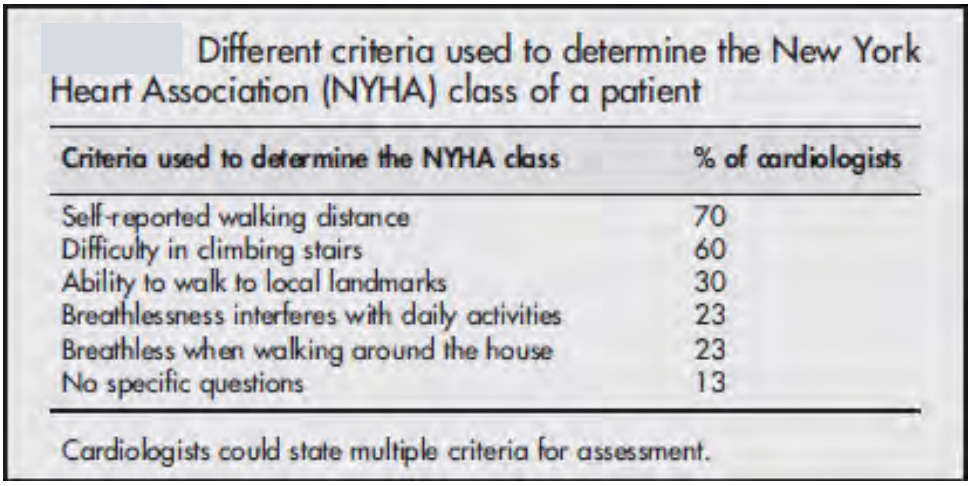
Despite this, echocardiography measures remain popular in clinical trials for CRT, although there is a drive to develop other imaging predictors of CRT response. Left ventricular work asymmetry by echocardiography and septal

viability by cardiac magnetic resonance (CMR) were shown to correlated to left ventricular end systolic volume (LVESV) in one recent trial (n=200)(Aalen et al, 2020). Importantly, this study used a single endpoint of 15% reduction in LVESV, the evidence for which has yet to be proven. However, CMR is even less accessible than echocardiography as a routine tool for assessing CRT response (Aalen et al, 2020; O'Donnell et al, 2020). Furthermore, whilst most newly implanted devices are MR conditional, not all hospitals have adapted protocols to cater for this patient group. Additionally, there is a large group of patients with legacy devices or redundant leads who are contraindicated for CMR (Aalen et al, 2020). In clinical practice there appears to be a divide between those that favour clinical measures and those preferring imaging or echocardiography measures. This means that emerging models of measuring CRT response vary between institutions, making comparisons difficult.

In real life, clinical and functional measures are simple, efficient and easy to access in the clinical setting. Arguably, they may provide more valuable information to the care team whose predominant goal is to manage patient wellbeing (Tomassoni, 2016a; Daubert et al, 2012). Crucially for non-CRT patients, clinical measures are used as standard in assessing a patient's response to HF medication. There are three main techniques to assess functional capacity in this cohort: Cardiopulmonary Exercise Testing (CPET), New York Heart Association (NYHA) classification and Six Minute Walk Test (6MWT). The gold standard measure of functional capacity is CPET (Giannitsi et al, 2019). This measures exercise tolerance by direct cardiorespiratory assessment of peak oxygen consumption (peak VO2) via a symptom limited exercise test. This is often performed using an exercise bicycle, but a treadmill can also be used. Conversely, many HF patients are contraindicated due to severe functional limitations or comorbidities. Furthermore, this test is expensive and requires specialist equipment and personnel, hence is not widely utilised in this patient group.

The most universally adopted measure in clinical practice is the NYHA classification, which was first proposed in 1928 (Raphael et al, 2007). NYHA features in multiple, large clinical trials regarding morbidity and mortality, often as both an inclusion and outcome measure (Giannitsi et al, 2019; Pocock et al, 2013; Raphael et al, 2007). In a large meta-analysis of almost 40,000 heart failure patients (data from over 31 studies), NYHA was identified as a strong predictor of mortality (Pocock et al, 2013).

Table 3 Different criteria used to assess NYHA class. This was reproduced from Raphael et al (2007). In this study, Cardiologists were shown to use different criteria when assessing NYHA Class and poor standardisation.



Different criteria used to determine the New York Heart Association (NYHA) class of a patient

Criteria used to determine the NYHA class	% of cardiologists
Self-reported walking distance	70
Difficulty in climbing stairs	60
Ability to walk to local landmarks	30
Breathlessness interferes with daily activities	23
Breathless when walking around the house	23
No specific questions	13

Cardiologists could state multiple criteria for assessment.

NYHA is an assessment of the patient's physical capacity based on limitations of daily activities. This can be self-assessment or more often physician-reported but is based on the patient's perceived limitations, incurring an element of subjectivity (Fu et al, 2016). It has been suggested that a more standardised approach to assessing NYHA is required. Raphael et al (2007) reported poor concordance between Cardiologists, particularly in assessing NYHA class II and class III. This study had a small sample size of 50 patients and class I and IV were not well represented. However, it highlighted significant variation in how NYHA is assessed as shown in Table 3 and suggested that self-reported walking distance from the patient has little

correlation to functional measures. Despite its weaknesses, NYHA is a quick, efficient and cheap technique which can be applied without specialist training.

An alternative to the physician derived measure of functional capacity, is the patient self-assessment. This can be achieved in the form of a questionnaire. The Minnesota Living with Heart Failure Questionnaire (MLHFQ) is a well established tool which has been used in several studies of HF (Fu et al, 2016). The MLHFQ is a series of questions in which patients are asked to grade the degree of quality of life impairment whilst performing different activities of daily living. A score between 0 and 105 will be determined, with higher scores relating to more significant HF symptoms. Repeating the MLHFQ before and after treatment can give an indication of progress. Various health related quality of life questionnaires (HRQL) have been developed to explore patient perceptions of wellbeing (Bilbao et al, 2016). The MLHFQ is the most widely adopted and has been translated into multiple different languages, emphasising its universal use (Bilbao et al, 2016). A systematic review of seven common HRQL questionnaires identified MLHFQ as one of the best, in conjunction with the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the Chronic Heart Failure Questionnaire (CHFQ) (Garin et al, 2014). The MLHFQ gives an overall score which critics have suggested is unidimensional, however it has also been argued that MLHFQ also covers physical, emotional and social dimensions (Bilbao et al, 2016). The validity and reliability of MLHFQ has been shown by a large cohort of HF patients (n=2565) at different hospitals (Bilbao et al, 2016).

The Six Minute Walk Test (6MWT) is a more widely adopted measure of functional capacity. The 6MWT is simple, inexpensive functional test that is well tolerated by patients with advanced disease states (Giannitsi et al, 2019). Standard methodology for 6MWT was proposed in 2002 the American Thoracic Society (ATS, 2002). These guidelines were later updated by both the American Thoracic Society and European Respiratory Society (Holland et

al, 2014). The 6MWT has prognostic value in morbidity and mortality and can be used before and after treatment in many patient populations (Giannitsi et al, 2019).

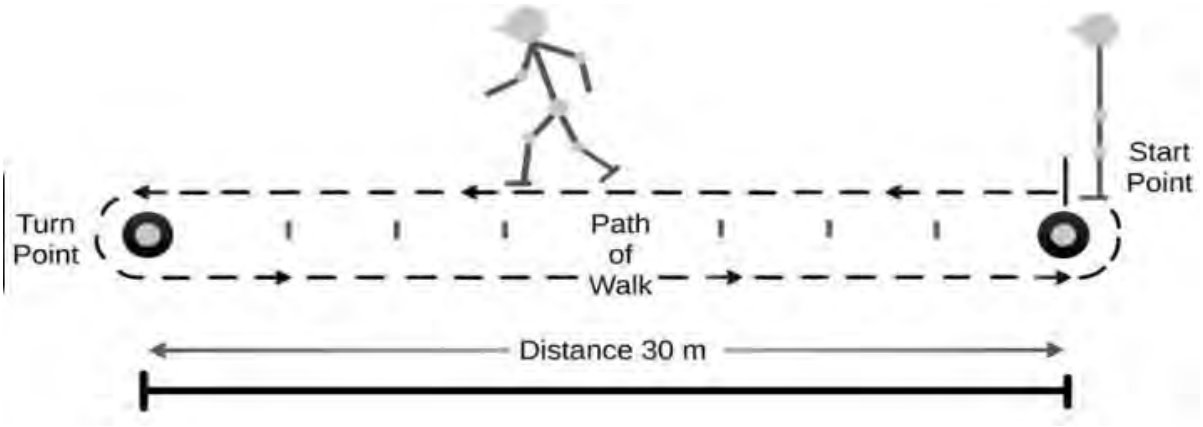


Figure 6 An example of a 6MWT circuit.
This diagram shows a typical 30 metre circuit. These are usually marked out by cones. The patient is asked to walk for a far as they can within 6 minutes; they can stop as many times as they need to but the clock will keep going. The patient should walk at their own walking pace. The total distance walked is measured in metres and known as the six minute walk distance (6MWD).

The test is performed on a flat circuit, usually 30 metres long and marked out by cones, as shown in Figure 6. Shorter circuits (e.g. 15 metres) can be used but are thought to increase the 6MWD due to an increased number of turns. Hence, these should not be directly compared to 30 metre circuits. The patient is asked to walk at their own pace for as long as they can within 6 minutes, stops are allowed. The total distance walked is known as the 6MWD (in metres). There have been suggestions of a learning affect, particularly in paediatrics but this is less significant in older patients (Giannitsi et al, 2019). Studies have shown good reproducibility providing adherence to a set protocol (Giannitsi et al, 2019).

Research has concluded that CPET parameters, such as peak VO2 or anaerobic threshold are the best markers of functional capacity in the HF population, particularly those with reduced EF (Giannitsi et al, 2019). Importantly, several studies have shown correlation between 6MWD and peak aerobic capacity (which is known as peak VO2) measured by CPET in this patient group (Giannitsi et al, 2020; Guyatt et al, Cahalin et al). Conversely, one trial found that 6MWD did not correlate with CPET parameters in patients with HF and preserved ejection fraction (Maldonado-Martin et al, 2017). Nevertheless, 6MWT is accepted as a submaximal test which provides prognostic information, similar to peak VO2 in the absence of CPET or a marker of maximal exercise in those with severe functional impairment, specifically in patients with HF and reduced LVEF (Giannitis et al, 2019).

The relationship between NYHA and 6MWT is less well established, with multiple studies indicating a mild/moderate inverse correlation between the two (Uszko-Lencer et al, 2017; Wegrzynowska-Teodorczyk et al, 2013). A systematic review further supports an inverse correlation, particularly in NYHA class II-IV (Yap et al, 2015). Greater overlap was found between NYHA classes I and II (Yap et al, 2015). Furthermore, there are other factors which have been associated with reduced 6MWD, notably advancing age, female sex, low body mass index, anaemia, high resting heart rate, diabetes and renal insufficiency (Giannitsi et al, 2019). Importantly, depression has also been shown to negatively impact 6MWD (Omar et al, 2017; Ingle et al, 2006). The link between depression and chronic conditions such as HF is well established, hence performing the test during low mood may result in underestimation of functional capacity. If 6MWD was used to assess functional improvement to CRT alone, a depressive episode may result in a patient being classed as a non-responder, leading to increased follow-up and further compromising mental state in a downward spiral.

The overall 6MWD has been researched and the evidence suggests that a distance of 300 metres or less is indicative of a poor prognosis (Cahalin et al, 1996, Rostagno et al, 2000). One meta-analysis showed a moderate relationship between 6MWD and quality of life with an increase in 6MWD of approximately 80 metres translating into improved quality of life. A much more conservative increase of 30-50 metres has been shown to improve morbidity and mortality in HF patients (Ciani et al, 2018). The MADIT-CRT study showed that patients with a baseline 6MWD of <350 metres were most likely to benefit from CRT (Brenyo et al, 2012). Conversely, in the study centre, a small, unpublished trial of 64 patients identified that NYHA was the only significant predictor of response (Wilburn et al, 2020).

The strengths and weaknesses of different measures of CRT response have been discussed. There is no consensus of opinion and experts are split on which is the preferred method (Daubert et al, 2017). The study centre had recently adopted a system for measuring CRT response. This was a clinical composite score (CCS) to overcome subjectivity in the individual methods (NYHA, MLHFQ, 6MWT). Positive response was defined as 2/3 of the following: ≥10% improvement in 6MWD, ≥1 class improvement in NYHA and ≥15 point improvement in MLHFQ. There was little available evidence of CRT response being measured in everyday practice, hence the study centre was trail blazing in this capacity.

Currently, the assessment of CRT response in real world practice is highly variable and not well described. UK guidelines for device follow-up were updated in 2020 to include the statement *'Follow-up services should have a protocol to measure CRT response and identify non-responders'* (BHRS, 2020). However, there is no further guidance on this subject and certainly they do not suggest a timeline (BHRS, 2020). Assessment of CRT response in UK device clinics is thought to be largely neglected and opportunity for CRT optimisation is frequently overlooked.

1.4 Achieving Optimal CRT

The goal of CRT is to restore electrical synchrony in patients with poor ejection fraction and a delay in ventricular activation (Varma et al, 2018). Achieving a reduction in QRS duration seems intuitive to achieve a superior outcome from CRT (Varma et al, 2018). Reducing the QRS width by CRT has been shown to favour a positive response (Gold et al, 2012). Evidence shows that the greatest percentage reduction in QRS duration is associated with improved response and is the only predictor of response in some series (Rickard et al, 2011; Rickard et al, 2013). Importantly, a recent large randomised controlled trial showed that QRS narrowing can now predict long- term survival in patients with LBBB (Jastrzebski et al, 2018). However, QRS narrowing in CRT is not a new concept. In 2005, Lecoq et al (2005) demonstrated that QRS shortening was the only independent predictor of CRT response in 139 participants.

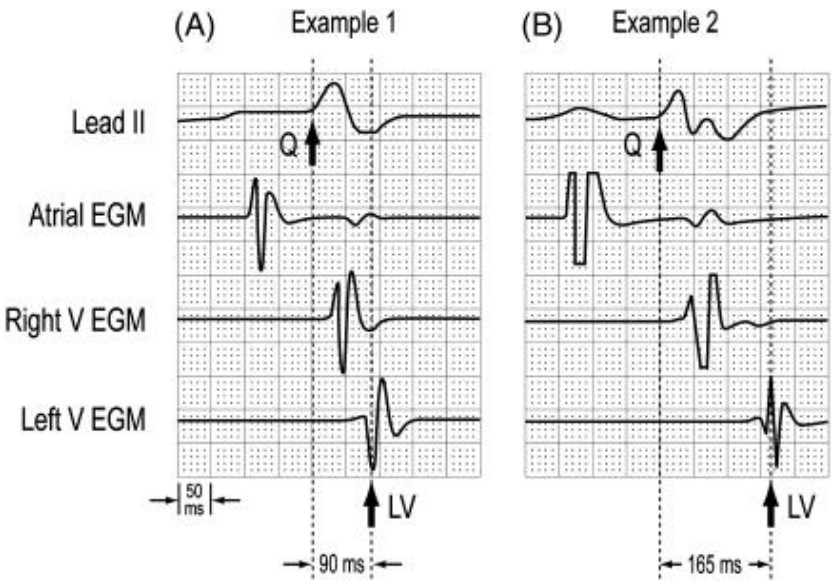


Figure 7 Measurement of QLV.
This is measured from the onset of the QRS on the surface ECG (shown by Lead II) to the first large deflection on the LV electrogram (shown by Left V EGM). In example 1 [A] QLV measures 90 ms, whereas in example 2 [B] QLV measured 165 ms. QLV is measured during implantation, to determine that the lead is positioned at a late point of activation; aiming for 2/3 of the duration of the baseline QRS (ms).

Much attention has focussed on the technical aspects during implant to achieve best CRT; such as the placement of the LV lead away from scar and efforts to pace the left ventricle at the site of latest activation by measuring QLV (interval from QRS onset to first large deflection of the LV electrogram) (Rademakers et al, 2010; Khan et al, 2012, Daubert et al, 2012; Zanon et al, 2016). The measurement of QLV is shown in Figure 7. Roubicek et al (2015) showed that a QLV within the terminal 30% of the intrinsic QRS complex is associated with a reduction in heart failure mortality and all-cause mortality during long-term follow-up. For this reason, operators aim for a QLV which is two thirds of the baseline QRS duration. Electrical programming of CRT devices post implant is becoming an area of great interest, with particular focus on atrioventricular (AV) and interventricular (VV) timing intervals (Varma, 2016; Trucco et al, 2018). Figure 8 describes AV and VV timing intervals.

The best method to optimise AV and VV timing of CRT devices post implant remains unproven (Brignole et al, 2013). Methods to electrically optimise CRT settings by either echo-guided programming or static device-based algorithms have yielded inconclusive results (Varma et al, 2018; Brignole et al, 2013). This is most likely because these techniques are performed at a single point in time and do not account for dynamic changes to AV timing which occur during activities, medication or disease progression (Gras et al, 2009; Thibault et al, 2019). The iterative method of Doppler echocardiography to optimise AV and VV delays was formerly classed as the reference measure, although large multicentre studies have shown this is largely ineffective (Sieniewicz et al, 2019). Overall, echo optimisation of CRT is time-consuming, unreliable and impractical in routine clinical practice and is restricted to use in clinical non-responders currently (Trucco et al, 2018; Gras et al, 2009).

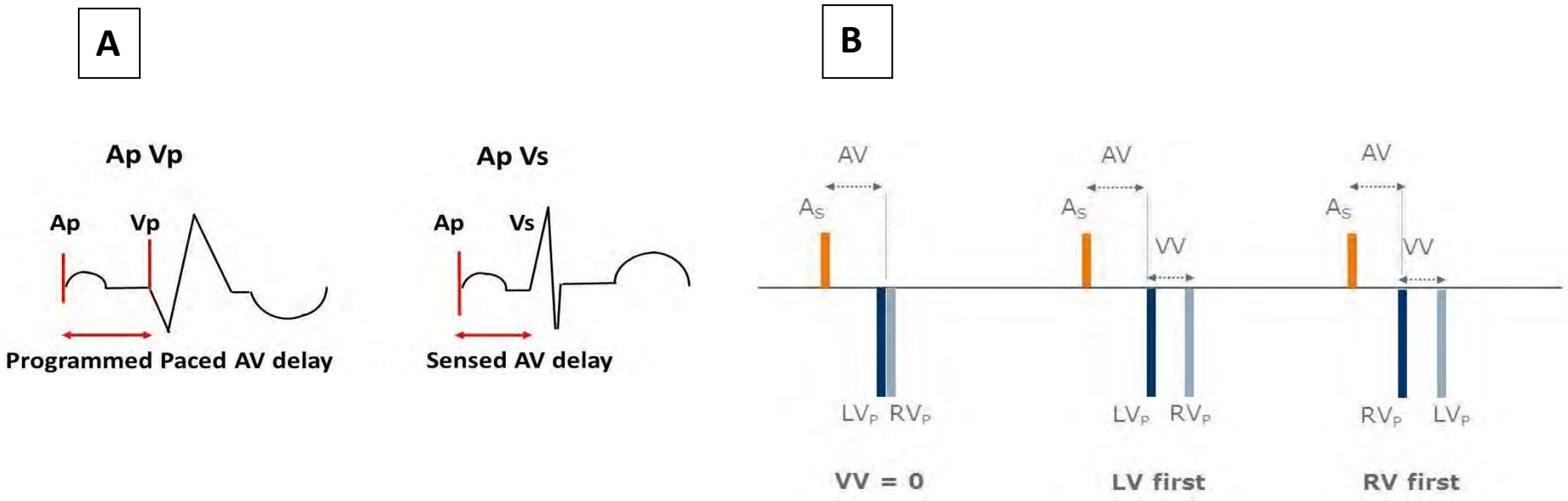


Figure 8 Atrioventricular (AV) and interventricular (VV) timing. Diagram [A] AV timing refers to the interval between the start of the P wave and the start of the QRS (whether paced or sensed). Too long an AV delay and the intrinsic QRS may conduct through; a long AV delay can also promote diastolic MR. Too short an AV delay and atrial contraction may not be fully complete before the ventricles contract, reducing the atrial component to cardiac output. Diagram [B] VV timing refers to the interval and sequence between RV (RVp) and LV (LVp) pacing stimulation. VV=0 means that both ventricles are stimulated simultaneously; or the LV can be stimulated before the RV to overcome the delay caused by LBBB, alternatively the RV can be stimulated before the LV. The interval between LV and RV pacing (VV duration) is programmable in ms. The intrinsic activation sequence is patient specific, hence optimal VV timing can vary between individuals. [A] reproduced from Cardioscan, accessed by: https://uk.cardioscan.co/blog/resource/the-bizarre-atrioventricular-av-delay/ ; [B] reproduced from Biotronik and accessed by: https://slideplayer.com/slide/276837/

Within the United Kingdom, CRT follow-up is led predominantly by Cardiac Scientists (BHRS, 2020). Current guidelines offer limited programming recommendations for CRT optimisation and there is only a small amount of research in this area (Varma et al, 2018; Brignole et al, 2013; BHRS, 2020). Hence, device programming and optimisation is left to the discretion of the operator and settings are often left at nominal or suboptimal parameters (Varma et al, 2018; Gras et al, 2009; Brignole et al, 2013). Furthermore, QRS narrowing (as a surrogate for best CRT) is affected by patient specific factors such as PR interval, intrinsic QRS duration, QLV and site of depolarisation (Varma et al, 2018). Hence a universal strategy for programming AV and VV intervals will be ineffective (Varma et al, 2018; Thibault et al, 2019). There is a wide range of CRT programming options available to Cardiac Scientists, as shown in Table 4; hence additional guidance is necessary for optimal therapeutic use (Thibault et al, 2019; Varma et al, 2018).

Table 4 Common Electrical Programming Options for CRT.
Typical options for programming CRT devices; ranges from default settings to manual adjustment and special manufacturer specific techniques. There is little national guidance for programming CRT.

Common Electrical Programming Options for CRT
Nominal Out of the Box settings
Manual AV and VV timing adjustment
Static automated device-based algorithms e.g. QuickOpt, SmartDelay
Echocardiography guided AV and VV Optimisation
Automated dynamic device-based algorithms (fusion pacing) e.g. SyncAV or AdaptivCRT
Single-point biventricular pacing
Multi-point biventricular pacing (MPP)
Contractility sensor-guided automatic optimisation e.g. SonR

In 2013 ESC guidelines recommended empirical settings for CRT programming with fixed AV delays at 100-120 ms and simultaneous VV timing (Brignole et al, 2013). However, in clinical practice this advice is considered largely outdated, and operator preference and manufacturer guided programming is becoming more common (BHRS, 2020). BHRS updated their guidelines for Device Follow-Up in February 2020 (BHRS, 2020). The lack of guidance for Physiologists is acknowledged and whilst reference is made to utilising algorithms for AV/VV timing and specifying end goals (such as QRS narrowing); there is still no definitive advice on CRT optimisation.

1.5 Fusion pacing

The latest research to emerge from a small number of studies, suggests that best CRT can be achieved by fusing intrinsic ventricular activation with biventricular pacing stimulation to obtain narrower QRS complexes (Trucco et al, 2018; Varma et al, 2018; Thibault et al, 2019). Figure 9 describes the activation sequence in biventricular and fusion pacing.

The study by Trucco et al (2018) was performed in a standard CRT population and had a relatively large sample size of 180 patients and evenly matched randomisation groups. In this study, AV and VV intervals were manually adjusted to achieve a fusion interval as demonstrated by QRS narrowing. The results showed that fusion pacing achieved greater LV remodelling and QRS narrowing, than nominal settings using a follow-up period of 1 year and assessing CRT response by a composite endpoint (>10% increase in 6MWT or 1 class improvement in NYHA; plus decrease of LVESV of ≥15%). There was no significant difference noted in clinical response, although this was defined by an increase in only one of two measures (>10% increase in 6MWT or 1 class improvement in NYHA). A combination of two or more clinical measures may have been more sensitive to changes in functional capacity and counter subjectivity. The echocardiography measures of LVEF and LV

volumes were obtained by biplane Simpson's rule from apical 4 and 2 chamber views. Arguably, these parameters are difficult to obtain consistently in HF patients and it is unclear whether the full echo dataset was obtained in all patients.

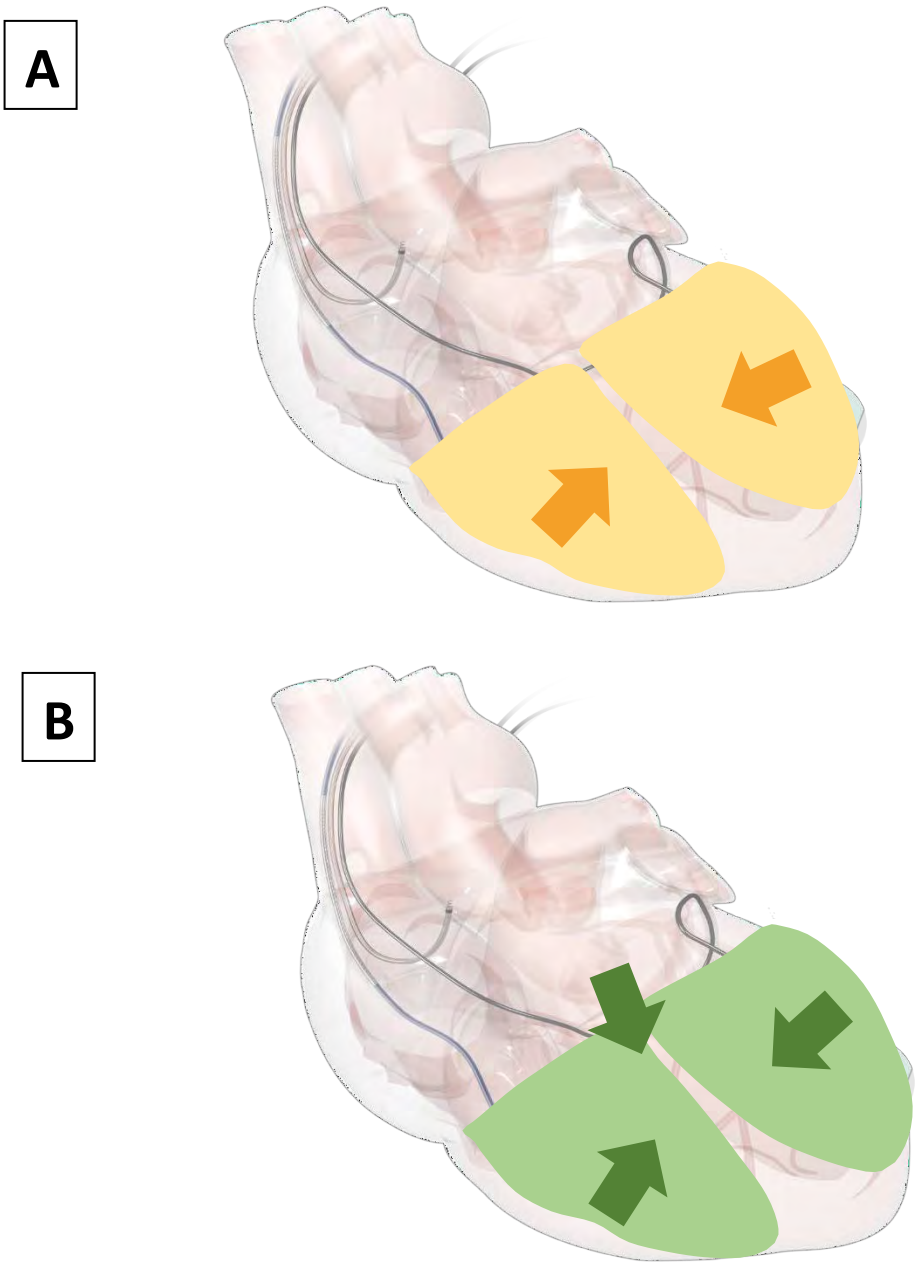


Figure 9 Activation wavefronts in biventricular and fusion pacing.
[A] shows single point biventricular pacing with two activation wavefronts; one from RV pacing and one from LV pacing. [B] shows fusion pacing with three activation fronts allowing depolarisation from bundle of HIS to the proximal bundle branches plus RV and LV pacing. The timing of wavefronts (fusion interval) can influence contribution of intrinsic depolarisation towards the resulting ventricular contraction.

A key factor was that the fusion methodology used in this study was not dynamic, hence was unable to respond to natural physiological variation over time. This may result in suboptimal CRT until the next in-house clinical assessment (Thibault et al, 2019). Despite this, the results demonstrate that fusion pacing, in particular individually optimised fusion intervals, may be beneficial in CRT patients with intact AV conduction. An important benefit of utilising a manual method to achieve fusion, is that it can be applied across all manufacturers of CRT devices to enhance its application into clinical practice, whereas automated methods are manufacturer specific and may come at a premium cost.

SyncAV CRT is a device-based algorithm that automatically and dynamically adjusts the AV timing to achieve fusion pacing, hence has advantages over the manual method described above (Varma et al, 2018). Nominal SyncAV measures intrinsic PR intervals and reduces AV timing by a 50 ms default, although SyncAV delta can be adjusted to achieve individualised SyncAV fusion timing. Varma et al (2018) assessed acute impact of SyncAV compared to nominal settings using QRS narrowing as the endpoint. This study utilised a small sample size of 75 patients but was adequately powered and showed that individualised SyncAV programming was superior to both nominal CRT and nominal SyncAV settings to achieve maximal QRS narrowing. The standard CRT population was studied, hence the results are transferable. SyncAV CRT is trademarked, hence is applicable to one device manufacturer only, but this created consistency in the results. This study however did not consider how the different strategies influenced patient outcomes, which is the main objective of CRT.

An earlier study from 2014 demonstrated that normalisation of the QRS in leads V1 and V2 can be used to predict positive ventricular remodelling in patients with LBBB (Sweeney et al, 2014). The biventricular wave propagation sequence is reflected in the characteristics of the QRS complex in the surface

ECG, hence fusion pacing restores synchronous activation and the resulting waveform can appear to normalise, as shown in Figure 10 (Sweeney et al, 2014). This study categorised the resulting QRS morphologies post CRT into 3 types: Type 1 (conformation change), Type 2 (normalisation) and Type 3 (persistent LBBB). Type 2 waveforms gave the strongest prediction of remodelling followed by Type 1, which gives a biphasic waveform in V1 and is the waveform most frequently obtained for best single point biventricular pacing. This suggests that fusion pacing is superior to single point biventricular pacing for predicting outcomes and the study was relatively large with 375 patients.

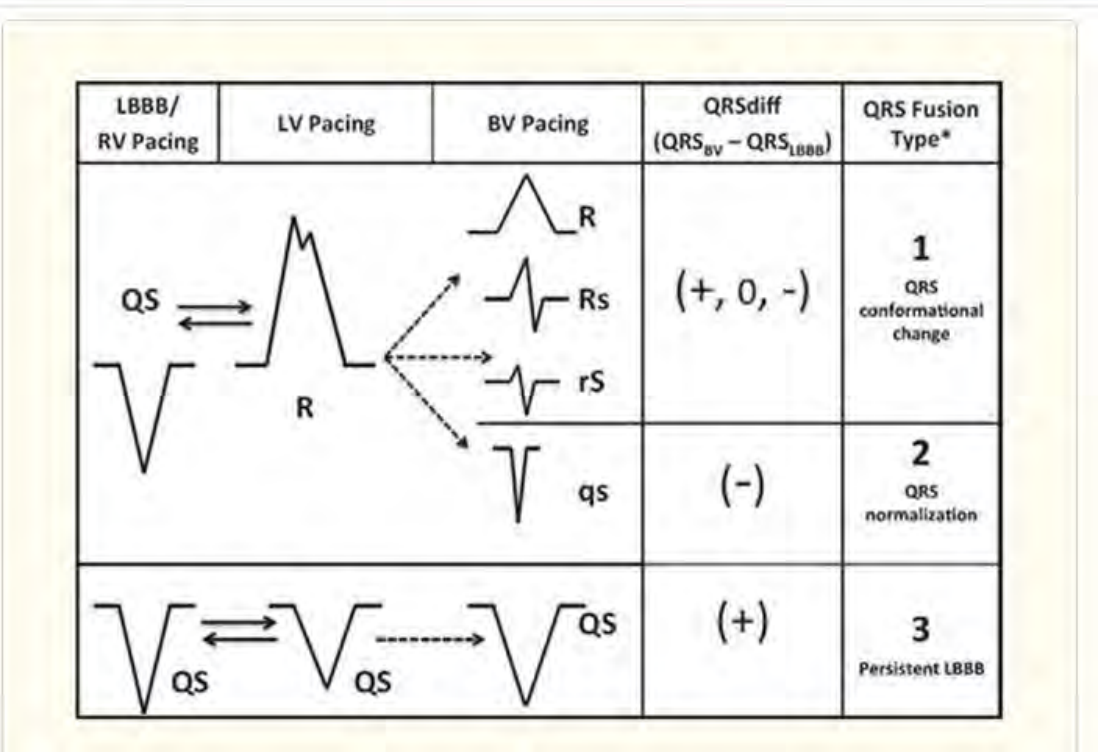


Figure 10 Type I, II and III CRT waveforms.
Wave interference for QRS fusion analysis. Type 1 corresponds to best single point biventricular pacing. Type 2 corresponds to the waveforms commonly seen with fusion pacing. Type 3 shows LBBB waveforms unchanged by biventricular pacing. Reproduced from Sweeney et al (2014). Accessed by: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4956362/

However, in this study the atrioventricular delay, hence fusion interval, was manually optimised using echocardiography. The protocol used to achieve fusion is not clearly specified, although a narrow AVD range of 100-120 ms was described. This method of fusion is not practical in clinical use and is not dynamic to adapt to daily physiological variation. Furthermore, this study utilised LV remodelling by echocardiography as the endpoint with a 10% reduction in LVESV at 6months. This was the only measurement tool used in the assessment of response. It is well established that clinical response can differ from reverse remodelling and may not reduce death or exacerbation of heart failure. Whilst the study population evenly represented ischaemic and non-ischaemic aetiologies with broad LBBB (>150 ms) and severe LVSD, participants were largely male. This is not representative of the real world CRT population and differences in response between sexes has been shown (Arshad et al, 2011). This study also demonstrated that QRS narrowing is favourable in LBBB, with the probability of remodelling increasing with greater QRS narrowing (Sweeney et al, 2014).

A more recent study supports the benefits of SyncAV with regards to LV remodelling (AlTurki et al, 2020). This study had a very small sample size (n=34) but interestingly focussed on chronically implanted CRT devices, with a mean time from CRT implant to fusion optimisation of 17.8 months. This study identified a statistically significant improvement in LVEF of 10% and decrease in LVESV by 15% compared with baseline programming, these are stricter cut-offs when compared to other studies. This suggests that optimised fusion pacing can be advantageous over and above the initial benefit gained from a new biventricular implant. Interestingly, no significance difference was noted in NYHA classification after optimisation and responder status was classified as improvement in LVEF by 10% only. This further supports the discrepancy between quantitative measures of CRT response and clinical benefit. Importantly, the patients in this study were not shown to feel better.

In the study by AlTurki et al (2020), the degree of LV remodelling was assessed after 6 months by echocardiography using Simpsons biplane method in apical 4 and apical 2 views. Importantly, baseline programming of the CRT devices was not standardised. Some devices were programmed at nominal settings whereas others were programmed according the operator preference. None of the devices utilised SyncAV prior to the study. The study utilised an optimised SyncAV offset, with the ideal offset selected based on narrowest QRS duration. Interestingly, QRS duration was measured automatically by a 12 Lead ECG machine and the measurement was validated by an operator blinded to programming (standard paper speed and calibration). This method is quick and easily applied in clinical practice, however automated measurements are often inaccurate (De Pooter et al, 2016). The long-term benefit of SyncAV programming remains unproven.

Patient specific programming using individualised SyncAV is further supported by a recent multi-site study by Thibault et al (2019). This study (n=90) had similar inclusion criteria to the previously described studies. The study showed that SyncAV can improve QRS narrowing beyond conventional CRT in the acute setting. Interestingly, this study also showed that selection of the LV pacing cathode on a quadpolar lead is not influential in the response to fusion pacing. Arguably, the results suggest that the LV activation sequence is not a major component in fusion pacing, hence multipoint pacing of the LV may follow suit. Greater research is required to fully explore this aspect. Importantly, this study focussed on QRS narrowing alone and did not assess patient response. Consequently, the impact of SyncAV on acute and chronic clinical outcomes remains unproven.

Overall, there is a growing evidence base that fusion pacing may be beneficial in specific patients in CRT.

1.6 Multipoint Biventricular Pacing

Multipoint pacing (MPP) therapy describes stimulation of the left ventricle at two different sites to capture a larger area of myocardium. This is facilitated by quadpolar LV leads which are now commonplace in clinical practice. Multipolar LV leads have four electrodes and can deliver pacing stimuli with varying intraventricular (LV to LV) and interventricular (LV to RV) delays. Various manufacturer and lead models are commercially available with different spacing intervals between electrodes. Figure 11 shows the Abbott family of quadrapole leads. The use of quadpolar leads enables greater pacing configurations to overcome high thresholds and phrenic nerve stimulation. Quadpole leads also facilitate a more basal pacing site which has been associated with improved patient outcomes (reduced hospitalisations and death) to apical pacing sites (Singh et al, 2011; Thebault et al, 2012). However, one more recent large study (n=1189) has suggested the contrary (Leyva et al, 2018). Despite this, pacing the LV from a more basal pacing site remains the consensus in clinical practice.

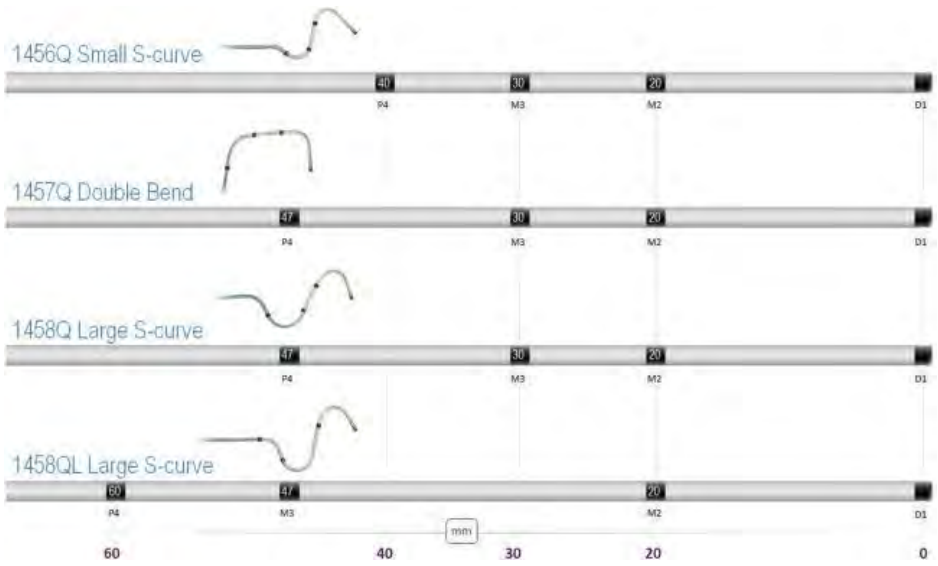


Figure 11 The family of Abbott Quadpolar LV leads and different electrode spacing. Reproduced from Leclercq et al (2019). Accessed from: https://www.sciencedirect.com/science/article/pii/S0002870318303387#f0005

Multisite LV pacing was first described using multiple LV leads, but added technical risk to the procedure and the results were variable (Leclercq et al, 2019). MPP using a quadpole lead has been the focus of several studies in recent years. The principles of MPP are shown in Figure 12. One small study (n=21) showed greater acute haemodynamic response (measured by LV dP/dtmax) in 72% of patients with MPP compared to conventional CRT (Thibault et al, 2013). Similar improvements in LV dP/dtmax were obtained in another small study (n=29) by Zanon et al (2015). In fact, MPP alone has been shown to be advantageous over conventional CRT by several trials (Tomassoni et al, 2016b; Leclercq et al, 2018; Forleo et al, 2017; Niazi et al, 2017). Echocardiographic measures of dyssynchrony have been significantly improved using MPP (Rinaldi et al, 2013; Osca et al, 2016), with the latter study also showing acute improvement on LVEF. Reduction in LVESV and increase in LVEF have been shown in other studies (Pappone et al, 2015; Forleo et al, 2017).

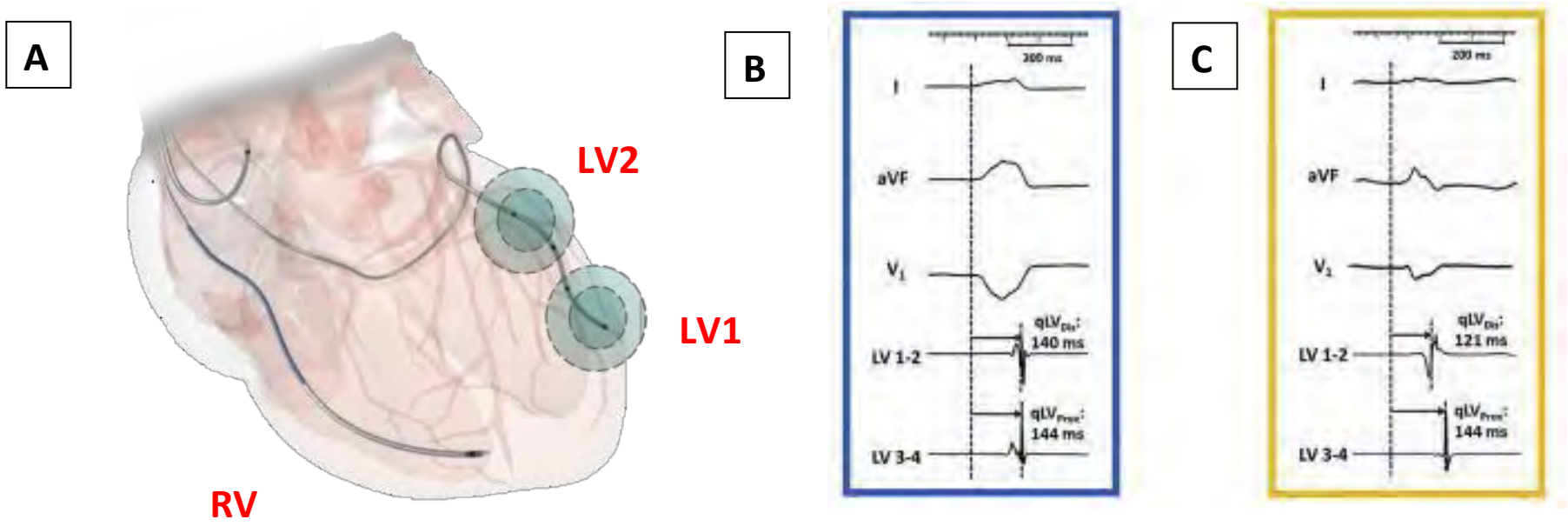


Figure 12 The principles of MPP. [A] shows how MPP is delivered from a quadrapole lead by pacing from 2 different sites of the LV from the same lead. The two sites are known as LV1 and LV2 and the timing intervals between these is programmable. It is thought that MPP captures a greater portion of the myocardium. The poles of the LV lead are labelled 1-4; where 1 is the distal tip and 4 is the proximal pole [B] In this example the QLV from the start of the surface QRS to the largest deflection on the LV electrogram is roughly the same for the 2 LV pacing sites (140 ms vs 144 ms. [C] In this example, QLV varies between the 2 LV pacing sites (121 ms vs 144 ms). Images adapted from: https://els- jbs-prod-cdn.jbs.elsevierhealth.com/cms/attachment/ae217499-89a5-4c96-80ba-647fc11abc25/gr3.jpg

MPP has also been shown to improve remodelling and CRT response over longer periods of up to 12 months (Zanon et al, 2016; Forleo et al, 2017; Niazi et al, 2017). The IRON-MPP study was a large (n=507 patients), multisite study highlighting an improvement in both LVEF and clinical response for patients using MPP (Forleo et al, 2017), although the downside is greater likelihood of stimulating the phrenic nerve. The IDE study was another large, multicentre study (n=506) which demonstrated that MPP is safe and non-inferior to standard biventricular pacing up to 9 months post implant (Tomassoni et al, 2016b). Research has started to show the circumstances in which MPP was preferable. In the IDE study, the benefit of MPP was most pronounced in patients with a spatial separation exceeding 30 ms and those with only a 5 ms timing delay between the 2 LV pacing sites, known as LV1-LV2 (Tomassoni et al, 2016b). Similarly, the Multipoint Pacing Trial (n=381) showed that MPP with wide anatomical spacing had a higher response rate and greater conversion rate of non-responders to responders (Niazi et al, 2017). Furthermore, studies have shown that MPP is most beneficial in patients with LBBB and a QRS duration >150 ms, in patients of non-ischaemic origin or those in NYHA III or IV (Tomassoni et al, 2016b; Forleo et al, 2017; Leclercq et al, 2018). Moreover, data has suggested that MPP can not only reduce the number of non-responders (Tomassoni et al, 2016b) but can boost the number of super-responders (Leclercq et al, 2018).

However, the long-term impact of MPP has yet to be established (Leclercq et al, 2019). The first large, randomised, multicentre trial assessing the long-term impact of MPP is the MORE-CRT MPP trial, which remains ongoing (Leclercq et al, 2019). This is specifically looking at the clinical benefit of MPP after 12months in patents previously considered non-responders to CRT and aims to enrol >5000 subjects. Importantly, this study will assess response by a single echocardiography measure: a reduction in left ventricular end systolic volume (LVESV) of at least 15%. To counter measurement bias, this will be analysed off site by blinded operators. The design of this study acknowledges image resolution challenges in this patient group and states that single plane

measurement of the modified Simpsons method for LVESV can be used where biplane is unavailable. Contrast echocardiography will be used where endocardial definition remains inadequate. The limitations of both echocardiography measures and also single measures of response have already been discussed, but this highlights how echocardiography remains the go-to method of assessing response in CRT clinical trials.

Many of the studies for MPP utilised echocardiography or imaging methods to assess response to CRT. This is most likely due to the need to assess acute benefit which cannot easily be achieved using a CCS or conventional clinical measures. However, future studies assessing the longer-term benefits of MPP may also focus on echocardiographic parameters; this is an important difference between the studies supporting fusion pacing. Conversely, both the IRON-MPP registry and Multipoint Pacing Trial demonstrated superiority of MPP over conventional CRT using a CCS (Niazi et al, 2017; Forleo et al, 2017). The Multipoint Pacing trial utilised a CCS including NYHA, Patient Global Assessment (PGA) score, HF events and death (Niazi et al, 2017). Echocardiography, notably velocity-time integral of transmitral inflow, was used during randomisation as it has the closest correlation to LV dP/dtmax (Niazi et al, 2017). IRON-MPP used a CCS of LVEF improvement of 5%, NYHA class and HF events (Forleo et al, 2017). Interestingly, the composition of the CCS also varies between studies.

Crucially, the trials also started to report evidence of QRS shortening with MPP, albeit a smaller number. Zanon et al (2015) found significant QRS narrowing with MPP in addition to improved haemodynamic benefit in the acute setting. Menardi et al (2015) also reported reduced QRS duration and subsequent activation time using MPP. However, the IRON-MPP trial was a large, multicentre registry (n=507) across Italy which showed that MPP reduced QRS duration (Forleo et al, 2017). Importantly, the method used to program MPP was not standardised across these studies, which may prevent

extrapolation of the results. In the trial by Zanon et al (2015), a fixed AV and VV interval was used. Whilst Rinaldi et al (2013) trialled different VV timings via MPP, the study used a fixed, non-physiological AV delay of 25 ms. In the IRON-MPP trial, programming was left at the discretion of the operators (Forleo et al, 2017).

The optimal programming of MPP is not yet known (Forleo et al, 2017). Clinical application of MPP may be more difficult than single point biventricular pacing due to patient specific factors. MPP is thought to overcome some anatomic (e.g. scar) and electrical barriers (e.g. high thresholds) by capturing a larger volume of myocardium (Niazi et al, 2017). However, for the same reasons it has also been associated with a greater likelihood of phrenic nerve stimulation and anodal capture (Niaizi et al, 2017; Forleo et al, 2017). Consequently, it is not surprising that the programming of MPP is not covered by BHRS guidelines, hence in UK clinical practice, manufacturer specific programming is adopted. This may result in suboptimal programming or even limited application of MPP. On the other hand, programming MPP with a focus on QRS narrowing may be an untapped resource to optimise CRT devices. There is call for more practical, non-invasive methods to program MPP to ensure that it is accessible to a wider audience (Rinaldi et al, 2013).

Consideration must be given to the impact on battery life because stimulating the LV from 2 consecutive poles is thought to increase current drain (Akerstrom et al, 2018; Forleo et al, 2019; Tomassoni et al, 2016b). One study suggested that this was in the region of 18 months, hence MPP may result in additional generator replacements (Akerstrom et al, 2018). This may be significant considering that average lifespan of a CRT patient is already abbreviated and battery changes are associated with an increased risk of complications (Forleo et al 2019). Fears over battery longevity and lack of clarity on programming may be barriers to the application of MPP in the real-world setting, with some clinicians preferring to use MPP in non-responders

only (Forleo et al, 2019, Tomassoni et al, 2016b). However, sub-analysis from the IRON-MPP registry (n=237) found that MPP was associated with less than 1 year reduction in battery life compared to conventional CRT (Forleo et al, 2019). The authors suggested that this should not prevent more widespread use of MPP in clinical practice given the potential benefits (Forleo et al, 2019).

Interestingly, the studies on battery drain in MPP focus on a cohort of patients with standard output settings of 2.5v or less. It is acknowledged that in patients with higher outputs, the impact on battery longevity will be more significant (Forleo et al, 2019; Akerstrom et al, 2018). Considering that high thresholds are common with LV pacing, the battery drain from MPP in a real world population may be more significant than the IRON-MPP sub-analysis suggests. The output cut-off of 2.5v is suggested to avoid the need of a voltage multiplier; this is common practice in device follow-up, particularly with anti-bradycardia pacemakers (Forleo et al, 2019). Importantly, one large ongoing trial (MORE-CRT MPP) defines a high capture threshold of 4.5v at the device default pulse width (Leclercq et al, 2019). This is likely to negatively impact battery longevity but may provide more transferable data to real-world practice.

Overall, MPP is a promising technique to improve response to CRT. However, there is little guidance on programming and several factors may impact its success in clinical practice.

1.7 Measurement of QRS duration

Accurate measurement of QRS duration is crucial in CRT to identify eligible patients and to assess for QRS narrowing (De Pooter et al, 2017). Despite this, there is no agreed technique to measure QRS and different methods are described in the clinical trials (De Pooter et al, 2017; Turagam et al, 2013; Tomlinson et al, 2009; De Guillebon et al, 2010). Some of the various methods

include automated measurement from ECG software, single lead measurement, widest complex and average of certain leads (Kashani and Barold, 2015); these are shown in Table 5.

Table 5 Snapshot of different methods used to measure QRS duration in clinical Trials. Various techniques have been described with no consensus as to best practice.

Author	Year	Number of Patients	Brief Description of methods
Dupont et al	2012	496	Automated QRS from ECG software
Bleeker et al	2006	144	Manual measurement of widest QRS from leads II, V1 and V6 (at standard paper speed) on surface ECG
Molhoek et al	2004	61	Manual measurement of widest QRS from leads II, V1 and V6 (at 50mm/sec)
Gold et al	2012	610	Manual measurement of mean QRS in leads II, V1 and V6
De Pooter et al	2016	52	Digital calipers and global QRS method at 50 mm/sec and 20 mm/mV
Forleo et al	2017	507	Global QRS method applied by 2 investigators. Exact methodology is not well documented and unclear whether digital calipers used. Unclear sweep speed and Gain
Thibault et al	2019	90	Global QRS method using digital calipers at 100 mm/sec
Varma et al	2018	52	Global QRS method using digital calipers. Sweep speed 100 mm/sec. 8-12 simultaneously recorded leads (V2-V5 optional)
Trucco et al	2018	180	Global QRS method using digital calipers over 12 leads. Screen velocity 300 mm/sec. 2 observers. Mean of 3 consecutive cycles
Stephansen et al	2019	40	Manual measurement of widest QRS in any of the 12 ECG leads. Intrinsic ECGs performed at 25 mm/sec and 10 mm/mV. Paced ECGs performed at 50 mm/sec and 10 mm/mV.

There is controversy over the different measures due to accuracy. Due to this, automated measurements calculated by the ECG equipment are becoming more popular, although the precision and reproducibility remains under debate (Vancura et al, 2017). Studies into automated QRS measurement overall

showed low concordance with manual QRS measurement, systematic differences between different manufacturer equipment and varying levels of precision (Vancura et al, 2017, De Guillebon et al, 2010, Tomlinson et al, 2009). One study showed greater concordance with manual measurement for narrower QRS durations of less than 120 ms (i.e. not the CRT population) (Tomlinson et al, 2009). This variation in methodology may lead to inconsistencies, inaccuracy and poor transferability between studies and into the clinical environment (Turagam et al, 2013).

The American Heart Association states that measurement using global QRS duration methodology '*from the earliest onset to the latest offset of the waveform in all leads*' is desirable (Surawicz et al, 2009). This technique has been adopted more consistently in recent clinical trials for CRT and has been shown to have superior inter and intra-operator variability when compared to individual ECG leads (De Pooter, 2016). Narrowing of global QRS has also been shown as the best predictor of response (De Pooter, 2016; Tamborero et al, 2009; Tamborero et al, 2011). However, global QRS duration is less easily measured without specialist software which has digital calipers and the ability to vertically align all ECG leads, hence it is not used commonly in routine practice. Furthermore, greater inter-operator variability has been described for global QRS in LBBB and paced complexes when compared to narrow QRS (De Pooter et al, 2017). Figure 13 demonstrates both global QRS methodology and single lead ECG measurement.

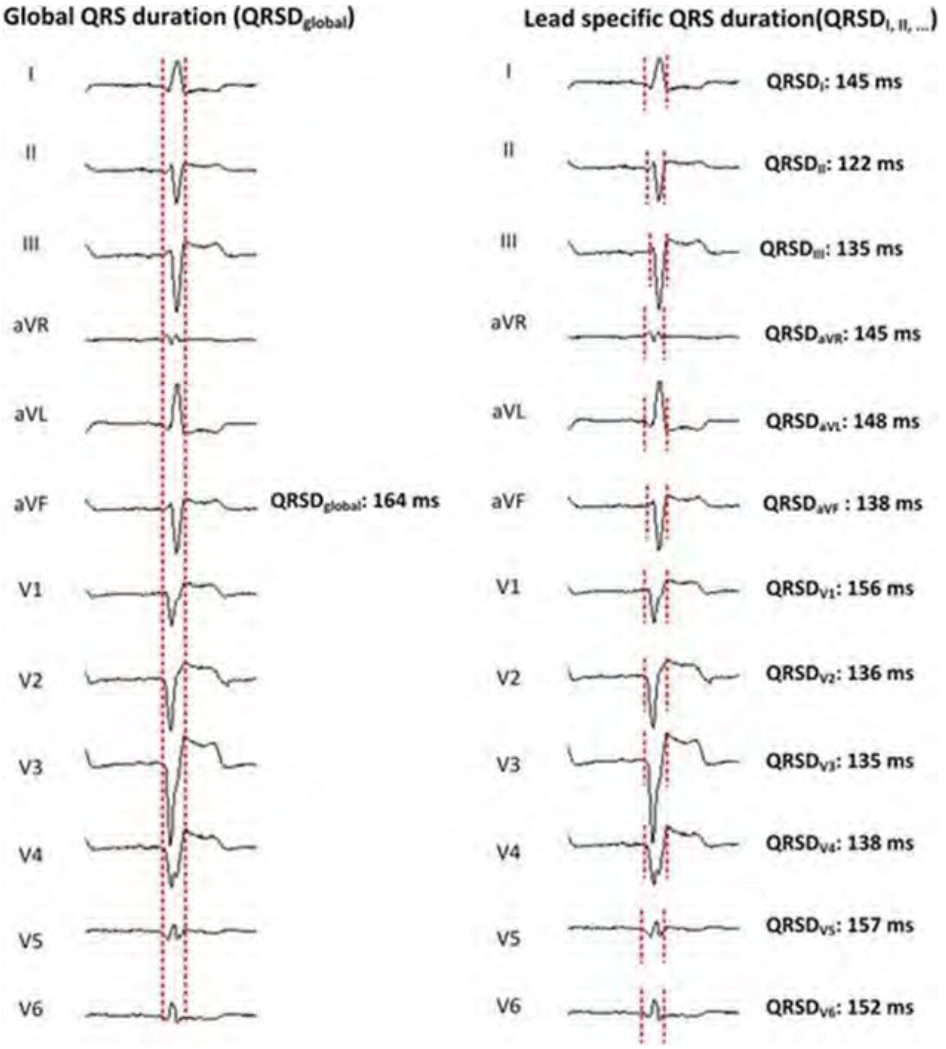


Figure 13 Global QRS methodology versus single lead ECG measurement. For global QRS a single set of calipers is applied from *the onset of the QRS in any lead to the offset in any lead*. For individual lead measurement, a different set of calipers is used to measure each of the 12 leads. Reproduced from De Pooter et al (2016). Accessed by: https://pubmed.ncbi.nlm.nih.gov/26391903/

Conversely, single lead measurement of QRS duration is commonplace in clinical practice, often from a paper copy of the 12 lead ECG (Turagam et al, 2013; Stephansen et al, 2019). The onset of the QRS is defined at the first positive or negative deflection from the isoelectric line and the offset is defined as being the J point (Stephansen et al, 2019). However, manual measurement in this way may underestimate QRS duration due to isoelectric segments

according to QRS vector, making the onset/offset difficult to differentiate (De Pooter et al, 2016). This may be more difficult in the CRT population due to slow directional changes in the terminal portion of the QRS (Vancura et al, 2017). Consequently, several studies have shown significant variability in manual assessment of QRS duration (Vancura et al, 2017; De Guillebon et al, 2010; Turagam et al, 2013; Tomlinson et al, 2009). In contrast, one more recent study indicated clinically acceptable inter and intra-operator variability of manual single lead measurement of QRS in a CRT cohort (Stephansen et al, 2019).

Manual QRS measurement by the single lead method is influenced by lead selection, although it has been suggested that intra- and inter-operator variability can be reduced by using a longer sweep speed of 50 mm/mV (De Pooter et al, 2016; De Pooter et al, 2017; Tomlinson et al, 2009). One study reported intra-operator variability in median QRS duration on the 12 lead ECG of 35ms at 25mm/sec; reducing to 22.5 ms at 50 mm/sec (Tomlinson et al, 2009). This reduced further to 12.5 mm/sec based on chest lead measurement (V1-V6) regardless of paper-speed (either 25 mm/sec or 50 mm/sec). However, in limb leads alone, the intra-observer variability was reported as 20 ms (range 10-35 ms), with a median inter-observer variability of 40 ms (range 30-40 ms) (Tomlinson et al, 2009). Conversely, it has been suggested that increasing sweep speed in LBBB and paced patients may not make it easier to determine onset/ offset of the QRS, as more gradual changes in ECG deflections in this cohort may be exacerbated by longer sweep speeds (Stephansen et al, 2019). Importantly in the same study, a sweep speed of 50 mm/sec was used as standard for CRT optimization and 25 mm/sec used for assessment of intrinsic QRS duration.

There is little evidence for the number of QRS complexes which should be reviewed when measuring QRS duration. Variation is seen during clinical trials from measuring a single lead (Tomlinson et al, 2009) to the median of 4

measurements (Guillebon et al, 2010). In other studies, the number of ECG cycles is not specified (Stephansen et al, 2019). A study from 2004, concluded that measurements of RR interval and QT interval made by a trained observer over 1 cardiac cycle accurately reflected those averaged over a larger number of cycles. This was a very small study performed in dogs in sinus rhythm and it is acknowledged that QRS duration was not one of the measured intervals (Hamlein et al, 2004). Hence its external validity is limited.

Despite single lead measurement being common in real world practice, there is no consensus or guideline specifying which lead should be used, which may cause variation (Tomlinson et al, 2009). Studies suggest that for single lead measurement, QRS duration should be the *widest QRS* in any lead (Stephansen et al, 2019; De Guillebon et al, 2010). In clinical practice, this usually means an 'eye-ball' assessment of QRS width and actual measurement in one lead only. This may lead to bias towards particular ECG leads by different operators. In one study, Cardiologists were demonstrated to favour V1-V4 to measure QRS duration, although reported variation in lead selection was thought to influence measurement variability (Tomlinson et al, 2009). Hence, comparisons of ECG duration may be significantly disadvantaged if the target lead is not standardised. Importantly, single lead measurement in V5 has been shown to be a reasonable surrogate for global QRS in CRT patients, although this study had a small sample size (De Pooter et al, 2016).

Importantly, the inter and intra-operator variability associated with QRS measurement may result in patients with borderline QRS durations being denied access to CRT (Tomlinson et al, 2009; Turagem et al, 2013, Vancura et al, 2017, De Guillebon et al, 2010). There is little evidence investigating the impact of QRS measurement in electrical CRT optimisation. One recent study, suggested adequate reproducibility and repeatability for manual QRS measurement during VV optimisation with a mean of 22 ms (Stephansen et al,

2019). However, it was also noted that inter-operator results varied by up to 80 ms, which may result in more than one VV interval being considered optimal (Stephansen et al, 2019).

The discussion regarding the method used to measure QRS is dependent on the type of ECG monitoring used. For Cardiologists assessing QRS duration and suitability for CRT, the 12 Lead ECG with the default 4 x 3 lead display is most commonly used at 25 mm/sec (Turagam et al, 2013). As discussed, QRS duration is often taken from the automated measurement or manual measurement from a single lead (Turagam et al, 2013; Tomlinson et al 2009). A standard paper ECG in this format restricts accurate QRS analysis and relies largely on unsophisticated manual assessment. Global QRS measurement cannot be applied because the ECG leads are not vertically aligned and it is uncommon for clinicians to have access (or the time) to use digital calipers. Manual calipers can be used but these are known to be bias to preferential numbers and have variable accuracy (Turagam et al, 2013). Digital ECG tracings and on-screen electronic calipers are preferred in clinical trials for interval measurement, but even these are thwarted if the baseline is distorted (Turagem et al, 2013).

During CRT implantation, the type of ECG monitoring used is also thought to vary between hospitals, although there is little published data to support this. Until recently, limb leads alone were commonly used during CRT implant. The use of a single chest lead (usually V1) gained popularity to help differentiate LV pacing from RV pacing (Barold, 2015). However, the use of 12 lead ECG during implant has been less widely adopted. This requires compatible equipment and radiopaque ECG leads that do not interfere with fluoroscopy. Importantly, positioning ECG electrodes in standard positions can overlap with defibrillation pad placement. Latest BHRS guidelines do not provide clarity, and state that 12 lead ECG or a chest lead should be *considered* when assessing biventricular pacing (BHRS, 2020). Interestingly, these guidelines

focus on CRT follow-up alone and do not make any recommendations specifically related to implantation. Nevertheless, the use of limited ECG leads during implant or using equipment without digital capability will restrict the method used to measure QRS duration. This in turn, may influence device programming and lead to suboptimal patient outcomes. There is an important assumption here that the CRT is optimised during implantation. Access to specialist digital software outside of the operating room environment is thought to be even less common.

In the study centre, the manual measurement of global QRS over 5 ECG leads (I,II,III, AVF, V5) on the device programmer has been more recently adopted into clinical practice. This so-called *abbreviated* global QRS is thought to overcome some of the challenges associated with individual lead measurement, although a literature search could find no evidence to support this. Importantly, in the Varma trial (2018), global QRS was measured over 8-12 leads, also indicating an abbreviated version of the global QRS method initially described by the American Heart Association. The use of the abbreviated global QRS method was recommended by the manufacturer. Importantly, the device programmer is used in both the implantation and follow-up environment and offers an opportunity to enable QRS analysis using digital calipers, without the need for additional specialist equipment.

In summary, greater research is required to identify the best method to measure QRS using standard equipment in routine clinical practice.

1.8 Current Practice

A common theme during the literature search was variation in clinical practice. A disconnect was also noted between the methodology in clinical research and real-world application. This disparity was noted through all aspects of the

CRT pathway, particularly for optimisation of CRT devices, assessment of CRT response and measurement of QRS duration during implantation. These are all areas which are predominantly performed by Cardiac Scientists.

In the UK, cardiac device programming and follow-up is almost entirely performed by Cardiac Scientists, Cardiac Physiologists and Cardiac Practitioners. This group of Healthcare Scientists have specialist and often expert-level knowledge and work autonomously in the technical and clinical management of cardiac device patients. However, ultimate responsibility for implanted devices remains with the designated Consultant. This is typically a Consultant Cardiologist, however in the future it will likely fall under the remit of a Consultant Cardiac Scientist (BHRS, 2020). This is a new role developed by Modernising Scientific Careers to acknowledge and build on the high level skills developed by this specialist group (BCS, 2015). Consultant Scientists are doctorate-level candidates and the training route is via completion of a five-year clinical doctorate called the Higher Specialist Scientist Training (HSST) programme (BCS, 2015). The Lead Cardiac Scientist at the study centre is one of the first HSST candidates specialising in Cardiac Science in the UK.

In 2018, the study centre was commissioned as the second complex cardiac device implantation and follow-up centre within the region. Consequently, the department sought a best practice approach and implemented a manufacturer guided programming strategy for CRT implantation focussing on QRS narrowing. This included using fusion pacing and MPP as part of the routine CRT programming pathway. In addition, a protocol to measure CRT response during Device Clinic was introduced using a CCS, where a responder was defined as 2/3 of the following: ≥10% improvement in 6MWD, ≥1 class improvement in NYHA and ≥15 point improvement in MLHFQ. Assessment of response occurred at 5 months post implantation, in keeping with the departmental protocol for device follow-up. Whilst evidence based, these departmental approaches remained untested in real life, hence formed the

fundamental elements of the current study (optimal CRT programming and assessment of response). The observed experiences of the study centre were anticipated to be of great value to other Cardiac Scientists and Device Clinics within the UK.

Early observations of the adopted CCS in clinical practice suggested that the current criteria was biased towards those with more severe heart failure (NYHA Class III or IV). The criteria appeared less sensitive to the NYHA class I/II population because patients in NYHA class I were unable to improve their class beyond this category and patients with <14 points on MLHFQ at baseline could not improve by 15 points. This meant that those with very mild symptoms could not be classed as responders, even if their 6MWD increased significantly (they would be considered 1/3, hence classified as a non-responder). A small unpublished study (n=69) from the study centre confirmed these findings and a revised definition of CRT response was proposed, based on the same CCS parameters (Wilburn et al, 2020). Both sets of criteria are listed in Section 2.5. The revised criteria incorporated two additional response categories for super-responders (3/3) and non-progressors (1/3). It is important to evaluate and learn from any change in practice. At the time the study protocol was written, the revised criteria remained in development and had not yet been implemented in clinical practice.

Development of advanced practice roles within Cardiac Science has led to increased interest in Scientist-led clinical research in this area. Due to the infancy of these roles and pace of technological advance in this area, there is currently a knowledge gap and further high quality research is urgently needed to influence professional body guidance and improve patient pathways. This culminates in a lack of clarity in professional body guidelines by the British Heart Rhythm Society in this specific field (BHRS, 2020). Furthermore, there is no published benchmarking exercise led by the BHRS into current clinical practice of Cardiac Scientists. Of particular interest, is the type of ECG

monitoring and methods used to measure QRS duration. This may help improve protocols and ultimately improve the standard of care for CRT patients.

1.9 Research questions

Fusion pacing (especially dynamic algorithms such as SyncAV) and multipoint pacing are emerging as promising techniques to achieve optimal patient-specific CRT. Both pacing strategies have been shown to narrow QRS duration and improve patient outcomes, particularly in the acute to medium term. However, there appears to be a lack of evidence of whether combining the techniques can produce even better results. Theoretically, a combination of fusion pacing and MPP could create four wave-fronts to fuse intrinsic ventricular activation with multipoint, biventricular pacing stimulation to obtain narrower QRS complexes. This may optimise haemodynamics, improve resynchronisation, maximise reverse remodelling and generate an augmented response to CRT.

However, a thorough literature search could only locate one study to investigate both techniques. An abstract from O'Donnell et al (2016) suggested that mean QRS duration was shortest using Sync AV and a Multipoint Pacing approach (MPP). However, the final results of this study were not published until 2020 (O'Donnell et al, 2020). Consequently, the working hypothesis of this research project was whether individualised fusion pacing (SyncAV) plus MPP could achieve greater QRS narrowing when compared to standard biventricular pacing parameters.

Importantly, there were limited data regarding the how these programming techniques could influence patient response, particularly whether combining SyncAV and MPP could actually augment patient response to CRT therapy.

Quantifying response to CRT is not common practice in UK Device Clinics and there are few models in widespread clinical use. Hence this study planned to obtain data for CRT response for the programming options discussed above using the department's CCS of NYHA Class, MLHFQ and 6MWT. It is unclear whether the current departmental criteria or the proposed revision would be sensitive enough for both minimally symptomatic patients and those severely limited by the HF symptoms.

Moreover, the best method to accurately measure QRS duration in clinical practice, using standard equipment remained uncertain. Single lead ECG measurement was thought to be in widespread clinical use, despite evidence indicating unreliability. Global QRS over 12 Lead ECG is emerging as the preferred reference method but few hospitals have this capability on implantation and follow-up. Consequently, an abbreviated global QRS methodology over 5 leads via the device programmer may be a useful compromise in real world practice. However, this method had not been assessed.

Finally, there is little evidence of current clinical practice within the UK specifically related to ECG monitoring and QRS measurement by Cardiac Scientists involved in CRT. There is growing interest in CRT programming and the role of the Cardiac Scientist is becoming ever more important within this field. Hence assumptions have been made regarding clinical practice, based on anecdotal evidence and knowledge of local and regional practice. A survey of real world practice within this field would provide a useful standpoint.

1.10 Aims

The primary objective of the study was to determine the best programming options to individualise CRT and achieve the narrowest QRS, focussing on

MPP and Sync AV. This was achieved by a 'Mode' Comparison study; a comparison of CRT programming strategies. It was acknowledged that multiple programming options were commonly used in clinical practice, hence these should be assessed for a true comparison. In this study, 5 programming strategies were proposed, in keeping with the study centre's standard protocol (best single point pacing, standard SyncAV, individualised SyncAV, standard MPP, individualised SyncAV and MPP). The primary research question was therefore:

Is individualised CRT programming superior to conventional programming with respect to QRS narrowing?

The secondary endpoint was to determine whether abbreviated global QRS measured over 5 leads on the device programmer is comparable to individual lead measurements from the 12 lead ECG using digital calipers. This was achieved by a 'Method' Comparison study; a comparison of methodologies for measuring QRS duration. This study was conducted in the clinical setting using standard equipment, hence provided more credible information as to whether an abbreviated global QRS methodology using the device programmer could improve measurement accuracy in routine practice.

A further secondary objective was to determine whether CRT optimisation influences clinical response after a 5 month follow-up period determined by a clinical composite score of three parameters (two out of three of either: reduction of ≥ 15 points in Minnesota questionnaire score at 5months, ≥ 10% improvement in Six Minute Walk distance at 5 months, improvement of ≥1 class in the NYHA classification). This was the current criteria used by the study centre at the time of writing to assess response. In addition, a revised criteria including categories for super-responders and non-progressors would be evaluated.

A final objective was to undertake a national survey to gauge current clinical practice of Cardiac Scientists and Physiologists within the UK, with particular focus on ECG monitoring and the measurement of QRS duration.

Overall, the study goal was to help guide Cardiac Scientists to individualise CRT settings to obtain narrowest QRS and improve patient outcomes. The results may be of particular interest to Cardiac Scientists and Cardiologists and it was anticipated that they may influence future practice and protocol writing, to benefit patient care.

The results were to be submitted to a peer reviewed journal for publication and put forward for presentation at national conference.

2.0 Methodology

2.1 Design

This prospective study of current clinical practice was performed using an observational study design within a single centre. The observational design was specifically chosen for this study because there was little data available on real-life UK practice within the field of optimal CRT programming and assessing actual UK clinical practice was considered of key importance. There was also minimal guidance for UK Cardiac Scientists regarding programming of CRT devices. At the time when the study was conceptualised, BHRS guidelines made no reference to CRT optimisation (BHRS, 2018).

This was an observational study of current clinical practice, hence the standard patient care pathway remained unchanged. The study utilised data collected as part of the standard clinical dataset. A detailed study protocol (as submitted to IRAS) is listed in Appendix 2. The clinical dataset was collected over three scheduled clinical appointments (Pre-Assessment, Implantation, 5 month Follow-Up). Each assessment took approximately 15 minutes longer than a standard appointment. The study flow chart is detailed in Figure 14.

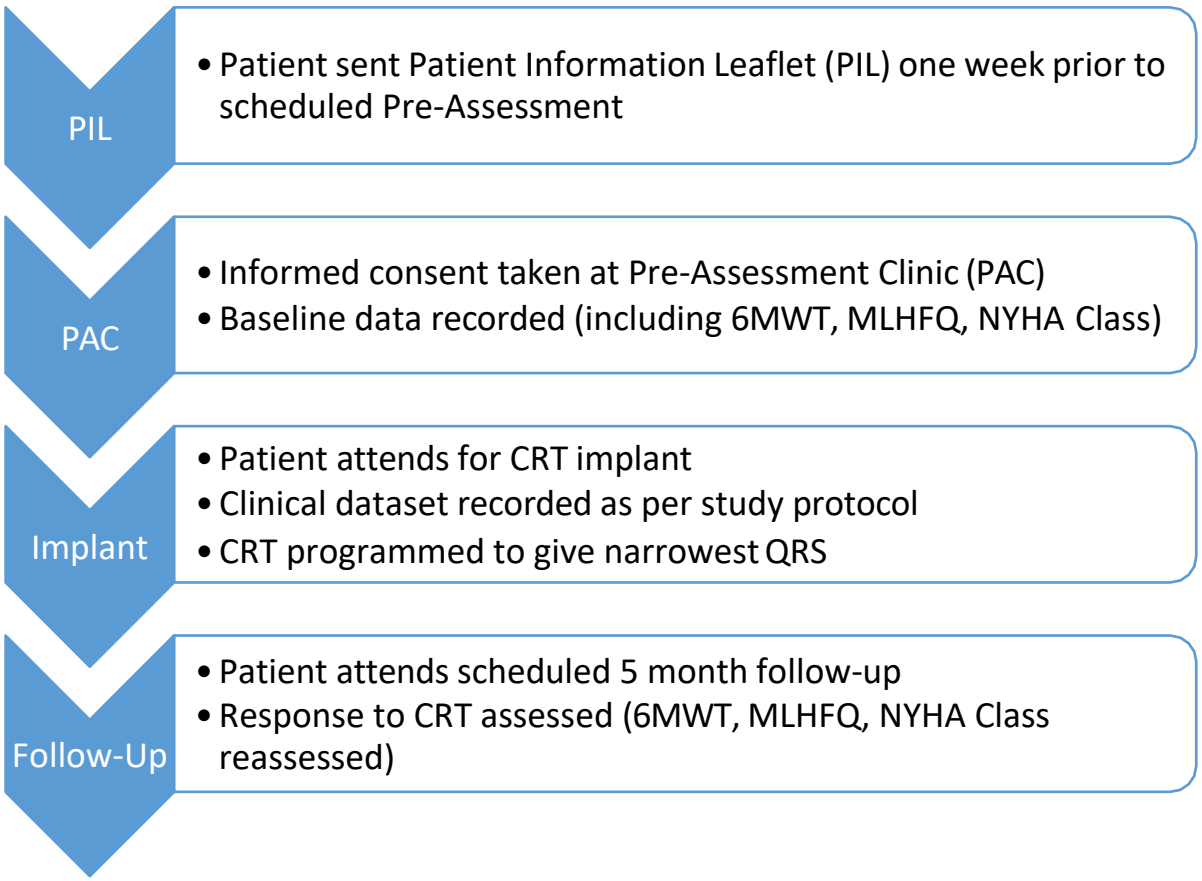


Figure 14 Study Flow Chart
This flow chart shows the steps included in the study and variables measured at each visit. Other scheduled attendances in Follow-up Clinic were excluded (such as the 4-6 week assessment performed post implant). After the 5 month follow-up, CRT follow-up continues as per departmental protocol and the patient exits the study.

2.2 Baseline clinical characteristics

Once written consent was obtained, baseline demographics were obtained at the Pre-Assessment Clinic. Research personnel recorded all clinical information for the whole study on the data collection sheet (as shown in Appendix 3).

The baseline clinical heart failure status was established using the departmental three measure approach: Minnesota questionnaire (MLHFQ), Six-Minute Walk Test (6MWT) and NYHA classification.

The Physiologist (or Cardiac Scientist) assessed NYHA Class during the Pre-Assessment Clinic and this acted as a baseline for assessment of CRT response. NYHA Class established by the Cardiologist on referral was used for inclusion. The NYHA class criteria listed in Table 6 was adopted in the study.

Table 6 Applied NYHA Class criteria.
This was the criteria used by Cardiac Scientist and Physiologists in this study.

Class	NYHA functional classification
I	Patients have cardiac disease but without the resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or angina pain
II	Patients have cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or angina pain
III	Patients have cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea or angina pain
IV	Patients have cardiac disease resulting in inability to perform any physical activity without discomfort. Symptoms of cardiac insufficiency syndrome may be present even at rest. If any physical activity in undertaken, discomfort is increased

Patients were given a paper version of the MLHFQ to complete during the clinic. Patients were encouraged to complete the questionnaire without input from relatives. The total score was recorded. A copy of the MLHFQ is listed in Appendix 4.

A 6MWT was performed over a flat 15 metre circuit as per departmental protocol. The circuit was marked out via cones. The patient was asked to walk at their own pace for as far as possible within 6 minutes and stops were allowed. Heart rate, blood pressure and patient symptoms were recorded pre and post 6MWT. The total distance walked was recorded in metres.

2.3 Method for CRT Programming

The core clinical dataset for the study was obtained during CRT Implantation (the patient's second appointment). Pacing leads were implanted via a standard transvenous approach under fluoroscopic guidance and ECG monitoring as described previously. Local protocol was to aim for a lateral or posterolateral LV lead position via the coronary sinus wherever possible. Basal vectors were preferred. LV lead position was guided by QLV to identify the site of latest activation (aiming to pace approximately two thirds into the baseline QRS complex). LV thresholds were obtained in multiple vectors (all 4 unipolar vectors and at least one bipolar vector). RV lead position was not specified in the study protocol and RV apical position was default, although a septal position may have been used in specific cases, operator preference.

Baseline readings of QRS duration were measured on the device programmer and 12 lead ECG prior to CRT implantation (using the methodology described in Section 2.4). Immediately following CRT implantation, the department's CRT optimisation protocol was followed. As part of this, five different programming strategies were temporarily applied and the data recorded as per standard clinical dataset. CRT optimisation was performed with the primary aim of the narrowest QRS duration, with the secondary aim of an R wave in V1, an S wave in lead I and optimal transition point in precordial leads. Abbreviated global QRS was the methodology used to establish narrowest QRS in this aspect of the study.

As part of the optimisation protocol, the site of latest activation was determined using the manufacturer guided algorithm (CRT Toolkit). The QuickOpt algorithm was activated to suggest optimal AV and VV timing but this was always manually verified by incremental adjustments for AV and VV timing continuously assessing the ECG and measuring QRS duration. The programming was built from best single point pacing (Mode 1) using the optimal AV and VV timings as a start point. For AV timing, a manual check was performed by measuring baseline P wave duration and adding an offset (30 ms if P wave duration >100 ms, 60 ms if P wave duration <100 ms). The QuickOpt measured AV delay was used as standard. However, if the QuickOpt derived AV delay was not appropriate (e.g. significantly different to the manual method, or allowed intrinsic conduction), then the manually derived AV delays were programmed. AV timing was always established first. For VV timing, QuickOpt derived values were used as a guide or starting point, but then were adjusted manually by small (10 ms) increments to identify the settings which gave the narrowest QRS.

SyncAV is a dynamic algorithm that automatically adjusts the AV delay to account for physiological changes in the PR interval during activities of daily living. This is achieved by measuring the intrinsic PR interval every 256 beats, by extending paced and sensed AV delays for 3 beats. The final PR interval of the third intrinsic beat is taken as the reference PR and a fusion delta is applied to calculate the paced AV delay for the next 255 beats. For nominal SyncAV, the delta is -50 ms, hence the SyncAV derived paced AV delay would be intrinsic PR interval -50 ms. The cycle is repeated every 256 beats, culminating in a dynamic adjustment algorithm. Individualised SyncAV is achieved by manually adjusting the delta by intervals of 10 ms and remeasuring QRS duration (using abbreviated global QRS methodology) to identify the delta which resulted in the greatest QRS narrowing. The programming of SyncAV is shown in Figure 15.

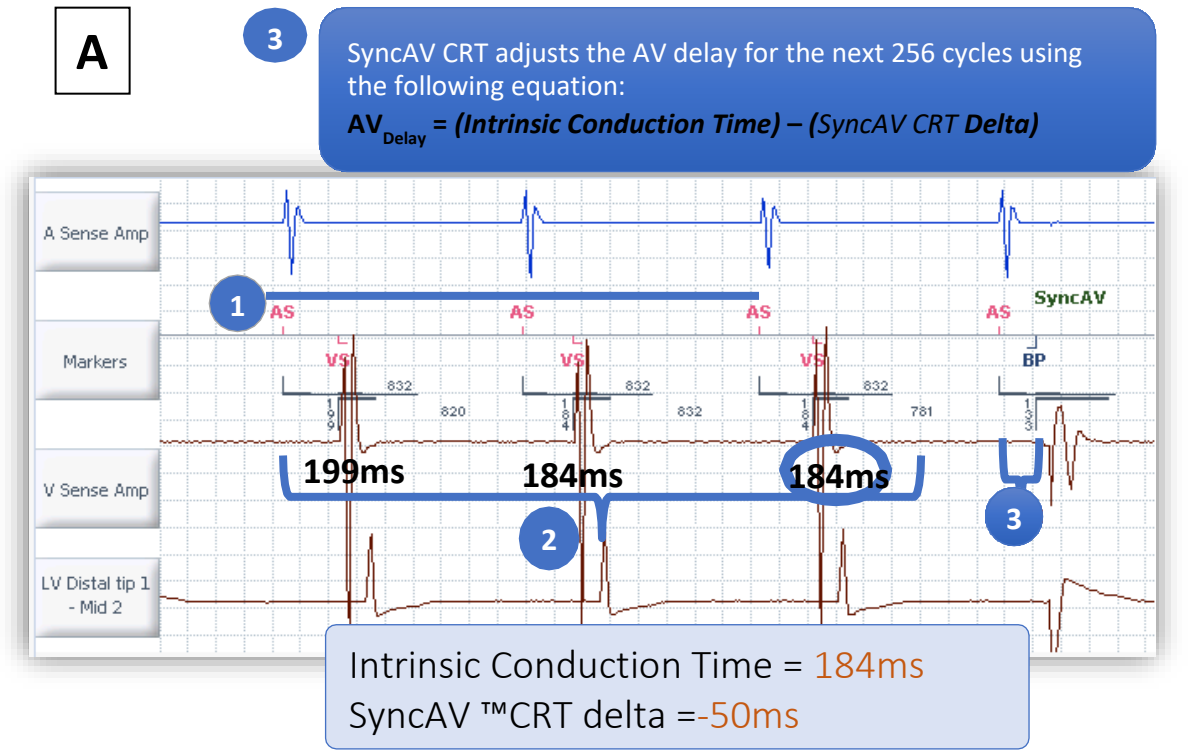


Figure 15 SyncAV Programming.
[A] The algorithm measures 3 x intrinsic PR intervals every 256 cycles. The last PR interval is used to apply the SyncAV delta. In this example, the PR interval is 184 ms and a -50 ms delta applied, so the resulting AV delay is 134 ms.
[B] shows the programming screen for SyncAV as displayed on the Abbott programmer. In this example, the last measured PR interval was 191 ms and a –50 ms SyncAV delta is selected. Images reproduced with permission from Abbott Medical.

For MPP modes, a minimum of 30 mm spacing was required between the 2 pacing sites on the LV lead. The 2 pacing vectors (LV1 and LV2) were selected from the available vectors at the operator's discretion. A 5 ms timing delay was applied between LV1-LV2 in keeping with the IDE study (Tomassoni et al, 2016b). If the patient displayed phrenic nerve stimulation, the QRS was still measured based on patient tolerance. However, MPP was not programmed if there was twitch or if the threshold was >3.5v at a pulse width of 0.5 ms. Multiple ECGs were measured each time and the five programming strategies are summarised in Table 7.

Table 7 Different pacing strategies applied in the study.
5 modes were applied to each patient and the QRSd measured. The modes built from best single point pacing (Mode 1) to default SyncAV (Mode 2), indivisualised SyncAV (Mode 3), standard MPP (Mode 4) and MPP with individualised MPP (Mode 5)

	Pacing Mode
Mode 1	Best Single Point BiV Pacing (AV/VV delays by QuickOpt or manual method to give narrowest QRS)
Mode 2	Best Single Point Pacing with nominal SyncAV (Offset -50 ms)
Mode 3	Best Single Point Pacing with Individualised SyncAV (offset -10, -20, -30, -40, -50, -60 or -70 ms)
Mode 4	MPP (AV and VV timing as derived in Mode 1 & 5 ms timing delay between LV1 and LV2)
Mode 5	MPP with individualised SyncAV (offset -10, -20, -30, -40, -50, -60 or -70ms) & 5 ms timing delay between LV1 and LV2

The programming strategy which achieved the narrowest QRS was permanently programmed, providing the electrical characteristics were within acceptable limits (i.e. narrowest QRS, absence of diaphragmatic twitch and

threshold <3.5v). In cases where electrical characteristics were not acceptable, the programming mode which gave the next best QRS narrowing was selected.

2.4 Method for Measuring QRS duration

Two methods of ECG monitoring were used to measure QRS duration during the CRT implantation: individual lead measurements over 12 Lead ECG and abbreviated global QRS using the programmer ECG.

12 Lead ECG measurements were made using Phillips Xper Flex haemodynamic recording system. In keeping with routine practice, radiolucent ECG cables were used to avoid interference with fluoroscopy images. Chest electrode positioning was in accordance with the professional standards of Society of Cardiological Science and Technology (SCST), as shown in Figure 16. Modified limb lead placement was used with lower torso for foot electrodes (F) and shoulders for left arm (LA) and right arm (RA) accordingly. This was to reduce muscle artefact as is standard practice. Paper speed was extended to 50mm/sec and gain was optimised to reduce measurement error. QRS duration was measured in all 12 ECG leads using digital calipers. The QRS_Max and QRS_Mean were documented offline. The onset of the QRS was defined as the first positive or negative deflection from the isolelectric line and the offset was defined as the J point.

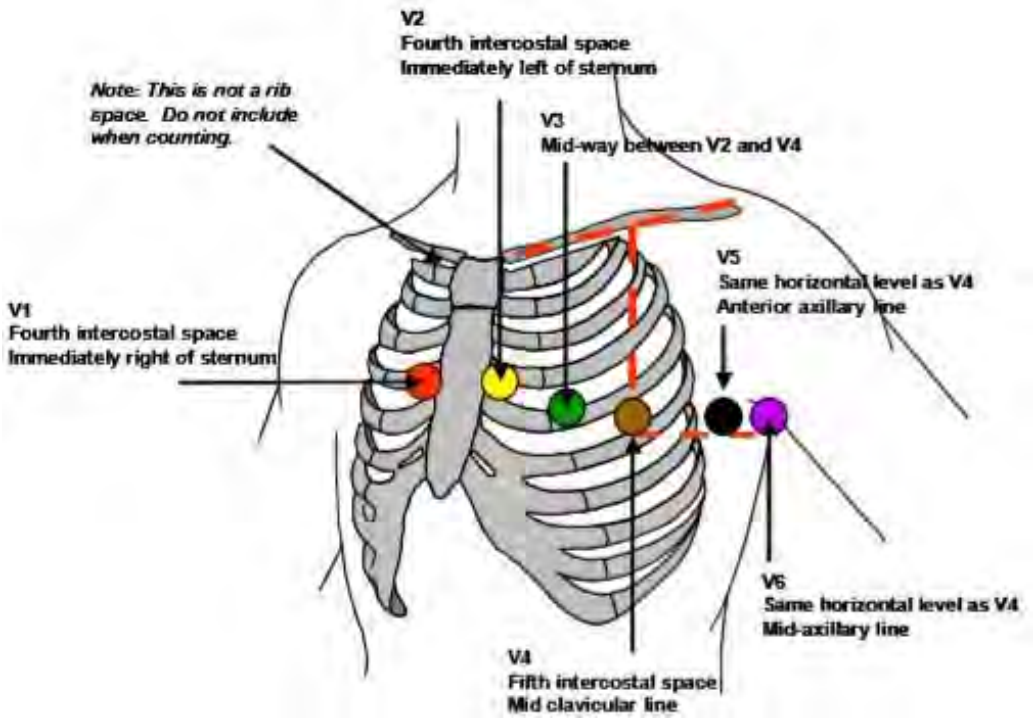


Figure 16 SCST Chest Positions. As used in the 12 lead ECG. Reproduced from British Cardiac Society (2010). Accessed by: https://www.bcs.com/documents/consensus_guidelines.pdf

Programmer measurements were made using a standard Abbott Merlin device programmer, which has 5 leads. The limb electrodes were located in identical positions to the 12 Lead ECG on lower torso and shoulders. The Abbott programmer has a single chest lead, this was positioned in the 'true' anatomical V5 position as per SCST guidelines. The V5 electrode from the 12 Lead ECG was positioned as close as possible to the true position. Using the programmer, the following ECG leads were used as standard I,II,III, AVF and V5, these were displayed in vertical alignment. V5 was selected as it had previously been shown to have the closest correlation to global QRS by a small study (De Pooter, 2016). 50 mm/sec paper speed was used and gain optimised to reduce measurement error. QRS duration was measured across all 5 electrograms using digital calipers. Abbreviated global QRS was defined as *from the earliest onset of QRS in any of the 5 simultaneously recorded and*

vertically aligned ECG leads, to the end of the latest QRS in any lead. Abbreviated global QRS was used for final CRT programming. Figure 17 shows examples of measurements taken on the departmental equipment.

Electrogram printouts were obtained from the patient lying supine at rest with stable haemodynamic parameters. Whilst an exact timeframe was not described per programming mode, measurements were only taken when uniform ECG waveforms were obtained. This was at the discretion of the programming Cardiac Scientist. A single QRS complex was measured by each method, in keeping with current clinical practice and respectful to the observational nature of the study. Two non-blinded operators were involved during ECG measurement to coordinate simultaneous recording of ECGs via each method (the equipment was not positioned side by side). The second operator was also used to verify measurements, verify uniformity of waveforms and overall reduce measurement bias. The position of the calipers was agreed by both operators together. For paced complexes, measurement of QRS was taken from the start of the waveform and not from the pacing spike.

Intra-operator and Inter-operator variability of abbreviated global QRS methodology was assessed using 15 ECGs; measured by two members of research personnel. This was performed in the clinic environment using 5 random ECGs from 3 patients. An independent observer displayed the 15 ECGs on the Abbott programmer in random order. Each operator was instructed to measure a specific QRS complex per ECG using abbreviated global QRS methodology. The operators were blinded throughout. In total 5 ECGs were measured 5 times by each operator. All measurements were obtained in one session.

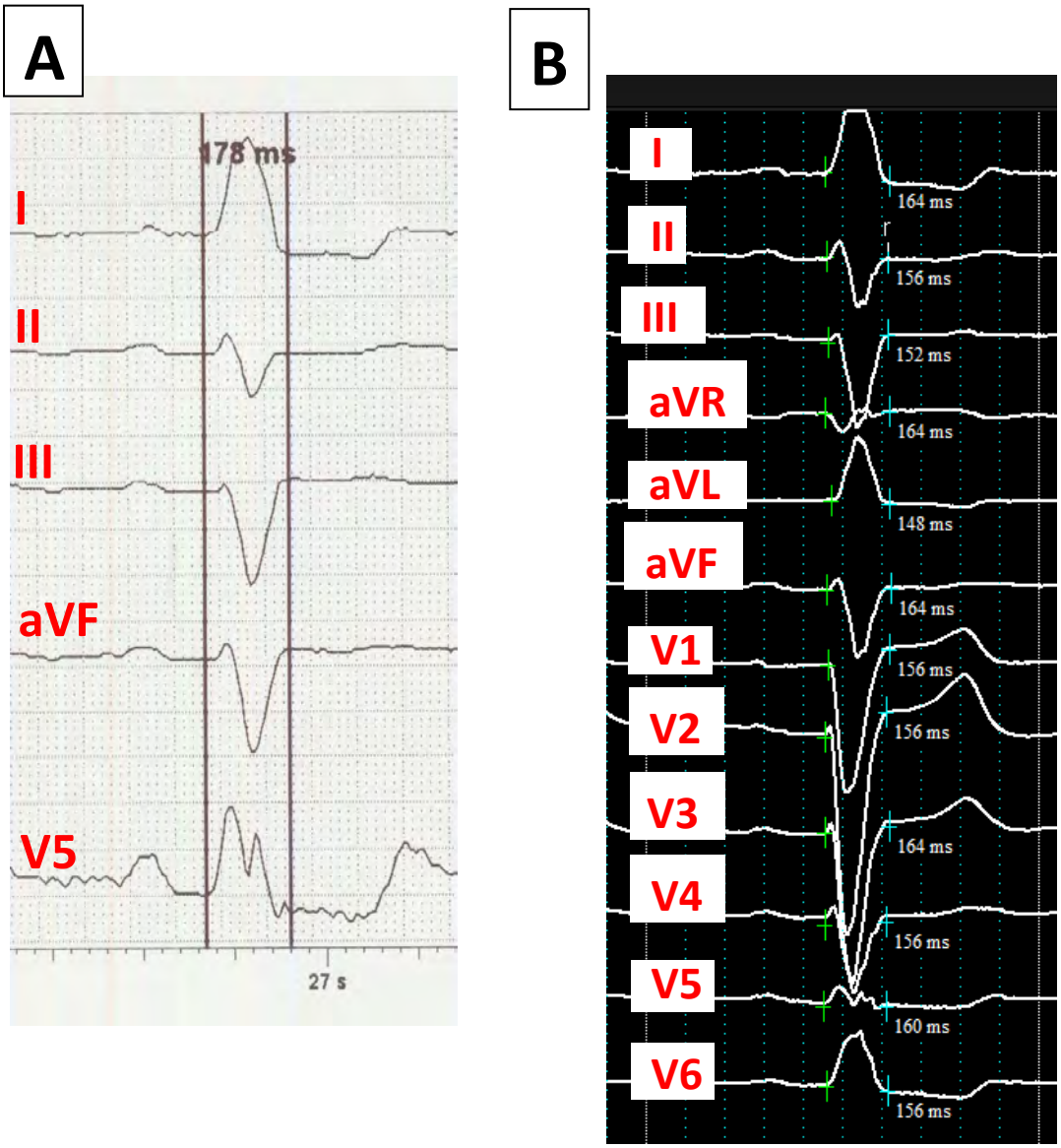


Figure 17 QRS duration measurement by two different techniques on the same patient (001)
{A} Shows abbreviated global QRS methodology on the Abbott programmer. This is measured from the earliest onset of QRS in any of the 5 simultaneously recorded and vertically aligned ECG leads, to the end of the latest QRS in any lead using a single set of digital calipers.
{B} 12 Lead ECG recorded on the Phillips haemodynamic system showing individual lead ECG measurement. The QRS duration is measured in all 12 ECG leads, each with a different set of digital calipers. The onset of the QRS was defined as the first positive or negative deflection from the isoelectric line and the offset was defined as the J point.

2.5 Assessment of Clinical Response to CRT

The final follow-up appointment was performed five months post implantation. Standard clinical follow-up was undertaken with repeat Minnesota questionnaire (MLHFQ), Six-Minute Walk Test (6MWT) and NYHA classification. CRT response was assessed at this point by comparing to baseline data and applying current departmental criteria as shown in Table 8. A responder was classed as having improvement in 2 out of 3 measures. The patient's future clinical care pathway beyond the study was based on this assessment.

Table 8 Current departmental criteria for Assessing CRT Response
A positive response in two out of three measures indicates a responder across the 3 clinical measures.

Assessment of Response	
Responder	≥2 of 3 measures: • Reduction in Minnesota questionnaire score at 5 months of 15 points • Improvement in Six Minute Walk distance at 5 months of 10% • Improvement of 1 step in the NYHA classification
Non-responder	0 or 1 of 3 measures: • Reduction in Minnesota questionnaire score at 5 months of 15 points • Improvement in Six Minute Walk distance at 5 months of 10% • Improvement of 1 step in the NYHA classification

Importantly, assessment in CRT response was only undertaken at this point if the patient was >90% biventricular paced at this visit and the lead tests were satisfactory.

For comparison, response to CRT was also assessed by applying the department's proposed revision to CRT Response criteria, this is shown in Table 9. However, this was not used to influence clinical decision making at this point.

Additional visits were not anticipated but the 6MWT and/or MLHFQ were offered on a separate visit if the participant was time-pressured or felt their health was not representative on the day. To eliminate confounding variables, this was performed within one week of the original planned visit.

Table 9 Revised Criteria for assessment of CRT response. This is more sympathetic to those who are minimally symptomatic and includes both a super-responder and non-progressor category.

Assessment of CRT Response ALIVE at 5 month Follow-Up plus:	
Super-Responder	**3 of 3 measures:** • Reduction in Minnesota questionnaire score at 5 months of ≥15 points (or if <14 points at baseline) • Improvement in Six Minute Walk distance at 5 months of ≥10% • Improvement of 1 step in the NYHA classification (or if class I at baseline)
Responder	**2 of 3 measures:** • Reduction in Minnesota questionnaire score at 5 months of ≥15 points (or if <14points at baseline) • Improvement in Six Minute Walk distance at 5 months of 10% • Improvement of 1 step in the NYHA classification (or if class I at baseline)
Non-Progressor	**1 of 3 measures:** • Reduction in Minnesota questionnaire score at 5 months of ≥15 points (or if <14 points at baseline) • Improvement in Six Minute Walk distance at 5months of 10% • Improvement of 1 step in the NYHA classification (or if class I at baseline)
Non-responder	**0 of 3 measures (no improvement or worse):** • Increase in Minnesota questionnaire score at 5 months or improvement ≤ 15 points • Decrease in Six Minute Walk distance at 5 months or improvement ≤ 10% • No Improvement in NYHA classification or worse class

2.6 Method for conducting a survey into CRT Practice

As part of this research study, a survey was undertaken using SurveyMonkey to document current practice in CRT implantation and follow-up focussing on the ECG. The survey questions are listed in Appendix 5.

The survey was circulated on social media platforms (Twitter and Facebook) on 28/04/2020. To account for potential selection bias, the survey was also circulated by the study centre's social media account. The final results were taken on 19/05/2020.

An online survey was selected to ensure rapid circulation and to reach a wide audience. SurveyMonkey is a free survey tool, hence is easily accessible by all. There was no restriction to participation, hence anyone could take part regardless of grade or job description. All responses were anonymous, although participants were asked to state their hospital.

Circulation on social media platforms conveys a personal approach and encourages cooperation by peers and colleagues. It was emphasized that the results would contribute towards the author's Higher Specialist Scientist Training doctorate-level thesis, which may have encouraged greater honesty and participation.

2.7 Statistical Analysis

The effectiveness of each CRT programming mode at narrowing QRSd was examined using descriptive measures and paired t-tests. The 10 different combinations of CRT programming modes were compared. Of greatest interest were differences in QRSd (ms) between conventional and individualised programming modes. Differences in QRSd were also assessed for each CRT programmed mode in comparison to baseline QRSd. The null hypotheses tested were of the form "*CRT programming mode 'x' is no different to programming mode 'y' with respect to QRS narrowing"*. Rejection of a null hypothesis implies there is a significant difference between the modestested. Values were taken to be significantly different when $p \leq 0.05$.

This analysis involved several comparisons between different mode pairs ("multiple comparisons"). There are different approaches to handling this kind of data statistically (Motulsky, 2017; Armstrong, 2014; Rothman 1990). In this thesis, particularly in view of the restricted number of paired comparisons of key clinical significance within the data, the approach taken was to present individual p-values and confidence intervals in detail but without routine mathematical correction for multiple-comparisons (Motulsky, 2017). This topic will also be addressed in later discussion.

This study also aimed to assess agreement for QRSd between individual-lead measurements and the abbreviated global QRS method. The methodology used in this analysis was based on Bland and Altman (1986), which has become the standard approach for method comparison studies (Hayes, 2010). The data were displayed graphically showing for each case, the difference between the two measurements, plotted against the mean of the two measurements ("Bland-Altman plot"). Quantities estimated were the mean difference between the measurements by the two methods, and the 95% limits

of agreement (LoA), defined as mean difference ± 1.96 x standard deviation (SD) of the differences. In addition, simple linear regression plots were used to demonstrate the relationship between the different methods of measuring QRSd, including estimation of the Pearson correlation coefficient (r).

Inter-operator variation (reproducibility) and Intra-operator variation (repeatability) of the abbreviated global QRS technique were assessed using the Standard Error of Measurement (SEM) method, as described by Popovic and Thomas (2017) and Glen (2016). This technique uses a two-way analysis of variance to calculate inter and intra-operator SEM from a dataset that contains repeated measurements from multiple observers. The standard error of measurement indicates the standard deviation of the test measurements around the “true” value and is measured in absolute units, in this case milliseconds (Glen, 2016). The 95% confidence interval for the measurement can be estimated as ± (1.96 x SEM).

The analysis is expected to be tolerant of mild or moderate departures from assumptions of normality due to adequate case numbers and the central limit theorem. Nevertheless, data were screened to exclude any major deviations from normality assumptions using graphical visual assessment and the Shapiro-Wilk test as explained by Ghasemi and Zahediasl (2012). Where indicated, selected results were confirmed with non-parametric tests such as the Wilcoxon Signed Ranks test and Sign test. Fisher Exact test was used in comparison of CRT response.

Data analysis was performed using standard statistical software including StatsDirect (StatsDirect Ltd, 2013) and “R” (R Core Team, 2020) with support packages (Wickham et al, 2019; Wickham, 2016; Schauberger and Walker 2020; Lemon, 2006; Yihui, 2014, Schloerke et. al.2020). Assistance in this statistical analysis was provided by Dr Mike Smith.

2.8 Power Calculation and Sample Size Estimate

A preliminary power calculation was performed at the outset of the study to provide a rough indication of the required sample size (Champely, 2020). The power calculation was based on detecting a clinically significant difference of 10 ms in QRS duration between pairs of CRT programming modes using a two- sided paired t-test. The calculation required an estimate of the standard deviation of paired differences between two different programming modes. This was estimated crudely from graphical data in the published study by Varma et al (2018), to be approximately 19 ms. This calculation necessarily involved a high degree of uncertainty, particularly due to the assumptions based on published data.

Given that the approach was to present data without routine mathematical correction for multiple comparisons, the significance level of <0.05 was applied. This resulted in an estimated a recruitment target of 30 patients to detect the required difference at 80% power. This was the minimum planned recruitment target for the study.

However, in acknowledgement of the multiple paired comparisons between five programming modes (i.e. 10 paired comparisons), a power calculation was also performed using the Bonferroni correction. This was for comparison purposes and used a highly conservative significance level of <0.005. With Bonferroni applied, the estimated recruitment target of 52 patients was required to detect the required difference at 80% power. Within the study timeframe, it was anticipated that recruitment would exceed the minimum target of 30 and reach n=52. The power calculation is shown in Appendix 6 and displays the estimated sample size at 80% power both with and without Bonferroni correction.

Effect sizes were calculated for each paired comparison using Cohens ‘d’, defined as the mean of the paired differences divided by the standard deviation of the paired differences. These are presented as the absolute valve ($|d|$).

2.9 Sampling/ Participants

The full inclusion and exclusion criteria are listed in Table 10.

Table 10 Inclusion and Exclusion Criteria

Inclusion	Exclusion
• Male / female aged 18 years upwards • Patients implanted with an Abbott or St.Jude CRT defibrillator (CRT-D) or CRT pacemaker (CRT-P) with Sync AV algorithm (CE marked) • Patients with a quadpole LV lead (CE marked) • Any commercially available RA & RV pacing or RV defibrillation lead • Scheduled for Class 1A Indication for CRT implant (NYHA Class II-IV; LVEF <35%, LBBB with QRS duration >12 0ms, preserved atrioventricular conduction with PR interval <250 ms; on optimal medical therapy) • Fully able to understand the nature of the study with sufficient chance to read PIL and commitment to follow-up schedule • Sinus rhythm at recruitment & implantation	• Under 18 years of age • Patients who do not have a quadpole LV lead in situ • Patients without an Abbott or St.Jude CRT generator • In Atrial fibrillation (AF) • Patients who are pregnant or plan to become pregnant during study period • Those with a PR interval >250 ms • Patients unable to complete a 6MWT • Patients with non-standard CRT indications • Patients taking part in other research studies during the study period • Inability to understand study requirements.

The target population in this study was patients listed for a Class 1A indication for CRT implantation in accordance with the criteria specified by NICE Technology Appraisal 314 (NICE, 2014). In keeping with NICE guidance, this population had severely impaired left ventricular systolic impairment, as determined by a Left Ventricular Ejection Fraction (LVEF) less than or equal to 35%. Patients also had delayed ventricular activation and dysynchronous

contraction, as determined by Left Bundle Branch Block (LBBB) morphology on the 12 Lead Electrogram (ECG) and a QRS duration of >120 ms. In addition, all patients were on optimal medical therapy by the time of referral to CRT (NICE, 2014).

This study focussed on patients in LBBB as this is the patient group most likely to benefit from CRT. Landmark studies that shaped the current guidelines for CRT specified QRS duration (typically >120 ms) for inclusion rather than QRS morphology (Brignole et al, 2013). However, later subgroup analysis emphasized that those with LBBB obtained greatest benefit from CRT with regards morbidity and mortality (Sipahi et al, 2011; Gold et al, 2012; Zareba et al, 2011; Tang et al, 2010). Furthermore, it was important to maintain consistency with other similar studies. QRS narrowing has been shown to improve mortality in LBBB patients only with an almost linear relationship between QRS shortening and mortality benefit (Jastrzebski et al, 2018). In the non-LBBB cohort of this study, there was no mortality or morbidity benefit from QRS narrowing (Jastrzebski et al, 2018).

This standard target group were deemed symptomatic, as depicted by a NYHA class of II-IV and in accordance with NICE guidance. In NYHA Class I, CRT is indicated in patients with LVEF <35% and QRS duration >150 ms. NYHA Class was determined by the referring doctor at the time of referral for CRT Implantation and this was used for inclusion. Importantly, the Cardiac Physiologists reassessed NYHA class as part of the standard care pathway during Pre-Assessment. It was accepted that any discrepancy identified at this stage would not negatively affect inclusion, due to the observational nature of the study. Physiologist-derived NYHA Class was used in the assessment of CRT response.

Patients referred for CRT with non-standard indications for CRT were

excluded. There is a large body of evidence emphasizing the patient group most likely to respond to CRT, which is reflected in the current NICE guidelines for implantation. Importantly, there is a discrepancy between NICE guidelines and ESC guidelines regarding QRS duration. ESC guidelines recommend CRT in patients with a QRS of 130 ms or greater, whereas NICE guidance states >120 ms (Brignole et al, 2013, NICE 2014). Some studies have suggested that CRT in patients with a QRS < 130ms is less likely to result in a responder but may even be harmful (Ruschitka et al, 2013; Brignole et al, 2013). Hence at the study centre a cut-off of 130 ms was informally applied.

Importantly for the current study, patients must also be in sinus rhythm with intact atrioventricular (AV) conduction, as determined by a PR interval of <250 ms. This was essential to ensure that patients could benefit from all five programmable modes. Three of the modes involved a fusion pacing algorithm, called SyncAV. This mode fuses electrical stimulation of both the left and right ventricles with intrinsic QRS depolarisation. Hence, significant AV block is a contraindication to this algorithm and was a marker for exclusion. A PR interval cut-off of 250 ms was consistent with manufacturer guidelines. The Sync AV algorithm is specific to the manufacturer Abbott, hence all patients were required to be implanted with an Abbott CRT-P or CRT-D device, which had the full range of algorithms required for this study. It was not necessary that the implanted leads were manufacturer specific, but the implanted LV lead must be quadpolar to enable multi-point pacing (MPP). MPP features in two of the five programmable modes.

One consideration was if a patient's cardiac rhythm changed between recruitment and implantation. Disease progression and intermittent rhythm abnormalities in heart failure are not uncommon, but the SyncAV algorithm was dependant on being in sinus rhythm and absence of AV conduction disease. Hence, it was decided that patients must still satisfy this criteria at the start of the CRT implantation procedure, when baseline readings were obtained. Importantly, rhythm abnormalities may be induced as part of the implantation procedure. In particular, manipulation of the coronary sinus catheter can stun the AV node, causing AV block or ventricular standstill.

Manipulation of the right atrial lead can provoke atrial rhythm disturbances, particularly in the dilated atria often associated with heart failure. These rhythm disturbances are usually temporary and resolve by the end of the CRT procedure. Any haemodynamic consequences are usually easily overcome by pacing, as is the goal of CRT. Patients who remained in persistent atrial fibrillation by the end of the procedure would be excluded, as losing the atrial contribution to ventricular filling may significantly affect the ability to obtain maximum benefit from the programming options and can also affect the patient's response. However, patients who developed AV block that did not resolve by the end of the procedure were included, but programmed modes II and III were not possible. Any patient which became unstable during the procedure was excluded, at the discretion of the implanting physician.

Optimal medical therapy was defined as the maximum tolerated dose of medications in line with 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure (Ponikowski et al, 2016). At the time of the study, this included an Angiotensin Converting Enzyme Inhibitor (ACE) or Angiotensin II type I receptor blocker (ARB) if the patient could not tolerate an ACE; a beta-blocker and a mineralocorticoid receptor antagonist (MRA). These ESC guidelines were further updated in 2021 and first line treatment now consists of a beta-blocker, MRA, ACE or Angiotensin Receptor-Neprilysin Inhibitor (ARNI) and a Sodium- Glucose Co-transporter 2 inhibitor (SGLT2I) (McDonagh et al, 2021).

All devices commercially available within the UK must conform to CE marking. All patients in this study were new implants performed at the study centre, hence all the devices used in this study satisfied this criterion.

Complex device implantation within the locality of this study was delivered by a regional approach; this was a collaboration between two NHS institutions,

using a shared computerised waiting list. Importantly, the recruitment strategy for this study was aimed at a single NHS site within the network. The catchment for CRT implantation within the network had an estimated population of 1.4 million. Based on the latest data published by NICOR for the 2016/2017 period, the estimated number of new CRT implants (CRT-D and CRT-P) over a 1 year period was expected to be 208.6 per year in this region (using a UK average of 149 per million population) (NICOR, 2019). Based on existing tender specifications within the study centre which governed procurement of devices per manufacturer, the target sample size of new CRT implants, using the single manufacturer Abbott, was considered very realistic within the study timeframe.

Consecutive patients newly referred for a CRT-P or CRT-D were identified from the shared waiting list and sent a Patient Information Leaflet (PIL) approximately one week prior to their Pre-Assessment appointment (as shown in Appendix 7). Research personnel (who were members of the direct care team) screened patients against the recruitment criteria during the Pre-Assessment appointment. This process is known as non-probability sampling, whereby investigators specifically select individuals who satisfy the inclusion criteria (Strauss et al, 2005). This may increase the chance of selection bias, although can be useful when the objective concerns the specific sample rather than the wider population (Altman, 1992). This type of sampling can be a viable alternative when a study is unable to adopt probability sampling, although external validity can be affected.

Importantly, patients who were found to be unsuitable for an Abbott device (or better suited to another CRT manufacturer based on clinical characteristics) were excluded. This was at the discretion of the direct care team. Whilst device manufacturers broadly offer the same range of software and hardware, there are subtle differences in algorithms and equipment which may suit different patients. The size and shape of the generator varies between manufacturers and may be better suited to particular body habitus. Battery composition also

varies; for example one manufacturer uses lithium magnesium and another uses lithium silver vanadium. Subsequent variation in battery longevity may influence device selection, particularly if a patient has multiple comorbidities and likely to be a poor candidate for future battery change. It is common practice to utilise the same manufacturer of leads and generator to maintain MR conditionality and only one manufacturer (Medronic) currently offers an active fix LV lead. These leads are used for targeted lead placement and can enable a basal position is a bigger vessel. Some operators have preferred manufacturers due to experience and handling of implantation equipment (such as LV lead delivery catheters and slitters).

2.10 Patient and Public Involvement

This study was discussed in detail with the trust's R&D Patient Ambassador on 03/07/18. No significant issues were identified because the data set was to be obtained as part of the routine assessment. Participation in the study was voluntary and all patients will be provided with a patient information leaflet and written consent obtained. It was suggested that the research study was discussed at the Pre-Device Counselling session and that the patient information leaflet was sent out in advance to give patient time to digest the information. Consequently, these views were incorporated into the study design.

2.11 Ethical Approval

Ethical approval was granted by the Research Ethics Committee (REC) and Health Research Authority (HRA). Local approval from the NHS study institution was also granted. Approval letters are listed in Appendix 8 (REC reference 19/LO/0448, Project ID: 260238).

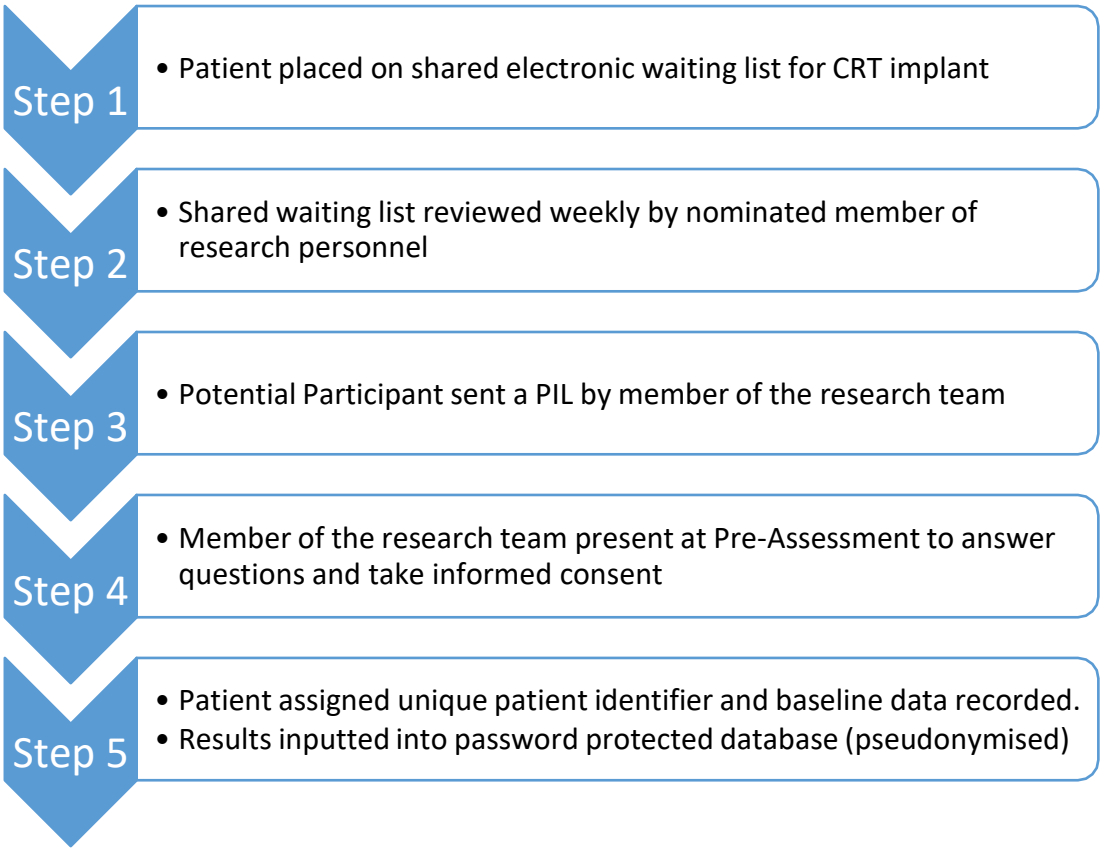


Figure 18 Recruitment Strategy
This flow chart shows how patients were identified for the study. Importantly, the research team were also members of the direct care team. Patients who did not wish to take part were not contacted further and received standard patient care.

Participation in this single-site study was entirely voluntary. The recruitment strategy is shown in Figure 18. Potential participants were first approached by a member of the direct care team, a specialist Device Physiologist. As already described, each participant was sent a Patient Information Leaflet (PIL) approximately one week prior to their routine Pre-Device Assessment appointment. The Pre-Assessment appointment was typically scheduled one to two weeks in advance of the CRT implantation procedure. This allowed participants sufficient time to consider the information. Qualified research/clinical personnel were available during Pre-Assessment to answer further questions and to take informed written consent. Qualified research personnel were defined as those who have undergone Good Clinical Practice

(GCP) Training and been fully trained in the study protocol / data collection methods by the investigatory team.

Patients who did not wish to take part were not contacted further about the study and their standard CRT care continued as planned. Patients who were unable to provide informed consent were not approached to take part in the study. A copy of the signed consent form was provided to the patient and a final copy stored in the research site file, an example is shown in Appendix 9.

No extra visits to hospital or outpatient care were required for this study. The operative process itself was entirely unchanged and therefore there was not an increased risk of complications through this study. In keeping with departmental protocol, CRT optimisation would be terminated in the event of any adverse symptoms. Any Serious Adverse Events, Serious Adverse Reactions or Serious Unexpected Serious Adverse Reactions would be recorded and actioned by members of the direct care team.

The anonymous online survey into CRT Practice did not require ethical approval. The survey was performed by the author and made no reference to the study centre.

To maintain confidentiality, all patients recruited to the study were anonymised and assigned a unique study identification code. Participants had the right to withdraw from the study at any point up to the commencement of data analysis. All investigators complied with the General Data Protection Regulation. Indemnity provision was not relevant as no harm was envisaged either prospectively or retrospectively, due to the observational nature of the study. The study design and data collection did not pose any safeguarding risk to participants or others. No children participated in the study. It

was specified that any safeguarding concerns raised as part of a patient's admission would be addressed by the clinical team as per Trust & National guidelines for safeguarding adults.

There is one disclosure for this study. A technical representative from Abbott Medical, who market the CRT devices used in the study, was present during device implantation, as is standard protocol for the study institution. However, Abbott had no involvement in the funding or interpretation of the results.

3.0 Results

Recruitment for this study commenced in March 2019. However, from 16th March 2020, data collection and further recruitment was suspended due to the COVID19 pandemic. Recruitment was re-opened in September 2020, although shortly afterwards COVID19 cases increased within the locality and South Yorkshire was placed into Tier 3 lockdown restrictions in October 2020. On 5th November 2020, the UK entered a second national lockdown until 2nd December 2020. Recruitment was again suspended and subsequently terminated early. There were no further volunteers to participate in the study since the first lockdown in March 2020. This is believed to be due to ongoing fear of COVID19 and reluctance to commit to any research which may require a commitment to a face to face hospital visit, despite this being part of the routine care pathway.

3.1 Study Population

In total, 31 patients were recruited to the study. One patient was incorrectly recruited and was having a pacemaker upgrade to CRT, hence did not satisfy inclusion criteria and was immediately excluded. A further patient was recruited in February 2020, but the implantation was delayed until July 2020 due to the COVID19 pandemic. Subsequently the initial pre-assessment data (6MWT & MLHFQ) was out of date, hence this patient was withdrawn. In one case, the coronary sinus was dissected during the implantation procedure and the patient was implanted with a HIS bundle CRT instead, hence was fully excluded.

In total, 28 of the recruited patients generated data that was used in analysis. A consort diagram of the study is shown in Figure 19. One patient was excluded during implantation because they developed complete AV block on positioning of the LV lead which did not resolve by the end of the procedure.

The patient became unstable, hence it was decided not to proceed to full CRT optimisation at that time. Consequently, their data was not included in the mode comparison study or that of CRT response. However, their baseline data taken pre-implant was valid for the method comparison study. One patient developed AV block during the procedure, but remained stable, hence it was possible to obtain data for Mode 1 and Mode 4 (all modes requiring AV conduction were excluded). In one patient, a programming conflict was observed when programming MPP, hence it was not possible to test Mode 4 and 5. However, data was included for Mode 1, 2 and 3. The full dataset for all five modes was achieved in 25 patients. Baseline clinical characteristics of the included patients is shown in Table 11.

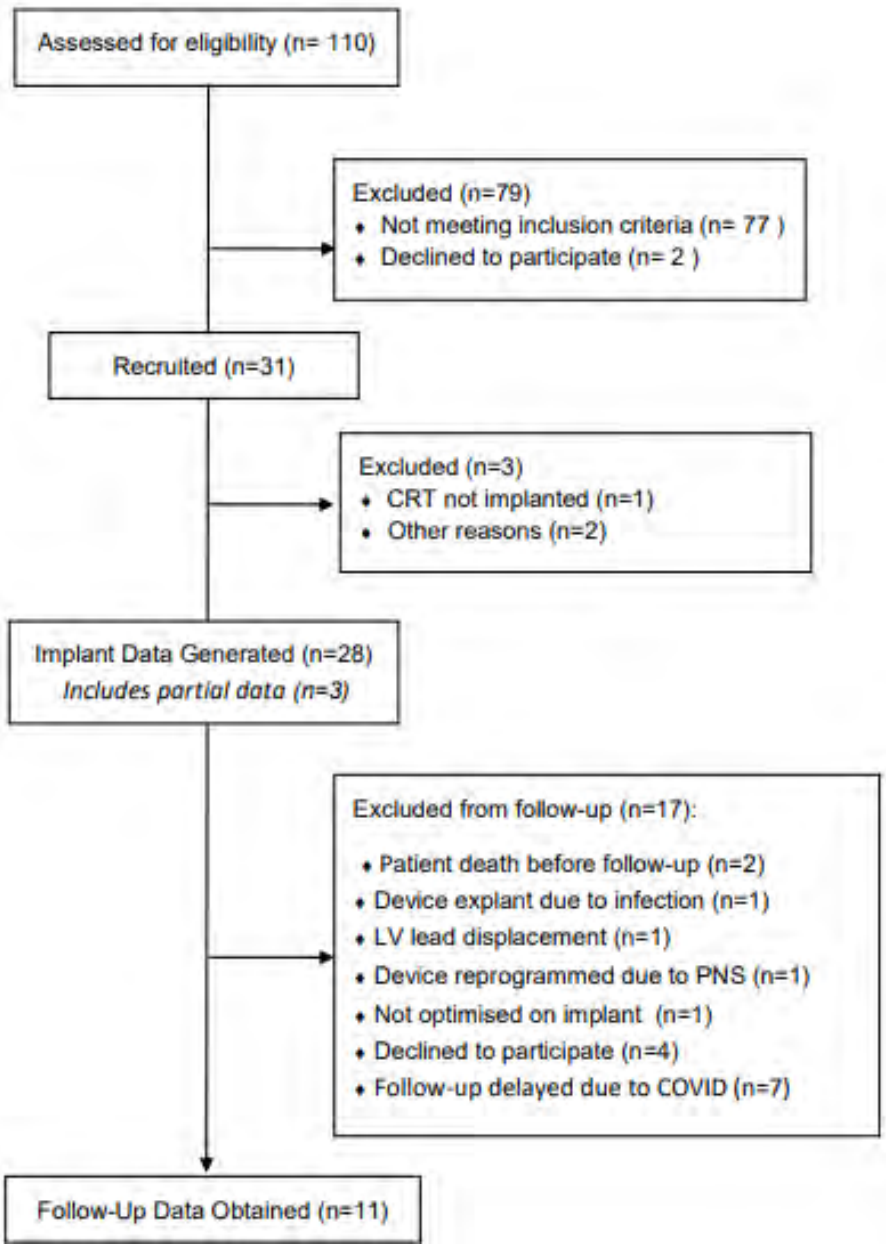


Figure 19 Consort Diagram
This flow chart displays the progress of participants in the study. It is based on the Consort 2010 statement. The total number of patients screened was 110 but of these only 31 were recruited. This was largely due to not meeting the inclusion criteria, only 2 eligible patients declined to participate. 11 patients completed the study to the 5 month follow-up stage.

Table 11 Baseline demographic data.
Clinical characteristics and demographic data from the study sample are shown in the table below; n=28. Percentage or SD shown in brackets where relevant.

Clinical Characteristics	Number (Percentage or SD)	Range
Patients (number)	n = 28	-
Age (years)	73.1 (± 10.7)	41-87 years
Male	19 (68%)	-
Ischaemic aetiology	15 (54%)	-
NYHA class		
I	3 (11%)	-
II	10 (36%)	-
III	15 (53%)	-
IV	0 (0%)	-
LVEF %	22.7 (± 7.5)	7-35
PR (ms)	187.3 (± 36.3)	113-248
P wave duration (ms)	121.4 (± 16.7)	66-148
Baseline QRS (aQRS_Global) (ms)	170.8 (± 18.9)	143-213
Baseline QRS (QRS_Max) (ms)	173.1 (± 21.2)	144-220
Baseline QRS (QRS_Mean) (ms)	155.1 (± 18.7)	127-192
Target Vein		
Lateral	15 (54%)	-
Posterolateral	7 (25%)	-
Posterior	2 (7%)	-
Anterolateral	4 (14%)	-
RV Lead position		
RV Apex	11 (39%)	-
RV Septum	16 (57%)	-
RV Free Wall	1 (4%)	-
Baseline 6MWD (metres)	252.7 (± 113.9)	45-495
Baseline MLHFQ (score)	39.5 (± 20.9)	4-88

28 patients were recruited between March 2019 and March 2020 with a mean age of 73.1 years (range 41 to 87 years). Nineteen patients (68%) were male and 15 (54%) displayed an ischaemic aetiology. The majority of patients were in NYHA class II (n=10, 36%) or III (n=15, 53%). None of the cohort were in

NYHA class IV pre-implant. Only 3 patients (11%) were in NYHA class I prior to CRT implantation. Mean LVEF was 22.7% with a range from 7-35%.

In terms of ECG characteristics, the mean P wave duration was 121.1 ms (± 16.7) with a range of 66-148 ms. Mean PR interval was 187.8 ms (± 36.3) with a range of 113-248 ms. Baseline QRS duration varied according to the measurement used: QRS_Global was 170.8 ms (± 18.9) with a range of 143-213 ms; QRS_max was 173.1 ms (± 21.2) with a range of 144-220 ms and QRS_mean was 155.1 ms (±18.7) with a range of 127-192 ms. Baseline mean 6MWD was 252.7 metres (± 113.9) and a wide range from 45-495 metres. Baseline MLHFQ score was 39.5 (±20.9) with a broad range from 4-88.

Optimal LV lead position was obtained in the majority of cases with 15 cases (54%) achieving a lateral vein; 7 cases (25%) achieving a posterolateral vein and 2 cases (7%) achieving a posterior vein. However, in 4 patients (14%) an anterolateral target vein was used indicating suboptimal LV lead placement. RV lead placement was predominantly in an RV septal position in 16 cases (57%) and RV apex in 11 cases (39%). In one patient, the RV lead was documented to be position at the RV free wall (4%).

3.2 Survey into CRT Practice

There were 31 responses received between 28/04/2020 and 19/05/2020. The participants represented 21 hospitals within the UK and Ireland. This showed wide geographical spread, as shown in Table 12. The results show that there was more than one response per hospital in some situations.

Table 12 Hospitals represented by the survey participants.
The table below lists the hospitals documented by the participants who responded to the survey. The participants themselves were anonymous.

Participating Hospitals	
Mid Yorks NHS Trust	Hermitage Clinic (Dublin)
Glenfield (Leicester)	University Hospital (Galway Island)
Nottingham University Hospitals NHS Trust	Barts Heart Centre (London)
Leeds Teaching Hospitals	Great Weston Hospital (Swindon)
James Cook Hospital (Middleborough)	Royal Brompton Hospital
Kings Mill Hospital (Mansfield)	St. Georges Hospital (Tooting)
Aberdeen Royal Infirmary	University Hospital (Southampton)
Diana Princess of Wales (Grimsby)	Essex CTC (Basildon)
University Hospitals (Birmingham)	Lincoln Hospital
Manchester Royal Infirmary	Rotherham NHS Foundation Trust
Blackrock Clinic (Dublin)	

97% of participants agreed that QRS narrowing was important in CRT. 84% measured QRS duration on implant, but only 55% measured QRS duration routinely at follow up. The type of ECG monitoring during CRT Implant varied between centres; 49% used 12 Lead ECG; 32% used limbs leads plus 1-2 chest leads and 19% used limb leads only. This is shown in Figure 20.

There was also variation in the type of ECG monitoring during CRT follow-up; 42% routinely used programmer ECG plus 12 Lead ECG; 16% used 12 Lead ECG only; 16% used programmer ECG only; 26% used programmer ECG with the addition of 12 Lead ECG on an individual basis.

Measurement technique for QRS duration varied on implant; 35% measured a single ECG lead using digital calipers; 10% manually measured a single ECG lead; 35% measured global QRS on the 12 Lead ECG using digital calipers; 13% measured abbreviated global QRS on the programmer using 4-7 leads with digital calipers; 3% used 'eyeball' assessment and 3% did not measure QRS duration. The written comments returned from the participants are listed in Appendix 10.

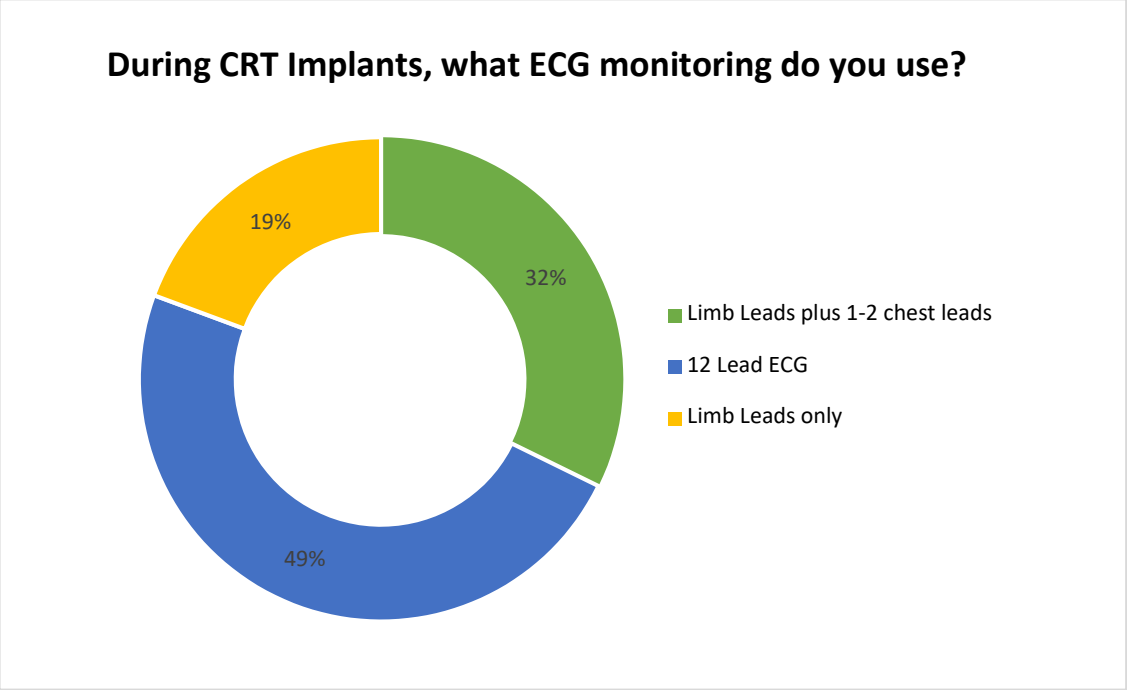


Figure 20 Survey Question 3.
This shows the wide variation in practice for ECG monitoring during CRT implant. 49%, 32% use limb leads plus 1-2 chest leads and 19% use limb leads only.

Similar variation in the measurement of QRS duration was noted during follow-up as shown in Figure 21. 14% used 'eyeball' assessment, 27% measured a single lead on the programmer or 12 Lead ECG sing digital calipers, 21% manually measured a single lead on the programmer or 12 lead ECG using digital calipers; 21% measured global QRS on the 12 Lead ECG using digital calipers, 14% measured abbreviated global QRS on the programmer using

digital calipers (e.g. 4-5 leads) and 3% selected other, but specified ‘automated ECG analysis-derived values which averages from all complexes’.

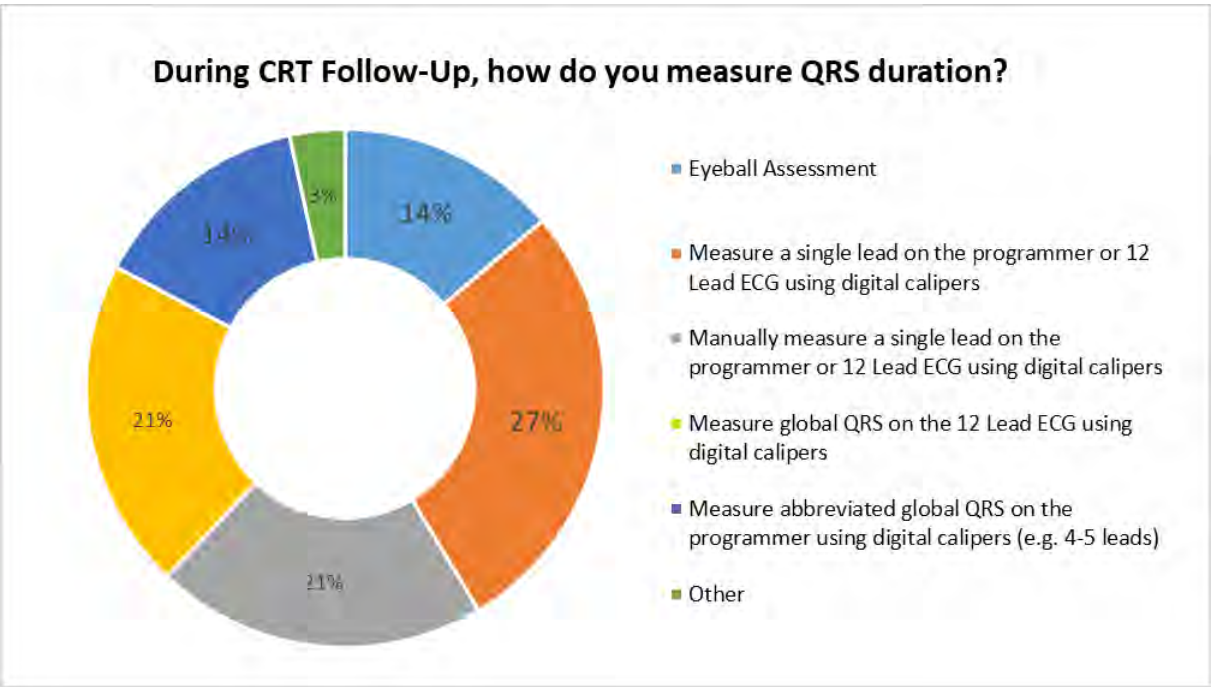


Figure 21 Survey Question 8
Significant variation in how the QRS duration is measured during CRT Follow-Up; the most popular method was measuring a single lead on the programmer or 12 lead ECG using digital calipers (27%).

3.3 Comparison of methodologies for measuring QRS duration

3.3.1 Abbreviated Global QRSd vs individual lead QRSd

Data from 28 patients was available for the method comparison study; which compared the abbreviated global QRS (QRS_aGlobal) method versus individual lead QRS method. Up to six sets of data were collected per patient to compare both methods of measuring QRS duration [Baseline, Mode 1, Mode 2, Mode 3, Mode 4 and Mode 5]. Only 3 patients did not have the full dataset available; of these one patient became pacemaker dependant after baseline readings were obtained; one patient developed AV block preventing

fusion pacing and in one patient programming conflicts were encountered which prevented programming of MPP.

Table 13 Correlation between the different methods for measuring QRSd. The measurements from abbreviated Global QRS (QRS_aGlobal) were compared to each of the 12 ECG leads plus the QRS_Max and QRS_Mean. This is a tabular presentation of Bland Altman Analysis; mean difference and Standard Deviation (SD) are shown in ms; the 95% Limits of Agreement (LoA) are shown in ms (plus upper and lower range). Pearson's correlation coefficient shows the strength of association between the datasets.

ECG Method Comparison	Bland-Altman Analysis			Pearson's correlation coefficient
	Mean difference (ms)	SD (ms)	95% LoA (ms) (Higher, Lower)	
QRS_aGlobal vs QRS_Max	-7.4	15.0	29.4 (+22.1, -36.8)	0.79
QRS_aGlobal vs QRS_Mean	8.4	13.8	27.1 (+35.5, -18.7)	0.82
QRS_aGlobal vs QRS_LeadI	14.2	18.2	35.6 (+49.8, -21.4)	0.7
QRS_aGlobal vs QRS_LeadII	8.3	19.1	37.5 (+45.8, -29.2)	0.67
QRS_aGlobal vs QRS_LeadIII	7.1	18.0	35.4 (+42.5, -28.3)	0.7
QRS_aGlobal vs QRS_aVR	9.4	17.9	35.1 (+44.5, -25.7)	0.72
QRS_aGlobal vs QRS_aVL	10.4	19.0	37.3 (+47.7, -26.9)	0.65
QRS_aGlobal vs QRS_ aVF	7.0	17.9	35.2 (+42.2, -28.2)	0.71
QRS_aGlobal vs QRS_ V1	8.4	15.5	30.5 (+38.9, -22.1)	0.78
QRS_aGlobal vs QRS_ V2	5.9	14.6	28.8 (+34.7, -22.9)	0.8
QRS_aGlobal vs QRS_V3	7.0	15.2	29.8 (+36.8, -22.8)	0.8
QRS_aGlobal vs QRS_V4	7.2	17.5	34.4 (+41.6, -27.2)	0.72
QRS_aGlobal vs QRS_ V5	8.3	18.0	35.4 (+43.7, -27.1)	0.7
QRS_aGlobal vs QRS_V6	7.3	16.8	32.9 (+40.2, -25.6)	0.73

There was a large volume of data available for this study and in total, 158 sets of ECG data were compared. The data sets were compared for each individual ECG lead vs QRS_aGlobal, with the addition of QRS_Max and QRS_Mean. Units are in ms. Results are presented by Bland Altman Analysis with 95% limits of agreement (LoA) and Pearson's Correlation Coefficient (r). A summary of the method comparison data is shown in Table 13. Graphical representation of paired ECG comparisons for QRS_V2, QRS_Mean and

QRS_Lead I are displayed in Figure 22. Appendix 11 shows the Bland Altman Analysis and correlation coefficient graphs for all other paired ECG comparisons.

The data distributions for inter-measurement differences were screened for non-normality as described in Section 2.7, the screening results are summarized in Appendix 12. The Shapiro Wilk test showed no significant deviation from normality ($p<0.05$) for all comparisons with the exception of slight deviations for the pairs QRS_aGlobal vs QRS_I and QRS_aGlobal vs QRS_V5. This could marginally affect the accuracy of the estimates for the Limits of Agreement for these pairs but would not affect the overall assessment of the data.

A Pearson's correlation co-efficient of +1 implies a perfect positive linear correlation, 0 describes no correlation between two variables and -1 describes a perfect negative correlation. If the coefficient lies between 0.5 and 1, there is considered to be a strong correlation. Pearson's correlation co-efficient showed strong correlation between all single lead measurements and QRS_aGlobal, as expected, because both techniques were designed to measure the same value on the same scale of measurement. Across all data sets, the r value ranged from 0.65 (QRS_aGlobal vs QRS_aVL) and 0.82 (QRS_aGlobal vs QRS_Mean).

The level of agreement between abbreviated global QRS and individual ECG leads is shown in the Bland-Altman plots (Figure 22). The scatterplots present paired differences (Y axis), plotted against pair-wise means (X axis). The reference line indicates the perfect average agreement, Y=0. The central dashed line indicates the mean difference between the 2 measurements, or mean bias. Upper and lower lines represent the mean ± 1.96 standard deviations (SD), or 95% limits of agreement.

Despite the high correlation between the different measurement scales, Bland Altman analysis highlighted substantial variation between the methods. Across all data sets, mean difference ranged from 5.9 ms (QRS_aGlobal vs QRS_V2) to 14.2 ms (QRSaGlobal vs QRS_LeadI). The LoA were broader and ranged from 27.1 ms (QRS_aGlobal vs QRS_Mean) to 37.5 ms (QRS_aGlobal vs QRS_LeadII). Standard deviation ranged from 13.8 ms (QRS_aGlobal vs QRS_Mean) to 19 ms (QRS_aGlobal vs QRS_aVL).

Lead I showed the largest mean difference between the methods at 14.2 ms with 95% LoA of ± 35.6 ms and SD of 18.2 ms. Importantly, the LoA are equal to 1.96 x SD, hence 95% of the time abbreviated Global QRS measured within 49.8 ms higher (14.2 + 35.6) and 21.4 ms (14.2-35.6) lower than the QRS measured by Lead I. 68% of the time, abbreviated Global QRS measured within 1 x SD of Lead I from +32.4 to -4.2 ms. In clinical practice, a difference of 10-20 ms is considered significant, hence this highlights variation of high magnitude between the methods.

Comparison of QRS_Mean against QRS_aGlobal demonstrated both the lowest SD at 13.8 ms and the lowest LoA of 27.1 ms (ranging from +35.5 to -18.7 ms). The mean difference between QRS_aGlobal and QRS_Mean was 8.4 ms. QRS_Mean also had the strongest correlation with QRS_aGlobal with a coefficient (r) of 0.82.

V2 demonstrated the smallest mean difference between the methods at 5.9 ms with LoA of ± 28.8 ms and SD of 14.6 ms. 95% of the time abbreviated Global QRS measured 34.7 ms higher (5.9 + 28.8) and 22.9 ms lower (5.9 - 28.8) than the value measured by V2. 68% of the time, abbreviated Global QRS measured within 1 x SD of V2 from +20.5 ms to -8.7 ms. Hence whilst V2 demonstrates the least mean difference and one of the strongest correlation coefficients, the variation between methods remains substantial. Variation of this magnitude and broad LoA were observed for all comparisons between

abbreviated Global QRS and individual leads.

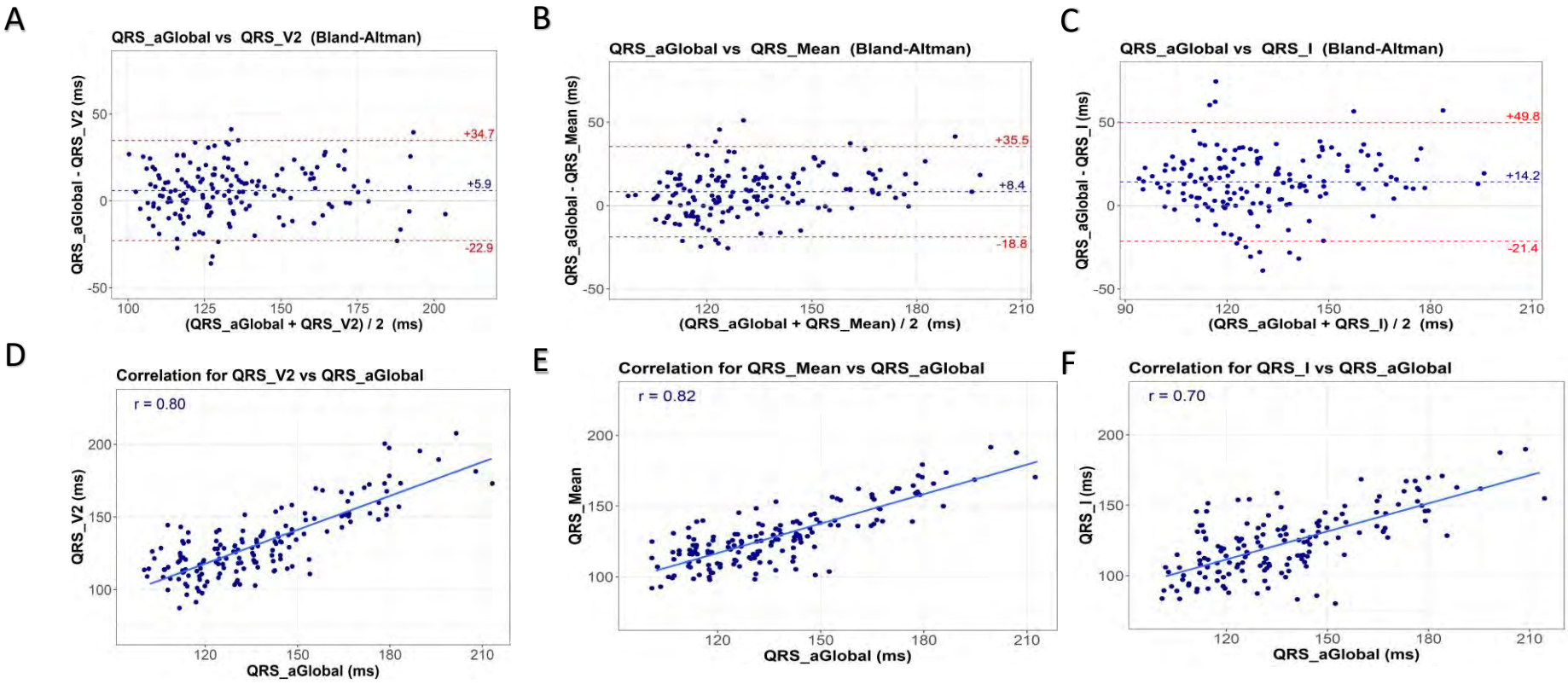


Figure 22 Comparison of methodologies for measuring QRS duration. (A) to (C) are Bland-Altman plots comparing single lead measurement in V2 (QRS_V2), mean QRS duration (QRS_Mean) and single lead measurement in lead I (QRS_I) respectively, against abbreviated global QRS (QRS_aGlobal). Horizontal lines indicate mean difference (blue) and upper/lower 95% limits of agreement (red). (D) to (F) show correlation for the same variables. “r” is the Pearson correlation coefficient. Slight random jitter has been applied to the point positions to minimise overlap.

3.3.2 Variation between individual ECG leads

Evaluation of the individual lead measurements across the 12 Leads (plus QRS_Max and QRS_Mean) showed inconsistent results. Some ECGs displayed modest variation across the 12 Leads whereas others displayed significant differences between individual leads. For example, in patient 001 the baseline QRS_Mean was 158 ms and the standard deviation across all leads from Lead I to V6 was 5.3 ms. This indicates that 68% of measurements fall within 1 x SD (5.3 ms) and 95% within 1.96 x SD (10.6 ms). This means that 95% of the time QRSd would vary by only 10.6 ms across all 12 leads in that example. Conversely, patient 023 (in mode 3) displayed much greater variation across all 12 leads during testing of mode 3; baseline QRS_Mean was 144 ms but the standard deviation was higher at 21.6 ms. This indicates that 68% of the measurements fell within 1 x SD (21.6 ms) and 95% within 1.96 x SD (42.3 ms). Hence, 95% of the time QRSd would vary up to 42.3 ms across the 12 leads. If individual lead measurement was used to guide CRT programming, the optimal CRT programming mode may be dependent on the ECG lead measured.

Overall, a broad range was observed across the individual leads, with the maximum SD at 21.6ms and the minimum SD was 3.98 ms. Importantly, the average SD across all 158 measurements in the dataset was reasonable at 10.6 ms. This means that on average, 68% of the measurements for a single lead measure within the mean SD 10.6 ms (1 x SD). However, approximately one third of patients fall outside of this and 95% of patients will measure within 20.8 ms (1.96 x mean SD). There were 158 measurements included in the full dataset for this aspect of the study; a summary is provided in Table 14.

Table 14 Summary of SD for individual lead measurements
The full dataset was a comparison of 158 measurements; these are summarized below. The maximum, minimum and average Standard Deviation (SD) is shown in milliseconds (ms).

SD	Value (ms)
Max SD	21.6
Min SD	3.98
Average SD	10.6

3.3.3 Variation of predicted optimum programmed mode

This analysis was undertaken to show how the programmed mode may vary depending on which individual ECG lead (or combination) was used to measure QRSd. The mode which would have been chosen based on the individual lead measurement of QRSd is shown in Table 15. Due to the wide variation demonstrated, the optimal programming mode for the narrowest QRS varied widely depending on the individual lead selected. In 8 cases (29.6%) the optimal mode varied across all 5 modes; in 11 cases (40.8%) the optimal mode varied across 4 modes; 6 cases (22.2%) varied by 3 modes and the final 2 cases varied by 2 modes (7.4%). This further supports that individual lead QRSd is suboptimal, particularly in CRT optimisation.

However, the median compared more favourably with the mode selected by narrowest QRS_aGlobal and predicted the mode in 74% of cases (20/27). This included 11 subjects in which narrowest QRSd (aGlobal_QRS) corresponded to more than one mode; the final programmed mode was left to operator discretion. The decision making process did consider battery longevity and MPP (mode 4 & 5) was avoided if there was an alternative mode which did not use MPP. Where mode 2 and mode 3 produced identical QRS narrowing, this meant that the optimal AV offset for the SyncAV algorithm is -50 ms. After

battery considerations, if greater than one mode produced the narrowest QRS, operators considered QRS morphology across the chest leads aiming for greater positivity across chest leads, particularly V1.

Frequency analysis on the optimal mode based on aGlobal_QRSd shows that Mode 3 was most frequently selected: Mode 1 [1], Mode 2 [4], Mode 3 [13], Mode 4 [2], Mode 5 [7]. Individualised modes (Mode 3 & Mode 5) were selected in 74% (20/27) of cases.

Table 15 Programmed mode based on narrowest QRSd by individual leads

Frequency analysis of the mode which would have been selected (based on narrowest QRS) if individual lead measurement was used rather than abbreviated global QRS. If the shortest QRSd was the same in different modes, both modes are listed (e.g. mode 3 or 5).

PATIENT	INDIVIDUAL LEAD QRS METHOD - Preferred mode based on narrowest QRS															GLOBAL QRS METHOD
	I	II	III	aVR	aVL	aVF	V1	V2	V3	V4	V5	V6	MAX	MEAN	MEDIAN	Mode with narrowest QRS
1	5	3	2	2	5	1	5	2	5	3	5	4	3	5	5	5
2	1	4	4	5	3	5	1	3	5	3	4	5	5	5	5	5
3	2	3	2	3	5	2	3	3	3	2	4	2	2	3	2 or 3	2 or 3
4	4	4	1	1	1	1	1	4	1	1	1	4	1	1	1	1
6	1	2	1	5	1	1	1	5	1	1	1	5	1	1	1	4 or 5
7	4	2	1	1	4	2	5	4	4	4	5	4	5	5	4	4
8	3	3	3	3	3	3	4	4	3	3	3	2	3	3	3	3 or 5
9	3	3	1	2	2	3	3	3	3	3	2	2	3	3	3	3
10	2	2	1	5	2	2	2	5	4	4	4	2	5	2	2	2 or 3
11	2	3	3	5	2	3	1	2	3	3	3	3	3	3	3	5
12	3	2	2	2	2	3	2	2	3	2	2	2	2	2	2	2 or 3
14	4	1	2	2	2	2	5	5	3	3	3	3	4	4	2 or 3	5
15	5	3	1	3	4	1	4	2	5	5	3	2	5	3	3 or 5	2,3 or 4
13	1	3	2	2	2	2	2	2	2	2	3	4	2	2	2	2 or 3
16	1	1	1	3	1	1	3	3	1	1	4	1	1	1	1	3
18	5	3	3	3	2	3	3	3	1	1	3	5	3	3	3	5
19	4	5	2	3	2	4	2	2	5	3	4	2	2	2	2	1,3 or 5
20	3	3	3	3	3	3	2	1	3	3	3	5	3	3	3	2 or 3
21	4	3	5	5	5	2	5	5	1	4	5	5	5	5	5	5
22	5	4	4	4	5	3	1	1	1	5	5	3	5	5	5	5
23	2	5	4	3	3	1	3	2	2	1	5	1	2	1	1,2 or 3	3
25	1	2	2	4	1	2	3	2	5	5	5	2	5	5	2 or 5	3
26	5	4	4	4	4	1	4	1	4	1	4	4	4	4	4	4
27	1	3	3	5	5	5	1	3	4	4	4	5	2	5	5	5
28	3	2	2	2	1	5	3	4	4	3	1	1	2	1	2	1, 2 or 3
30	1	1	1	1	1	1	1	1	2	1	1	3	3	1	1	1,2 or 3
31	4	5	5	5	5	2	4	3	5	2	3	3	5	5	5	5

3.4 Inter-operator and Intra-operator variability

Overall intra-operator and inter-operator variability was calculated as standard error of measurement (SEM) in this study, as shown in Table 16. SEM is measured in milliseconds (ms); the lower the SEM, the more reliable the test. Intra-operator variability for abbreviated global QRSd gave an SEM of 4.8 ms (± 9.5 ms LoA). Inter-operator variability for abbreviated global QRSd gave an SEM of 7.9 ms (± 15.5 ms LoA).

The 95% limits of agreement (or confidence intervals) were calculated at 1.96 x SEM. For example, when measuring intra-operator variability, a QRSd of 200msec would be measured within the range 191.5 to 209.5 ms, 95% of the time by the same operator. Two thirds of the time, it would be in the range 200± 4.8 ms.

Table 16 Inter-operator and Intra-operator variability.
Presented as Standard Error of Measurement (SEM) in milliseconds (ms) between operators and within the same Operator. The 95% Limits of Agreement (LoA) are also presented to show the range of differences.

	Standard error of measurement (SEM)	95% confidence interval / Limits of Agreement for measurement
Intra-observer variability (repeatability)	4.8 ms	± 9.5 ms
Inter-observer variability (Fixed+random effects)	7.9 ms	± 15.5 ms

The data for the individual ECGs (n=15) is shown in Figure 23. This is a visual display of the range of values obtained per ECG by each Operator. A small

amount of jitter was used on the graph to identify overlapping data points. Operator 2 appeared to measure QRSd slightly broader than Operator 1. There are 4 ECGs associated with a wider degree of measurement variation (ECG number 5, 9, 13, 14).

The source data is included in Appendix 13. The worst variation within the same operator was 13 ms for Operator 1 (ECG 7) and 30ms for Operator 2 (ECG 13). Although variation was much lower than this in most cases. The worst variation between 2 operators was 35 ms (ECG 9 Operator 1, reading 1 versus Operator 2, reading 3).

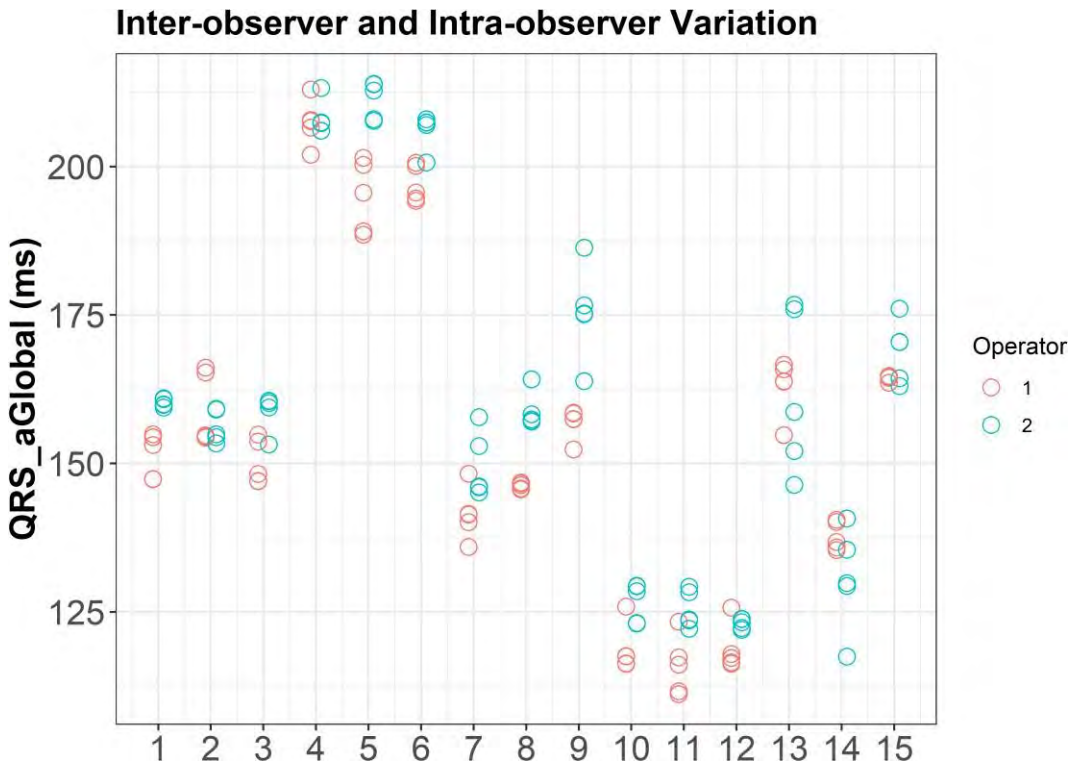


Figure 23 Inter-operator and Intra-operator variability.
This graph shows the individual measurements made by each operator per ECG (n=15). Each operator is represented by a coloured circle (Operator 1 is red, Operator 2 is blue). This is a visual display of the range of measurements obtained per ECG, Operator 2 tending to measure slightly longer than Operator 1.

3.5 Comparison of CRT programming modes

Data for the mode comparison study was collected on 27 patients until suspension of enrolment in March 2020 due to COVID-19. However, one patient developed atrioventricular block during the programming, hence was excluded from fusion pacing modes (Mode 2, 3 and 5). Data was included for Mode 1 and Mode 4. Another patient developed a programming conflict during CRT optimisation which prevented MPP parameters being tested, hence this patient was excluded from Modes 4 and 5. Data for Mode 1, 2 and 3 was included. All QRS duration (QRSd) analysis was performed using the abbreviated global QRS methodology (ms).

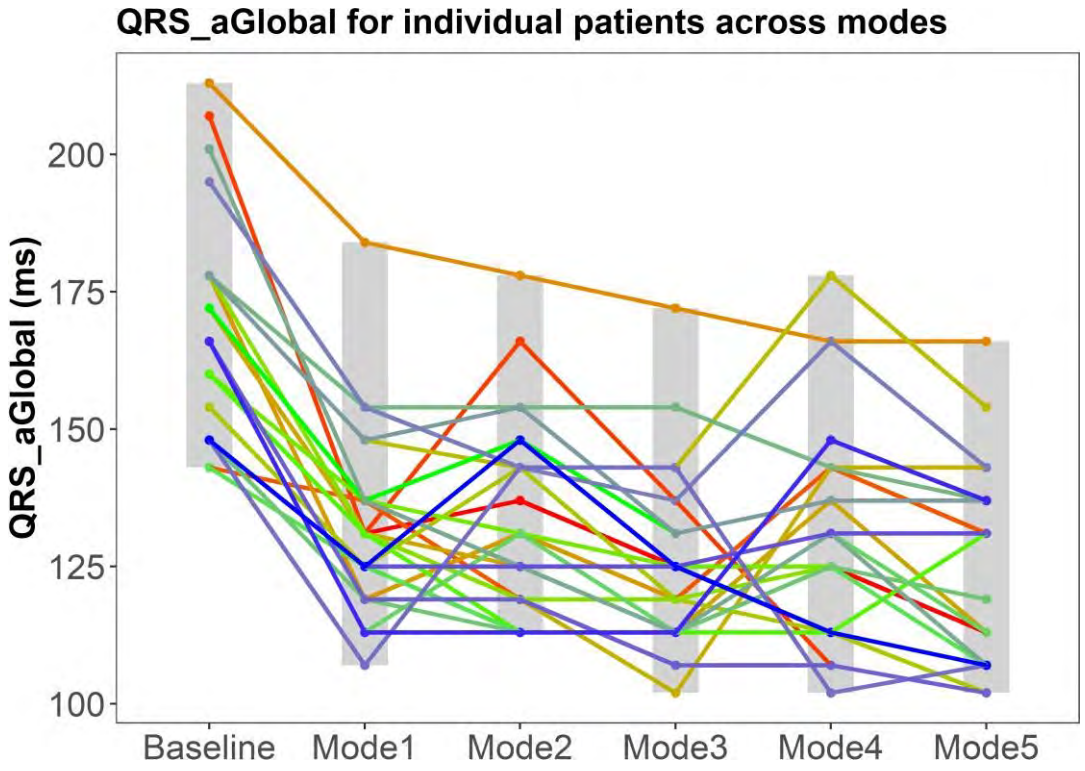


Figure 24 Ladder Plot showing QRSd shortening across the modes
This graph shows the reduction in QRSd from baseline across the 5 programming modes for all patients with complete data included in this aspect of the study. The X-axis shows the 5 programming modes as measured by abbreviated global QRS (M1_Global to M5_Global) plus the baseline QRSd measurement (BL_Global). QRS duration is displayed on the Y axis (milliseconds).

The results show some significant differences between modes. The ladder plot in Figure 24 shows how the QRSd changed for individual patients across the 5 programming modes in comparison to baseline. The graph gives a clear visual representation highlighting how all modes reduced QRSd from the baseline.

3.5.1 QRSd reduction compared to baseline

As expected all paced modes achieved highly significant reductions in QRSd ($p<0.0001$) compared to baseline. The largest mean reductions in QRSd compared to baseline were obtained with Mode 3 (individualised SyncAV) and Mode 5 (MPP and individualised SyncAV).

Table 17 Comparison of QRSd shortening between baseline and the five programmed modes. Mean difference and standard deviation (SD) are shown in milliseconds (ms) with upper and lower 95% confidence intervals. Significance levels calculated using paired t-test.

Mode Comparison	Mean Difference (ms)	Standard Deviation of difference (ms)	Lower 95% CI	Upper 95% CI	t-value	P	Significance
Baseline vs Mode 1	37.2	16.5	30.7	43.7	11.74	<<0.0001	****
Baseline vs Mode 2	36.0	16.9	29.2	42.8	10.87	<<0.0001	****
Baseline vs Mode 3	44.8	18.0	37.5	52.1	12.70	<<0.0001	****
Baseline vs Mode4	38.3	21.4	29.6	46.9	9.12	<<0.0001	****
Baseline vs Mode5	45.4	21.6	36.5	54.3	10.54	<<0.0001	****

Table 17 summarises QRSd shortening between baseline and the five programmed modes. The mean difference between each mode pair was

compared using paired t-tests. T-tests are used to show the difference between the mean of two groups. A larger T-value indicates greater difference between the groups. When comparing QRSd shortening across all five modes from baseline, the T-value ranged from 9.1 (Baseline vs Mode 4) to 12.7 (Baseline vs Mode 3). All five modes had a p-value of <<0.0001, but based on T-value alone, Mode 3 (individualised SyncAV) showed the greatest difference to baseline.

QRSd in Mode 1

In Mode I (best single point biventricular pacing), there was a significant mean reduction in QRSd from baseline by 37.2 ms (with 95% confidence intervals 30.7 ms to 43.7 ms, p=<0.001). This is shown in Figure 25.

QRSd in Mode 2

In Mode 2 (nominal SyncAV), a significant mean reduction in QRSd from baseline was observed at 36.0 ms (with 95% confidence intervals 29.2 ms to 42.8 ms, p=<0.001). This is shown in in Figure 25. These findings are similar to the reductions observed with Mode 1 (best single point pacing).

QRSd in Mode 3

In Mode 3 (individualised SyncAV), a significant mean reduction in QRSd from baseline was observed at 44.8 ms (with 95% confidence intervals 37.7 ms to 52.1 ms, p=<0.001). This is shown in Figure 25. Mode 3 reduced the QRS duration to a greater extent than Mode 1 and Mode 2, indicating that individualised SyncAV was superior.

QRSd in Mode 4

In Mode 4 (nominal MPP), a significant mean reduction in QRSd from baseline was demonstrated at 38.3 ms (with 95% confidence intervals 29.6 ms to 46.9 ms, p=<0.001). This is shown in Figure 25. These findings suggest mode 4 reduces QRS duration to a similar magnitude as Mode 1 and Mode 2.

QRSd in Mode 5

Mode 5 (individualised SyncAV and MPP) demonstrated the largest mean reduction in QRSd compared to baseline at 45.4 ms (with 95% confidence intervals 36.5 ms to 55.3 ms, p=<0.001). This is shown in Figure 25.

Mode 5 reduced the QRS duration to a greater extent than Mode 1, Mode 2 and Mode 4. Mode 5 reduced the QRSd to a similar magnitude as Mode 3, indicating that individualised programming was superior.

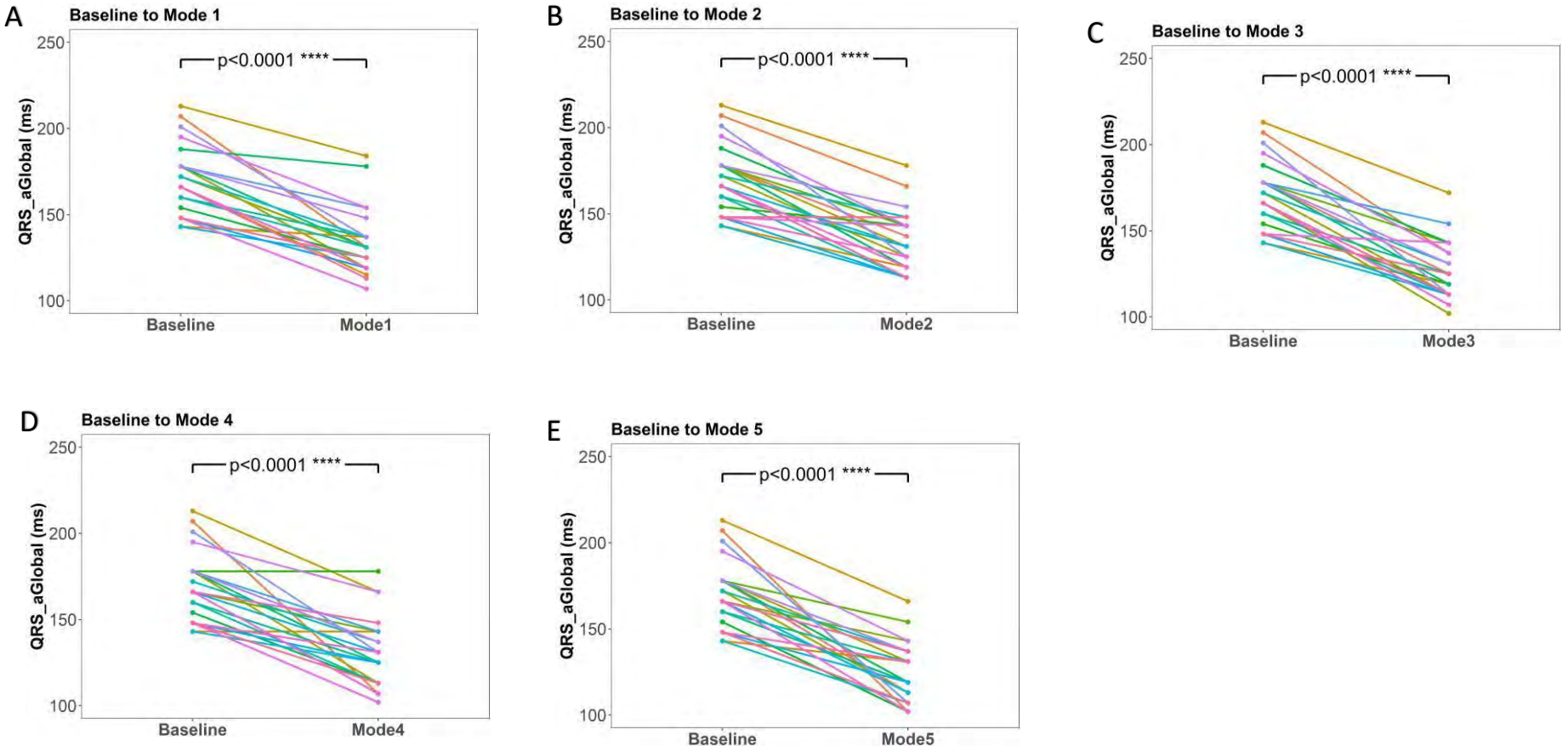


Figure 25 Comparison of programming modes against baseline. (A) to (E) show changes in abbreviated global QRS duration (QRS_aGlobal) for program modes 1 to 5 respectively, compared to the baseline value. Each line represents an individual patient. Significance levels ("p value") calculated using paired t-test.

3.5.2 QRSd reduction between pairs of CRT programming modes

The results highlighted significant differences between the different programming modes. These were compared as paired modes as shown in Table 18 and Figure 26. P-values ranged from non-significant to p<0.0001 (highly significant). T-values ranged from -0.22 (Mode 1 vs Mode 2) to 4.8 (Mode 2 vs Mode 3).

Table 18 Intercomparison of QRSd shortening between 'pairs' of programming Modes. Mean difference (Mean Diff) and standard deviation (SD) are shown in milliseconds (ms) with upper and lower 95% confidence intervals (CI). Effect size is stated as the absolute value ($|d|$). More significant results are represented by asterisks *** and NS means non-significant.

Mode Comparison	Mean Diff (ms)	SD (ms)	Lower 95% CI	Upper 95% CI	t-value	Effect size $\|d\|$	P	Significance
Mode 1 vs Mode 2	-0.7	16.3	-7.3	5.9	-0.22	0.04	0.8300	NS
Mode 1 vs Mode 3	8.1	12.9	2.9	13.3	3.21	0.63	0.0036	**
Mode 1 vs Mode 4	0.0	15.2	-6.1	6.1	0.00	0.00	1.0000	NS
Mode 1 vs Mode 5	7.7	14.6	1.7	13.7	2.63	0.53	0.0146	*
Mode 2 vs Mode 3	8.8	9.4	5.0	12.6	4.80	0.94	0.0001	***
Mode 2 vs Mode 4	2.8	23.4	-6.9	12.4	0.59	0.12	0.5601	NS
Mode 2 vs Mode 5	9.8	21.3	1.0	18.6	2.30	0.46	0.0301	*
Mode 3 vs Mode 4	-6.4	19.5	-14.5	1.7	-1.64	0.33	0.1140	NS
Mode 3 vs Mode 5	0.6	17.0	-6.4	7.6	0.19	0.04	0.8518	NS
Mode 4 vs Mode 5	7.0	11.4	2.3	11.7	3.10	0.61	0.0049	**

Effect size is an alternative indicator of the level of difference between each paired comparison. An effect size of 0.2 is considered a small effect, 0.5 is a medium effect and 0.8 or above is considered a large effect size. A large effect size is linked directly to a highly significant difference. Overall, observed effect size ranged from 0.00 (Mode 1 vs Mode 4) to 0.94 (Mode 2 vs Mode 3). Findings with $p<0.05$ were associated with effect sizes from 0.46 (Mode 2 vs Mode 5) to 0.94 (Mode 2 vs Mode 3). Consequently, these results showed limitations in terms of effect size and the data should be interpreted accordingly.

The data distributions for inter-mode QRSd differences were screened for non-normality as described in Section 2.7. The screening results are summarised in Appendix 12. There were no major deviations from normality. Minor deviations to normality were identified in 3 cases (Baseline-Mode 5, Mode 1-Mode 3 and Mode 2 Mode 3). Parametric statistics were still appropriate. However, the probability values were also evaluated using non-parametric methods and the results were almost identical to the parametric analysis: Baseline-Mode 5 (Wilcox $p<0.0001$, sign test $p<0.0001$, t-test $p<0.0001$); Mode 1-Mode 3 (Wilcox $p=0.0025$, sign test $p=0.0004$, t-test $p=0.0036$) and Mode 2-Mode 3 (Wilcox $p=0.0007$, sign test $p<0.0001$, t-test $p<0.0001$).

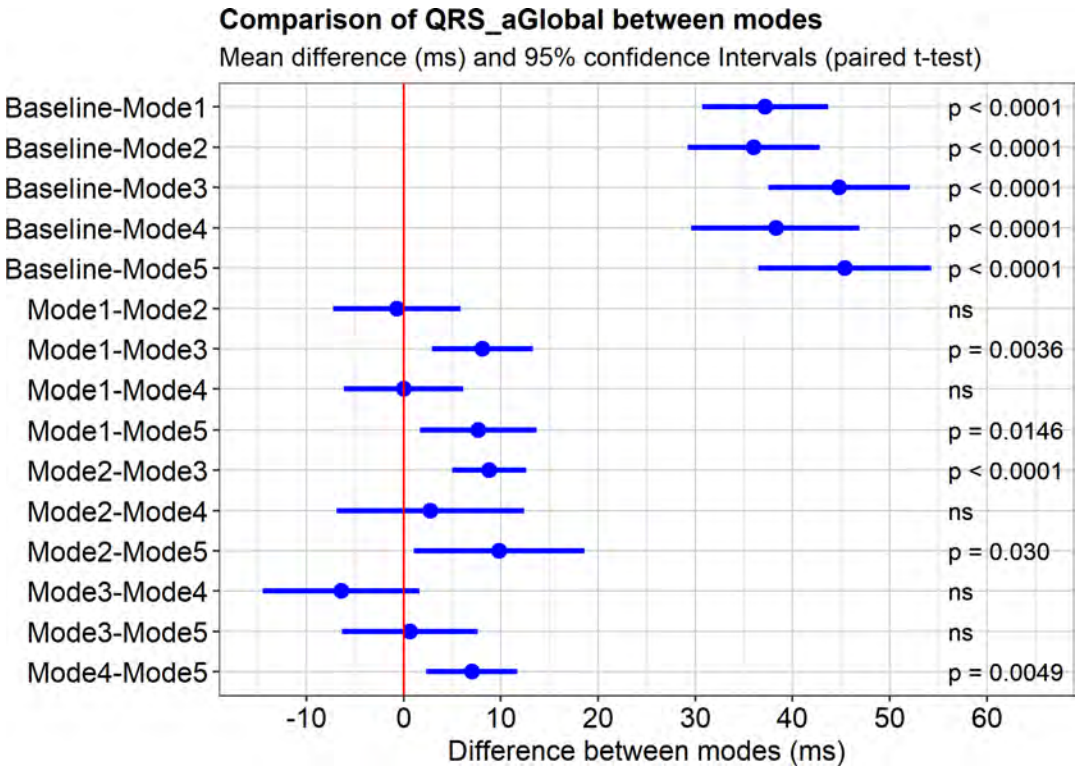


Figure 26 Summary Plot showing effectiveness of QRSd shortening between different pairs of programming modes. Confidence intervals are shown by the blue bars. The X axis shows QRS shortening in ms. The red line represents zero QRS narrowing. Bars to the right of the red line display significant QRS narrowing (significance ranging from p<0.0001 to p=0.03). Bars which overlap the red line are not significant (ns).

Mode 3 showed a significant reduction in QRSd when compared to Mode 1 (p=0.0036) and Mode 2 (p<0.0001). Importantly, the results for Mode 3 vs Mode 2 were the most significant in the series with a p-value of p<0.0001. Mode 5 also showed significant reduction in QRSd when compared to Mode 1 (p=0.0146), 2 (p=0.0301) and 4 (p=0.049) with corresponding elevated T-values. This shows that modes with greater individualisation are associated with greater QRS narrowing (Mode 3 and Mode 5). There was no statistically significant differences between Modes 1 and 2 and the mean reduction between the 2 modes was negligible at -0.69 ms CI (-7.26-5.88, p=0.8300). This suggests that nominal SyncAV has no benefit beyond best single point biventricular pacing. Similarly, Mode 1 and Mode 4 were almost identical with

a mean QRSd of 0 ms CI (-6.14-6.14, p=1.0). Based on these findings, nominal MPP programming is equivalent to best single point pacing and may not be worth the risk of phrenic nerve stimulation or impact on battery longevity. Mode 2 and Mode 4 also showed no significant difference with a mean QRSd of 2.76 ms CI (-6.88 – 12.4, p=0.5601). Individual ladder plots of comparisons between the modes are shown in Figure 27.

There was no significant difference in QRSd narrowing between Mode 3 and Mode 4 with a mean reduction of -6.4 ms CI (-14.45 – 1.65, p=0.1140). However, the summary plot in Figure 26 shows a trend towards Mode 3 and a larger sample size may be beneficial in this case.

Importantly, no significant difference was detectable between Mode 3 and Mode 5; with a mean reduction in QRSd 0.64 ms CI (-6.36-7.74, p=0.8518). These 2 modes accounted for the most individualised programming settings and the study failed to show superiority of Mode 5 (individualised SyncAV and MPP) over Mode 3 (individualised SyncAV). This suggests that individualised SyncAV has a greater contribution to QRS narrowing than MPP alone.

Furthermore, the magnitude of the QRSd narrowing between modes was more conservative when compared to baseline reductions. All mean reductions in QRSd between modes were < 10ms.

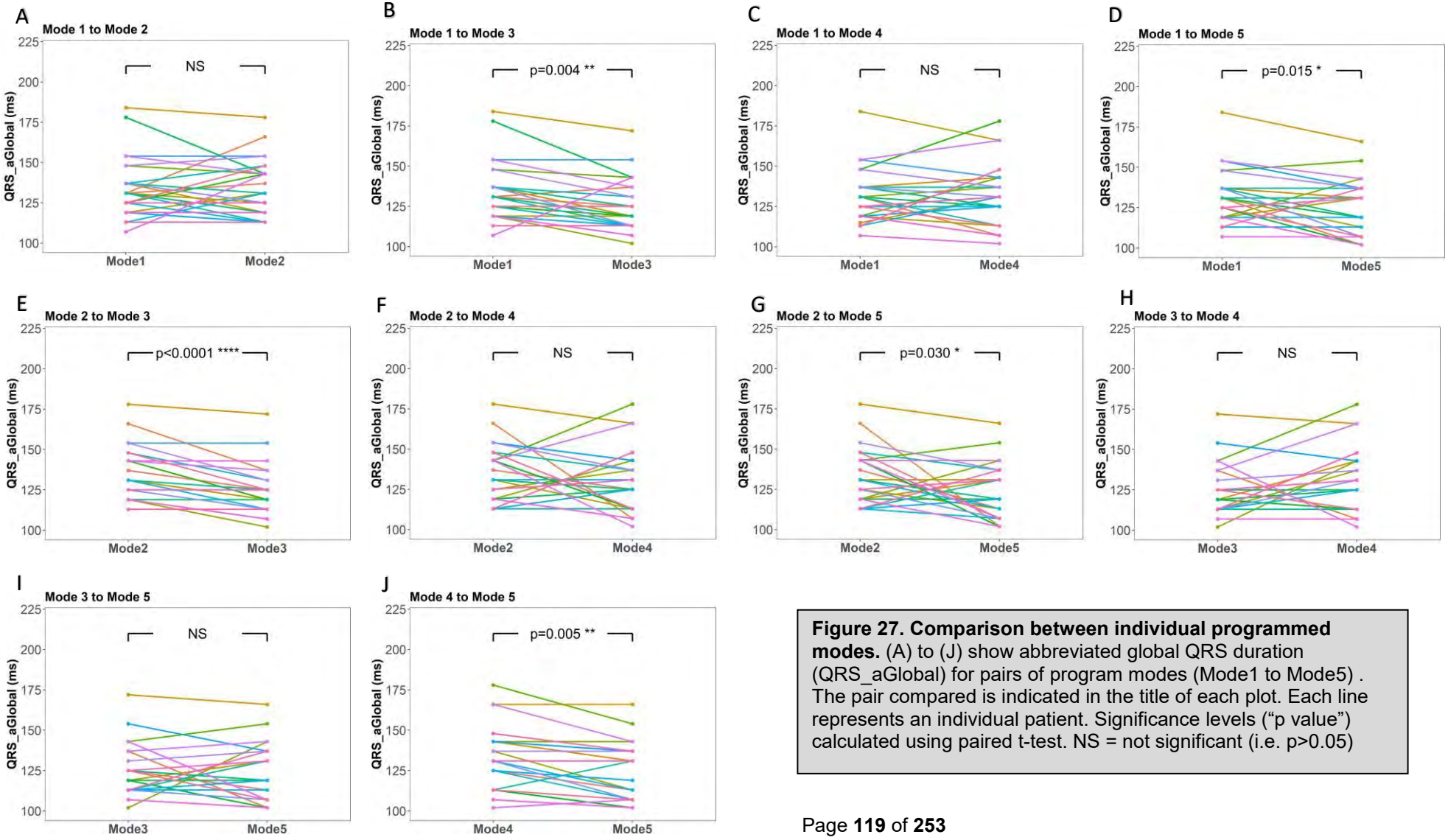


Figure 27. Comparison between individual programmed modes. (A) to (J) show abbreviated global QRS duration (QRS_aGlobal) for pairs of program modes (Mode1 to Mode5) . The pair compared is indicated in the title of each plot. Each line represents an individual patient. Significance levels ("p value") calculated using paired t-test. NS = not significant (i.e. p>0.05)

3.6 Clinical Response to CRT

Assessment of CRT response was a secondary endpoint in this study. Due to COVID-19, there was a much reduced sample size reaching this secondary endpoint. Of the initial 28 patients included in data collection, 6 patients were excluded from CRT response analysis for non-COVID reasons. 2 patients died before their follow-up appointment; 1 patient developed AV block on implant and did not undergo device optimisation; 1 patient had their device explanted prior to follow-up due to infection; 1 patient had an LV lead displacement and 1 patient had their device reprogrammed due to phrenic nerve stimulation.

Of the remaining 22 patients, only 11 underwent assessment of CRT response prior to the COVID-19 pandemic. The remaining enrolled patients were scheduled to attend for their 5 month follow-up during the COVID-19 pandemic. However, in keeping with the NHS and trust guidelines, all patients attending for non-essential face-to-face hospital appointments were postponed between March 2020 and July 2020 (trust flowchart displayed in Appendix 14). The 5 month technical device follow-up was achieved by remote assessment instead. These patients were sent a MLHFQ in the post, but none were returned. Patients were invited to attend clinic when routine hospital appointments were resumed. However, 7 patients were excluded from analysis because CRT response was assessed beyond the 5 month follow-up. A further 4 patients were excluded because response data was not assessed despite patients physically attending follow-up in the early stages of the COVID pandemic. The reasons are unclear, but thought to be due to patient choice and concerns regarding the safety of performing 6MWT during COVID.

Table 19 CRT Response Data: Comparison of criteria. The table shows the 6MWD percentage increase (%), MLHFQ decrease (points) and NYHA Class (number of classes improved by) for all patients attending for assessment of response (n=11). The Initial Responders Class was based on the study centres response criteria and was used for clinical practice. The Revised Responder Class was based on the proposed criteria and was for comparison only.

Patient ID Number	6MWD Increase (%)	MLHFQ decrease (points)	NYHA increase (class)	Initial Responder Class (2/3)	Revised Responder Class
1	10.7	18	1	Responder (3/3)	Super Responder
2	51.5	34	1	Responder (3/3)	Super Responder
3	36.2	41	1	Responder (3/3)	Super Responder
7	34.8	13	1	Responder (2/3)	Responder
9	20.4	43	2	Responder (3/3)	Super Responder
6	300	46	2	Responder (3/3)	Super Responder
4	25	4	2	Responder (2/3)	Responder
8	3.8	22	1	Responder (2/3)	Responder
10	39.1	21	2	Responder (3/3)	Super Responder
11	1.6	20	same	Non-Responder (1/3)	Non-Progressor
12	8.5	35	1	Responder (2/3)	Responder

Despite the small sample size, the results were interesting. Of the 11 patients, 10 were classed as responders to CRT according to existing departmental protocol. Only 1 patient was classed as a non-responder. The results are shown in Table 19. Interestingly, when the revised response criteria was applied, 6 patients were classed as super-responders, 4 patients were classed as responders and 1 patient was classed as a non-progressor. None of the patients did worse and none were classed as non-responders under the revised criteria.

Despite the very small sample size, the level of response was compared to final programmed mode and total reduction in QRS duration. 7 of the 11

patients achieved maximum QRS narrowing using an individualised programming mode (Mode 3 or Mode 5) as shown in Table 20.

Table 20 Comparison of QRSd shortening and Programmed Mode in CRT Response. This table shows the revised response class against the final programmed mode and absolute reduction in abbreviated global QRSd (ms) n=11

Patient ID Number	Revised Responder Class (2/3)	Final Mode	QRS Reduction in ms (by aGlobal_QRS)
1	Super Responder (3/3)	5	65
2	Super Responder (3/3)	5	105
3	Super Responder (3/3)	2	24
7	Responder (2/3)	3	59
9	Super Responder (3/3)	3	64
6	Super Responder (3/3)	5	47
4	Responder (2/3)	1	51
8	Responder (2/3)	3	59
10	Super Responder (3/3)	2	35
11	Non-Progressor (1/3)	5	52
12	Responder (2/3)	2	45

The utility of statistical analysis of the response data in this study is severely limited by the low numbers. Nevertheless, the study response rate (11/12 i.e. 92%) did appear to be higher than that found from routine audit of clinical practice in our department (44/69 i.e. 64%) (Wilburn et al, 2020). This bordered on statistical significance (p=0.056, Fisher Exact Test).

This study was not designed to assess hard outcome measures, such as mortality of Heart Failure Hospitalisation (HFH). However, it was noted that out of the 28 patients initially included for data analysis, a total of 3 patients

(10.7%) died within 12 months of their CRT implant. The cause of death is not known. All three patients were NYHA Class III at baseline and all had ischaemic aetiology (2 males aged 63 years and 78 years and 1 female aged 79 years). All achieved significant QRS narrowing on implant ranging from 23ms to 41 ms; baseline QRSd ranged from 148 to 178 ms. HFH was not measured.

4.0 Discussion

4.1 Study Population

The patient demographics are largely comparable to those in similar studies, such as Varma et al (2018) and O'Donnell et al, (2020). The key similarities are 68% male participants and 89% being in NYHA class II or III pre-implantation. No patients were NYHA class IV prior to implantation. The mean age is slightly older at 73.1 years (± 10.7) and the study group had a greater proportion of patients with ischaemic aetiology at 54%. Importantly, females and non-ischaemic cardiomyopathy patients have been shown to have greater benefit from CRT (Brignole et al, 2013). These individuals are less well represented in this cohort.

Optimal LV lead placement was achieved in 86% of cases (24 patients), however in 14% (4 patients) an anterolateral vein was selected. RV lead position was split based on operator preference with 39% (11 patients) implanted at the RV apex and 57% (16 patients) implanted in the RV septum. RV apical pacing is well known to have a deleterious effect on LV function and it has been suggested that non-apical RV lead pacing is preferable, although there is no definitive guidance at this time (Brignole et al, 2013).

Mean baseline QRS duration (QRSd) varied according to the method used: 170.8 ms by QRS_aGlobal, 173.1 ms by QRS_Max and 155.1 ms by QRS_Mean. Standard deviation was similar by each method. The mean baseline QRSd was long (>150 ms), indicating a good likelihood of improvement and subsequently QRS shortening was achieved across all programming modes with highly significant findings.

Mean baseline 6MWD was 252.7 metres, indicating a good opportunity for a positive response to CRT. One study showed that patients with a baseline 6MWD of <350 metres are most likely to benefit from CRT (Brenyo et al, 2012). Interestingly, the observed response rate was very high at 92%, although the sample size was much reduced (n=11).

This study was aimed at patients with Class 1A indication for CRT but surprisingly 77/110 patients were excluded because they did not meet the inclusion criteria. The reasons for this were not documented. However, research personnel reported exclusions such as PR intervals exceeding 250msec, the presence of permanent AF, non-LBBB morphology and a high proportion of patients referred for CRT upgrade who already had a pacemaker or implantable defibrillator. There were also patients excluded because they were unable or unwilling to complete a 6MWT due to mobility issues or comorbidities. This was a single site study but the study centre was part of a regional service and had visiting implanters. Some patients were excluded because they chose to be followed up at a different hospital in the region and this is largely thought to account for the high rate of exclusions. This could have been overcome by applying for the necessary approvals to extend the study across two hospitals. However this also may have created challenges in consistency in this observational study due to different operational protocols across each hospital.

4.2 Survey of CRT Practice within the UK and Ireland

The results of the survey highlight wide variation in practice across the UK and Ireland. QRS narrowing was considered important in CRT by all bar one participant (97%). Several large trials have shown that a reduction in QRS post CRT is associated with a more positive outcome (Gold et al, 2012; Rickard et al, 2011; Rickard et al, 2013; Jastrzebski et al, 2018). This appears widely known amongst the 23 participants which explained their reasoning, however one responder commented that there was ‘no evidence from clinical trials to

demonstrate efficacy'. Interestingly, 84% of participants measured QRS duration on implant and there were 3 comments which stated that this was operator dependent in their study centre and was not mandatory.

There was wide variation in the type of ECG monitoring used during CRT implant, which in turn led to a broad mix of methods used to measure QRS duration. The American Heart Association states that global QRS over 12 leads is the most desirable method for measuring QRS duration (Surawicz et al, 2009). Despite this, only 35% measured global QRS on the 12 Lead ECG using digital calipers. 49% of participants utilised 12 Lead ECG on implantation, but not all implanting centres will have the software with the technical capabilities to measure global QRS. Studies have shown that single ECG lead measurement can be unreliable (De Pooter et al, 2016, De Pooter et al, 2017). Despite this, the most common technique to measure QRS duration on implant was via a single ECG lead either manually or using digital calipers (45%). Unfortunately, the survey did not ask participants whether they used the same lead pre and post CRT; or to state which lead they preferred (if any).

Thirteen percent of participants used abbreviated global QRS methodology to measure QRS duration in their clinical practice during CRT implant. Whilst this is a smaller group, the results indicate the emergence of this technique across the UK and Ireland. However, there is no published literature comparing abbreviated global QRS measurement to global QRS measured via 12 lead ECG. This remains an area of interest.

Similar variety was observed in the type of ECG monitoring used during CRT follow-up, with 57% of participants using 12 Lead ECG, whether alone or in conjunction with programmer ECG. Only 18% of participants actually measured QRS duration during follow-up. Comments indicated that the remaining participants often performed this on a case-by-case basis, such as

during optimisation or during troubleshooting. Unsurprisingly, there was similar variation noted in the technique used to measure QRS duration during follow-up. 50% of participants measured a single ECG lead either on the programmer or 12 lead ECG. 19% measured Global QRS on 12 Lead ECG. As expected, fewer hospitals measured global QRS on follow-up, most likely because this requires specialist software which may not be universally available in the outpatient clinic environment. The abbreviated global QRS technique was used in 16% of cases via the programmer. Importantly, the programmer is common to both implantation and follow-up and is ideally placed to offer a compromise for QRSd measurement.

The latest BHRS guidelines from 2020 state that careful consideration should be given to the 'use of 12 lead ECG or a chest lead' when assessing biventricular pacing (BHRS, 2020). However, the technique used to measure QRSd is not specified. Consequently, the wide variation in practice across the UK and Ireland is likely to persist. The optimal electrical characteristics of CRT are best assessed using 12 Lead ECG, but this is not universally adopted in clinical practice. There is inconsistency in both the type of ECG monitoring and the methods used to assess QRS narrowing in both implant and follow-up. Studies have shown that QRS duration can vary depending on the measurement technique, with global QRS considered superior to single lead measurement. CRT Optimisation clinics are growing in popularity and it may be beneficial to standardise the type of ECG assessment and also the measurement of QRS duration to ensure quality and consistency.

From a methodology perspective, there are limitations in seeking voluntary feedback from a survey in this manner. Firstly, online surveys favour individuals who are IT literate and in particular have social media accounts. More specifically, this survey was biased to those using Facebook and Twitter. The survey may have failed to reach other staff members who were less 'tech savvy' or who do not have a social media presence. The short timeframe of the study (22 days) may also have excluded people who were less active on

social platforms. Importantly, the results were voluntary and there is no guarantee of accuracy or honesty. It is possible that individuals may have completed the survey with their ideals for clinical practice rather than actual practice. Whilst the study was anonymous, people were asked to disclose their hospital and it is possible that staff may have tried to protect their workplace or risk being identified via this route.

The author was unable to identify any other published survey findings relating to the practice of Cardiac Scientists and Physiologists during CRT implantation. Crucially, this survey was intended as a snapshot of CRT practice to provide a rapid overview. There was good participation (n=31) and wide geographical spread from 21 hospitals throughout the UK and Ireland. Hence overall, it was considered a reasonable sample of national practice. Free and instantaneous access via the online link may have encouraged greater participation and the informal nature of the survey may have encouraged more honest feedback. It was never intended as a coordinated national benchmarking exercise and the results should be considered accordingly.

However, given the wide variation in practice identified by this survey, the author recommends a more formal benchmarking exercise within the UK, ideally coordinated by the professional body, the British Heart Rhythm Society (BHRS). An exercise of this type may be useful to guide development of future professional recommendations and may emphasise specific areas for improvement in line with evidence based medicine. If the results of the current study are reproduced, it is clear that professional body guidelines should incorporate more specific references to CRT Optimisation including standardisation of ECG Monitoring and measurement of QRS duration as a minimum.

The timeframe of the survey may also have been significant and was undertaken early in phase one of the COVID pandemic (28th April 2020 -19th May 2020). During this period, most routine complex device implantations were postponed, meaning that Cardiac Scientists may have been more willing to take part in an online survey and more candid with their responses.

4.3 Comparison of methodologies for measuring QRS duration

QRS duration is crucial in CRT but the measurement techniques vary between research and clinical settings (De Pooter et al, 2017). The results of the survey highlighted wide variation in clinical practice across the UK and Ireland. Even within the study centre, two methods of measuring QRS duration were used in clinical practice: single lead ECG measurement and abbreviated global QRS duration. As with many hospitals, prior to this study there was no standardisation in departmental protocol, leading to the methods being used interchangeably with little thought. This study compared both of these methods using a 'method comparison' design. Bland Altman analysis is the standard methodology to evaluate whether measurements from a new process are consistent with those from an established technique (Linnet, 1999; Bland and Altman, 1986). It is essential to determine the magnitude of any differences between the methods which could be of clinical significance (Linnet, 1999). Since neither method measures the precise quantities, determination of the method closer to the true values is unknown (Altman, 1992). Limits of agreement (LoA) are particularly useful in evidence based medicine and describe a range of values either side of the estimate in which it is certain that the true values lies (Altman, 1992; Strauss et al, 2005).

The most widely used QRS measurement technique in clinical practice is single lead ECG measurement, but the evidence shows this can be unreliable (De Pooter, 2016). Significantly, the study protocol implemented features to improve accuracy in single lead ECG measurement by enhancing gain and increasing paper speed to 50 mm/sec. In this study, single lead measurement

of QRS duration was performed for all 12 ECG leads, plus the QRS_Max and QRS_Mean. However, in usual practice, QRS duration in only one lead would be measured. Despite there being no published literature of abbreviated global QRS, this technique is already in use in clinical practice as demonstrated by the survey. The device programmer is essential for all CRT assessments during implantation and follow-up, hence is ideally placed for QRS measurement in clinical practice. The device programmer has the technical attributes to facilitate abbreviated global QRS measurement such as digital calipers, 5 x ECG leads on a vertically aligned display and facility to adjust scale and sweep speed to 50 mm/sec. It is understandable why this technique is of interest to form a practical compromise to overcome measurement concerns in clinical practice.

As expected, there was high degree of correlation between the two methodologies (0.65 to 0.82), because both measure the same variable on the same scale of measurement. The mean differences between abbreviated global QRS and single lead measurement of QRSd were reasonable and ranged from -7.4 ms (QRS_Max) to 14.2 ms (Lead I). At its best, mean abbreviated global QRSd was only 5.9 ms higher than lead V2; at its worst, mean abbreviated global QRSd was 14.2 ms higher than Lead I. In practical terms, a difference of ≤10 ms would be considered largely insignificant in clinical practice with regards measurement error. One study quoted 20 ms as the clinically accepted difference in QRSd between measures (Stephansen et al, 2019), however this seems a little high when the margins of QRS narrowing are so small. Importantly, the mean difference was <10 ms in 12 of the 14 assessed single lead measurements (except Lead I and aVL). However, the 95% LoA did show much more significant variation ranging from 27.1 ms (QRS_Mean) to 37.5 ms (Lead II). The magnitude of variation is similar to that reported by De Pooter et al (2016) comparing individual lead vs global QRS over 12 leads, with variation up to 29 ms. Variation of this degree would be significant in clinical practice, hence the two methods should not be used interchangeably. There is little published literature comparing these two

specific methodologies (QRS_aGlobal vs QRS_individual lead).

Similarly, the results found variation in QRSd between the individual leads on the same 12 lead ECG. The mean SD across the entire dataset was 10.6 ms, meaning that in 95% of cases QRSd would measure within 20.8 ms across all 12 ECG leads (2 SD). This is certainly pushing the boundaries of clinical acceptability and some ECGs showed even greater variation; in one case the QRSd varied by 42.3 ms. This highlights a weakness of the individual lead methodology. Importantly any inaccuracy or poor repeatability in one method will result in poor agreement between the two (Altman, 1992). It cannot be assumed that individual lead QRSd measurement provides the true reference value, none of the methods used in QRS measurement are strictly precise, hence the 'true' measurement of QRS duration actually remains unknown. In clinical terms, this means that a patient could be classed as having a successful CRT implant simply because the QRS duration was measured by a different method or even a different ECG lead in comparison to baseline. These results are in keeping with published literature in which QRSd was found to be dependent on the measurement technique used (Tomlinson et al 2009, De Pooter et al, 2016). It could be argued that the true value of QRSd is less valuable than standardisation of the measurement methodology used in daily practice (i.e. ensuring the same method is always used per patient).

The limitations in methodologies are particularly significant because single lead ECG measurement remains the most popular method of measuring QRSd in clinical practice (used 45% of the time during CRT implant and 50% of the time during CRT follow-up). However, single ECG lead measurement is known to be unreliable (De Pooter et al, 2016, De Pooter et al, 2017). Chest lead V5 has previously been shown to be a reasonable surrogate for global QRS (De Pooter et al, 2016). However, this was not supported by the current study. V5 was found to have one of the weakest correlation coefficients (by Pearsons) at 0.7 and widest LoA of 35.4 ms, although the mean difference in QRSd was 8.3 ms. However, in this study the V5 electrode from the 12 Lead

ECG was placed as close as possible to the SCST position, but the true anatomical V5 position was taken by the programmer chest lead. The single lead which was most comparable to abbreviated global QRS was V2 with a correlation coefficient of 0.8, the smallest mean difference of 5.9 ms and one of the lowest LoA at 28.8 ms. The reason for this is unclear, although the study by De Pooter et al (2016) found V2 as the next best single lead to V5 in predicting QRS reduction. Chest leads have also been shown in other studies to be more accurate in measuring QRSd (Tomlinson et al, 2009).

The results for QRS_Max and QRS_Mean demonstrated some of the least variation in comparison to abbreviated global QRS. QRS_Max had a correlation coefficient of 0.79, mean difference of -7.4 ms and LoA of 29.4 ms; QRS_Mean had the strongest correlation coefficient of 0.82, mean difference of 8.4 ms and narrowest LoA of 27.1 ms. QRS_Max is the maximum QRS duration of all 12 leads, whereas QRS_Mean is the average of all 12 leads. It is intuitive that these techniques can overcome measurement error, such as in isoelectric segments in individual leads. Importantly, both QRS_Max and QRS_Mean have been used to measure QRSd in other published studies (Bleeker et al, 2006, Molhoek et al, 2004, Gold et al, 2012; Tomlinson et al, 2009). However, both these techniques require the operator to measure all 12 individual ECG leads, which is largely impractical in a day-to-day setting in terms of time and availability of suitable software. Abbreviated global QRS may form a practical compromise, with rapid QRS assessment over 5 leads within both the implant and follow-up environment.

Global QRSd measured over 12 leads has become the preferred measurement technique in clinical trials and is endorsed by AHA standards (Surawicz et al, 2009; De Pooter et al, 2016). It is defined by '*measuring the onset of the QRS in any lead to the offset in any lead*'. This technique is thought to overcome measurement error caused by isoelectric segments in individual leads and is reported to have much improved inter-operator and intra-operator

variability when compared to single lead ECG measurement (De Pooter et al, 2016). It was hypothesised that these benefits would also apply to the abbreviated global QRS method over 5 leads, but perhaps to a lesser extent. For this reason, abbreviated global QRSd was used as the reference method for QRSd measurement in the mode comparison study. Whilst some limitations of this methodology have been described when compared to individual lead QRS measurement, the most important factor is that the method was applied consistently for comparison of CRT programming modes.

It may have been useful to compare *abbreviated* global QRSd to *standard* global QRSd over 12 leads. This would have maintained consistency with other clinical trials. However, the specialist software required was not available in the study institution, and more importantly the results would not be representative of routine clinical practice. One alternative to overcome the lack of specialist equipment, would be to print 12 ECGs in vertical alignment and analyse them offline using a downloaded App for global measurement such as EP Calipers or Cardio Calipers. However, this would prevent immediate programming in the clinical setting which was an essential component of the observational study design. Also, the use of offline tools would require ECGs to be accurately scanned and individually calibrated, introducing potential for further measurement error. Consequently, this study did not intend to assess the accuracy of the abbreviated global QRS method against the standard 12 Lead Global QRS method. Interestingly, one study suggested that Global QRS (over 12 leads) actually showed greater inter-operator variability in paced and LBBB patients (De Pooter et al, 2017). This means that the benefits of global QRS methodology may be less applicable to the CRT population. This may require further exploration.

Previous studies have highlighted the need for standardisation in the measurement of QRSd, but these typically focus on the identification of patients for CRT (Turagam et al, 2013; De Pooter et al, 2016). In fact, some

Cardiologists in the study centre still admit to using the automated QRSd measurement from the ECG machine to identify candidates for CRT. The current study emphasises the importance of accurate QRSd measurement for Cardiac Scientists involved in the programming of CRT. The literature review could only find one study which addressed the reproducibility of QRSd measurement with respect to CRT optimisation and this showed acceptable inter and intra-operator variability in manually measured intervals on the 12 Lead ECG although LoA were wide (Stephansen et al, 2019). This highlights how the type of ECG monitoring and measurement technique for QRSd is frequently overlooked within the field. The concern is that this may lead to suboptimal CRT programming and ultimately influence the patient outcome.

The author recommends better education across the range of disciplines regarding the accuracy of QRSd measurement. Measuring QRSd is often viewed as a routine and menial task that it is often performed with little thought. Physiologists may not be aware of the limitations of single lead ECG measurement and may not have considered alternative forms of measurement. Professional body guidelines should be updated to improve standards; a minimum should be to quote the target ECG lead if using individual lead QRS but ideally the guidelines should encourage global QRS measurement using digital calipers. This may in turn help departments to get appropriate ECG monitoring equipment and obtain protected time post implant to optimize CRT devices. Consistency of measurement technique is also recommended between implantation and follow-up, to enable comparable QRSd measurements between serial ECGs. The device programmer is commonly used in both settings and could be used to measure abbreviated global QRS duration to standardise measurement throughout the patient's journey. The inter-operator and intra-operator variability of the abbreviated global QRSd methodology is a key factor for whether this technique is suitable for clinical practice. Significantly, there is no published evidence of the inter and intra-operator variability for this method, hence the current study will provide a usual standpoint; it is discussed in the next section.

Applying these findings to the clinical environment, Cardiac Scientists typically record resting 12 Lead ECG on the haemodynamic system at the start of a CRT implantation. Baseline QRS duration is measured at this point, but the method and equipment used to measure QRS duration has not been standardised. It is convenient to measure individual lead QRSd when the 12 Lead ECG is recorded. Immediately following CRT implantation, whilst the patient is being sewn up, the Cardiac Scientist will apply the departmental CRT optimisation protocol and QRS duration will be measured. Since the Cardiac Scientist is already using the programmer, it is convenient to measure the final QRS duration using abbreviated global QRS. Based on the potential magnitude of difference between the two methodologies, this study recommends that serial measurements of QRS duration are made using the same methodology e.g. individual lead measurement with a nominated target lead or abbreviated global QRS. The author recommends that departmental protocol is updated with immediate effect.

There were some technical challenges that may have affected the method comparison study. Firstly, MPP introduced a greater degree of artefact on the ECG, which in some instances made accurate measurement difficult. However, this appeared to affect both abbreviated global QRS and individual lead measurement equally. Secondly, some individual leads had isoelectric segments making true onset and offset difficult to identify. Difficulties in identifying the onset and offset of paced complexes due to pacing artefact has been described in other studies (Stephansen et al, 2019; De Guillebon et al, 2010). Nevertheless, measurements were obtained in 100% of patients, hence some values may have been suboptimal. This may have influenced results. Measurement error in these leads may have also impacted QRS_Max and QRS_Mean.

There were some technical considerations associated with the Phillips haemodynamic system; notably the measurement cursor (in the shape of a cross) was large and sometimes tricky to manoeuvre and position with

absolute accuracy. Moreover, clusters of identical values were noted. This was unusual as QRSd was on a continuous measurement scale and it was subsequently found that the digital calipers on the programmer measure in increments of 6 ms. Furthermore, when measuring individual leads on the 12 lead freeze frame, it was not possible to erase an individual measurement. In practical terms, this meant re-measuring all intervals on the entire ECG or measuring a different complex. Due to time pressures, suboptimal measurements may have been accepted. This is a downside of an observational study but is reflective of actual real life practice.

Whilst paper speed was extended to 50 mm/sec each time, this sometimes made the onset and offset of the QRS complex more difficult to identify in the CRT cohort. This has been observed in a previous study (Stephansen et al, 2019). However, in other studies an extended paper speed has been shown to enhance inter and intra-operator agreement (De Pooter et al, 2016, De Pooter et al, 2017, Tomlinson et al, 2009). It was sometimes difficult to optimize gain in all leads due to signal amplitude exceeding the minimum gain of the haemodynamic system. This meant that on some occasions, ECG leads were overlapping which made single lead measurement difficult. Importantly, only one ECG complex was measured, which may have been prone to error. Efforts were made to ensure morphology was stable, but in some other studies QRSd has been measured over multiple ECG complexes and averaged the results to improve accuracy (Jastrzebski et al, 2018).

Another limitation of the method comparison study is that operators were non-blinded. This may have introduced measurement bias, although the study was observational and immediate QRS measurement and optimisation was essential as part of the routine care pathway. Offline and blind analysis of each method may have resulted in more accurate measurements, but it would be impractical to delay the procedure whilst this was undertaken. It was also beneficial to reflect the challenges of real life clinical practice. Importantly, a second operator was used to counter bias and verify measurements, although

in practice, there was very little disagreement. This meant that either all measurements were accurate, or more likely, the second operator assumed a more passive role. One alternative would have been for both operators to measure independently and produce a combined, averaged measure, but again time pressures would have made this impractical in an observational study of this type.

Abbreviated global QRSd is a composite measurement of QRS duration which includes of the '*start of the QRS in any lead to the end of the QRS in any lead'*. For this reason, it was anticipated that the abbreviated global QRS measurement would be greater than the individual lead measurement alone. However this was not the case and on some occasions the aQRS_Global measured shorter than the individual lead, for example in lead I. This is particularly unusual when the individual lead was included in the aQRS_Global composite. This reasons for this are unclear and most likely due to measurement error in the individual lead. One possibility is that a different cardiac cycle was measured, although every effort was made to measure the same beat. Importantly, any uncertainty in the onset/offset of a QRS complex in an individual lead would be countered by having other leads to compare to in the abbreviated measurement. Nevertheless this was an interesting observation.

4.4 Inter-operator and Intra-operator variability

To the author's knowledge, this is the first study to report inter and intra-operator variability for abbreviated global QRSd methodology over 5 leads. This study found the standard error of measurement (SEM) was reasonable for both intra-operator variability (4.8 ms, LoA 9.5 ms) and inter-operator variability (7.9 ms, LoA 15.5 ms). Repeatability and reproducibility are key components of any measuring technique.

The SEM observed for *abbreviated* global QRSd methodology in this study were comparable to those reported for *standard* global QRS methodology over 12 leads. Jastrzebski et al (2018) reported mean intra-operator variability of up to 6.4 ms (± 4.7 ms) and mean inter-operator variability up to 9.4 ms (± 7.6 ms) using standard global QRS methodology. De Pooter et al (2016) reported slightly greater inter-operator variability (11 ms ±4 ms) with global QRS over 12 leads, but the LoA were narrow; mean intra-operator variability was impressively low (4 ms ± 1 ms). The limits of agreement in the current study were notably wider for abbreviated global QRS (9.5 ms for intra-operator variability; 15.5 ms for inter-operator variability). The clinically accepted limits of agreement for QRSd between 2 different operators or repeat measurement by the same operator are reported to be in the region of ± 20ms (Stephansen et al, 2019). In fact, Tomlinson et al (2009) demonstrated median inter-operator variability of 22.5 ms using 12 lead ECG at 50 mm/sec. Stephansen et al (2019) demonstrated LoA of ± 20ms in 12 Lead ECGs. Hence the LoA for abbreviated global QRS are comfortably within this range, indicating that the methodology is acceptable for use in clinical practice.

However, this directly conflicts with the level of QRSd shortening that is considered to be clinically significant, which has been described as 10 ms (Vancura et al, 2017) and 14 ms (De Pooter et al, 2016). Importantly, the magnitude of QRS narrowing achieved by the different modes of CRT programming in the current study was also modest (<10 ms). In clinical terms, this means that there is little margin to detect optimal QRS narrowing when performing CRT optimisation. This applies to all methodologies for measuring QRSd and is not a specific barrier for abbreviated global QRS. Conflict of this nature is not unusual in CRT; in echocardiography an increase of ≥5% in LVEF is sometimes used in CRT response criteria, despite 5% being the accepted level of inter-operator variability in assessment of LVEF (Mollo et al 2013).

Studies reporting inter and intra-operator variability for QRSd measurement by individual leads describe inconsistent results. There is a discrepancy in how inter-operator and intra-operator variability is presented in some studies, which makes direct comparison difficult (Vancura et al, 2017; Popović and Thomas, 2017). The recent study by Stephansen et al (2019) reported impressive mean inter-operator variability of 3ms (mean LoA -20, 27 ms) for individual lead QRS measurement and intra-operator variability of -2.5 ms (-20, 20 ms), however LoA were at the edge of clinical acceptability. A greater number of studies report much more significant inter and intra-operator variability (Tomlinson et al, 2009; De Pooter et al, 2016; De Guillebon et al, 2010). Tomlinson et al (2009) reported a median intra-operator variability of up to 25 ms (range 10-50 ms) and a median inter-operator variability of 35 ms (range 20-50 ms) at a paper speed of 25 mm/sec. De Guillebon et al (2010) reported a 50 ms absolute variability between operators using the widest QRS technique in individual leads; and up to 40 ms absolute variability within the same operator. De Pooter et al (2016) reported wide inter-operator variability of single lead ECG measurement with mean variation 35 ms ±12 ms; intra-operator variation was 11 ms± 6 ms. The variability reported with single lead ECG measurement is considerable, yet this is the most commonly used technique for measuring QRSd in the UK and Ireland as shown by the survey.

One reason that single lead ECG measurement of QRSd is so commonplace is because it is easy and quick. It can be manually performed in any clinical setting using standard ECG equipment, although the use of digital calipers is preferable. One problem with the uptake of standard global QRS methodology is that it requires specialist software with digital calipers and vertically aligned ECG leads. Some haemodynamic systems in the cardiac catheterization suite may have this technology, but the technique is certainly less applicable outside of the implant setting. Most ECG machines do not have digital calipers. Many hospitals, including the study centre, will not have the equipment to measure global QRS during CRT implant. The profession needs to address these practical challenges if more accurate measurement of QRSd and better optimisation of CRT is to be encouraged.

Based on these findings, abbreviated global QRS may offer a practical compromise to improve the accuracy of QRSd measurement. The interoperator and intraoperator variability demonstrated is superior to single lead ECG measurement, although has wider LoA when compared to Global QRS. The device programmer is readily available during CRT implantation and follow-up to facilitate rapid measurement. This study assessed abbreviated global QRSd measurement using the Abbott programmer. It is expected that the same technique could be applied to other manufacturers of device programmer, although the number of ECG leads varies between manufacturers and the increment of measurement is not known on other systems. This may require further research. There may be some value in exploring whether a different combination of leads can improve measurement accuracy, for example using V2 instead of V5 based on the lower levels of variation reported.

The programmer was observed to measure in 6ms increments, rather than on a continuous measurement scale, hence it is easy to see how LoA may broaden even if measurements differ by only one increment. However, during a clinical session of CRT optimisation, QRS measurement is usually performed by a single operator meaning that the more conservative level of variation would apply (4.8 ms, LoA 9.5 ms). If comparing QRSd between implant and follow-up in the presence of a different operator, the higher level of variation would be expected (7.9 ms, LoA 15.5 ms). In a practical sense, variation between operators could be reduced by taking 2-3 measurements of QRSd and calculating the mean. This would be a quick and simple method to introduce into clinical practice.

Increasing the paper speed to 50 mm/sec has been shown to improve repeatability both between and within operators (De Pooter et al, 2016; Tomlinson et al, 2009). However, in this study, extending paper speed sometimes made the onset and offset of the QRS complex more difficult to

identify; a finding also observed in previous studies (Stephansen et al, 2019; Guillebon et al, 2009). In future practice, it may be necessary to adjust paper speed on a case by case basis to optimise visualisation of QRS onset and offset. A key advantage of global QRS methodology is the ability to compensate for isoelectric segments in individual leads (De Pooter et al, 2016), hence more attention to the ECG display may improve measurement accuracy regardless of which technique is used.

All ECGs measured in this study were from the study cohort and the ECG was recorded in either of intrinsic rhythm with LBBB morphology or during biventricular pacing. The study protocol stated that for paced beats, measurements would start at the first deflection of the QRS rather than the pacing spike. The artefact associated with the pacing spike can make interpretation of the onset of the QRS difficult, hence in these cases the pacing spike may have been used. This may explain the greater interoperator variability seen in the study. Furthermore, the gradual onset and offset associated with broader paced beats and LBBB can affect precision of measurements in this cohort (Stephansen et al, 2019). Only 2 of the published studies described above were specifically performed in CRT patients (Stephansen et al, 2019 and De Pooter et al, 2016). Hence the reported levels of inter-operator and intra-operator variability may be further hampered if repeated within the study population.

Inter and intra-operator variability was not performed for individual lead QRS methodology in the current study. This may have facilitated direct comparison of methods between the same observers. However, as already described there is considerable published data for the inter-operator and intra-operator variability of QRSd using single lead ECG measurement. Hence it was decided this would not add value to the current findings. The sample size used in the inter-operator and intra-operator variability study (n=15 ECGs) was slightly smaller than intended (target n=20). This was due to a smaller number of study participants attending clinic in the advent of COVID. The target of 20 ECGs

was chosen in keeping with similar studies, such as Stephansen et al (2019). However, smaller samples have been described in some trials; De Pooter et al (2016) used a sample of 12 ECGs with 4 observers and Tomlinson et al (2009) used 7 ECGs with 6 observers.

4.5 Comparison of CRT Programming Modes

The design of this aspect of the study was similar to the trial by Varma et al (2018) who compared nominal biventricular parameters with SyncAV over 4 programming strategies. The study had similar objectives regarding comparison of CRT programming with the focus on achieving narrowest QRS. The sample size was a little larger (n=75) but the rationale and study population were similar with regards the comparison of CRT programming modes. The trial by Varma et al (2018) was appropriately powered and the results applicable to the wider population of patients implanted with an Abbott CRT device. However, Varma et al (2018) also assessed an off-label programming strategy which was intended to replicate Medtronic's AdaptiveCRT algorithm (LV only pacing plus nominal SyncAV -50ms). The observational nature of the current study using Abbott devices only, meant that application of an off-label strategy would not be possible and would not add benefit to the study objectives.

The current study supports the view that individualised CRT programming (Modes 3 and 5) can produce maximal QRS narrowing. These were the only two programming strategies to show significant superiority over best single point BiV pacing (Mode 1). Whilst there was no significant difference between Modes 3 and 5, the combination of MPP with individualised SyncAV (Mode 5) was associated with some of the best individual improvements. Clinically, MPP is not suitable for all patients due twitch or myocardial viability, and in this situation, individualised SyncAV (Mode 3) appeared equally effective in selected patients. From these data, individualised SyncAV appears more

important than MPP in reducing QRSd, but further research is needed in this area.

A recent study (O'Donnell et al, 2020) published in August 2020 (n=103) was the first of its kind to assess the relationship between individualised SyncAV and MPP. The external validity of the trial is strong when compared to the current study. Importantly, O'Donnell et al (2020) also showed significant reduction in QRSd when using individualised fusion offsets. However, the trial also demonstrated that the combination of individualised SyncAV and MPP further increased QRSd reduction, a finding which the current study was unable to support. However, the magnitude of additional QRSd reduction when MPP was combined with individualised SyncAV was smaller than the benefit of individualised SyncAV alone (O'Donnell et al, 2020). This does support the findings of the current study which indicates that SyncAV is the most important determinant of QRS narrowing in this patient cohort. The smaller sample size of the current study means that it was possibly underpowered to measure significant differences between Mode 3 and Mode 5. A larger sample size may have yielded similar results to the trial by O'Donnell et al (2020).

Overall, the results supported the findings of other recent studies, particularly with regards to fusion pacing (Varma et al, 2018, Thibault et al, 2019, AlTurki, 2020, Trucco et al, 2018). Varma et al (2018) also reported that individualised SyncAV pacing was superior to nominal biventricular pacing and nominal SyncAV settings in terms of QRS narrowing. This study demonstrated a greater magnitude of mean QRSd reduction compared to baseline. For Mode I (best single point pacing), Varma et al (2018) demonstrated a mean reduction of 20ms, whereas this study reported 37.22 ms. For Mode 2 (nominal SyncAV), Varma et al (2018) reported a mean reduction of 30 ms, whereas 36 ms was demonstrated in the current study. Finally, for Mode 3 (individualised SyncAV), Varma et al (2018) found a mean QRSd reduction of 39 ms, whereas 44.81 ms was demonstrated in the current study. The reasons for this may be due to fixed AV/VV delays programming in Modes 1 and 2 in the study by Varma et

al (2018), whereas in the current study a degree of individualisation was allowed to achieve best single point pacing.

Importantly, the inclusion criteria from Varma et al (2018) allowed intrinsic PR intervals up to 300 ms. Achieving fusion within the presence of profound first degree AV block may have affected the magnitude of QRSd reduction, particularly when a fixed SyncAV delta was applied. A PR interval of 300 ms exceeds manufacturer recommendations for SyncAV, hence a more conservative cut-off of <250 ms was applied in the current study. Importantly, mean baseline QRSd was 162 ms in the trial by Varma et al (2018), compared to 170.8 ms in the current study, another factor which favours greater QRS narrowing. QRSd was measured by global QRS methodology over 8-12 leads in the trial by Varma et al (2018) compared to abbreviated global QRS over 5 leads in the current study.

The results of the current study were also consistent with those reported by Thibault et al (2019). Maximum QRSd reduction was observed with individualised SyncAV, in comparison to nominal BiV pacing versus BiV pacing and nominal SyncAV. Again, the magnitude of QRSd reduction in the current study was greater than that observed in the trial by Thibault et al (2019) when compared to baseline. For nominal BiV pacing, Thibault et al (2019) reported a mean QRSd reduction of 17 ms, whereas the current study observed 37.22 ms. Nominal SyncAV gave a mean reduction of 22 ms compared to 36 ms in the current study. Finally, individualised SyncAV gave a mean QRSd reduction of 32 ms, compared to 44.81 ms in the current study. In contrast to the trial by Varma et al (2018), Thibault et al (2019) used more conservative PR intervals in keeping with intact AV conduction (<250 ms). However, the degree of individualisation in modes 1 and 2 in the current study may account for the greater QRS reduction observed. Furthermore, mean baseline QRSd was much shorter in the trial by Thibualt et al (2019) at 155 ms (170.8 ms in the current study).

Importantly, the current study was unable to demonstrate benefit of nominal SyncAV (fixed offset of -50 ms) over best single point pacing. This is not in keeping with the findings by both Varma et al (2018) and Thibault et al (2019), who both demonstrated modest QRSd reduction. In practical terms, a fixed fusion offset is less likely to benefit a wider patient group due to patient specific factors such as intrinsic PR interval and dynamic physiological changes. Much of the evidence suggests that optimised fusion pacing intervals are superior. Trucco et al (2018) manually adjusted AV and VV delays to achieve individualised fusion intervals, which showed benefit over nominal BiV pacing. Early studies, such as Sweeney et al (2014) demonstrated that normalisation of the morphologies in V1 using fusion intervals were better at predicting outcomes. The manual methodologies applied in the latter studies support individualised programing. The downside of manual methodologies is the lack of dynamic adjustment to the daily physiological variation in PR intervals. This means that manually derived fusion intervals may become suboptimal once the patient leaves clinic.

The results also failed to demonstrate the benefit of standard MPP (Mode 4) over best single point biventricular pacing (Mode 1) with regards QRS narrowing. This is not in keeping with other published literature (Zanon et al, 2015, Menardi et al, 2015, Forleo et al, 2017). It is acknowledged that the current study was slightly underpowered due to the smaller sample size, which means that the results should be interpreted with caution. However, many of the trials supporting MPP assessed reverse LV remodelling by echocardiographic parameters or LV dP/dtmax, rather than QRS reduction (Pappone et al, 2015; Forleo et al, 2017; Zanon et al, 2015; Rinaldi et al, 2013; Osca et al, 2016; Thibault et al, 2013). Arguably, utilising a reduction in QRSd as an end point in this study was a disadvantage to MPP. However, mode 5 (MPP and individualised SyncAV) was associated with some of the greatest reductions in QRSd, meaning that it may be highly beneficial in specific patients. Further research is required in this area. The study population was slightly biased towards those with an ischaemic aetiology (54%) which may have affected the impact of MPP due to scar burden.

However, the magnitude of QRSd narrowing between the different CRT programming modes was smaller than the baseline reductions; mean reductions across all 5 modes were <10 ms. The clinical benefit of such a modest reduction in QRS is debatable. Studies have shown that the greater the reduction in QRSd, the greater the likelihood of CRT response (Rickard et al, 2011, Rickard et al, 2013). Notably, narrowing the QRS has not been demonstrated to cause harm in any series. QRS narrowing in this arm of the study was measured by a standardised ECG technique, abbreviated global QRS, to overcome measurement error between different methods.

This study allowed a degree of operator discretion and patient individualisation during the programming of each mode. For example, even best single point pacing (Mode 1) allowed different AV and VV timing per patient. Since the operators were not blinded to QRS duration, this may have introduced bias, despite the verification by a second operator. Significantly, operator discretion during programming has been a feature of many key clinical trials assessing CRT programming, particularly those assessing MPP. For example, both the IRON-MPP trial (Forleo et al, 2017) and the Multipoint Pacing trial (Niaizi et al, 2017) gave operators full discretion on programming. A very large ongoing trial into MPP with an enrolment target of >5000 subjects (MORE- CRT MPP-PHASE III), also allows implanters to select AV and VV timing according to operator preference (Leclercq et al, 2019). Crucially, in the current study the outcome goal was clear: to achieve the narrowest QRS. Based on the published methodology, the goals for MPP programming in the above studies were more ambiguous.

There is an obvious knowledge gap in how to best program MPP, consequently there is no published guidance. However, this is a wider problem affecting CRT programming in general. Consequently, operator discretion and manufacturer guidance remains standard in clinical practice at this time. The lack of guidance for CRT programming is acknowledged by the latest BHRS guidelines published in February 2020. Careful consideration for 'adjustments

to AV/VV timing utilising dynamic adaptive algorithms where appropriate' is suggested (BHRS, 2020). This general statement promotes the use of the SyncAV algorithm and similar algorithms from other manufacturers (e.g. Medtronic's AdaptivCRT). However, the guidelines do not mention MPP. Importantly, BHRS guidelines (2020) refer readers to the evidence-based guidance from the 2012 HRS/EHRA Consensus paper (Daubert et al, 2012).

This paper is over 8 years old and will not incorporate the newer technologies and developments of recent years. Consequently, until more up to date guidance is available from the professional groups within this specialist field, improvements in CRT programming in clinical practice are unlikely.

4.6 Clinical Response to CRT

Disappointingly, this study was unable to achieve its secondary endpoint of assessing patient response to the different programmed modes. This was caused by suspension of the study due to COVID19 and subsequent (understandable) reluctance of the patient group to enrol or attend. There is a clear knowledge gap related to the assessment of CRT response, particularly with respect to QRS narrowing and individualised SyncAV. This study was unable to contribute to the knowledge base and it remains a key area of interest.

Only 11 patients completed the full dataset prior to suspension of the study in March 2020. This reduced sample size (n=11) means that the results should be treated with caution and may be bias. The response rate within the study sample at this point was 92%. This is much higher than values reported in clinical trials and should be treated with caution considering the much reduced sample size. An unpublished study (n=69) from the study centre gave an overall response rate of 64% which is considered to be much more representative and had borderline statistical significance p=0.056 (Wilburn et al, 2020). This unpublished study utilised the original departmental criteria for CRT response within the study centre (2/3 of the following ≥10% improvement

in 6MWD, ≥1 class improvement in NYHA and ≥15 point improvement in MLHFQ).

Research trials using similar definitions of response have witnessed response rates analogous to this. Norabartolo et al (2004) demonstrated a response rate of 69% using a 2/3 definition of response at 3 months post CRT: ≥50metre improvement in 6MWD, ≥1 class improvement in NYHA and/or ≥15 point improvement in MLHFQ. Lecog et al (2005) observed a response rate of 73% using the definition of alive at 6 months, without HF hospitalisation and with ≥ one of the following: ≥ 1 class improvement in NYHA, ≥10% improvement in peak oxygen uptake (pVO2) and/or ≥10% improvement in 6MWD.

The best method to assess response to CRT remains unknown (Sieniewicz et al, 2019). The original definition of CRT response used in the study centre was based on clinical and functional improvement. Arguably, these criteria was biased towards those with more severe HF symptoms (NYHA Class III/IV). There are four landmark studies for CRT which clearly document improved functional capacity, quality of life and symptom improvement: MIRACLE, MIRACLE ICD, CONTAK CD and MUSTIC SR. These all focussed on patients with NYHA Class III/IV symptoms. In the MIRACLE study, improvements were reported in 6MWD, VO2 max, MLHFQ and NYHA class after 6 months for patients with CRT-P and class III/IV heart failure (Abraham et al, 2002). In MIRACLE ICD, the same patient group receiving CRT-D displayed improvement in peak VO2, MLHFQ and NYHA at 6 months (Young et al, 2003). The CONTAK CD trial showed similar results in class III/IV patients with CRT-D noting improvements in 6MWD, peak VO2 and NYHA after 6 months (Higgins et al, 2003). The MUSTIC SR study showed increased 6MWD, peak VO2 and MLHFQ after 6 months, in class III patients who received CRT-P (Cazeau et al, 2001).

For patients with less severe HF symptoms (NYHA I/II), the benefit of CRT tends to be focused on reduced mortality and Heart Failure Hospitalisation (HFH) rather than significant improvements in functional capacity, quality of life and symptom relief (Linde et al, 2008; Moss et al, 2009). Any symptomatic relief may occur over a longer timeframe (Curtis et al, 2016) and only subtle changes may be present after 5 months. This is demonstrated by the REVERSE trial, whereby NYHA class I/II patients receiving CRT-P or CRT-D did not demonstrate significant improvements in exercise tolerance or quality of life after a longer follow-up period of 12 months (Linde et al, 2008). Furthermore, In the MIRACLE ICD II study, patients in NYHA class II implanted with CRT-D did not demonstrate significant improvements in peak VO2, 6MWD or MLHFQ after 6 months (Abraham et al, 2004).

CRT response was assessed in the current study 5 months post implantation. In keeping with the observational approach for the study, this was aligned with departmental protocol. The literature review found that most studies assess CRT response between 6-12 months post implantation, with 6 months being commonly accepted as standard (Leclercq et al, 2019, Forleo et al, 2017, Niazi et al, 2017). Consequently, a timeframe of 5 months was considered in line with the consensus and helped to maximise the sample size within the study timeline. However, this may have underestimated true response to CRT, particularly individuals with less severe heart symptoms. The observed 92% response rate does not support this theory, but is likely to be misrepresentative due to the small sample size.

It is possible that patients who were feeling better were more willing to undergo MLHFQ and 6MWT. 4 patients declined to engage in assessment of CRT response at their 5 month follow-up. The reasons were unclear but thought to be patient choice and safety concerns over COVID19. The study protocol gave patients the option to return on a later date (within one week) to undergo assessment of CRT response, particularly if they felt their health was not representative on the day. However, no patients took this opportunity, possibly

due to convenience and to minimise time within the hospital in the advent of COVID19. Depression associated with long-term illnesses can limit 6MWD (Omar et al, 2017) and intuitively may affect MLHFQ scores. The Physiologists observed some limitations of MLHFQ in practice. Firstly, patients found it difficult to differentiate symptom limitation caused by HF from other comorbidities, which may have produce falsely elevated scores. In addition, patient answers appeared to be influenced on some occasions by their accompanying relatives or carers. The questionnaires themselves can be time-consuming in a clinic setting, particularly in the HF population which is largely elderly.

Arguably, there is another class of patients whose disease progression has halted but not reversed, leading to stasis in functional capacity or symptoms. Identification of 'unchanged' patients is recognised in other clinical trials (Daubert et al, 2017). Packer's CCS has been validated in landmark CRT trials and classifies patients as worsened, unchanged or improved (Daubert et al, 2017). Unfortunately, the current CRT criteria does not address these patients. This group could be defined as 'non-progressors' or 'no change' and correspond to 1/3 of the current CCS. For example, no worsening of NYHA class and one of the following: improved 6MWD of ≥10% or increase in MLHFQ of ≥15 points. These patients would be classed as non-responders on the original CCS criteria. Essentially, some clinicians would interpret no change as a positive response to CRT.

Patients which have a particularly impressive response to CRT form another classification group. These have been labelled 'Super-Responders' and are associated with the best outcomes. The definition of a super-responder varies in literature, probably related to the uncertainty surrounding the definition of a responder. One study suggested that patients should have functional recovery and an LVEF >50% (Castellant et al, 2008). Conversely, another study used a more comprehensive criteria assessed as 6months: ≥ improvement in NYHA class, ≥ two-fold increase in LVEF or to an absolute value >45%, and a

decrease in the LVESV >15% (Antonio et al, 2009). This group is less well studied in literature, although most studies use echocardiographic criteria. There is little evidence of the definition of a super-responder using clinical measures. Nevertheless, based on the CCS used by the study centre, patients who show improvement in all three measures (3/3) could be classified as Super-Responders.

Daubert et al (2017) supports the use of CCS, where multiple components to assess functional and quality of life measures are preferred over a single indicator. It has been suggested that CCS should encompass all aspects of therapeutic response, such as functional assessment, hard outcome measure and quality of life (Daubert et al, 2017). The original CRT response criteria does not address hard outcome measures such as mortality or HFH. These are debatably the most unbiased measure of CRT response. However, the measurement of HFH can be challenging in ongoing clinical practice, particularly within the typical 6 month timeframe used to assess response. It can be difficult and time-consuming to review admission data for every patient and patients may present to different hospitals. The assessment of all- cause mortality at the end of the follow-up period is a more realistic indicator in real life. The department's revised CRT response criteria was designed to overcome many of the challenges discussed above and includes categories for non-progressors and super-responders. It also incorporates a hard outcome measure by specifying that the patient was alive at the end of the follow-up period.

There was the notable absence of an echocardiography based endpoint in the department's CCS. Evidence supporting echocardiography in assessment of CRT is inconclusive and the latest guidelines do not recommend imaging techniques for this purpose (Aalen et al, 2020; Ponikowski et al, 2016). Furthermore, due to service pressures on the echocardiography service at the study institution, measurement of LV remodelling post CRT was not part of the routine patient pathway. Echocardiography is used however, for the

assessment of non-responders at the study centre. Its utility in this capacity is of interest but outside the remit of this thesis.

The response criteria used by the study centre was designed to be efficient and easy to follow, to be achievable within a single hospital visit and to make best use of hospital resources. However, to those who favour echocardiographic parameters, this criterion may appear too simplistic and may falsely elevate response, as clinical measures are thought to produce greater outcomes (Sieniewicz et al, 2019).

Consequently, using the original response criteria, it may have been more difficult to classify patients in NYHA I/II as responders. Of the 11 patients, 5 were NYHA class II at baseline and 6 were NYHA class III at baseline. Only one patient was classed as a non-responder and this was a patient in NYHA II. The revised CRT criteria was designed to be more sympathetic to minimally symptomatic patients. Interestingly, when the revised response criteria was applied, 6 patients were classed as super-responders, 4 patients were classed as responders and the previous non-responder was re-classified as a non-progressor. The responders were defined by improvement in 2/3 measures and this group was comprised of 3 x NYHA class III patients and 1 x NYHA class II patient at baseline.

The patient reclassified as a non-progressor was an 87 year old male in NYHA class II at baseline. This patient had a 20 point decrease in MLHFQ but remained in NYHA Class II and only achieved a 1.6% increase in 6MWD (1/3). Comorbidity data was not collected as part of this study but failure to increase 6MWD by 10% could well be due to mobility issues or other comorbidities. The impact of comorbidities may influence other clinical measures in a similar way. For HF patients with low LVEF, having a degree of breathlessness is largely expected, hence remaining in NYHA class II post CRT should not necessarily be considered a negative. CRT is not a cure and in many cases, patients do not become symptom free (and achieve NYHA class I). Consequently, this

case highlights how the revised response criteria may be more applicable to real-life situations and prevent minimally symptomatic patients being inappropriately labelled as non-responders. More research is required in this area, although it is acknowledged that the results may have high internal validity but be of less use to a wider audience due to the variable nature of CRT response criteria used in clinical practice. Nevertheless, it is recommended that the revised CRT response criteria is implemented in the study centre with immediate effect.

Response to CRT is also based on expectation (Daubert et al, 2012). The NYHA classification used in this study considers symptoms from ordinary activities. The level of normal activity for a retired 87 year old is likely to differ from a 50 year old in an active job. The Physiologist's assessment was used for NYHA classification with regards CRT response. This was deliberate to ensure consistency between baseline and follow-up. It was not documented whether the NYHA class at baseline differed to the Consultant's assessment on referral. However, one study suggested there is considerable variation in how Cardiologist's assess NYHA (Raphael et al, 2007). Assessing NYHA is a new role for the Physiologists in the study centre, hence it was perhaps easier to standardise the approach in this group using set criteria. It may be difficult to apply the same NYHA classification criteria to experienced Cardiologists with historical practices. There was also sometimes a time lag between referral for CRT and attendance for Pre-Assessment, hence it is entirely possible that NYHA may have changed in that interval.

Unfortunately, 3 patients died within 12 months of their CRT Implant (10.7%). The cause of death is unknown. All three patients were NYHA Class III at baseline indicating significant symptomatic impairment from their heart failure. Ischaemic aetiology was present in all cases, although without the cause of death it is difficult to comment further. Significant QRS narrowing was achieved in all three implants with the absolute QRS narrowing ranging from 23 ms to 41 ms. Baseline QRS ranged from 148 ms to 178 ms, providing a high

likelihood of achieving a positive CRT response. Interestingly one of the patients was assessed as a responder (and super-responder based on the revised criteria) but died approximately one month after assessment in CRT Follow-Up clinic. 2 of these patients had individualised CRT programming (Mode 3 and Mode 5), the final patient was programmed in Mode 2 but this gave the same QRS reduction as Mode 3.

In February 2020, revised BHRS guidelines for device follow-up introduced a new recommendation that hospitals 'have a protocol to measure CRT response and identify non-responders'. However, the guidelines stopped short of suggesting a suitable pathway, evidently due to the lack of consensus. This means that individual hospitals, like the study centre, will develop their own protocols and result in a heterogenous mix of definitions for CRT response. Whilst this enables hospitals to develop pathways within their available resources, it prevents direct comparison between centres. Conversely, the lack of direct guidance may limit uptake of this recommendation. Interestingly, whilst the knowledge base is evolving in this area, it does create an ideal opportunity for further research.

All 11 patients reaching the 5 month following up period had a high percentage of biventricular pacing and absence of persistent atrial fibrillation. In keeping with local protocol, assessment of response would have been delayed if biventricular pacing was <90%. Biventricular pacing >98% has been shown to be a major factor in the success of CRT and better clinical outcomes (Hayes et al, 2011; Ousdigian et al, 2014). Atrial fibrillation (AF) is frequently associated with faster intrinsic ventricular rates and is a well-established cause of low biventricular pacing (Ousdigian et al, 2014). In a large meta-analysis, AF was associated with higher all-cause mortality when compared to CRT patients in sinus rhythm (Wilton et al, 2011). Similar findings were reported by Ousdigian et al (2014). Furthermore, the risk of non-response in the AF cohort is greater than that in sinus rhythm (Wilton et al, 2011).

4.7 Limitations

This study was limited by a smaller sample size due to COVID-19. This particularly affected the assessment of CRT response (n=11). The impact of COVID-19 is discussed in more detail in section 4.9. However, useful data was obtained for all parts of the study that may form the blueprint for further research in these areas.

When the study was conceptualised, two power calculations were performed: one with a significance level of $p<0.05$ which gave a sample size of 30 and another with a significance level of $p<0.005$ which gave a sample size of 52. It was initially proposed to present the data with the Bonferroni correction ($p<0.005$), but subsequently it was decided that this was unnecessarily conservative and a sample size of 30 was used as the minimum target. Despite multiple pair-wise comparisons, Bonferroni correction recommended P value was not used and unfortunately the higher sample-size recommended was not achieved. This remains a limitation of the study.

The 'mode' comparison study tested 10 pairs of CRT programming modes to determine which obtained greatest QRS narrowing. Some statisticians prefer to perform mathematical corrections when testing multiple comparisons in this way; to correct for the probability of a significant result occurring by chance (Motulsky, 2017; Armstrong, 2014). One of the most common, yet conservative models, for mathematical correction is the Bonferroni method (Motulsky, 2017; Armstrong, 2014). In this thesis, the data was presented without mathematical correction because there was a limited number of pairs which were of particular clinical interest, and because of the capacity of such correction methods to obscure differences of importance (Armstrong, 2014). Interestingly, even had the Bonferroni correction been applied, the paired modes identified as achieving the highest significance levels would have remained the same (i.e. Mode 1-Mode 3; Mode 2-Mode 3, Mode 4-Mode 5), and these would have remained significant at least to the $p<0.05$ level even

with correction. The modes achieving borderline significance using the t-test (i.e. Mode 1 - Mode 5, Mode 2 - Mode 5) would no longer be significant when corrected. However, the Bonferroni method has been criticised due to a high rate of false negatives (falsely classing results as non-significant), hence should not be used routinely (Armstrong, 2014). In summary, the Bonferroni correction did not change the broad conclusion that individualised fusion CRT programming can produce greater QRS narrowing that conventional CRT programming.

As this was an observational study, on some occasions there were time pressures performing all measurements post implantation. This was due to workload pressures and turnaround time within the Cardiac Catheterisation Suite. Whilst all measurements were obtained for the study, it highlighted the challenges affecting Cardiac Scientists who are applying this methodology in current practice. The precision of the measurement for QRSd is crucial and is thought to influence the patient response to this therapy, hence it seems counter-intuitive to perform these measurements at haste. This may be due to a lack of understanding by other members of the multidisciplinary team, where less respect is given to the CRT programming than the implantation procedure itself. Unfortunately, this may result in suboptimal programming and ultimately prevent a patient achieving their best possible chance of response to CRT. This can only be overcome through education and a change in culture. It is difficult to change historical practices whereby CRT implantation relied greatly on the skills of the implanting physician alone and CRT programming post implant was considered optional. Workload pressure means there is a conflict between the duration of each CRT implant procedure and emphasis of quality CRT programming. However, professional body guidance should change to reflect the shift in paradigm and support Cardiac Scientists to deliver high quality programming and give patients the best chance of a positive response.

Patients with LBBB were targeted in this study because this cohort of patients has been shown to have the best response to CRT and is the focus of latest

CRT guidelines (Ponikowski et al, 2016, NICE, 2014, Brignole et al, 2013, Daubert et al, 2012). Importantly, QRS narrowing has been shown to give prognostic benefit in LBBB only (Jastrzebski et al, 2018). However, the inclusion criteria did not specify the definition of LBBB and this was left to the discretion of the referring clinician. Consequently, patients with less definitive LBBB may have been included and limited the ability to achieve QRS narrowing. Conventional ECG definition of LBBB is a QRS duration ≥120 ms, QS or rS in lead V1, and a monophasic R wave with no Q waves in leads V6 and I (Stipdonk et al, 2015). It has been suggested that a more specific criteria should also include notched or slurred R waves in lead I, aVL, V5, or V6 to avoid non-LBBB patients diluting the sample (Strauss et al, 2011; Stipdonk et al, 2015). The evidence for CRT in non-LBBB groups is less compelling (Jastrzebski et al, 2018; Brignole et al, 2013).

This study also does not assess the ability of the programming strategies to narrow QRS in Right Bundle Branch Block (RBBB) or other forms of inter-ventricular conduction delay. As already described, the evidence for CRT in non-LBBB cohorts is weak (Brignole et al, 2013). There are fewer studies of this particular sub-group and RBBB patients are generally thought not to benefit (Brignole et al, 2013). The decision to implant a CRT in non-LBBB is controversial and should be on a case-by-case basis. Importantly, ESC guidelines recommend CRT in non-LBBB with very broad QRSd of >150 ms at the class IIa level of evidence.

Patients in atrial fibrillation (AF) were excluded from the study. The evidence for the benefit of CRT in AF is weaker than in sinus rhythm, as discussed previously (Brignole et al, 2013). However, AF is the most common arrhythmia seen in HF and appears related to disease severity with up to 20% in mild/moderate HF and up to 50% in patients with advanced disease (Brignole et al, 2013). AF is associated with worse mortality and lower likelihood of symptomatic benefit (Wilton et al, 2011; Ousdigian et al, 2014). However, fusion pacing cannot achieved in this patient group, hence CRT

personalisation would relate to adjustments in VV timing only.

For this reason, it may have been useful to collect data on AF burden during the follow-up period prior to assessment of CRT response. Patient having significant episodes paroxysmal atrial fibrillation are less likely to obtain symptomatic benefit and it would not be possible to assess the impact of individualised fusion pacing in this group. It is widely assumed that Remote Monitoring (RM) is of great value in patients with reduced ejection fraction and AF due to early detection and intervention. In line with this, it is departmental protocol that all device patients are provided with RM on discharge. However, the results of the recent REM-HF study did not identify any mortality benefit for patients undergoing remote monitoring (Zakeri et al, 2020). Conversely, the study also identified a potential increase in all-cause mortality and a higher rate of unplanned cardiovascular hospitalisation within the persistent AF group under remote monitoring. The reason for this is unclear but the REM-HF study adopted weekly data transmission rather than daily monitoring. This may have prevented earlier intervention in this group.

This study focused on fusion pacing in patients with intact AV conduction. Personalised CRT programming was not assessed in patients with AV block in whom fusion pacing is not possible. The benefit of CRT in patients with bradycardia indications for AV block is less clear. ESC guidelines indicate upgrade to CRT for pacemaker patients with LVEF <35% and high percentage ventricular pacing in NYHA III/IV despite optimal medical therapy (Brignole et al, 2013). De novo CRT is indicated in HF patients with reduced LVEF and expected high percentage pacing to decrease the risk of worsening HF as class IIa indication (Brignole et al, 2013). The BLOCK-HF study identified superior outcomes for CRT over RV pacing in patients with AV Block (Curtis et al, 2016). It is unclear whether individualised VV timing would be beneficial in this group.

Patients in this study were implanted with a CRT device from a single

manufacturer only (Abbott). The results of the mode comparison study may not be applicable to other manufacturers for two reasons; firstly, because not all manufacturers offer the same array of programming options and secondly, because algorithm function may vary slightly between manufacturers. However, the methodology for optimising QRSd using manual adjustment of AV and VV timing is applicable to all devices and indeed is used as standard in the study centre. This study does not consider fusion pacing or MPP in patients with LV only pacing. The device manufacturer, Medtronic, is able to deliver LV only pacing as fusion with intrinsic conduction as part of the AdaptivCRT algorithm. This algorithm also features dynamic AV adjustment similar to SyncAV. The evidence shows AdaptiveCRT is non-inferior to conventional biventricular pacing and may increase CRT response and clinical outcomes (Birnie et al, 2017; Brignole et al, 2013).

The ability of observational studies to influence clinical practice is much debated (Tai et al, 2014). Observational research involves the direct observation of individuals in their natural setting, and variables are not directly manipulated. This means that alternative explanations for a causal relationship must be considered, a process called confounding (Carlson and Morrison, 2009). Observation studies often have high external validity because they are often better representative of the patient population (Carlson and Morrison, 2009; Tai et al, 2014). However, the internal validity can be reduced by the lack of a control group, hence any relationship may be attributed to an alternative cause (Carlson and Morrison, 2009). For example, heart failure is a progressive condition and patient disease status may be affected by non-CRT parameters such as medication and comorbidities. It may have been useful to assess compliance with medication, and/or prescription changes, during the follow-up period to assess this variable on patient response. However, with so many contributory and patient-specific factors, this would have been very difficult. The impact of comorbidities may also have been of use over the follow-up period. For example, this may have influenced the patient's exercise tolerance during the 6MWT.

In 2018, the results of a large observational study into CRT practice were published and included 11088 patients from across Europe (Dickstein et al, 2018). The study included contributions from 42 countries, including 571 patients from the UK, and showed largely good compliance with ESC guidelines for CRT implantation. As expected, the results showed that CRT is largely being implanted in men with LVEF <35%, LBBB and broad QRS (Dickstein et al, 2018). However, the results also showed some deviation from the guidelines with 8% of patients having a QRS <120 ms and a quarter of patients having underlying atrial fibrillation (Dickstein et al, 2018). Worryingly, CRT in patients with narrow QRS is widely considered to be harmful. This may be explained by clinicians extrapolating data from clinical trials into slightly different patient populations with the intention of providing best treatment (Dickstein et al, 2018). Observational studies therefore have an important role in providing an insight into real world practice, both positive and negative aspects. This can be seen in the current study which has highlighted significant variation in CRT practice across the UK.

4.8 Scientist Led Research

Within Cardiac Physiology, there is little by the way of research outside of the tertiary centre environment. The Modernising Scientific Careers framework is addressing this via the most recent academic pathways in the profession, such as the Scientist Training programme (STP) and Higher Specialist Scientist Training (HSST) programme. These courses have a much greater focus on research and teach students vital research and critical appraisal skills which are lacking the historical training routes. However, many practising Cardiac Scientists (or Physiologists) have had little exposure to research aside from what their clinicians have been involved with. Professional bodies are actively addressing this and the agenda for the annual 2020 conference for both the British Society of Echocardiography (BSE) and Heart Rhythm Congress (HRC) had a clear focus on Research for Cardiac Scientists.

This emphasises the importance of this thesis within the field of Cardiac Science, not only as resource for new knowledge but also to promote research within the profession. This study had three entries at HRC 2020 with two posters and an abstract presentation (Broadhurst, 2020; Broadhurst et al, 2020a, Broadhurst et al, 2020b); the posters are shown in Appendix 15 & 16). Furthermore, the author was invited to present about her experience of research and doctorate level opportunities within Cardiac Science at HRC 2020. This highlights the growing appetite for Scientist-led research, particularly that which may influence the clinical practice of Clinical Scientists and Cardiac Physiologists.

4.9 Covid-19

The COVID-19 epidemic had a significant impact on this study. Both recruitment and the data collection phase were initially postponed in March 2020 and subsequently terminated early. In line with government and NHS England guidelines, routine face-to-face appointments were suspended in March 2020. The department underwent a strict review of the criteria for patients who should still physically attend the hospital, this was in keeping with BHRS guidelines published at the time and routine in-person CRT follow-up was not considered essential. The department routinely offered all patients remote monitoring and for this reason, patients underwent remote assessment in lieu of physical attendance. This meant that NYHA and the 6MWT was not performed. The department sent out MLHF questionnaires to patients but none were returned. Only patients deemed as clinically urgent e.g. remote data suggesting impaired device function or significant patient symptoms were invited to attend the hospital at this time.

The study population fell into one of the most vulnerable groups identified by the government and patients were advised to shield for a period of approximately 3 months during phase I of the COVID-19 outbreak (BHF,

2020). Evidence shows that patients were very anxious to attend the hospital for any reason, figures for admissions for all conditions during the height of lockdown show great reductions, even for myocardial infarctions (BHF, 2020). In July 2020, the department resumed face-to-face appointments with strict infection control measures in place, in keeping with government recommendations. Despite this, the department experienced a high number of failed attendances (Did Not Attend). Importantly, recruitment for the study re-opened in September 2020 but no further patients were enrolled since March 2020. The direct care team reported a distinct reluctance of patients to commit to a research project, particularly one where face-to-face attendance was required (despite this being part of the routine care plan), as the facility of remote follow-up was particularly attractive.

In October 2020, South Yorkshire reported increasing COVID transmission rates and hospital admissions and was subsequently placed under Tier 3 restrictions. By the 5th November 2020, the UK entered a second national lockdown until 5th December 2020. At this point, it was decided to terminate the study early. Subsequently the UK entered a third national lockdown on 4th January 2021.

The pandemic is known to have widely affected a broad range of research projects worldwide (Myers et al, 2020). Research resources world-wide have been channelled into COVID-19 to reduce transmission, improve treatments and ultimately develop a vaccine. Between Spring and Summer 2020, Ethics approval boards were only approving projects into Covid-19. Furthermore, healthcare professionals were redeployed to the frontline to provide direct care. The author fell into the last category, hence in keeping with reduced patient compliance, the decision to terminate the study early was the most sensible option in the circumstances.

5.0 Summary, Recommendations and Conclusions

This study supports the view that individualised programming for CRT can have the greatest influence on QRSd and the author promotes individualised CRT programming in clinical practice. In the study population, dynamic fusion pacing via SyncAV appeared to have the greatest contribution to QRS narrowing. The combination of MPP and individualised SyncAV was not shown to augment QRS narrowing when compared to individualised SyncAV alone, although this is contrary to a more recent study with a larger sample size (O'Donnell et al, 2020). Further research is recommended into the combination of MPP and SyncAV.

The results highlight wide variation in clinical practice across the UK and Ireland with regards the type of ECG monitoring used in CRT and the method used to measure QRSd. Crucially, limitations were also identified in two common methods for the measurement of QRSd. Both these factors may influence patient outcomes.

The author recommends that the method for measuring QRSd should be standardised and local protocols updated. As a minimum, the target ECG lead should be quoted if using single lead measurement and the same methodology should be used for serial readings. The author recommends the use of abbreviated global QRS methodology when using the Abbott device programmer, as a reasonable alternative to single lead ECG measurement. The device programmer is ideally placed in both the implant and follow-up environment to provide a practical compromise to improve measurement accuracy. Further research may be required to evaluate abbreviated global QRSd against standard global QRSd.

The patient's clinical response to QRS narrowing by individualised CRT programming remains a key area of interest which was not effectively

assessed by the study due to COVID-19. Further research is required. However, this study did evaluate patient response in a small group and the revised criteria proposed may form a pragmatic approach to measuring CRT response. The author recommends this is incorporated into departmental protocol and may be of interest to other centres, in the absence of professional body guidance.

The author urges the BHRS to update professional body guidelines. A more sophisticated benchmarking exercise is recommended to formally document variation in clinical practice and drive the need for change. Local standardisation of the method for measuring QRSd is strongly recommended. The guidelines should be more explicit with regards CRT optimisation with greater acknowledgement of modern programming options such as MPP. A suggested pathway for measuring CRT response may also be beneficial.

Overall, better education is encouraged across in all disciplines and Cardiac Scientists are best placed to lead service development within our own profession.

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7.0 Appendices

Appendix 1 CRT Animation

CRT is a dynamic process and can be best appreciated using an animation. In the short video clip below, the heart can initially seen to have dysynchronous contraction of the ventricles. However, once CRT is enabled, the ventricles can be seen to pump simultaneously. Thus improving improving the efficiency of the heart.

HF4 - CRT Therapy On-Off-On Animation - YouTube

Appendix 2 Study Protocol

C1 –DOCTORAL RESEARCH PROTOCOL V1

Optimal programming for Cardiac Resynchronisation Therapy

IRAS Project ID: **260238**

Lay Summary

Cardiac Resynchronisation Therapy (CRT) has been shown to improve cardiac performance and quality of life in specific patients with heart failure. These patients have poor cardiac pumping capacity and their pumping chambers contract out of sequence, due to a delay in the natural electrical system across the ventricles. The goal of CRT is to reduce the electrical delay and restore synchronisation between the heart chambers. A CRT coordinates contractions between the atria and the ventricles by delivering artificial electrical signals. The main timing intervals are known as the atrioventricular (AV) and interventricular (VV) delay. The best method to optimise the timing of these electrical signals remains unproven. Hence, device programming is left to the discretion of the operator and often remain at out of the box settings.

Importantly, not all patients respond favourably to CRT and approximately 30% are considered non-responders. Multiple factors can influence response to CRT and research has previously focussed on patient selection and lead placement. However, electrical programming of CRT devices post implant has become an area of great interest. Patient specific characteristics can influence electrical timing. Hence a universal strategy for device programming will be ineffective. This study will compare five programming strategies tailored to the individual and optimal CRT will be considered as the maximal reduction in ventricular delay. The study may help guide operators to best optimise CRTs in routine practice and how electrically optimised CRT can influence patient outcomes.

This data is recorded as part of our routine clinical dataset for patients undergoing standard CRT implantation. Participants will benefit by contributing towards improving protocols. The study will be completed at Rotherham NHS Foundation Trust and will be completed within 48 months.

Background

Heart failure describes a clinical syndrome characterised by structural and/or functional abnormalities resulting in impaired cardiac output or elevated intracardiac pressures (Ponikowski et al, 2016). Typical symptoms include breathlessness, ankle swelling and fatigue (Ponikowski et al, 2016). The prevalence

of heart failure is 1-2% of adults in developed countries, rising to greater than 10% of the older population (over 65 years) (Ponikowski et al, 2016). 12 month Mortality rates range between 7-17% and the rate of hospitalisation within 12 months ranges from 32-44% (Ponikowski et al, 2016). Most deaths are due to cardiovascular causes, particularly sudden death and pump failure (Ponikowski et al, 2016).

Cardiac Resynchronisation Therapy (CRT) has been shown to improve cardiac performance and quality of life in specific patients with heart failure (Cleland et al, 2013; Ponikowski et al, 2016; Moss et al, 2009). CRT is also known to reduce heart failure hospitalisations (HFH) and death (Cleland et al, 2013; Cleland et al, 2005). Two large randomised controlled trials (CARE-HF and Companion) have shown a morbidity and mortality benefit with CRT when compared to optimal medical therapy alone (Cleland et al, 2005; Bristow et al, 2004). Moss et al (2009) showed that the morbidity and mortality benefit even extends to those with only minimal HF symptoms due to reverse remodeling of the left ventricle.

However, not all patients respond favourably to CRT (Ponikowski et al, 2016). It is widely considered that up to 30% of patients are thought to be clinical non-responders and up to 50% do not achieve reverse remodelling (Trucco et al, 2018). Daubert et al (2012) pooled data from multiple CRT trials which highlighted the great variation in CRT non-responder rates between 15-45%. Importantly, non-responders have worse outcomes due to lesser degrees of ventricular remodelling but super responders do extremely well (Ponikowski et al, 2016; Moss et al, 2009). Multiple factors are thought to influence response to CRT and landmark studies have defined the patient populations most likely to benefit, hence have manifested in the current criteria for CRT implantation (Ponikowski et al,2016; Daubert et al, 2012). Cleland et al (2013) showed that QRS duration was a strong predictor of CRT response based on morbidity and mortality and also showed increasing benefit with longer QRS durations.

The goal of CRT is to restore electrical synchrony in patients with reduced left ventricular ejection fraction (LVEF) and left ventricular dyssynchrony (Varma et al, 2018). Delayed left ventricular activation gives rise to prolonged QRS duration and the typical left bundle branch block (LBBB) morphology on the resting electrogram (ECG). Achieving a reduction in QRS duration seems intuitive to a superior outcome from CRT (Varma et al, 2018). A meta-analysis has shown that reducing the QRS width on CRT favours a positive response (Korantzopoulos et al, 2016; Coppola et al, 2016). One study also shows that the greatest percentage reduction in QRS duration is associated with improved response (Rickard et al, 2011). Data also shows that reducing QRS duration is the only predictor of response in some series (Rickard et al, 2013). Importantly, a recent large randomised controlled trial showed that QRS narrowing can predict long-term survival in patients with LBBB (Jastrzebski et al, 2018).

Much attention has focussed on the technical aspects during implant to achieve best CRT, such as the placement of the LV lead (Rademakers et al, 2010; Khan et al,

2012) and efforts to pace the left ventricle at the site of latest activation by measuring qLV (interval from QRS onset to first large deflection of the LV electrogram) (Khan et al, 2012, Daubert et al, 2012; Zanon et al, 2016). However, electrical programming of CRT devices post implant is also an area of great interest, with the goal of reducing QRS duration (Varma, 2016).

The best method to optimise atrioventricular and interventricular timing of CRT devices post implant remains unproven (Brignole et al 2013). Methods to electrically optimise CRT settings by either echo-guided programming or device-based algorithms have yielded inconclusive results (Auricchio et al, 2018; Varma et al, 2018; Brignole et al, 2013). This is most likely because these techniques are static and do not account for dynamic changes to AV timing which occur during activities, medication or disease progression. Furthermore, echo optimisation is time-consuming, unreliable and impractical in routine clinical practice (Trucco et al, 2018).

The range of programming options on CRT devices is vast and there is little guidance in the literature (Varma et al, 2018; Brignole et al, 2013). Hence, device programming and optimisation is left to the discretion of the operator and settings are often left nominally (Forleo et al, 2017). However, manufacturers have designed novel ways to deliver electrical signals via to adapt to the patient's individual characteristics. The latest research suggests improvements in reverse remodelling can be achieved by fusing intrinsic ventricular activation with biventricular pacing to obtain narrower QRS complexes (Trucco et al, 2018; Varma et al, 2018). Abbott Medical have developed an algorithm sympathetic to the natural variation in PR interval, called Sync AV, which guides fusion pacing of this type.

An alternative programming option to optimise CRT, is to deliver pacing stimuli at two sites within the left ventricle, this is known as multipoint pacing (MPP). This is facilitated by quadpolar LV leads which are commonplace in clinical practice. MPP alone has been shown to be advantageous by several trials (Tomassoni et al, 2016; Leclercq et al, 2018; Forleo et al, 2017). MPP has been shown to reduce QRS duration and subsequent activation time (Menardi et al, 2015). Echocardiographic measures of dyssynchrony have been significantly reduced using MPP (Rinaldi et al, 2013; Osca et al, 2012), with the latter study also showing acute improvement on LVEF. Furthermore, data has suggested that MPP can not only reduce the number of non-responders but can boost the number of super-responders (Pappone, 2015; Leclercq et al, 2018).

MPP has also been shown to improve remodelling and CRT response over longer periods (Zanon et al, 2016). The IRON-MPP study highlighted an improvement in both LVEF and response for patients using MPP (Forleo et al, 2017), although the downside is greater likelihood of stimulating the phrenic nerve. Tomassoni et al (2016) demonstrated that MPP is safe and non-inferior to standard biventricular pacing. Importantly, the benefit of MPP was most pronounced in patients with a

spatial separation exceeding 30 msec and those with only a 5 msec timing delay between LV1-LV2 (Tomassoni et al, 2016). This is useful evidence for clinical practice. Overall, studies have shown that MPP is most beneficial in patients with LBBB and a QRS duration >150 msec or in patients of non-ischaemic origin or those in NYHA III or IV (Tomaassoni et al, 2016; Forleo et al, 2017; Leclercq et al, 2018).

However, the longterm impact of MPP is not yet known. Consideration must be given to the impact on battery life because stimulating the LV from 2 consecutive poles is likely to increase current drain (Akerstrom et al, 2018). Data suggests this is in the region of 18months, which means that an estimated 1 in 7 patients will have an additional generator change due to MPP (Akerstrom et al, 2018). This may be significant considering the average lifespan of a CRT patient. There is also an ongoing study called MPP VARR assessing medium term remodelling with MPP and incidence of ventricular arrhythmias.

Evidence supports the use of these individual programming strategies, but combinations of these algorithms are also possible. The knowledge gap for this study is whether combining MPP and fusion pacing (SyncAV) can produce the greatest narrowing in QRS duration. In theoretical terms, the combination of Sync AV and MPP will create four wave-fronts to optimise haemodynamics, improve resynchronisation, maximise reverse remodelling and generate an augmented response to CRT. An abstract from O'Donnell et al (2016) suggested that mean QRS duration was shortest using Sync AV and a Multipoint Pacing approach (MPP). However, the final results of this study were not published and no further evidence is currently available.

Research Question

Is optimised fusion pacing (SyncAV &±MPP) superior to optimise biventricular pacing (±MPP) with respect to QRS narrowing when compare to nominal settings?

Aims

- The main aim of the project is to determine the best programming options to optimise Cardiac Resynchronisation Therapy (CRT) and achieve the narrowest QRS, focussing on Multipoint Pacing (MPP) and fusion pacing (SyncAV).
- A secondary objective is to determine whether this influences patient response after a 5month follow-up period.

Method

This is a prospective study of 52 patients implanted with an Abbott Medical CRT implanted due to standard CRT indications {Preliminary power calculation to detect 10msec difference in QRS suggests a sample size of 52 patients at 80% power}.

Baseline demographics, ECG characteristics, Minnesota questionnaire and Six-Minute Walk Test (6MWT) will be obtained at the scheduled Pre-Assessment visit.

Immediately following CRT implantation, five different programming strategies will be temporarily applied and the data recorded as per standard clinical dataset. [1. Single point BiV pacing with the AV delay optimised either using QuickOpt or a manual method (P wave duration plus 30 msec) to give narrowest QRS; 2. BiV pacing with nominal SyncAV; 3. BiV pacing with optimised SyncAV; 4. Optimised BiV pacing with MPP; 5. Optimised BiV pacing with MPP and SyncAV]. This is summarized in the table below:

	Mode 1	Mode 2	Mode 3	Mode 4	Mode 5
Pacing Mode	Single Point BiV	Single Point BiV	Single Point BiV	MPP	MPP
AVD	By QuickOpt or manual P wave measurement plus 30 msec	Nominal Sync AV (offset 50 msec)	Individualised SyncAV (offset 10, 20, 30, 40, 50 or 60 msec)	By QuickOpt or manual P wave measurement plus 30 msec	Individualised SyncAV (offset 10, 20, 30, 40, 50 or 60 msec)

Electrograms from the device programmer will be analysed using digital calipers, 50mm/sec paper speed and global QRS measurement method (i.e. from the earliest onset of QRS in any of the 5 simultaneously recorded and vertically aligned ECG leads, to the end of the latest QRS in any lead). These will be compared to individual QRS measurement measured from the 12 lead ECG on the haemodynamic recording system measured with digital calipers. Global QRS duration must be verified by two operators at the time of assessment. As per standard practice, patients will be permanently programmed at the optimal settings (i.e. narrowest QRS, absence of diaphragmatic twitch and threshold <3.5v).

Standard follow-up will be performed five months post implantation with repeat Minnesota questionnaire, Six-Minute Walk Test (6MWT) and NYHA classification. A responder will be classed as having improvement in 2/3 measures.

This dataset will be collected at three scheduled clinical appointments and it is expected that each assessment will take approximately 15minutes longer than normal. Additional visits are not anticipated but it is plausible that the 6MWT and/or Minnesota questionnaire could be collected on a separate visit if the participant is short of time. To eliminate confounding variables, this must be performed within one week of the original planned visit.

Each participant will be sent a Patient Information Leaflet (PIL) approximately one week prior to their routine Pre-Device Assessment appointment. This is usually one to two weeks in advance of the CRT implantation procedure. This will allow participants sufficient time to consider the information. Qualified research/clinical

personnel will be available during Pre-Assessment to answer further questions and to take informed consent. Qualified research personnel are defined as those who have undergone Good Clinical Practice (GCP) Training and been fully trained in the study protocol / data collection methods by the investigatory team. The study utilises data collected as part of the standard clinical dataset.

Challenges and Study Design

This study will compare the main five programming strategies used in CRT optimisation at our institution [1. Nominal simultaneous biventricular pacing with the AV delay optimised either using QuickOpt or a manual method (P wave duration plus 30msec) to give narrowest QRS; 2. nominal biventricular pacing as described above with nominal SyncAV setting; 3. nominal biventricular pacing with optimised SyncAV; 4. Optimised biventricular pacing with MPP; 5. Optimised biventricular pacing with optimised SyncAV]. The outcome measure is QRS duration and the strategy which gives the shortest duration will be permanently programmed, providing the electrical characteristics are within acceptable limits as stated by local protocol (threshold <3.5v, absence of diagphramatic twitch).

The study will focus on new patients implanted with a CRT made by the manufacturer Abbott. This is the primary manufacturer used by the centre and has the full range of programming options. Other manufacturers will be excluded because they do not provide the same range of programming options or the algorithms differ slightly preventing direct comparison. The use of Abbott devices also gives the best chance of recruiting adequate patient numbers within the study timescale.

The method for QRS measurement was an important consideration. It is common practice to measure QRS duration from a single ECG lead. However, studies have shown that techniques to measure QRS duration may influence the result. Narrowing of global QRS has also been shown as the best predictor of response. Global QRS has been shown to have superior inter and intraoperator variability when compared to individual ECG leads. However, global QRS methodology often requires specialist electrophysiology equipment to enable vertical alignment of 12 ECG leads and digital calipers to align the start of the QRS in any lead to the offset of the waveform in any lead. Hence, it is not routinely used in clinical practice. This study aims to use standard equipment within the clinical setting, hence the device programmer can simultaneously display five vertically aligned ECG leads and electronic calipers can be used to apply global QRS methodology. QRS duration will be measured in milliseconds. These will be compared to individual QRS measurement measured from the 12 lead ECG on the haemodynamic recording system.

To minimise the potential for measurement bias, two operators must agree on the QRS measurement for each programming strategy. This will be the Highly Specialist

Cardiac Physiologist performing the programming and the implanting Consultant Cardiologist or second specialist cardiac physiologist. It is not possible to blind operators to the programming strategy used because the exact timing intervals are essential as part of the optimisation process. Inter and Intra-operator variability will be assessed offline by measurement of global QRS over 20 ECGs.

The timing of data collection was another consideration. The full clinical dataset is obtained at both the time of implantation and also during specialist CRT Optimisation Clinics which take place regularly for several months post implantation. However, because this study also aims to assess patient outcomes following programming, it was decided to utilise the dataset from implantation. This means that the response to CRT can be assessed in comparison to baseline. The length of the follow-up period is a key consideration. It is well established that response to CRT is variable. It was decided to use a follow-up period of 5months to ensure a reasonable time for response but accepting that the response time to CRT can vary significantly from 3months to 18months. This is also in keeping with the study timescale and South Yorkshire' current follow-up protocol.

Standard protocol for CRT implantation will minimise the influence of patient selection and technical considerations on QRS narrowing. New CRT patients should satisfy standard NICE or ESC criteria for implantation. Optimal lead placement will be selected and guided by the site of latest activation (QLV). This data is recorded as part of our routine clinical protocol for all new patients undergoing standard CRT implantation, hence there is no change to the patients care pathway. Participants will benefit from taking part by contributing towards
improving protocols.

The project was assessed by the trust's Patient Research Ambassador who agreed with the study design and recommended that the Study Information Leaflet was distributed to patients prior to their appointment in Pre- Assessment Clinic, hence this was adopted into study design. The research will be undertaken by the Highly Specialist Device Physiologists who are members of the direct care team.

One consideration was to omit a programming strategy which utilises LV only pacing and nominal SyncAV settings, similar to Medtronic's Adaptiv CRT algorithm. However, RV and LV fusion has been shown to be superior to LV only pacing (Varma et al, 2018). Furthermore, LV only pacing is not available on Abbott devices and this can only be achieved by programming the RV output to sub-threshold, which would be an off license use of the device.

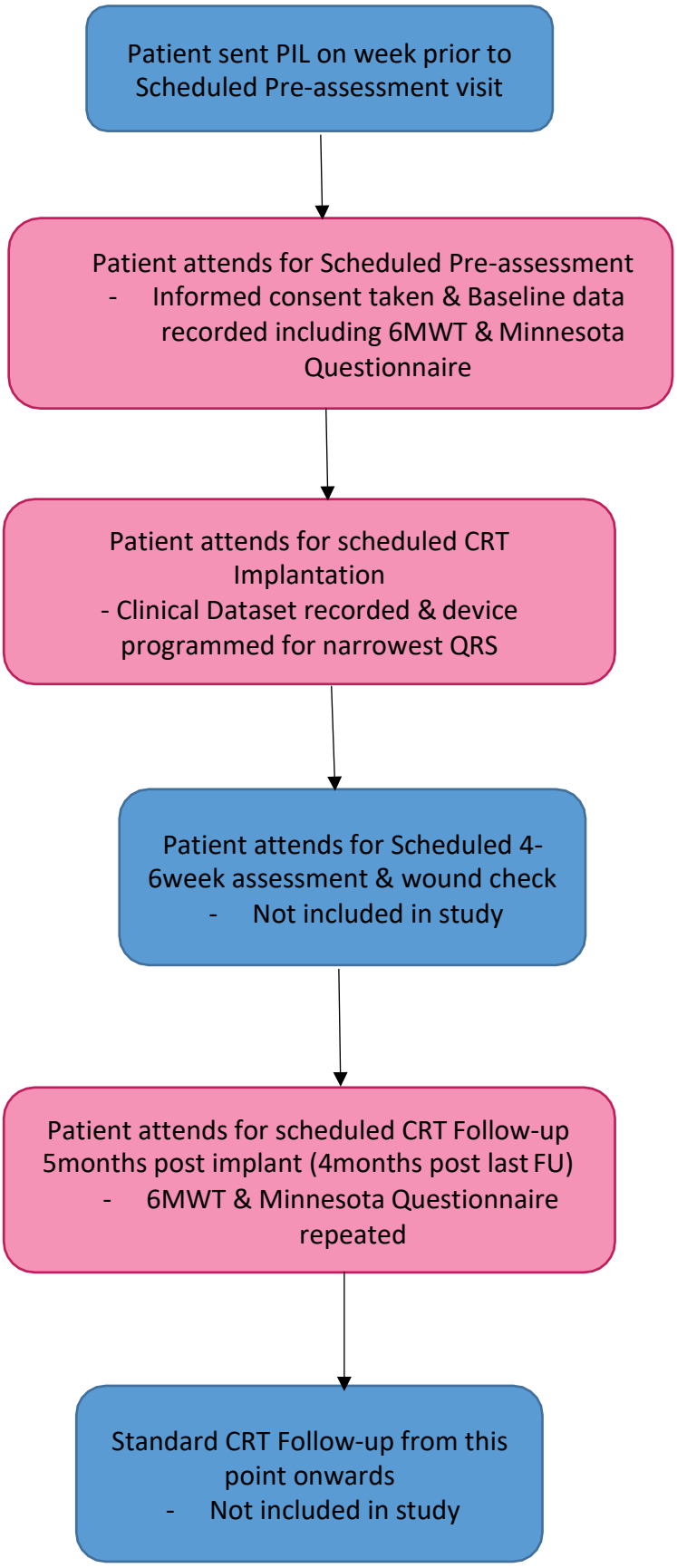
In summary, a universal programming strategy for CRT is ineffective because QRS narrowing is influenced by patient specific characteristics. The range of programming options available is vast and there is little guidance for optimal programming describe in the literature. This study may help guide Cardiac Scientists to individualise CRT settings to obtain narrowest QRS. Previous studies (such as Varma et al, 2018) utilise specialised electrophysiology equipment to

measure QRS interval. This study is conducted in the clinical setting using standard implantation equipment (i.e. Phillips Xper Flex haemodynamic recording system and device programmer), hence will provide more credible information to whether these techniques are viable in routine practice. Furthermore, this study may show how electrically optimized CRT settings can influence patient outcomes.

Inclusion and Exclusion Criteria

Inclusion	Exclusion
• Male / female aged 18 years upwards • Patients implanted with an Abbott or St.Jude CRT defibrillator (CRT-D) or CRT pacemaker (CRT-P) with Sync AV algorithm (CE marked) • Patients with a quadpole LV lead (CE marked) • Any commercially available RA & RV pacing or RV defibrillation lead • Scheduled for Standard CRT implant (NYHA Class II-IV; LVEF <35%, LBBB with QRS duration >120msec, preserved atrioventricular conduction with PR interval <250msec; on optimal medical therapy) • Fully able to understand the nature of the study with sufficient chance to read PIL and commitment to follow-up schedule	• Under 18 years of age • Patients who do not have a quadpole LV lead in situ • Patients without an Abbott or St.Jude CRT generator • In Atrial fibrillation (AF) • Patients who are pregnant or plan to become pregnant during study period • Those with a PR interval >250msec • Patients unable to complete a 6MWT • Patients with non-standard CRT indications • Patients taking part in other research studies during the study period • Inability to understand study requirements.

Study Flow Chart/ Organisation



Primary and secondary outcome measures

Primary:

- To establish which programming regimen achieves the narrowest QRS

Secondary:
Two out of three measures classed as a responder:

- Reduction in Minnesota Questionnaire score at 5months
- Improvement in 6MW distance at 5months
- Improvement in NYHA clasification

Statistics and Sample Size.

Data will be analysed using standard statistical software. It is intended to examine differences in QRS interval between different device program modes using descriptive measures and appropriate hypothesis tests, for example paired t-tests and one-way ANOVA with Tukey-Kramer model for paired comparisons.

A preliminary power calculation was performed to detect a clinically significant difference of 10 ms in QRS duration. This calculation was based on a standard deviation of paired differences between two different program modes of approximately 19ms. This is a rough estimate based on data presented in the study by Varma et al (2018). For two-tailed $p<0.005$ significance at 80% power, the sample size is estimated at 52 patients (64 for 90% power). The significance level of 0.005 was chosen to allow overall detection at the $p<0.05$ level in the presence of multiple paired comparisons (Bonferroni method).

All statistical modelling will be overseen by an experienced medical statistician based within the Manchester Metropolitan University.

Data and sample storage.

Once enrolled into the study following consent processes, each participant will be assigned a unique study identification number. Patient identifiers and personal details (i.e name, date of birth, etc.) will be stored separately from the unique study ID on password protected computer files. Only the unique study ID will be used on the paper data collection sheets and ECG tracings stored specifically for the study. Study data will be recorded onto password protected hospital network database using study ID only. Physical study related material will be stored in the site file in a keypad protected office within hospital (which has standard security). Password

protected computerised 'back-ups' will be created of all documentation and these will be stored separately in a similarly protected environment in the Hospital in case of loss of physical data in a major event (e.g. fire, flood).

Project timetable and estimated recruitment strategy.

The anticipated timescale is shown in the table below:

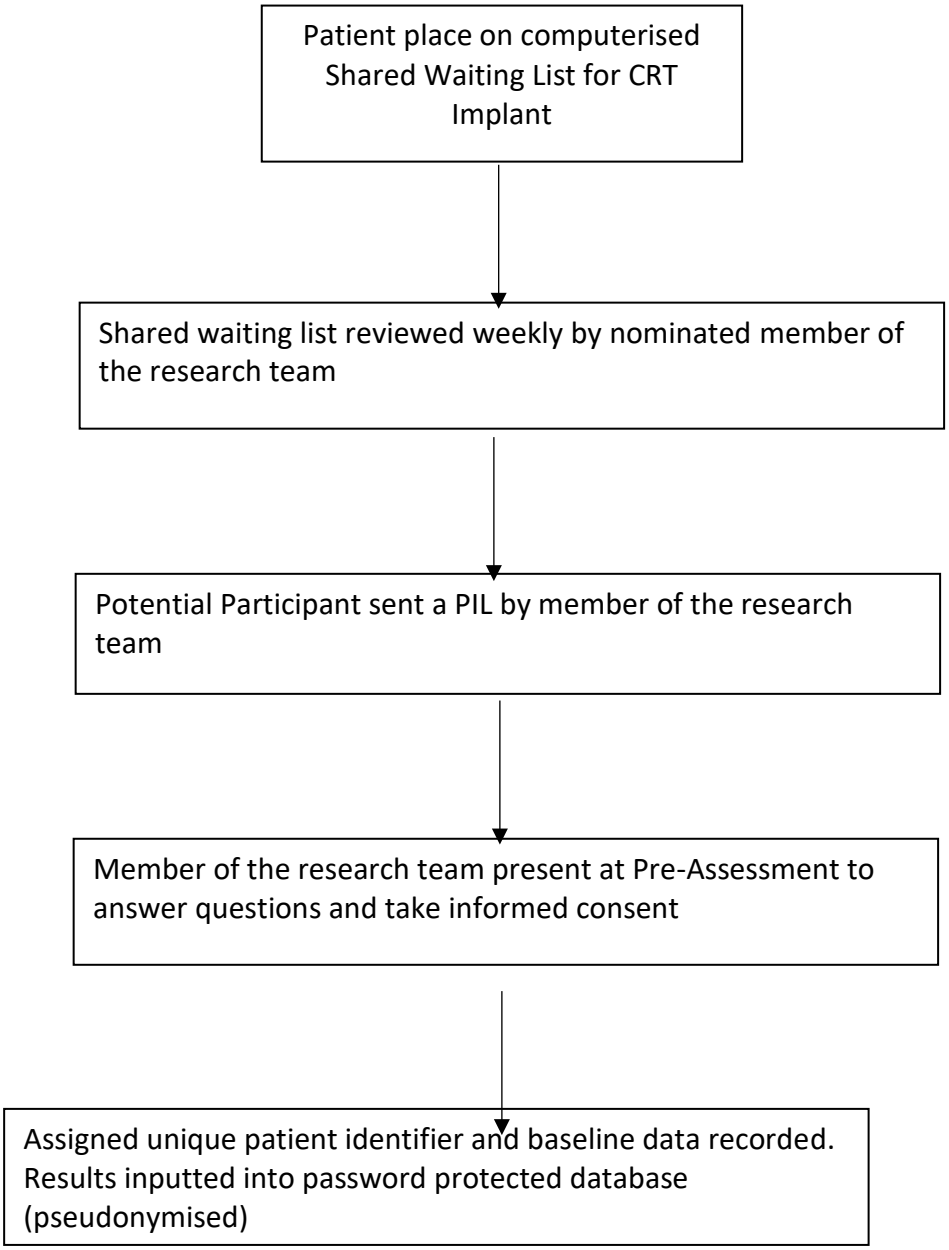
INCLUSIVE MONTHS	DESCRIPTION
0-3	Ethical approval, recruitment of the research team and staff training (commenced Nov 2018)
3-15	Recruitment and Data collection.
15-20	Recruitment completed and collection of remaining follow-up data
20-24	Statistical analysis of data including medical statistician input. Beginning of study write-up.
24-30	Compilation of final reports / papers. Conference presentation of results.

South Yorkshire has a regional approach to complex device implantation and CRT devices are implanted at Rotherham General Hospital and Sheffield Northern General Hospital from a shared computerised waiting list. The recruitment strategy for this study is aimed at Rotherham General Hospital only. The catchment for CRT implantation therefore covers the whole of South Yorkshire with an estimated population of 1.4 million. Based on implantation data published by NICOR, estimated numbers of new CRT implants (CRT-D and CRT-P) over a 1 year period is 208.6 per year (UK average of 149 per million population). This study is based on the current manufacturer usage based on existing tender specifications, hence a minimum sample size of 52 (and maximum sample size of 64) St.Jude/Abbott new CRT implants is reasonable within the study timeframe.

Potential participants will be identified from the shared waiting list and will be sent a PIL approximately one week prior to their Pre-Assessment appointment. This includes all patients referred for new CRT-P or CRT-D who satisfy basic inclusion criteria as specified on referral information. Importantly, patients who are found to be unsuitable to a St.Jude/Abbott device (better suited to another CRT manufacturer based on clinical characteristics) will be excluded.

A research assistant at Rotherham General Hospital will be identified to support the investigatory team. Recruitment to terminate when maximum sample size reached or after recruitment period of 1 year (whichever occurs sooner). Figure 1. outlines the proposed strategy for recruitment.

Figure 1: Recruitment Strategy



Roles and Responsibilities study team.

The chief investigator (Miss Lucy Broadhurst) has ultimate responsibility for ensuring that the study meets the structure as outlined in the proposed methods and is completed within the desired timeframes. The chief investigator will also ensure research staff assigned to the study undergo necessary training and obtain relevant support. The chief investigator will chair regular research team meetings (monthly) to ensure the safety and efficacy of the project. The day to day co-ordination and execution of the study will also be led by the chief investigator in this study, who will manage all study related documentation and recruitment targets.

Dr Simon Smith will provide expert clinical support and guidance to the research team. He will be an integral member of the investigatory team, particularly in data analysis and discussion of results with respect to clinical impact. Dr Mike Smith, Consultant Physicist, will provide support with statistical analysis. The academic supervisor of the study is Dr Martin Stout from Manchester Metropolitan University. He will provide expert supervisory support and guidance, particularly with statistical analysis and write up of results.

The research assistant (band 7 cardiac physiologist) will play a fundamental role in the recruitment and data collection phase of the study. It is envisaged that the research assistant will ensure all research related tasks are carried out effectively. They will be responsible for identification of participants, supporting informed consent, collecting and recording clinical data. They will report any concerns to the chief investigator.

Patient and Public Involvement

This study was discussed in detail with the trust's R&D Patient Ambassador on 03/07/18. No significant issues were identified because the data set will be obtained as part of the routine assessment. Participation in the study is voluntary and all patients will be provided with a patient information leaflet and written consent obtained. It was suggested that research study was discussed at the Pre-device Counselling session and that the patient information leaflet was sent out in advance to give patient time to digest the information.

Expected Value and Impact

This study is expected is provide valuable information regarding the optimal programming of CRT devices in clinical practice. This will be of particular interest to Cardiac Scientists, Physiologists and Cardiologists and may be used to guide further practice and protocol writing, which may benefit patient care.

Ethical and regulatory considerations

There is minimal risk from the data collection. The data collection and consent process will be performed in a clinic room to maintain patient confidentiality.

Assessment and management of risk

The study design and data collection should not pose any safeguarding implications for participants or others. No children will participate in the study. Should any safeguarding concerns be raised as part of a patient's admission these will be addressed by the clinical team as per Trust & National guidelines for safeguarding adults.

No extra visits to hospital or outpatient care are required for this study. The operative process itself is entirely unchanged and therefore there is no increased risk of complications through this study.

Research ethics committee (REC) review & reports

Before commencement of the study, approval will be sought from a Research Ethics Committee (REC) and Health Research Authority (HRA). Any amendments to the study following approval will not be implemented until any further review by the REC/HRA and R&D department. All REC/HRA correspondence will be retained for future review if necessary. At the conclusion of the study, a report will be produced and the REC will be informed by the Chief Investigator.

Regulatory compliance

The Chief Investigator will apply for Ethics Approval, Health Research Authority approval and Trust permission prior to commencement of or enrolment of any patient into this study

Data protection and patient confidentiality

All investigators will comply with the General Data Protection Regulation.

Indemnity

No harm to patients can be envisaged for this study, or attributed to it retrospectively, and therefore indemnity provision is not relevant.

Amendments

If any substantial amendments to the REC/HRA application or the supporting documents are necessary, a valid notice of amendment to the REC will be submitted. Amendments will also be notified to the R&D department.

Communication will then be made in writing to the R&D department and/or REC and HRA. Any amendments to the protocol will be reflected in the data collection tool to note which version was in use for that patient.

Dissemination Policy

Rotherham retains ownership of the data generated by this study.
It is envisaged that the results will be disseminated by peer-reviewed journal and presentation at the Heart Rhythm Congress.

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Appendix 3 Data Collection Form

The Rotherham NHS
NHS Foundation Trust

Cardiac Device Suite, Level A
Moorgate Road,
Rotherham S60 2UD
Tel: 01709 427670

Chief Investigator: Lucy Broadhurst
lucy.broadhurst@nhs.net

Optimal CRT Programming Study- CASE REPORT FORM

****VISIT 1 PRE-ASSESSMENT****

CLINICAL CHARACTERISTICS

Participant ID Code			

Male □ Female □

Age:_____years

Height: _____ Weight: _____ BSA: _____

Indication for CRT	
Cardiovascular history	
Symptoms	
LVEF % & Scan date	
Relevant Echo findings	
Other imaging findings e.g. MRI	
Presenting rhythm & Rate	
QRS Morphology	□ LBBB □ IVCD □ Other
ECG Data	QRS Duration _____msec PR Interval _____msec P wave duration_____msec
Arrhhythmias?	
Symptoms:	
Other comments	□ Requires further psychological support

Heart Failure Medications:

□ B-Blocker (e.g. Atenolol, Bisoprolol): _____
□ ACE-Inhibitor (e.g. Lisinpopril, Ramipril): _____
□ Aldosterone Antagonist (e.g. Spironolactone, Eplerenone): _____
□ Angiotensin II Receptor (e.g. Candesartan, Losartan): _____
□ Hydrazaline + Nitrate: _____
□ Entresto _____

Satisfies Criteria? □ **Yes (proceed to study)** □ **No (debrief & discharge)**

Participant ID Code			

INFORMED CONSENT

Informed Consent Obtained Yes □ No □ _____

FUNCTIONAL STATUS

	Performed Yes/ No	Results
Six Minute Walk Test		Metres
Minnesota Questionnaire		
NYHA Class		

**** VISIT 2 - DAY OF PROCEDURE****

Participant ID Code			

PRE-TEST QRS DURATION

Intrinsic rhythm > Verified by 2 observers > Paper speed 50mm/sec

Individual Lead QRS 12 lead haemo kit (msec)	I	II	III	aVR	aVL	aVF	Max	Mean
	V1	V2	V3	V4	V5	V6		
Global QRS (msec) 5 lead programmer								
P wave duration								
PR interval								

IMPLANTED CRT SYSTEM DETAILS

	Manufacturer/ Model	Serial Number	Date Implanted
Device (with Sync AV&MPP)			
RA			
RV			
LV (Quadpole)			

Target Vein for LV: _____

RV Lead position: □ RV Septum □ RV apex

IMPLANT DATA

	Sensing	Impedance	Threshold
RA			
RV			

Vector	LV Threshold	QLV	PNS
D1 – Uni			
M2 – Uni			
M3 – Uni			
P4 - Uni			

Participant ID Code			

MEASURED DATA

	D1	M2	M3	P4
RV-LV Conduction time				
Vector chosen		**Vector Threshold**		
QuickOpt	**AV Delay**		**VV Delays**	
Manual AV delay	P wave duration ≥ 100msec **+ 30msec**		P wave duration ≤ 100msec **+60msec**	

RESULTS

*QRS duration measured with paper speed of 50mm/msec > Verified by 2 operators

Mode I – Optimised Single Point BiV Pacing								
Vector Chosen								
AVD								
VV Offset								
Individual Lead QRS duration - 12 lead (msec)	I	II	III	aVR	aVL	aVF	Max	Mean
	V1	V2	V3	V4	V5	V6		
Global QRS (msec) 5 lead programmer								

Mode II – Optimised Single Point BiV Pacing with nominal SyncAV (50msec)								
Vector Chosen								
Measured PR								
AVD (PR -50msec)								
Individual Lead QRS duration - 12 lead (msec)	I	II	III	aVR	aVL	aVF	Max	Mean
	V1	V2	V3	V4	V5	V6		
Global QRS (msec) 5 lead programmer								

Participant ID Code			

Mode III – Optimised Single Point BiV with optimised SyncAV								
Measured PR								
Sync AV Delta								
AVD								
Individual Lead QRS duration - 12 lead (msec)	I	II	III	aVR	aVL	aVF	Max	Mean
	V1	V2	V3	V4	V5	V6		
Global QRS (msec) 5 lead programmer								

Mode IV– Optimised BiV with MPP								
AVD								
LV1 Vector & Threshold			LV2 Vector & threshold					
VV Offset								
Electrode Spacing								
Individual Lead QRS duration - 12 lead (msec)	I	II	III	aVR	aVL	aVF	Max	Mean
	V1	V2	V3	V4	V5	V6		
Global QRS (msec) 5 lead programmer								

Mode V– Optimised BiV with MPP & Optimised Sync AV								
Programming comments								
Individual Lead QRS duration - 12 lead (msec)	I	II	III	aVR	aVL	aVF	Max	Mean
	V1	V2	V3	V4	V5	V6		
Global QRS (msec) 5 lead programmer								

FINAL PROGRAMMING

Participant ID Code			

FINAL PROGRAMMING MODE CHOSEN (I-V)
COMMENTS

ADVERSE EVENTS

Symptoms reported □ YES □ NO

Testing terminated □ YES □ NO

Adverse Event Form Completed □ YES □ NO

FINAL PROGRAMMING

Optimal settings programmed as per protocol □ YES □ NO

If no, explain reasons:_____
_____
_____
_____

DEBRIEF

Full debrief performed and patient discharged home □

Final comments:_____
_____
_____

****VISIT 3 - 5 MONTH FOLLOW-UP****

FUNCTIONAL STATUS

	Performed Yes/ No	Results	Improvement?
Six Minute Walk Test		metres	
Minnesota Questionnaire			
NYHA Class			
Responder (Y/N) (*Must have 2/3)*			

*** END OF STUDY****

Appendix 4 Minnesota Living with Heart Failure Questionnaire (MLHFQ)

Patient Name…… Hospital Number……Date……

The following questions ask how much your heart failure (heart condition) has affected your life during the past month (4 weeks). After each question, please circle the number (0-5) to show how much your life has been affected.

	Did your heart failure prevent you from living as you wanted during the past month (4 weeks) by:	**No**	**Very Little**				**Very Much**
		0	**1**	**2**	**3**	**4**	**5**
1.	Causing swelling in your ankles or legs						
2.	Making you sit or lie down to rest during the day						
3.	Making your walking about or climbing stairs difficult						
4.	Making your working around the house or garden difficult						
5.	Making it difficult to go places away from home						
6.	Making it difficult to sleep well at night						
7.	Making relating to or doing things with your friends and family difficult						
8.	Making working to earn a living difficult						
9.	Making recreational pastimes, sports or hobbies difficult						
10.	Making sexual activities difficult						
11.	Making you eat less of the foods you like						
12.	Making you short of breath						
13.	Making you tired, fatigued or low on energy						
14.	Making you stay in hospital						
15.	Giving you side effects from treatments or medications						
16.	Making you feel you are a burden to your friends or family						
17.	Making you feel a loss of self control in your life						
18.	Making you worry						
19.	Making it difficult for you to concentrate or remember Things						
20.	Making you feel depressed, down or fed up						

Appendix 5 Survey Questions

Below is a manuscript of the questions asked in the SurveyMonkey questionnaire.

Questions	Answer Format
1. What hospital do you work at?	• Freetext
2. Is QRS narrowing important to you during CRT?	• Yes/No • Please explain your reasoning
3. During CRT implants, what ECG monitoring do you use?	• A single chest lead plus limb leads • 12 Lead ECG • Limb leads only • Other (please specify)
4. During CRT Implants, do you measure QRS duration (or narrowing)?	• Yes/No • Other
5. During CRT Implants, how do you measure QRS duration?	• Eyeball assessment • Measure a single ECG lead on the programmer or 12 lead ECG using digital calipers • Manually measure a single ECG lead on the programmer or 12 lead ECG • Measure Global QRS using digital calipers on the 12 Lead ECG • Measure abbreviated Global QRS on the programmer using digital calipers (e.g. over 4-5leads) • Other (please specify)
6. During CRT Follow-Up, what ECG monitoring do you use?	• Programmer ECG Only • 12 Lead ECG only • Programmer ECG and 12 Lead ECG • Other (please specify)
7. During CRT Follow-Up, do you measure QRS Duration (or narrowing)?	• Yes/No • Other (please specify)
8. During CRT Follow-Up, how do you measure QRS Duration?	• Eyeball assessment • Measure a single ECG lead on the programmer or 12 lead ECG using digital calipers • Manually measure a single ECG lead on the programmer or 12 lead ECG • Measure Global QRS using digital calipers on the 12 Lead ECG • Measure abbreviated Global QRS on the programmer using digital calipers (e.g. over 4-5leads) • Other (please specify)

Appendix 6 Power Calculation

Introduction

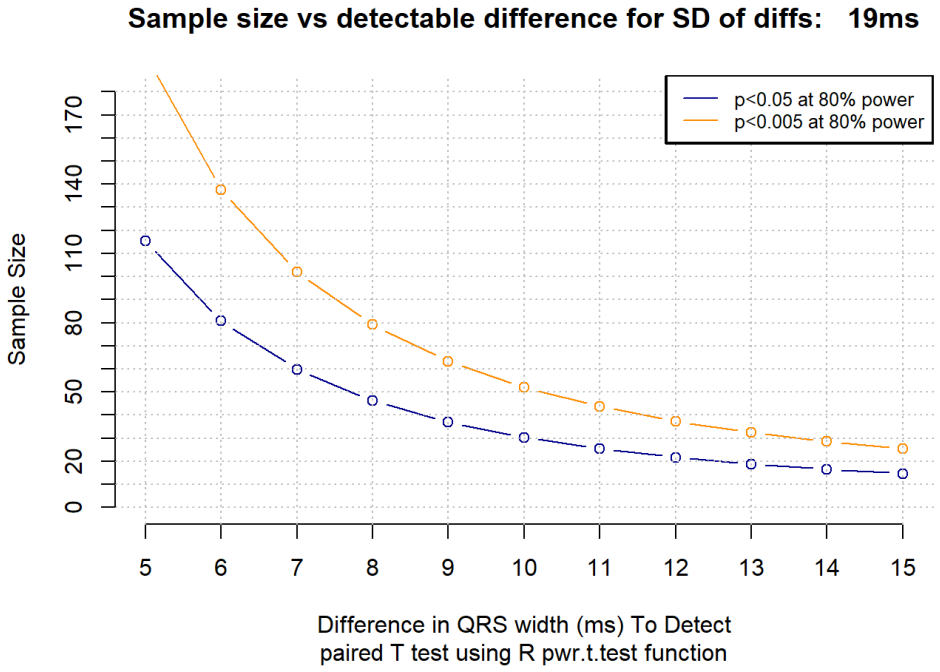
Criteria for power calculation (rationale as described in main text):

- Minimum mean difference in QRS (ms) between treatment modes that it is required to be able to detect: ***10 ms***
- Estimate of the standard deviation of the QRS differences (ms) between pairs of treatment modes: ***19 ms***
- [i.e. required effect size to detect = 10/19 =0.526]
- Required significance levels: ***p < 0.05 / p < 0.005***
- Required detection power: ***80%***
- Statistical test to be used: two-tailed paired t-test

Methodology

- Calculations performed using pwr.t.test function from "pow" package for R software (Champely, 2020)

Results



Conclusion

To detect a mean difference of 10ms at 80% power, the required sample sizes are: N=30 (for p< 0.05) or N=52 (for p < 0.005)

Appendix 7 **Participant Information Sheet**

OPTIMAL CRT PROGRAMMING STUDY

The Rotherham NHS Foundation Trust

IRAS Project ID: **260238**

You are invited to take part in this research project. Participation is entirely voluntary. Please read the following information and feel free to ask questions.

What is the purpose of the study?

Cardiac Resynchronisation Therapy (CRT) has been shown to improve quality of life and survival in certain patients with heart failure. However, previous research has shown that not all patients respond favourably to CRT and approximately 30% of patients do not feel improvement.

The programming of CRT devices can influence the heart's performance, especially if tailored to the individual. Despite this, the best methods to program CRT devices are not yet proven, hence programming is at the discretion of our highly trained specialists. This study aims to explore whether a patient-specific programming strategy can improve response to CRT.

Why have I been asked to participate?

You have been invited to participate because you have been referred for a CRT pacemaker (CRT-P) or CRT defibrillator (CRT-D) to manage your cardiac condition.

What would taking part involve?

All patients who have a CRT implanted are regularly assessed in the Cardiac Device Suite as part of their routine care package. If you volunteer to participate, routine data collected as part of three scheduled appointments will used as part of the research study, these are discussed below:

1. Pre-Assessment Clinic

   Prior to having your CRT implanted, you will attend a Pre-Assessment Clinic to learn more about this therapy and ask any questions you may have. During this visit, you will complete a questionnaire about your heart failure symptoms. You will also be asked to demonstrate how far you can walk, this is called a Six Minute Walk Test. This test involves walking at your normal pace along a 15metre circuit on the flat - you

can stop as many times as you need to. The walking test will last no longer than six minutes. If you would like to take part in this research study, further information can be provided and you will be asked to sign a consent form. Your Pre-Assessment visit may take up to 1 hour and 30minutes.

2. CRT Implantation

   Your CRT will be implanted a few weeks after your Pre-Assessment visit. Once your CRT is implanted, the Physiologists will adjust the settings of the CRT to suit your individual needs using a special computer. The data collected during the personalisation of your CRT will be analysed as part of the research study. This may take up to 20minutes.

3. Device Clinic - 5 month Follow-Up

   Five months after your CRT is implanted, you will attend Device Clinic for a routine follow-up. During this appointment, you will be asked to repeat the questionnaire about your heart failure symptoms and complete another Six Minute Walk Test. This appointment will take up to 45minutes.

Please note that these appointments form part of the routine care pathway and there are no additional hospital visits required for the research study. However, your appointments may take up to ten minutes longer than normal. Data collected at the three appointments will be anonymised to be included in the research study. You will be required to attend Device Clinic more frequently than this as part of your routine care, but only these three appointments form part of the research.

What are the advantages and disadvantages of taking part?
By taking part in this study, it will help us to understand the best ways of programming your CRT. This may directly benefit you in the future. Other than the time you give to participate, there are no specific disadvantages in taking part. As with any of your appointments, should you experience any discomfort, testing can be stopped.

Do I have to take part?
No, it is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. Deciding not to take part or withdrawing from the study will not affect the healthcare that you receive.

Can I withdraw from the study at any time?
You are free to withdraw at any time until commencement of data analysis, without giving a reason and without affecting your ongoing care. Once data analysis has started, your anonymised data cannot be withdrawn. If you wish to withdraw, please contact Lucy Broadhurst on 01709 424794 and quote your unique identification number.

Who is organising and funding this study?
This study is being conducted by Lucy Broadhurst (Cardiac Device Lead at Rotherham NHS Foundation Trust) as part of her doctorate level studies at Manchester Metropolitan University. The study is being supervised by Dr Simon Smith (Consultant Cardiologist at Rotherham NHS Foundation Trust) and Dr Martin Stout (Academic Program Lead DClinSci at Manchester Metropolitan University).

Will the information obtained in the study be confidential?
The Rotherham NHS Foundation Trust is the sponsor of the study. The research is part of an academic study; the academic institute is The Manchester Metropolitan University. We will be using information from your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

We will collect your information from your medical records according with our instructions and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from the trust and regulatory organisations may look at your medical and research records to check the accuracy of the research study. The only people in the trust who will have access to information that identifies you will be people who need to contact you to about the study. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.

All information gathered will be anonymised and you will be given a unique identification number. Your confidentiality will be maintained at all times. The information will be stored securely at Rotherham NHS Foundation Trust and only accessible by the study researchers and supervisor. Following completion of the study all personal data will be destroyed in an appropriate manner. The Rotherham NHS Foundation Trust will keep and store

identifiable information about you for 5 years after the study ends. Data will be archived and securely stored. You can find out more about how we use your information on the trust website.
http://www.therotherhamft.nhs.uk/research/.

What will happen to the results of the study?
The results of the study will be analysed and reported as they may guide future practice. The results of this study will form part of Lucy's doctoral level studies. Results may be presented at conferences and submitted for publication in a peer-reviewed journal. You will be able to request a summary of the study results from Lucy on the contact details below.

Who has reviewed this study?
Ethical approval has been granted by London - Brent Research Ethics Committee REC Ref: 19/LO/0448.

If you are dissatisfied with any aspect of the study please make your concerns known to the Study team at based in the Cardiac Device Suite at Rotherham NHS Foundation Trust, Tel: 01709 424794. If you wish to make a formal complaint, please contact the Patient Experience Team on 01709 424461 or email your.experience@nhs.net

You can also write to: Patient Experience Team, The Oldfield Centre, The Rotherham NHS Foundation Trust, Moorgate Road,
Rotherham, S60 2UD

Contact Details
Lucy Broadhurst (Cardiac Device Lead), Cardiac Device Suite, Level A, Rotherham NHS Foundation Trust, Moorgate Road, Rotherham, South Yorkshire, S60 2UD, Tel: 01709 424794, Email: lucy.broadhurst@nhs.net

Appendix 8 Approval Letters - HRA Approval

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Miss Lucy Broadhurst
Clinical Scientist - Cardiac Device Lead
Rotherham NHS Foundation Trust
Cardiac Device Suite, Level A
Rotherham General Hospital
Moorgate Road, Rotherham
S60 2UD

Email: hra.approval@nhs.net
Research-permissions@wales.nhs.uk

08 April 2019

Dear Miss Broadhurst

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Is individualised CRT programming superior to nominal settings in the optimisation of biventricular pacing with respect to QRS width?**
IRAS project ID:	**260238**
Protocol number:	**1**
REC reference:	**19/LO/0448**
Sponsor	**Rotherham NHS Foundation Trust**

I am pleased to confirm that HRA and Health and Care Research Wales (HCRW) Approval has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report

(including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **260238**. Please quote this on all correspondence.

Yours sincerely,

Natalie Wilson
Approvals Specialist

Email: nrescommittee.london-brent@nhs.net

Copy to: *Ms Ferzanah Salim, Rotherham NHS Foundation Trust, Sponsor contact*

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
IRAS Application Form [IRAS_Form_22022019]		22 February 2019
Other [Data Collection Form]	1	31 January 2019
Other [Cover Letter]		22 March 2019
Other [GCP Training Certificate for CI]	1	28 January 2019
Other [GCP Training Certificate for Researcher]	1	13 February 2019
Other [Short CV for Researcher]	1	05 February 2019
Participant consent form [Patient Consent Form]	3	20 March 2019
Participant consent form [Patient Consent Form]	3	20 March 2019
Participant information sheet (PIS) [Participant Information Sheet]	3	20 March 2019
Participant information sheet (PIS) [Participant Information Sheet]	3	20 March 2019
Referee's report or other scientific critique report [Peer Review Form]		05 February 2019
Research protocol or project proposal [Research Proposal]	1	31 January 2019
Summary CV for Chief Investigator (CI) [Short CV for CI]		31 January 2019
Summary CV for student [Short CV for CI]		31 January 2019
Summary CV for supervisor (student research) [Short CV for Academic Supervisor]		31 January 2019

IRAS project ID	260238

Information to support study set up

The below provides all parties with information to support the arranging and confirming of capacity and capability with participating NHS organisations in England and Wales. This is intended to be an accurate reflection of the study at the time of issue of this letter.

Types of participating NHS organisation	Expectations related to confirmation of capacity and capability	Agreement to be used	Funding arrangements	Oversight expectations	HR Good Practice Resource Pack expectations
Activities and procedures as detailed in the protocol and supporting study documents will take place at participating NHS organisations.	This is a single site study sponsored by the participating NHS organisation. You should work with your sponsor R&D office to make arrangements to set up the study. The sponsor R&D office will confirm to you when the study can start following issue of HRA and HCRW Approval.	As the only participating NHS organisation is also the study sponsor, no study agreements are expected.	No external funding application.	A Principal Investigator (PI) is expected at participating NHS organisations.	This is a single site study sponsored by the participating NHS organisation. You should work with your sponsor R&D office to make arrangements to set up the study. The sponsor R&D office will confirm to you when the study can start following issue of HRA and HCRW Approval. For research team members only administering questionnaires or surveys, a Letter of Access based on standard DBS checks and occupational health clearance would be appropriate.

Other information to aid study set-up and delivery

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales in study set-up.
The applicant has indicated that they do not intend to apply for inclusion on the NIHR CRN Portfolio.

Approval Letters - REC Approval

NHS
Health Research Authority

London - Brent Research Ethics Committee
80 London Road
Skipton House
London
SE1 6LH

Telephone: 0207 104 8241

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

08 April 2019

Miss Lucy Broadhurst
Clinical Scientist - Cardiac Device Lead
Rotherham NHS Foundation Trust
Cardiac Device Suite, Level A
Rotherham General Hospital
Moorgate Road, Rotherham
S60 2UD

Dear Miss Broadhurst

Study title:	**Is individualised CRT programming superior to nominal settings in the optimisation of biventricular pacing with respect to QRS width?**
REC reference:	**19/LO/0448**
Protocol number:	**1**
IRAS project ID:	**260238**

Thank you for your letter of 25 March 2019, responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the sub-committee.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact please contact hra.studyregistration@nhs.net outlining the reasons for your request.

A Research Ethics Committee established by the Health Research Authority

Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA and HCRW Approval (England and Wales)/ NHS permission for research is available in the Integrated Research Application System, at www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe,

they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" above).

Approved Documents

The documents reviewed and approved by the Committee are:

Document	*Version*	*Date*
IRAS Application Form [IRAS_Form_22022019]		22 February 2019
Other [GCP Training Certificate for CI]	1	28 January 2019
Other [GCP Training Certificate for Researcher]	1	13 February 2019
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Summary CV for Chief Investigator (CI) [Short CV for CI]		31 January 2019
Summary CV for student [Short CV for CI]		31 January 2019
Summary CV for supervisor (student research) [Short CV for Academic Supervisor]		31 January 2019

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed

guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance

HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at:
https://www.hra.nhs.uk/planning-and-improving-research/learning/

19/LO/0448	Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely

PP
Dr Manish Saxena
Chair

Email: nrescommittee.london-brent@nhs.net

Copy to: *Ms Ferzanah Salim*

Appendix 9 Consent Form

IRAS Project ID: **260238**

The Rotherham NHS Foundation Trust
Cardiac Device Suite,
Level A
Rotherham Hospital
Moorgate Road
Rotherham
S60 2UD

CONSENT FORM

Optimal CRT Programming Study

Participant Identification Number for this trial:

_____

Please put your initials in the boxes to indicate your agreement with the corresponding statements:

1. I confirm that I have read the Participant Information Sheet (Version 3, Date 20/03/19) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time up to the commencement of data analysis, without giving reasons and without any of my medical care or legal rights being affected ☐

3. I acknowledge that my anonymity will be maintained at all times and all information will be confidential ☐

4. I understand that relevant sections of data collected during the study may be looked at by individuals from regulatory authorities and Rotherham NHS Foundation Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to this data. ☐

5. I accept that the information is only accessible to the study investigators and will be kept securely at Rotherham NHS Foundation Trust for the duration of the study. I understand that all personal information will be destroyed on completion of the study, in a manner to preserve my confidentiality. ☐

6. I agree to take part in this study ☐

Signature of participant: .....Date:.....

Name (Block Letters): .....

Signature of investigator: .....Date:.....

Name (Block Letters):.....

Appendix 10 Participants Comments from the Survey

Question 2 Is QRS narrowing important to you during CRT? Please explain your reasoning

Studies have shown better outcomes in patients with narrowing of the QRS post CRT implant.

We are adopting a new process of device optimisation to specifically target narrowing of QRS and comparing to EF

It is when trying to improve symptoms

Any narrowing of QRS used as indicator potential responder

Electrical therapy as such you should look at electrical parameters for response

Demonstrates good resyncronisation of the ventricles and this better cardiac output for the patient. Eve more beneficial to see R wave in V1 if possible

No point spending time implanting the lead and not getting it to work to its optimal capacity

Optimise response to CRT

Global QRS measurement used, based on

should lead to better response

Some data on reduction in QRS, not conclusive outcome data

An indicator of mitigating the effects of dysynchrony and LBBB

There is evidence that QRS narrowing in multipolar lead improves some end points (6MWT etc)

Displays biventricular synchrony

Indicates reduction in dysynchrony and therefore improved function.

More physiologically normal

Narrower QRS should lead to better LV function

It increases likelihood of response to CRT but should n be looked at in isolation

To try to get the most 'synchronised' pacing

Believed to be associated with improved outcomes.

There is some evidence to show narrowing QRS improves patient outcomes. QRS duration is still one of the only predictors of events in HF patients

05/05/2020, 06:48

QRS narrowing is indicative of electrical resynchronisation. We hope this in turn improves mechanical synchronisation and thus overall heart

05/05/2020, 06:10

No evidence from clinical trial to demonstrate efficacy

05/05/2020, 05:59

Part of our protocol

05/05/2020, 05:54

Question 4 During CRT Implants, do you measure QRS duration (or narrowing)?

If Other, please specify

Some do, some don't. It is not yet embedded into the impllant procedure. We are hoping to work this in in the future.

15/05/2020, 01:27

Depends on the operator. Will always measure if I have time to do a full vector set up

05/05/2020, 08:17

Currently some staff do And some do not, our SOP it changing so all will note it pre and post.

05/05/2020, 07:58

Question 5 During CRT Implants, how do you measure QRS duration?

If Other, please specify

Maclab screen using calipers

05/05/2020, 13:46

Measure global QRS using digital callipers on 7 lead (limb leads + chest lead)

05/05/2020, 06:50

We don't

05/05/2020, 05:59

Question 6 During CRT Follow-Up, what ECG monitoring do you use?

Comments

Programmer and limb leads plus 1 chest lead.

15/05/2020, 01:27

Normally programmer ECG however if troubleshooting 12 Lead ECG as well

14/05/2020, 07:03

Programmer for routine CRT FU and all is well, 12 lead ECG aswell if the patient is scored unchanged or worse on clinical composite score

05/05/2020, 08:48

Programmer ECG first, if broad then 12 lead to optimise

06/05/2020, 08:36

Depends on if optimisation is required. Programmer ECG and 12 lead of optimising

05/05/2020, 07:54

Programmer ECG including chest lead. 12 lead if uncertain of function, fusion etc.

05/05/2020, 06:50

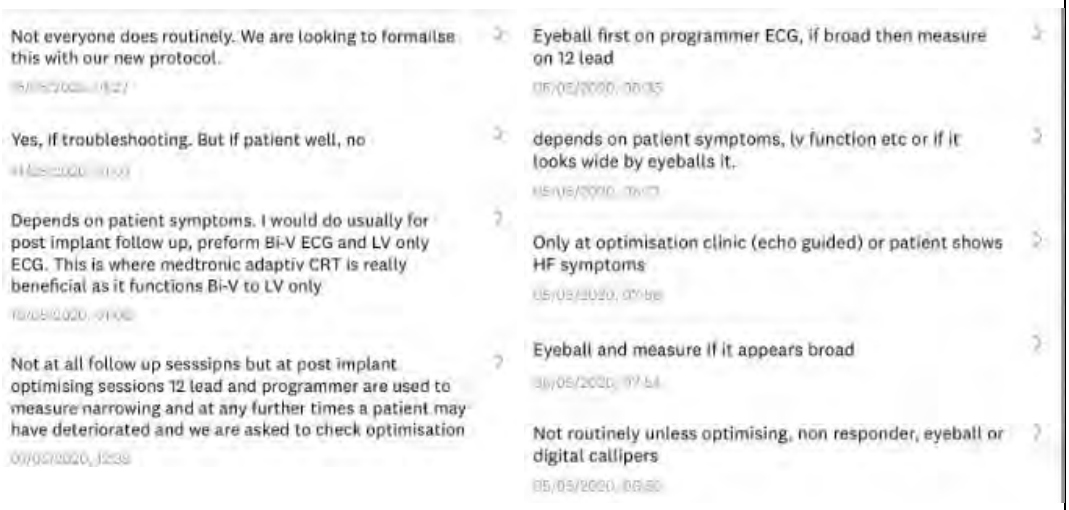
Programmer ECG. Would use 12 lead if I was optimising programming.

05/05/2020, 06:10

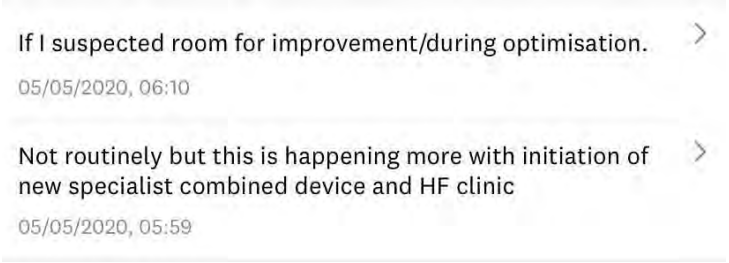
Programmer ECG but moving towards including more 12 lead

05/05/2020, 05:59

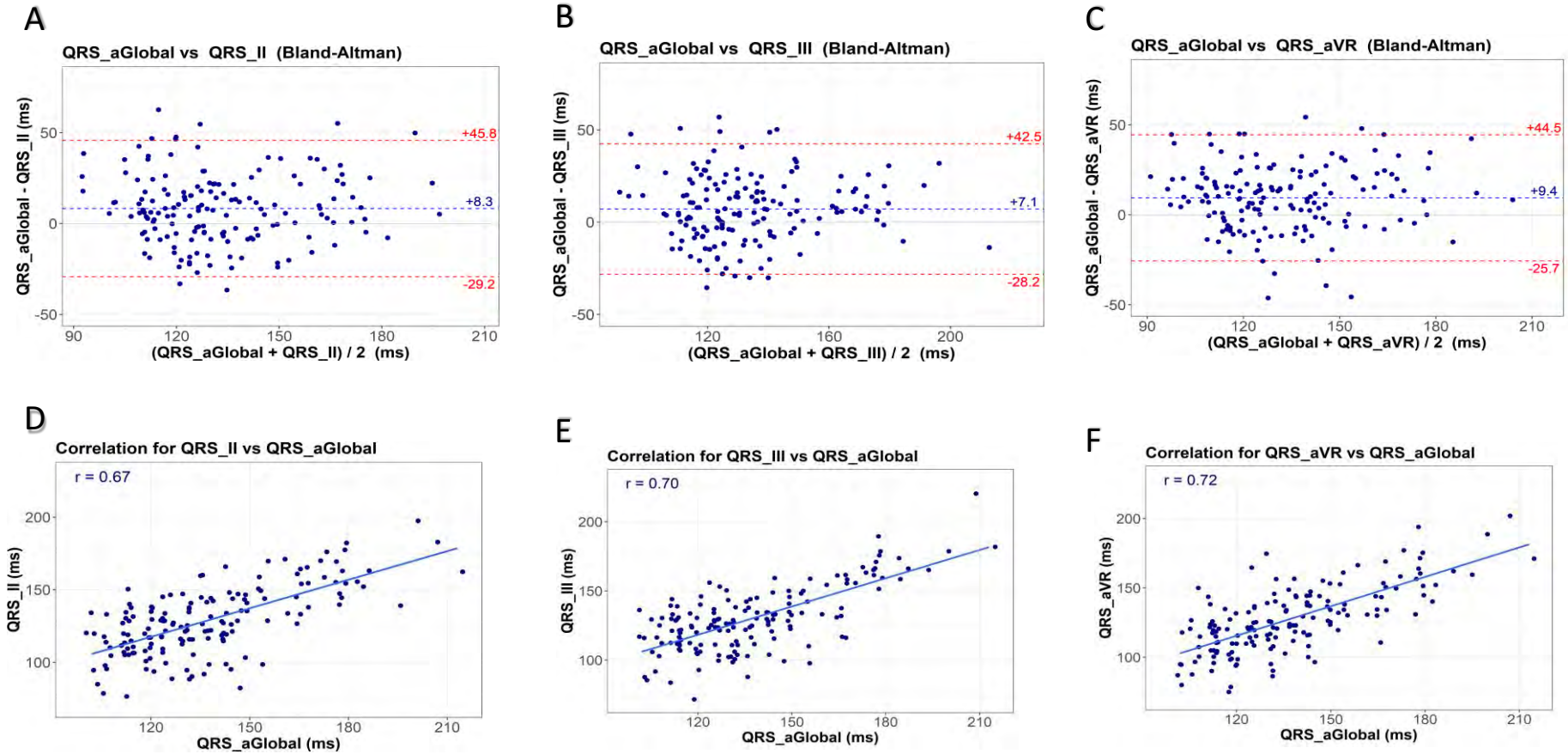
Question 7 During CRT Follow-Up, do you measure QRS Duration (or narrowing)? If Other, please specify



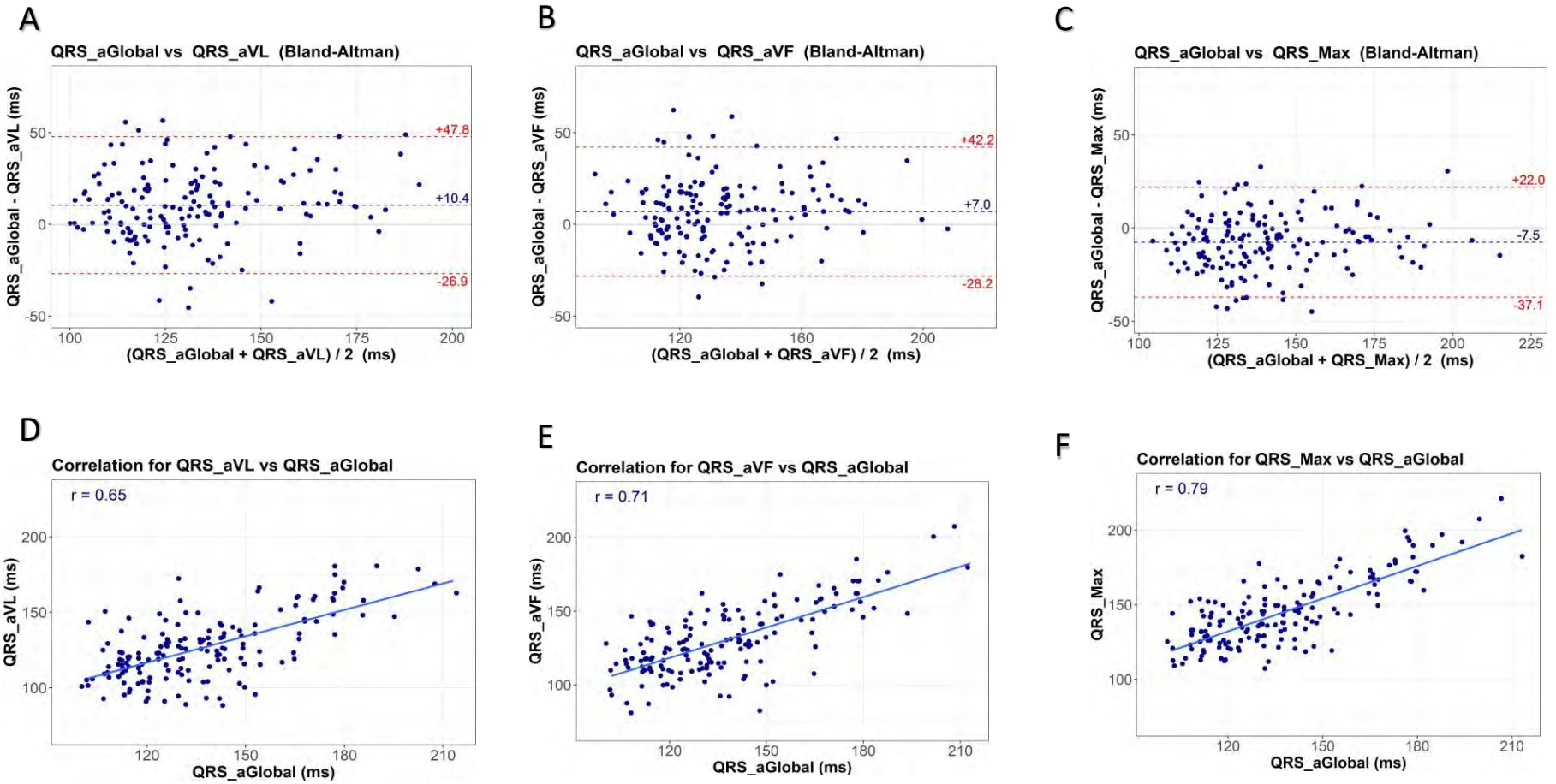
Question 8 During CRT Follow-Up, how do you measure QRS Duration?
If Other, please specify



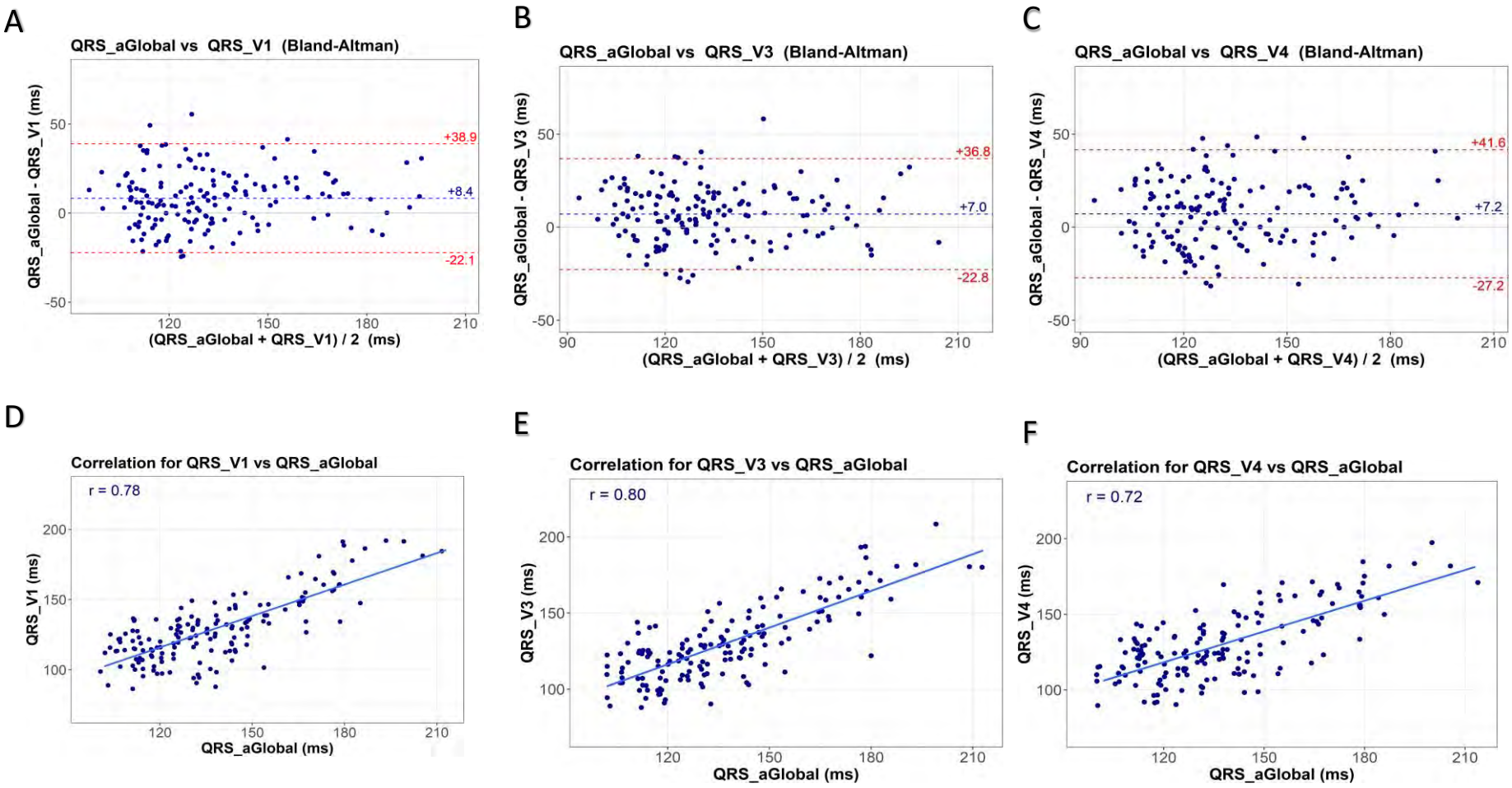
Appendix 11 Bland Altman Analysis for paired comparisons



Comparison of methodologies for measuring QRS duration. (A) to (C) are Bland-Altman plots comparing QRS duration (ms) from the individual lead named in the title to abbreviated global QRS (QRS_aGlobal). Horizontal lines indicate mean difference (blue) and upper/lower 95% limits of agreement (red). (D) to (F) show correlation for the same variables. "r" is the Pearson correlation coefficient. Slight random jitter has been applied to the point positions to minimise overlap.

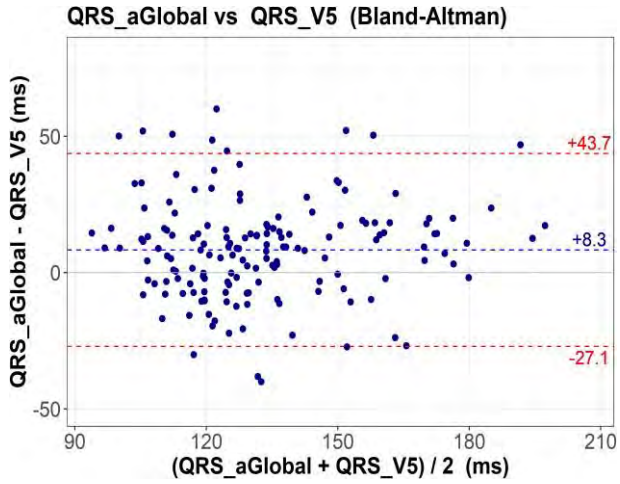


Comparison of methodologies for measuring QRS duration. (A) to (C) are Bland-Altman plots comparing QRS duration (ms) from the ECG lead named in the title to abbreviated global QRS (QRS_aGlobal). Horizontal lines indicate mean difference (blue) and upper/lower 95% limits of agreement (red). (D) to (F) show correlation for the same variables. “r” is the Pearson correlation coefficient. Slight random jitter has been applied to the point positions to minimise overlap.

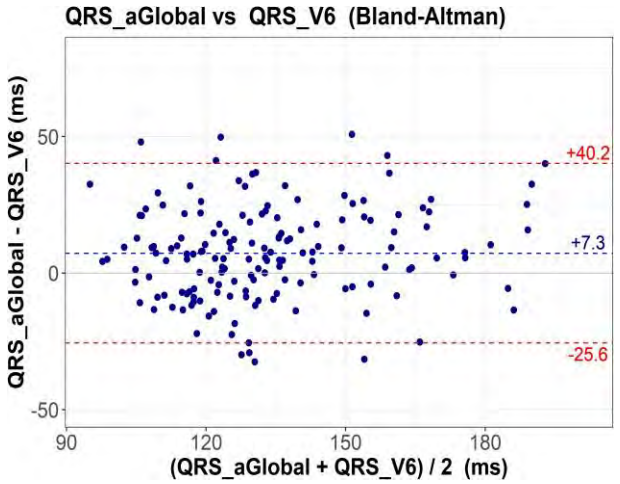


Comparison of methodologies for measuring QRS duration. (A) to (C) are Bland-Altman plots comparing QRS duration (ms) from the individual lead named in the title to abbreviated global QRS (QRS_aGlobal). Horizontal lines indicate mean difference (blue) and upper/lower 95% limits of agreement (red). (D) to (F) show correlation for the same variables. “r” is the Pearson correlation coefficient. Slight random jitter has been applied to the point positions to minimise overlap.

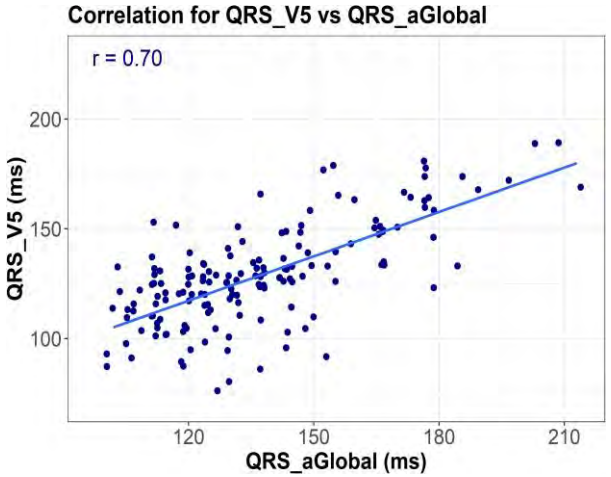
A



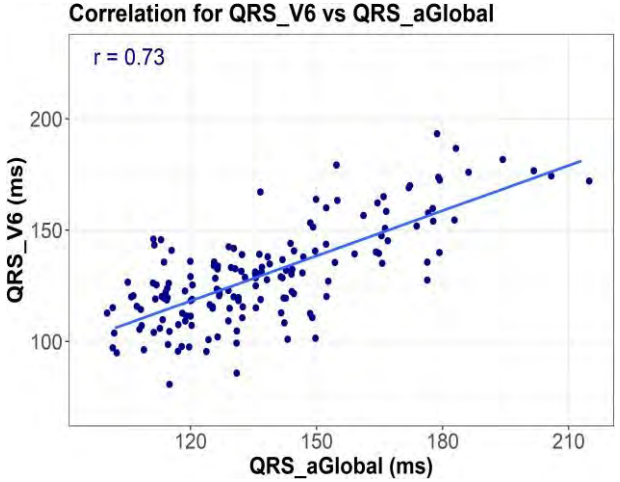
B



C



D



Comparison of methodologies for measuring QRS duration. (A) and (B) are Bland-Altman plots comparing QRS duration (ms) from the individual lead named in the title to abbreviated global QRS (QRS_aGlobal). Horizontal lines indicate mean difference (blue) and upper/lower 95% limits of agreement (red). (C) and (D) show correlation for the same variables. "r" is the Pearson correlation coefficient. Slight random jitter has been applied to the point positions to minimise overlap.

Appendix 12 Normal Distribution Analysis: CRT Programming Modes (Figure 6.1)

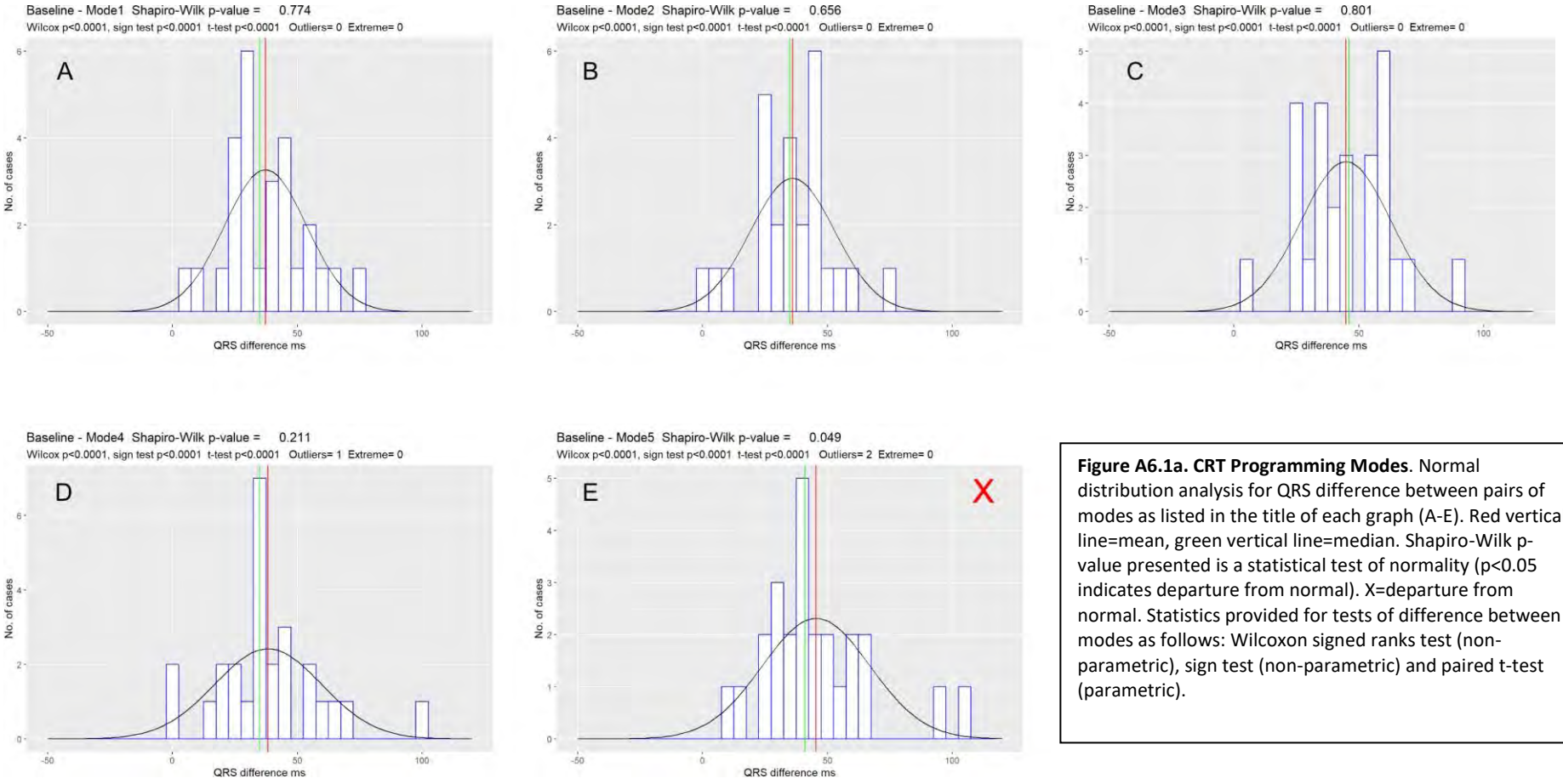


Figure A6.1a. CRT Programming Modes. Normal distribution analysis for QRS difference between pairs of modes as listed in the title of each graph (A-E). Red vertical line=mean, green vertical line=median. Shapiro-Wilk p-value presented is a statistical test of normality ($p<0.05$ indicates departure from normal). X=departure from normal. Statistics provided for tests of difference between modes as follows: Wilcoxon signed ranks test (non-parametric), sign test (non-parametric) and paired t-test (parametric).

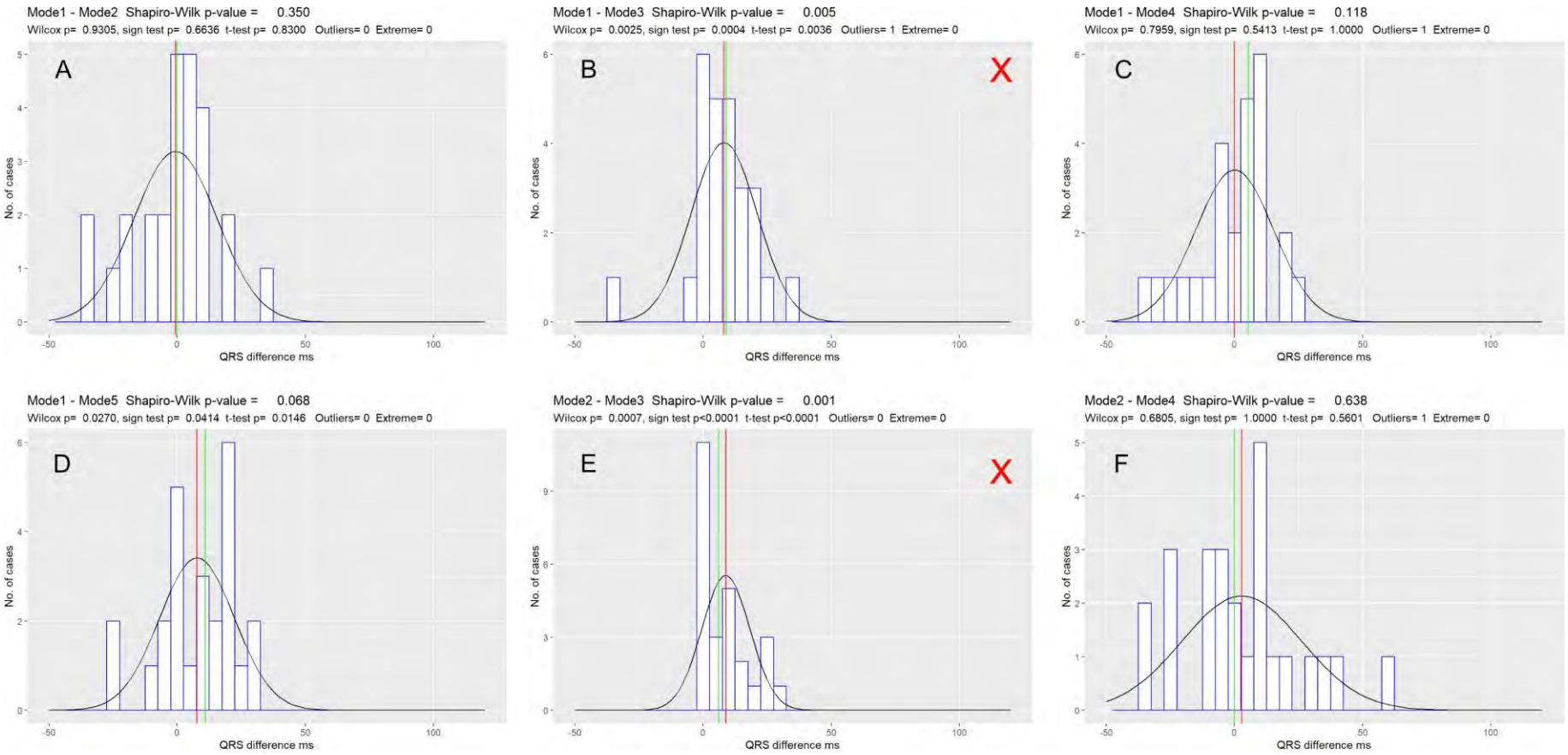


Figure 6.1b CRT Programming Modes. Normal distribution analysis for each paired mode as listed in the title of each graph (A-F). Red vertical line=mean, green vertical line=median. Shapiro-Wilk p-value presented is a statistical test of normality (p<0.05 indicates departure from normal). X=departure from normal. Statistics provided for tests of difference between modes as follows: Wilcoxon signed ranks test (non-parametric), sign test (non-parametric), and paired t –test (parametric).

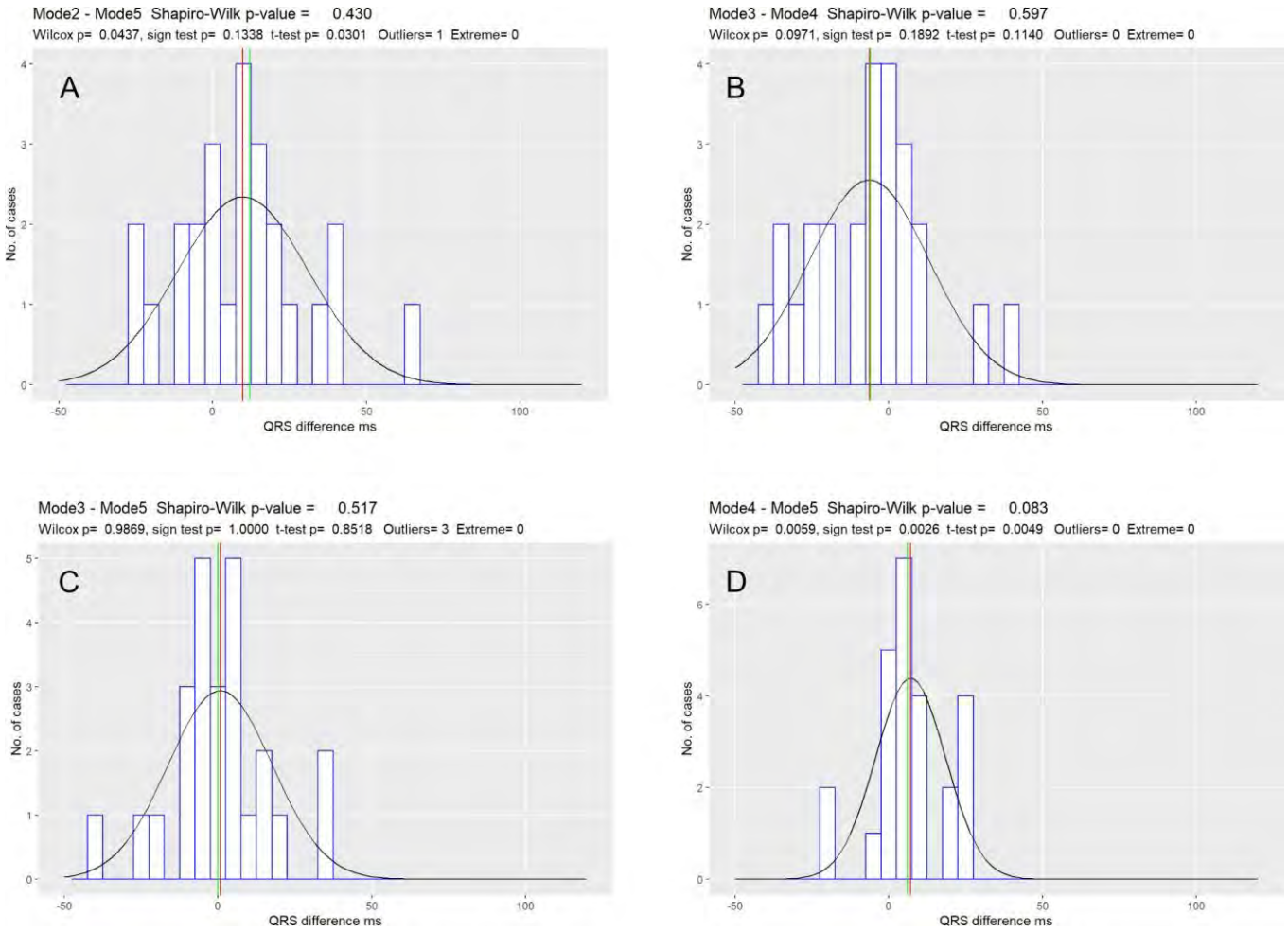


Figure 6.1c. Normal distribution analysis for CRT Programming Modes. Normal distribution analysis for each paired mode as listed in the title of each graph (A-D). Red vertical line=mean, Green vertical line=median. Shapiro-Wilk p-value presented is a statistical test of normality ($p<0.05$ indicates departure from normal). X=departure from normal. Statistics provided for tests of difference between modes as follows: Wilcoxon signed ranks test (non-parametric), sign test (non-parametric), and paired t-test (parametric).

Normal Distribution Analysis: Comparison of ECG Methodologies (Figure 6.2)

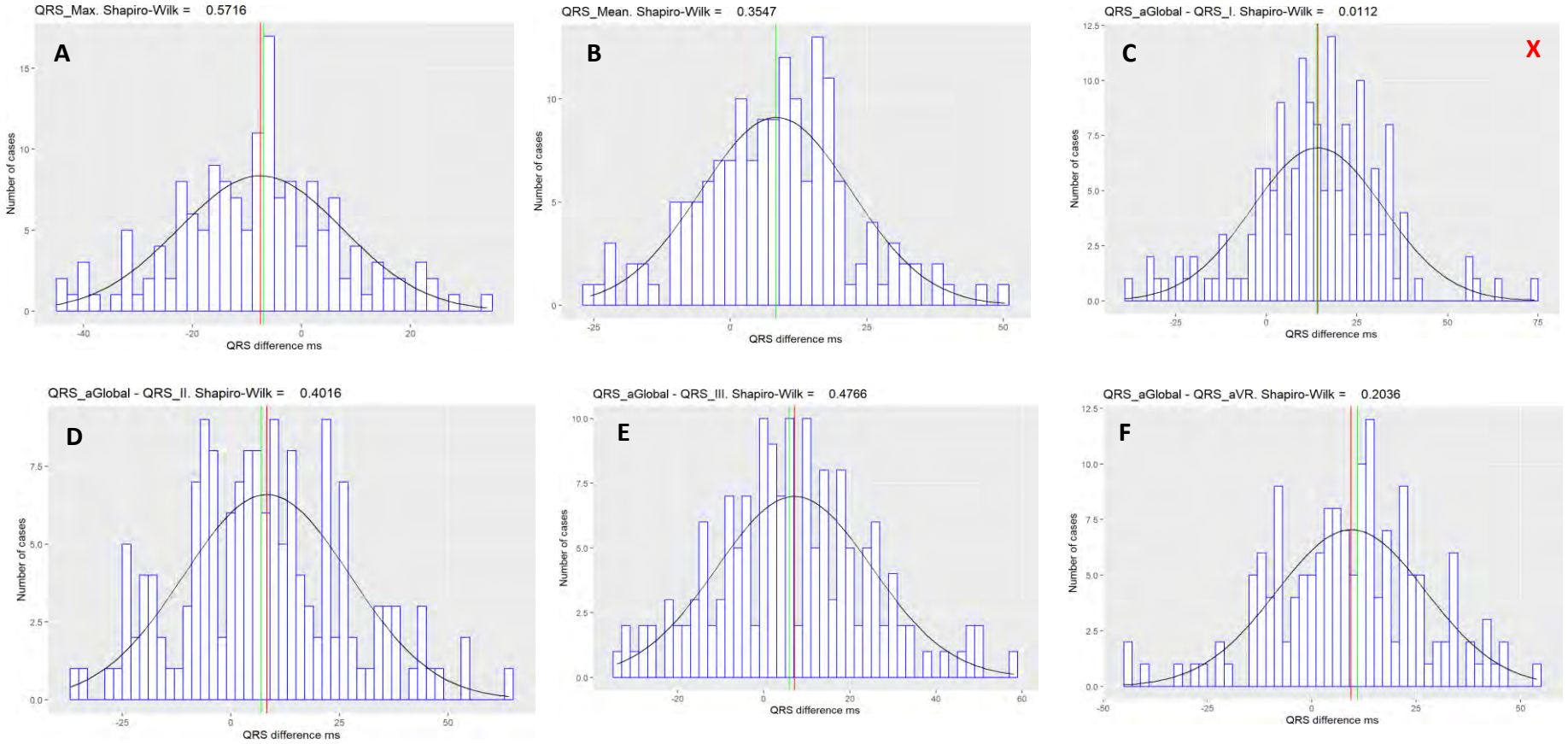


Figure 6.2a. Normal distribution analysis for comparison of QRS methodologies. Comparison of abbreviated global QRS and individual lead as listed in the title of each graph (A-F). Red vertical line=mean, Green vertical line=median, Shapiro-Wilk indicates p for Shapiro-Wilk normality test (p<0.05 indicates departure from normal). X=departure from normality.

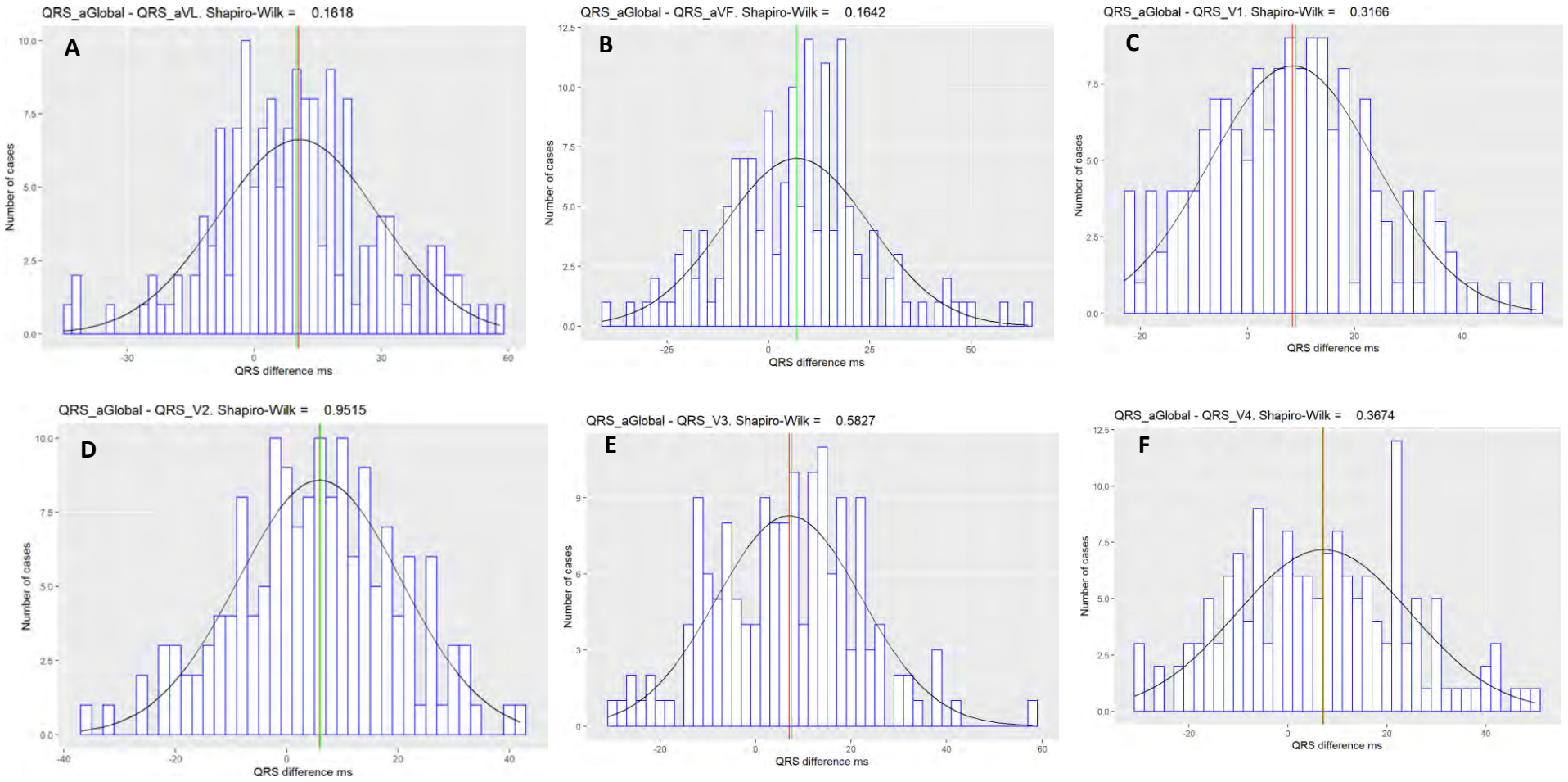


Figure 6.2b. Normal distribution analysis for comparison of QRS methodologies. Comparison of abbreviated global QRS and individual lead as listed in the title of each graph (A-F). Red vertical line=mean, Green vertical line=median, Shapiro-Wilk indicates p for Shapiro-Wilk normality test (p<0.05 indicates departure from normal). X=departure from normality.

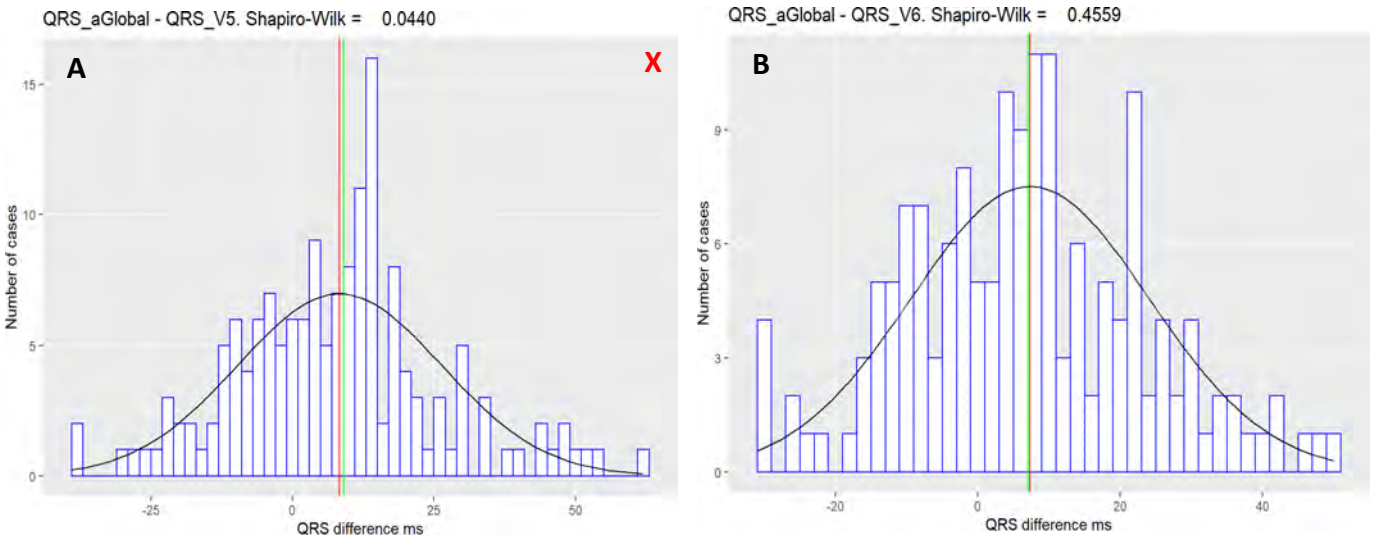


Figure 6.2c. Normal distribution analysis for comparison of QRS methodologies. Comparison of abbreviated global QRS and individual lead as listed in the title of each graph (A-B). Red vertical line=mean, Green vertical line=median, Shapiro-Wilk indicates p for Shapiro-Wilk normality test (p<0.05 indicates departure from normal). X=departure from normality.

Appendix 13 Inter-operator and Intra-operator Variability

Methodology as described by Popovic and Thomas (2017).
Source data is shown in the table below, where:

> "treatments" t1,t2 correspond to observer 1,2
> "repeats" r1,r2,r3,r4,r5 correspond to the 5 repeat measurements for each case by each observer

QRS measurements (ms) Per operator (t1,t2) and repeat measurrment (r1, etc)									
t1 (r1)	t2 (r1)	t1 (r2)	t2 (r2)	t1 (r3)	t2 (r3)	t1 (r4)	t2 (r4)	t1 (r5)	t2 (r5)
148	160	154	160	154	160	154	160	148	160
154	160	166	154	154	160	154	154	166	154
154	154	154	160	148	160	148	160	148	160
207	207	201	213	213	207	207	207	207	207
201	213	189	207	195	207	189	213	201	213
201	207	195	207	195	207	195	207	201	201
148	152	135	158	141	146	141	146	141	146
146	158	146	164	146	158	146	158	146	158
152	164	158	176	158	187	158	176	158	176
125	123	117	129	117	123	117	129	117	129
117	129	111	123	123	129	117	123	111	123
117	123	117	123	117	123	117	123	125	123
154	146	166	176	166	176	164	152	164	158
137	117	135	129	141	129	135	141	141	135
164	164	164	176	164	164	164	170	164	170

Software used: StatsDirect (v3.3.4):
Method: Replicate 2-way analysis of variance

Raw output from Statsdirect (additional red text links nomenclature in Povic paper to Statsdirect terminology)

Two way randomized block analysis of variance with repeated observations

Variables: (t1 (r1), t2 (r1)) (t1 (r2), t2 (r2)) (t1 (r3), t2 (r3)) (t1 (r4), t2 (r4)) (t1 (r5), t2 (r5))

Source of Variation	Sum Squares	Mean Square
Blocks (rows)	113,414.36	8,101.025714
Treatments (columns)	1,607.206667	1,607.206667 MSObserver (Popovic)
Interaction	1,707.293333	121.949524 MSOxS (Popovic)
Residual (error)	2,821.6	23.513333 MSE (Popovic)
Corrected total	119,550.46	

Note:
n = number of cases = 15
m = number of repeats = 5

Calculation of appropriate variances per Popovic table S7

[i] Repeatability (intra-observer repeatability) = MSE = 23.51

[ii] Reproducibility (observer variability) = (MSObserver - MSOxS)/(n * m) = 19.803

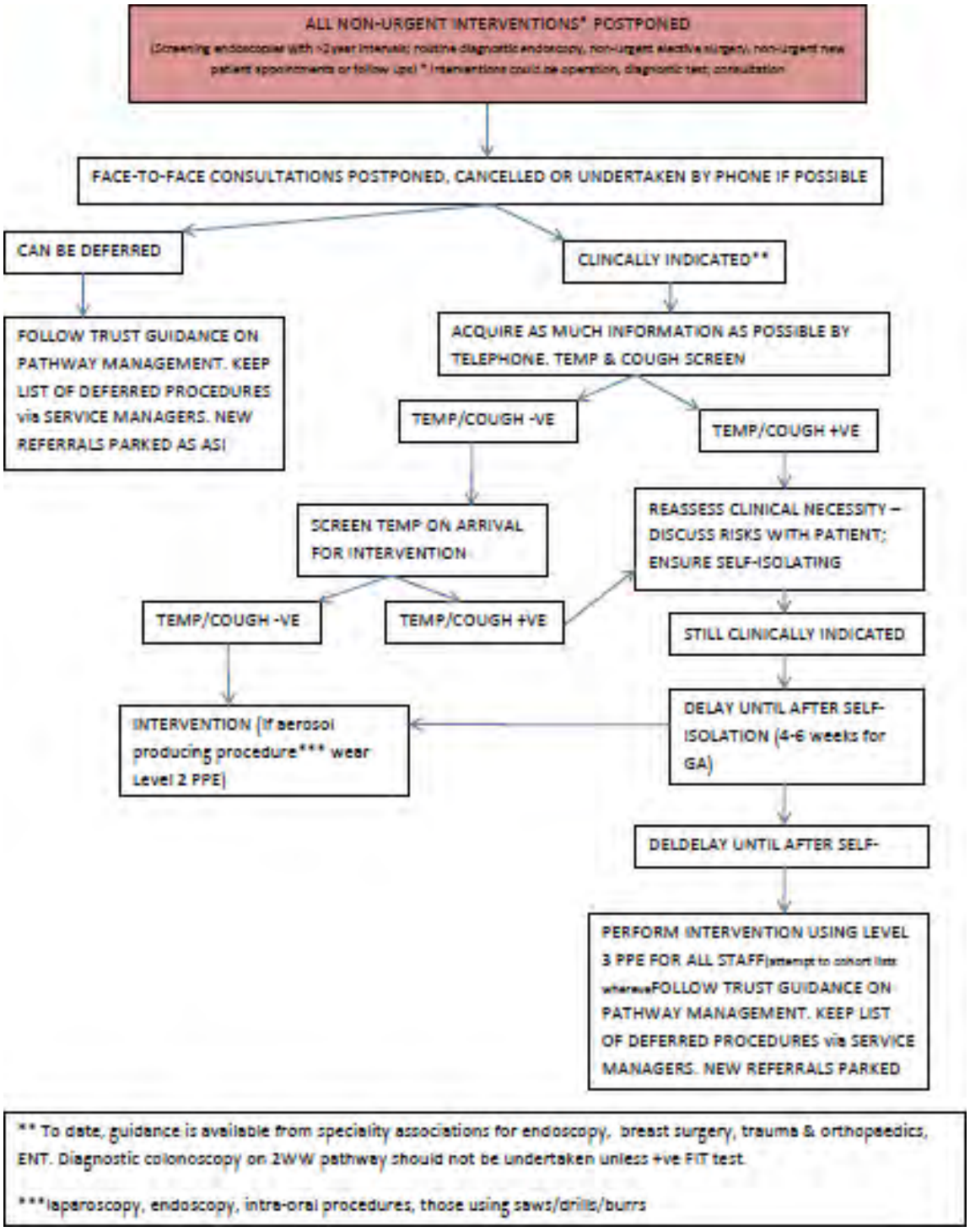
[iii] Interaction = (MSOxS - MSE)/m = 19.687

Total R&R interobserver variability = [i] + [ii] + [iii] = 63.003

Final standard error of measurement per Popovic table S8

SEM Intra = sqrt(i) = 4.849
SEM inter, fixed effects = sqrt (i + iii) = 6.572
SEM inter, random effects = sqrt(i + ii + iii) = 7.937

Appendix 14 Study Centre Flowchart for Postponement of appointments during COVID-19 (received in April 2020)



Appendix 15 Poster Accepted at Heart Rhythm Congress 2020 'Measuring the QRS – How hard can it be?'

IRAS Project ID: 260238 ORCHID ID: 0000-0002-0336-7612

The Rotherham NHS Foundation Trust

Measuring the QRS – How hard can it be? A Method Comparison Study

L Broadhurst, Dr S Smith, Dr M Smith
Cardiac Physiology Service, Rotherham NHS Foundation Trust

Introduction

Accurate measurement of QRS duration is crucial for electrical optimisation of CRT. Despite this, there is no agreed technique to measure QRS duration and different methods are used in clinical practice. Global QRS duration has been shown to have improved accuracy over individual lead measurement[1]. However, global QRS duration over 12 leads is less easily measured without specialist software, hence it is not routinely used in practice. This study compared whether an abbreviated global QRS measurement over 5 leads on the device programmer was comparable to individual lead measurements on 12 lead ECG.

Method

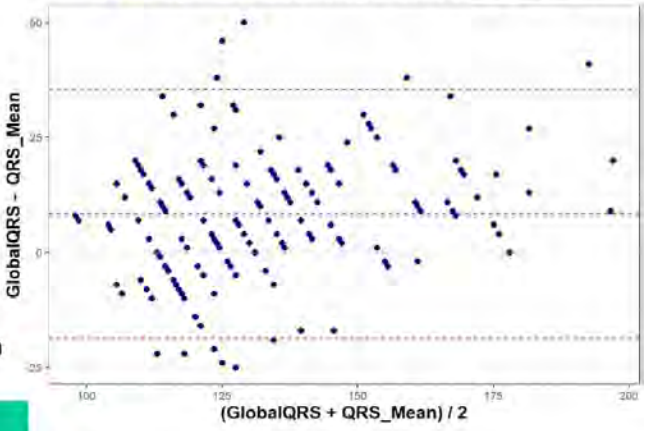
Comparison of ECG data for patients undergoing CRT implantation. Individual lead QRS duration from the 12 Lead ECG was compared to abbreviated global QRS duration measured on the Abbott programmer. Abbreviated global QRS duration was measured using digital calipers in **leads I, II, III, aVF and V5** '***from the earliest onset to the latest offset of the waveform in all leads***'. Individual lead QRS duration in all 12 ECG leads was measured using digital calipers via the Phillips haemodynamic system, together with the maximum (QRS _Max) and Mean (QRS_Mean) of the individual leads. 50mm/sec sweep speed and optimised gain was used to improve measurement accuracy. Each measurement technique was applied by a blinded operator and verified by a third independent operator. Bland Altman analysis was used for comparison.

References

1.De Pooter J, El Haddad M, Timmers L, Van Heuverswyn F, Jordaens L, Duytschaever M, Stroobandt R (2016). Different Methods to Measure QRS Duration in CRT Patients: Impact on the Predictive Value of QRS Duration Parameters. **Ann Noninvasive Electrocardiol** 2016; 21 (3):305-315

Results

Figure 1 Bland Altman Analysis of Global QRS vs QRS_Mean



158 sets of ECG data were compared. Importantly, there was considerable variation in QRS duration between the individual leads on the 12 Lead ECG, likely due to isoelectric segments specific to ECG vector. Compared to GlobalQRS, QRS_Mean averaged 8.4ms shorter with 95% confidence interval for the observed differences ± 21.7ms (**Figure 1**). Greater levels of variation were observed between GlobalQRS and individual lead measurements, e.g. GlobalQRS vs Lead I showed an average difference of 14.2ms with 95% confidence interval ±35.6ms.

Discussion

This study found substantial variation between different methods of assessing the QRS duration. We recommend further research and development of practical guidelines to standardise clinical practice. Where single lead measurement is used, the target ECG lead should be specified to avoid inaccuracies that may affect device programming. We also recommend consistency of measurement technique between implantation and follow-up. The device programmer is commonly used in both settings and could be used to measure abbreviated global QRS duration to standardise measurement throughout the patient's journey.

Appendix 16 Poster Accepted at Heart Rhythm Congress 2020

‘A Survey of current CRT Practice in Uk & Ireland’

IRAS Project ID: 260238 ORCHID ID: 0000-0002-0336-7612

The Rotherham NHS Foundation Trust

A Survey of Current CRT Practice within the UK & Ireland

L Broadhurst
Cardiac Physiology Service, Rotherham NHS Foundation Trust

Introduction

Methods for optimising CRT vary in clinical practice. Electrical optimisation of CRT is becoming more popular with QRS narrowing and favourable ECG characteristics emerging as markers of success[1]. The aim of this survey was to gauge current working practices of CRT within the UK and Ireland, with particular emphasis on the ECG.

Method

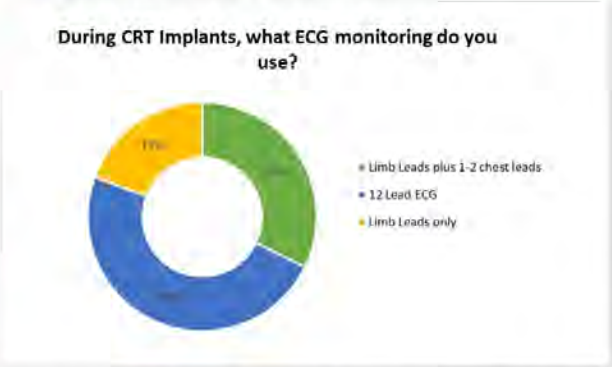
Voluntary completion of a short online questionnaire (8 questions) via Survey Monkey. This was circulated widely on two key social media platforms (Facebook & Twitter) and aimed at Cardiac Physiologists & Cardiology Clinicians. The survey remained open between 28/04/2020 and 15/05/2020.

Results

There were 31 responses representing 20 CRT centres within the UK and Ireland with wide geographical spread. 97% agreed that QRS narrowing was important in CRT. 84% measured QRS duration on implant, but only 55% measured QRS duration routinely at follow up.

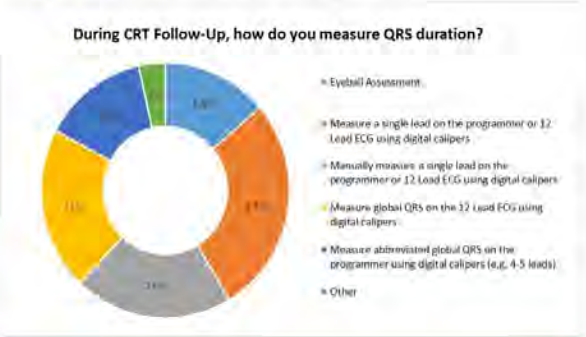
The type of ECG monitoring during CRT Implant varied between centres; 49% used 12 Lead ECG; 32% used limbs leads plus 1-2 chest leads and 19% used limb leads only (**Figure 1**). There was also variation in the type of ECG monitoring during CRT follow-up; 42% routinely used programmer ECG plus 12 Lead ECG; 16% used 12 Lead ECG only; 16% used programmer ECG only; 26% used programmer ECG with the addition of 12 Lead ECG on an individual basis.

Figure 1 ECG monitoring during CRT Implants



Measurement technique for QRS duration varied on implant; 35% measured a single ECG lead using digital calipers; 10% manually measured a single ECG lead; 35% measured global QRS on the 12 Lead ECG using digital calipers; 13% measured abbreviated global QRS on the programmer using digital calipers (e.g 4-5 leads); 3% used eyeball assessment and 3% did not measure QRS duration. Similar variation in the measurement of QRS duration was noted during follow-up (**Figure 2**).

Figure 2 Measurement of QRS during Follow-Up



Discussion

The results highlight wide variation in practice across the UK and Ireland. The optimal electrical characteristics of CRT are best assessed using 12 Lead ECG but this is not universally accepted in clinical practice. QRS duration is considered important during CRT, but there is inconsistency in both the type of ECG monitoring and the methods used to assess QRS narrowing in both implant and follow-up. Studies have shown that QRS duration can vary depending on the measurement technique, with global QRS considered superior to single lead measurement. CRT Optimisation clinics are growing in popularity and it may be beneficial to standardise the type of ECG assessment and also the measurement of QRS duration to ensure quality and consistency.

References

1. Sweeney MO, Hellcamp AS, van Bommel RJ, Schalij MJ, Borleffs CJW, Bax JJ (2014). QRS Fusion complex analysis using wave interference to predict reverse remodelling during cardiac resynchronisation therapy. **Heart Rhythm** 2014;11:806-816