"Cardiac Resynchronisation Therapy": Does the Haemodynamic Improvement of Biventricular Pacing Truly Arise from Cardiac Resynchronisation?

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Declaration of Originality

I declare that the work presented in this thesis is my own.

Dr S M Afzal Sohaib

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Dedication

I dedicate this thesis to my wife Uzma for her constant support and patience, our daughter Anya who blessed us with her arrival during this PhD, and to my parents, Mohammad Sohaib and Warsa Sohaib, and siblings, Aslam and Aram, who have supported and mentored me throughout my career.

Abstract

In this thesis I have explored some of the fundamental concepts which underpin biventricular pacing (commonly called cardiac resynchronisation therapy, CRT). As a therapy, its impact on survival, and symptoms is impressive. By adopting the name cardiac resynchronisation therapy, a common assumption is that these benefits come from ensuring resynchronisation of the ventricles in the failing heart. In this thesis I explore how biventricular pacing delivers its benefit, and whether there are other dimensions beyond resynchronisation which deserve more attention.

I first performed a meta-analysis to quantify what the actual symptomatic benefit from biventricular pacing is in the randomised controlled trials. A non-response rate of one-third is often quoted to biventricular pacing, but my analysis demonstrated that once the effect seen in the control arms is deducted the incremental symptomatic response rate is closer to 15%.

I explored more acute markers of response, and how they are used for optimisation of biventricular pacing. I composed a review of different technologies available for optimisation, and a developed a step wise approach to develop the ideal optimisation scheme. Left ventricular outflow tract (LVOT) Doppler is one commonly used measure for optimisation, and my analysis concluded that a much larger number of beats is required for precise optimisation., I evaluated a novel method to acquire and trace around large numbers of LVOT Doppler velocities, and assessed whether breath holding is required. I discovered that breath holding did not have a significant impact on the magnitude or variability of measurements, and quiet breathing may be the easier way to acquire a larger number of beats for precise measurements.

An algorithm using multiple alternations of systolic blood pressure between reference and tested pacing setting has been developed by my supervisors for reproducible AV optimisation, I used this technology to explore current techniques, and explore concepts in biventricular pacing: I evaluate the different methods for manufacturer specific electrogram-based AV optimisation. I found that agreement between the different methods is poor, and none agree with the haemodynamic optimum. I explored the apparent discrepancy studies have reported on the effect of VV optimisation. By performing VV optimisation by using four different methods for holding the AV delay constant (A-LV constant, A-RV constant, time to first ventricular lead constant, and time to second ventricular lead constant), I discovered that the acute haemodynamic effect was predominantly determined by the time

to the first paced ventricle. To explore the influence of pure AV optimisation in heart failure I examined a group of patients with PR prolongation and demonstrated a significant improvement in acute haemodynamic response with AV optimised pacing of the His bundle. Temporary pacing of the His allows us to maintain the same, narrow QRS morphology and thus examine the pure effect of AV optimisation, an mean increment of 4 mmHg in systolic pressure is seen, approximately 60% of that seen in heart failure with LBBB. This also demonstrates the pure effect of AV shortening without an associated adverse haemodynamic effect of right ventricular pacing. I explored the role of lead position and whether the AV optimum varies between different LV lead positions. The AV optimum, did not significantly differ, suggesting high precision measurements at one AV delay could be used to determine the best lead position which in my study was occasionally in a position which would usually be considered non-conventional (anterior basal wall).

I finally explored the role of biventricular pacing in non-LBBB morphologies looking at outcome studies. My analysis showed that biventricular pacing has a harmful effect in narrow QRS and the effect increases with the duration of time, indicating that this is due to a physiologically adverse effect of pacing. As this is the case, one can make a case for switching off biventricular pacing in such patients.

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List of Publications

The following peer reviewed publications were all generated as a result of the

research performed during this PhD:

Sohaib SMA et al. AV-optimised direct His bundle pacing improves acute hemodynamic function in patients with heart failure and PR prolongation without LBBB. J Am Coll Cardiol EP 2015;1:582–91

Dehbi HM, Jones S, Sohaib SM, Finegold JA, Siggers JH, Stegemann B, Whinnett ZI, Francis DP. A novel curve fitting method for AV optimisation of biventricular pacemakers. Physiol Meas. 2015 Sep;36(9):1889-900.

Sohaib SMA, Kyriacou A, Jones S, Manisty CH, Mayet J, Kanagaratnam P, Peters NS, Hughes AD, Whinnett ZI, Francis DP. Evidence that conflict regarding size of haemodynamic response to VV delay optimisation of CRT may arise from differences in how AV delay is kept constant. Europace. 2015;17(12):1823-33.

Sohaib SMA, Finegold JA, Nijjer SS, Hossain R, Linde C, Levy WC, Sutton R, Kanagaratnam P, Francis DP, Whinnett ZI. Opportunity to increase lifespan in narrow QRS Cardiac Resynchronization Therapy recipients by deactivating ventricular pacing: Evidence from randomized controlled trials. JACC: Heart Failure. 2015;3(4):327-36.

Finegold J, Bordachar P, Kyriacou A, Sohaib SM, Kanagaratnam P, Ploux S, Lim B, Peters N, Davies W, Ritter P, Francis DP, Whinnett ZI. Atrioventricular delay optimization of cardiac resynchronisation therapy: comparison of non-invasive blood pressure with invasive haemodynamic measures. Int J Cardiol. 2015;180:221-2.

Jabbour RJ, Shun-Shin MJ, Finegold JA, Sohaib SM, Cook C, Nijjer SS, Whinnett ZI, Manisty CH, Brugada J, Francis DP. Effect of study design on the reported effect of cardiac resynchronization therapy (CRT) on quantitative physiological measures: stratified meta-analysis in narrow-QRS heart failure and implications for planning future studies. J Am Heart Assoc. 2015;4(1):e000896

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Zolgharni M, Dhutia NM, Cole GD, Jones S, Sohaib SMA, Tai SB, Willson K, Francis DP. Automated Doppler Flow Tracing for Reproducible Research and Clinical Measurements. IEEE Transactions on Medical Imaging. 2014;33(5):1071-82

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Sohaib SMA, Chen Z, Whinnett ZI, Bouri S, Dickstein K, Linde C, Hayes DL, Manisty CH, Francis DP. Meta-analysis of symptomatic response attributable to the pacing component of Cardiac Resynchronization Therapy. Eur J Heart Fail. 2013;15(12):1419-28.

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1 Introduction

Since the initial case report in 1994, over 20 years ago, the treatment of heart failure has been revolutionised by the advent of biventricular pacemakers (Cazeau et al. 1994). Randomised controlled trials have since demonstrated that it improves symptoms, and prolongs life in certain patients with heart failure (Cleland et al. 2005). However, despite the passing of over 20 years, there are many elements of this treatment which continue to confuse us:

1. Whether an individual responds to biventricular pacing or not appears to drive much research and perplex clinicians in this field, particularly to predict which patients will respond, or managing those who appear not to respond after implant (Mullens et al. 2009).

2. The COMPANION (Bristow et al. 2004) and CARE-HF (Cleland et al. 2005) trials, the first to show a mortality benefit from biventricular pacing, both used protocols for AV optimisation. Small studies in the era prior to biventricular pacing indeed showed a benefit from AV optimized right ventricular pacing in heart failure (Brecker et al. 1992). However, there remains much confusion about how best to perform AV optimization. Randomized controlled trials have often failed to demonstrate a benefit from AV optimisation (Ellenbogen et al. 2010; Auger et al. 2013). The reproducibility of common echocardiography based methods is questionable (Jones et al. 2014; Raphael et al. 2013).

3. If the primary mechanism for benefit from biventricular pacing comes from resynchronising the ventricles we would expect a big effect from adjusting the timing of contraction between the right and left ventricle (VV optimisation). However, there

appears to be conflict surrounding the effect size of this. Some studies appear to show an important benefit (Bogaard et al. 2010; León et al. 2005), whereas meta-analysis data appears to show no long term benefit from VV optimisation (Auger et al. 2013).

4. There are differing reports on how best to place the left ventricular lead. Some studies suggest that the lateral wall is not always the best place (Derval et al. 2010; Spragg et al. 2010). If this is really the case, how do we reliably decide where to place the left ventricular lead?

5. It is not clear how beneficial, if at all, CRT is in non-LBBB morphologies. Despite previous encouraging studies to suggest biventricular pacing may benefit patients with narrow QRS and imaging evidence of mechanical dyssynchrony, it has become apparent that as more rigorous approaches to study design were applied, this benefit disappeared (Nijjer et al. 2012; Jabbour et al. 2015). While LBBB appears to confer a greater benefit over non-LBBB morphologies (Wokhlu et al. 2009), whether there is any benefit compared to controls in non-LBBB QRS widening is not entirely certain. One large meta-analysis suggests a benefit with very wide QRS regardless of morphology (Cleland et al. 2013). In the MADIT-CRT, however, a trend towards harm is seen in non-LBBB (Zareba et al. 2011).

6. In clinical practice, almost 20% of patients with biventricular patients have atrial fibrillation (Bogale et al. 2012), but only a relatively small number of patients with AF have been included in the large randomised trials assessing the effect of biventricular pacing, and the evidence of its benefit in this group is much more limited than in sinus rhythm (Leclercq et al. 2002; Tang et al. 2010). For this reason, this thesis predominantly focuses on patients in sinus rhythm.

In patients with atrial fibrillation the main benefit would potentially only be through delivery of be resynchronisation of the ventricles as the benefits of AV synchrony would be absent, so this may be an interesting group of patients to study.

With the extensive body of research work which has already been done on biventricular pacing, many of the answers may lie within the literature already, but some require more careful exploration with well designed experiments. A clearer understanding of the physiological mechanisms which underpin the benefits of biventricular pacing should help to resolve some of these questions.

This thesis aims to explore more closely how biventricular pacing delivers its physiological benefit. In particular I explore how much of the benefit comes from optimising the timing of atrial contraction and ventricular contraction, how much comes from restoring ventricular synchrony.

1.1 Challenges of quantifying response and optimisation.

There are two benefits to any medical intervention which matter to patients. The first is whether they have any impact on survival, the second is whether they make the patient feel better, i.e. give a beneficial symptomatic response. Quantifying survival reliably can only be done through large, randomised controlled with an appropriate period of follow up. While the overall concept is a simple one, the scale, cost, and logistics of organising these trials can be challenging and often other methods are sought to understand whether a medical intervention, or in the case of biventricular pacing, one element of a medical intervention, might be beneficial. When it comes to AV optimisation, where the benefit of one AV delay has to be chosen ahead of

another, this becomes impossible. The alternative is to measure response using other (acute) methods.

1.1.1 Long term response

Response in biventricular can be judged on a number of levels, each with its own advantages, and limitations. The simplest response is to judge symptom response, which can be quantified numerically using a variety of symptoms scores such as the Minnesota Living with Heart Failure Score (Rector & Cohn 1992). Again this can be used to assess longer term benefits from biventricular pacing, but will be of limited value when doing head to head comparisons of AV delay for example.

Echocardiographic markers can also be used to quantify response. This can include markers of function such as ejection fraction, or an evaluation of the effect on structure such as left ventricular dimensions (Foley et al. 2009). When response is mentioned in the context of biventricular pacing, what is often mentioned is a "non-responder" rate. A value is such as 30% is often ascribed to this without defining whether this is compared to a control arm. To be more precise, separate terms can be used to describe response, and response once the effect of the control arm is deducted. The latter could be defined as the "effect" rather than "response" (Bouri et al. 2014). Quantifying this value more accurately is important both for clinicians and researchers in the field. It would allow clinicians to provide accurate information when consenting patients for an implant which in itself is an invasive procedure with a complication rate (Ahsan et al. 2013). It is also important for researchers who may be investigating ways of improving selection criteria or novel methods of delivering biventricular pacing from assuming that response rates are high, and small improvements might make it complete. If subtracting the effect in the control arm

leads to a much smaller effect than widely assumed, and the quoted response rates are greater than their true value, there may yet much a much greater room for improvement when it comes to improving the delivery and optimisation of biventricular pacing.

1.1.2 Acute response and optimisation

Response can be judged acutely also. Effective methods for judging acute responses are necessary for judging therapeutic decisions with multiple choices and where the effects may be smaller. It also provides a rapid way of assessing the efficacy novel approaches to biventricular pacing such as lead position studies. For biventricular pacing markers of acute response have been used most widely with AV and VV optimisation. Just as we need to rigorously need to judge how we assess long term response, a similar approach is also needed to assess short term response.

A wide range of different physiological markers of response can be used in this context. Echocardiographic markers can be used including mitral valve inflow (Ritter et al. 1999), tissue Doppler (Vidal et al. 2007), left ventricular outflow tract (LVOT) Doppler (Waggoner et al. 2008). Invasive haemodynamic markers can be used (Auricchio et al. 1999; Berberian et al. 2005; Wang et al. 2011) and non invasive markers of blood pressure (Zachary I Whinnett et al. 2006), and peak endocardial acceleration, a measurement derived from the loudness of the first heart sound is currently also undergoing evalution in a randomised controlled trial for biventricular pacemaker optimisation (Ritter et al. 2012).

Invasive markers of haemodynamics have been used in studies of lead position in biventricular pacing (Derval et al. 2010; Spragg et al. 2010). In general, however,

markers of acute response have been used more widely in studies of biventricular pacemaker optimisation.

Up until now, there has been some doubt about the value of AV and VV optimisation. When a range of trials are examined, there appears to be little prognostic benefit of this process (Auger et al. 2013), suggesting that when these acute measures are used to select a setting, this is not translated into a longer term benefit. Failure to demonstrate success in long term trials does not necessarily indicate that markers of acute response have no role in this field if the protocols used during an optimisation are weak. There is a risk that the substantial resources are allocated in a large trial on a strategy that is mathematically or physiologically implausible. When any acute marker of response is being used to judge whether any one setting is better than another, a series of questions must be asked. When a method is used to select one of a series of settings as the optimal setting, is a single region or value selected? Is this value reproducible? Is the value physiologically plausible? Does this method agree with another method?

When we analyse the different schemes for optimisation, we find that the general approaches for using these measurements to select the optimum are fundamentally very different. Broadly speaking there are four different approaches. The first is to visually analyse the measurement and spot the pattern which appears to be consistent with the best setting. This is the case with mitral valve inflow (Ritter et al. 1999). The second is to take a range of measurements across a range of AV or VV delays, and choose the setting corresponding to the highest measurements. Such a process can be applied to left ventricular outflow tract Doppler (Waggoner et al. 2008). The third is to take a range of measurements across a range of AV delays, and fit a curve. The peak of this curve can be used to identify the optimum (Z I Whinnett et al. 2006).

The fourth similarly takes a range of measurements across AV delays, and a sigmoid curve is fitted, with the inflection point chosen as the optimum (Ritter et al. 2012). Another set of methods also exist which technically do not use markers of acute response, but use a set of electrogram based methods to predict the optimum (Krum et al. 2012; Baker et al. 2007; Gold et al. 2007). These have been derived using markers of acute response, but when applied to patients assume the same effect holds.

In this thesis, I analyse the different approaches to the use of acute response to select an optimum, judging their benefits and weaknesses and set out a set of quality markers required of an optimisation scheme.

1.2 High resolution methods to probe the current methods

Two methods for optimisation are widely used in contemporary practice. Doppler based methods which use mitral valve inflow or left ventricular out flow tract (Waggoner et al. 2008), and a range of methods built in to the devices which use electrogram based parameters to predict the optimum (Krum et al. 2012; Baker et al. 2007; Gold et al. 2007). Both have failed to show a benefit from optimisation in large randomised controlled trials (Ellenbogen et al. 2010; Abraham et al. 2010). It is tempting to deduce that there is little value in performing an optimisation, but another approach is to step back and to have another look at the very methods themselves, by collecting de novo data, and probing these methods from first principles experimentally, using high resolution methods. If there are improvements which could be made at this fundamental level, these methods may yet have more to offer.

1.2.1 Left ventricular outflow tract Doppler for optimisation

Doppler measures are part of guideline protocols for optimisation of AV and VV delay in cardiac resynchronization therapy pacemakers (Gorcsan et al. 2008). There

are recommendations to average at least 3 beats in sinus rhythm or 5 beats in atrial fibrillation should be averaged (Baumgartner et al. 2009). Examples can show the process being performed using one beat per setting (Waggoner et al. 2008). We often find that variability between beats at a single setting even when the three beats are acquired can be substantial (Pabari et al. 2011). With single beat data sets, plotting VTI measurements can in fact show a series of local maxima and minima, rather than on single consistent optimum. Much of this variability can be attributed to noise, a consequence of measurement variability and genuine biological noise. To allow us to distinguish signal from noise, a much larger number of beats is usually required than the 3-5 recommended. Physiological responses such as pressure and flow tend to follow a parabolic pattern associated with changes in AV delay (Z I Whinnett et al. 2006; van Geldorp et al. 2011). Knowledge of the magnitude of this curvature, and beat-to-beat variability allows us to calculate the number of beats required to make a precise measurement (Francis 2013b) and the number is usually well in excess of three and in fact closer to hundreds. While this does not exclude us from using Doppler measures for optimisation, or indeed for any other assessment of response where LVOT Doppler is used as a physiologically marker, manually tracing each of the these beats almost becomes prohibitively labour intensive. However, a reliable method for automated tracing has been developed in our group which allows large numbers of beats to undergo automated tracing (Zolgharni et al. 2014). This technology can be applied to any manufacturer. Such a technique potentially allows us to dramatically improve the precision by which echocardiography is used in for biventricular pacing.

Before we can apply this directly to biventricular pacing we need to evaluate how best such technology should be used. To collect 100 beats for a measurement would require the operator to hold the probe still in one position for over a minute. How

long is it reasonable to ask an operator to hold a probe still before the probe starts to drift? It is better to take multiple measurements instead? Importantly what is the importance of breath holding when making these measurements? A variety of approaches have been described when Doppler measurements have been used in biventricular pacemaker optimisation. Some describe patients to breath hold during Doppler measurements (Jansen et al. 2006; Thomas et al. 2009), and other do not (Dubin et al. 1990; Hardt et al. 2007; Riedlbauchová et al. 2005).

Breath holding limits the duration of measurement that can be acquired. This in itself can be a significant limitation when it is large numbers of beats, and hence long recordings which are required. It can also be difficult for some patients to comply with, and may be a particular problem in the heart failure population who are, as their predominant symptom, breathless.

By investigating long runs of measurement can we explore the effects of breath holding on measurement variability and magnitude, and whether prolonged durations of measurement are viable. Once we have the answers to these questions, we can then apply these more effectively to investigate response and optimisation in biventricular pacing.

1.2.2 Electrogram based methods for optimisation

While we attempt to improve the precision of Doppler measurements to assess response and optimisation, non-invasive blood pressure has been established within this group as a reproducible method to calculate the AV optimum (Zachary I Whinnett et al. 2006). Non-invasive blood pressure measured from the finger can be measured much more easily allowing large number of beats to be analysed at different settings. By performing multiple replicates and using automated software to measure and plot the results allows the AV optimum to be identified with high precision and

test-retest reproducibility. The precision of this technique allows us to probe other optimisation protocols on the market to assess their validity.

One area where this may be a particularly useful tool is in the evaluation of different electogram based methods for AV optimisation. The different manufacturers have published at least three different types of automated electrogram based optimisation methods. Currently algorithms include QuickOpt^{TM} by St Jude Medical (Anselmino et al. 2009; Abraham et al. 2010; Baker et al. 2007), AdaptivCRT^{TM} by Medtronic (Krum et al. 2012; D. Birnie et al. 2013; Khaykin et al. 2011; Jones et al. 2010), and a series of algorithms by Boston Scientific. The Boston Scientific algorithms began with the method used in the COMPANION Trial (Bristow et al. 2004) which appears not to have been published. The second was ExpertEase for Heart Failure Plus (EEHF+^{TM})(Gold et al. 2007). The third is SmartDelay^{TM} (Ellenbogen et al. 2010) which is present on current devices.

Many of these methods are said to have been developed or validated using echocardiographic methods for AV delay optimisation (Anselmino et al. 2009; Khaykin et al. 2011; Jones et al. 2010; Baker et al. 2007). Unfortunately those echocardiographic methods for optimisation in themselves as we have discussed can sometimes be an uncertain gold standard (Jones et al. 2014; Raphael et al. 2013). It is difficult to understand how two different electrogram methods agree with echocardiographic based optimisation when the echocardiographic measures do not agree with themselves.

When two different methods are assessed for agreement, it is essential that the two AV optima are plotted against each other and not measures of cardiac function (Stegemann & Francis 2012; Sohaib, Whinnett, et al. 2013). Otherwise there is a risk of falsely assuming the two methods correlate. This is because different patients with

have very different values of, as an example cardiac output, and the difference between patients is likely to be bigger than the effects of AV delay adjustment, so any plot of the cardiac output obtained using one method versus another method will automatically show a strong correlation (Stegemann & Francis 2012). In this thesis I explore whether first, the different methods for electrogram based optimisation agree with each other, and second whether they agree with the reproducible method of haemodynamic optimisation.

1.3 Resolving controversies using high resolution physiology

A more powerful reason to use high resolution physiological methods in the field of biventricular pacing is to answer some of the fundamental mechanistic questions that continue to confuse us. Many of these ultimately require us to decipher how much of the benefit of biventricular pacing comes from shortening of the AV delay, which by definition will happen when biventricular pacing is instituted in any patients in sinus rhythm, and how much comes from restoring ventricular synchrony? There are three situations that can be considered suitable for examination in this manner. The first is resolving questions surrounding VV optimisation, and why it is not seen consistently to have a much larger effect than predicted. The second is to investigate the importance of lead position, especially when it is considered in the context of the AV optimum - does the AV optimum differ substantially between positions? And if it is performed to a high resolution in both positions, is there a difference in the haemodynamic benefits between different lead positions. Thirdly I consider how the pure effects of AV optimisation can be considered when the element of ventricular resynchronisation is removed. Patients with narrow QRS and a long PR interval provide a model for us to understand this.

1.3.1 Relative changes in beat-to-beat systolic blood pressure to judge differences between pacing configurations

To investigate these controversies in the field of pacing in heart failure, an adequately high resolution method is required to detect potentially small changes between different pacing configurations with sufficient signal-to-noise ratio to give a meaningful answer. I use a protocol initially developed for AV optimisation (Zachary I Whinnett et al. 2006) but have adapted this to address the questions outlined. Non-invasive beat-to-beat blood pressure is measured using a finger photoplethysmograph (Finometer). Multiple alternations are performed between a reference setting on the

pacemaker and a tested AV delay. The relative change in systolic blood pressure is plotted against the AV delay and tends to follow a parabolic pattern (Z I Whinnett et al. 2006). The AV delay closest to the peak of the parabola has been used to select the AV optimum. The non-invasive haemodynamic method is undergoing comparison to echocardiographic based methods for optimisation as part of the multicentre BRAVO Trial (Whinnett et al. 2014). The BRAVO trial is a non-inferiority study and the primary outcome measure is peak $V0_2$ measured using cardiopulmonary exercise testing.

The haemodynamic optimization method described produces reproducible values for the AV delay identified as optimal (Zachary I Whinnett et al. 2006). A range of haemodynamic measures can be generated by the Finometer device including cardiac output, systolic blood pressure, diastolic blood pressure, pulse pressure, and mean arterial pressure. Of these five, systolic blood pressure has been shown to have the best characteristics in terms of efficiency and reproducibility (Whinnett, Davies, et al. 2008). This alternation protocol has also been used for a range of invasive markers of acute haemodynamics including LV dP/dt_{max}, LV systolic BP, and LV pulse pressure (Whinnett et al. 2013). All three methods have comparable reproducibility, and precision for all three is improved by increasing the number of replicate measurements between and tested and reference setting. Signal to noise characteristics for dP/dt_{max} are not as good as systolic BP. Correlation of change in blood pressure measurements between invasive and non-invasive is good (Kyriacou, Pabari, Whinnett, et al. 2012).

Correlation between optima obtained by different methods is different from correlation of those biological measurements themselves. Moreover LV dP/dt is an

entirely different physical property from systolic blood pressure and has different units. The distinction between them can be illustrated in a thought experiment. Two pressure curves are shown below (Figure 1-1), A and B, with their corresponding dP/dt curves. The dP/dt curve B was constructed by taking the dP/dt curve A, and stretching it three-fold in the time direction while decreasing its height two fold. The pressure curve B was then derived from the dP/dt curve B. Obviously the dP/dt_{max} of B is two times smaller than the dP/dt max of A. However, the pulse pressure of B is 1.5 times larger than the pulse pressure of A.

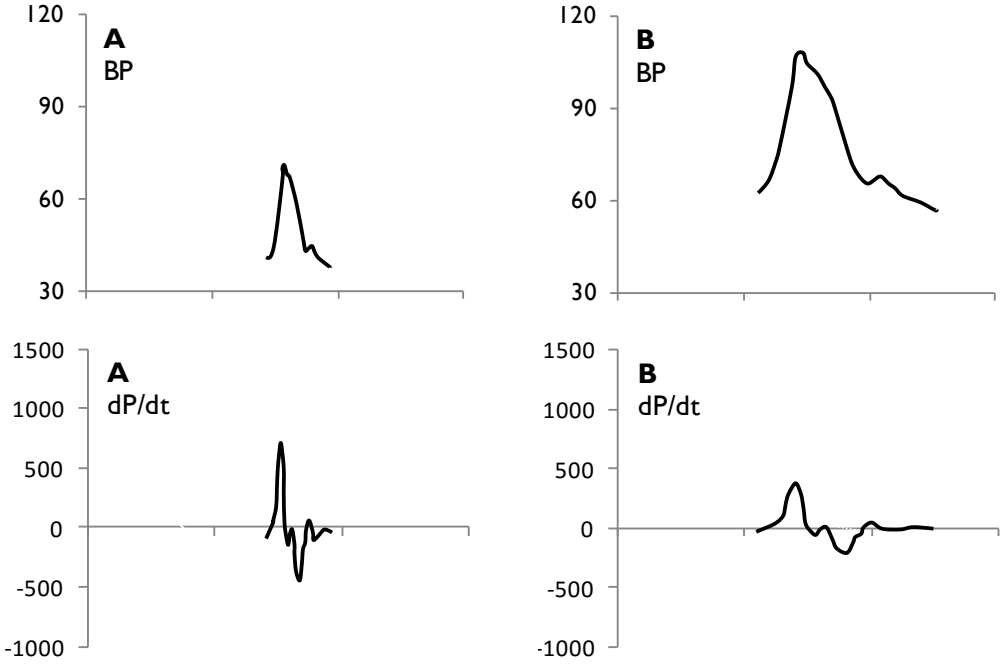

Figure 1-1 Proof that there is no necessity for pressure and dP/dt to change in the same direction, because they are different physical quantities with different dimensions

In this example the pressure wave form is increased in height by 50% and its duration is increased 3 fold. Because of the nature of dP/dt being ratio between change in pressure and unit of time, the peak dP/dt is necessarity halved.

Whether the peak systolic pressure is affected in the same way will depend on the baseline, but it is clear from this simple diagram that dP/dt_{max} and peak pressure are

different physical properties. They are both lower in patients with heart failure than normals but one is not an estimate of the other, they are merely properties that tend to move in the same direction. An increase in LV dP/dt_{max} does not require an increase in useful work done by the heart since it is only an instantaneous measure, rather than systolic blood pressure which is the accumulation of brief instance of instantaneous increase. Therefore given the choice between a higher LV dP/dt_{max}, and a higher blood pressure, other things being equal, the cardiac configuration which delivers a higher blood pressure is delivering more cardiac function.

Ultimately cardiac output would be a better variable to measure than blood pressure. However, there is no practical way and reliable way to measure beat to beat changes in cardiac output with more accuracy than blood pressure can be measured. The commercial algorithms within the Finapres that produce cardiac output values are designed not to sensitively between small changes, but rather produce an approximately correct value. It is for this reason that it requires the entry of variable such as the patient's body size and gender, without which it would not be able to produce a remotely plausible value. Because the Finapres derived output variable using the shapes of the parts of the blood pressure wave form and a mathematical computation, it is more vulnerable to biological and measurement noise in the pressure signal than is the algorithm that simply measures systolic blood pressure, as a result it is more noisy on a beat to beat basis. The unavoidable consequence of beat to beat noise is much greater unreliability of the optimum, as our group has recently reported (Finegold et al. 2014), because of the mathematical nature of calculating an optimum from a series of estimates that are hoped to form a curve. In fact the uncertainty in the optimum rises with the square of the amount of biological noise (Francis 2011). For this reason in this thesis I chose to use as the primary measure and index of immediate changes in cardiac function which was the least vulnerable to

noise, but capable of being measured invasively as well as non invasively. This was systolic blood pressure.

Haemodynamic optimization has not yet been demonstrated to produce longer term benefits on other clinical measures. Improvements in systolic blood pressure are likely to occur due to improvements in cardiac function. Sustained improvements in aortic flow are observed to occur with haemodynamic optimization (Manisty et al. 2012). Contrary to the general population, in the heart failure population increasing blood pressure is associated with improved outcomes (Raphael et al. 2009). Delivering CRT has been demonstrated to produce both acute improvements in systolic blood pressure (Auricchio et al. 1999) and this improvement is sustained in the longer term. In the treatment arm of the CARE-HF study systolic blood pressure was improved by 6.3 mmHg at 18 months (Cleland et al. 2005).

In order to demonstrate long term improvements in outcome measures with haemodynamic optimisation (compared to programming a nominal setting) a very large study would be required since the effect size of optimisation is smaller than the effect of turning on CRT in patients with LBBB. In addition in a large proportion of of patients the AV delay determined as optimal is likely to be within 40ms of nominal settings and therefore a very large study would be required.

The haemodynamic optimization method is being testing in the HOPE-HF study which is assessing whether haemodynamically optimised AV delay delivered with His pacing improves peak $V0_2$ in patients with narrow QRS duration, long PR interval and impaired heart function. This will allow us to further understand the direct predictive power of this method on clinical endpoints.

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1.3.2 Programming uncertainties with VV optimisation - understanding the influence of unconsidered changes in AV delay

Contemporary biventricular pacemakers allow the adjustment of the timing of the left and right ventricular leads (VV delay). If biventricular pacing works mainly by resynchronising the ventricle, one would anticipate that adjusting the timing between these two leads would increase the ability to achieve complete ventricular resynchronisation. Some researcher report large haemodynamic effects associated with VV adjustment (Bogaard et al. 2010; Lim et al. 2008; Vernooy et al. 2007) whereas other report a much smaller effect (Z I Whinnett et al. 2006). To understand why this conflict might arise, one needs to examine more closely what is meant by VV optimisation. Pacemaker optimisation is usually divided in a dichotomous manner in VV optimisation and AV optimisation. This gives the impression that there are only two timings that can be adjusted. The reality is, especially in the context of VV optimisation three different delays are undergoing adjustment: the time between the atrium and LV (A-LV), the time between the atrium and RV (A-RV), and the time between the LV and RV (the traditional interpretation of VV timing). VV optimisation can only occur if the timing between the atrium and one of the ventricles is kept constant while the other is adjusted, this can occur in four different combinations: the A-LV, the A-RV, atrium to the first paced ventricle, and atrium to second paced ventricle.

Studies have varied in their conventions for keeping these times constant. In some, the A-LV timing was kept constant and VV adjustment was done by changing the A-RV time (Bogaard et al. 2010; León et al. 2005). The opposite convention has also been used where the A-RV time has been kept constant (Rao et al. 2007). A common approach is to keep the time between the atrium and first paced ventricle constant and adjust the time to the second ventricle (Ritter et al. 2012; Boriani et al. 2006). This

distinction has not been considered important before, and therefore has not always been reported (Bogaard et al. 2010; Z I Whinnett et al. 2006). Whether the convention for keeping the AV delay constant influences the responses seen during VV optimisation has not been considered before (Bogaard et al. 2013; Vernooy et al. 2007). Exploring all these different combinations for keeping AV delay constant require some time, and a rapid, and reproducible technique is needed to investigate the range of settings. Non-invasive systolic blood pressure based optimisation offers such a tool and is investigated in this thesis.

1.3.3 AV Optimised His pacing

Patients with narrow QRS duration are no longer offered biventricular pacing because, when tested in a bias-resistant (Jabbour et al. 2015) manner, the outcomes have not been favourable (Ruschitzka et al. 2013; Thibault et al. 2013). However these studies did not specifically look at patients with long PR intervals, and instead selected patients on whether there was imaging evidence of mechanical dyssynchrony.

In otherwise healthy individuals, PR prolongation is associated with increased mortality regardless of QRS duration (Crisel et al. 2011; Park et al. 2013).

In heart failure with left bundle branch block (LBBB), shortening AV delay has a role in improving haemodynamics by improving LV filling (Kyriacou, Pabari & Francis 2012). A recent analysis of the MADIT-CRT trial, found that in patients where there was non-LBBB QRS prolongation, those with PR greater than 230 ms derived a prognostic benefit over controls compared to those who had a PR shorter than 230 ms (Kutyifa et al. 2014).

Direct His-bundle pacing has been demonstrated to be a feasible technique where normal ventricular activation patterns can be preserved (Deshmukh et al. 2000;

Kronborg et al. 2014; Catanzariti et al. 2013; Barba-Pichardo et al. 2010). This gives us a model to explore the pure effects of AV shortening without disrupting normal ventricular activation.

High resolution systolic blood pressure measurements provide us with the tool to assess acute haemodynamic improvement with AV optimised His pacing, compared to a baseline rhythm of first degree heart block and this is explored in this thesis.

1.3.4 Lead position

The question of where the left ventricular lead is placed is not only of interest because it affects clinical practice during implantation, but because it gets to the heart of what CRT is. Clinical practice is to site LV lead in the most lateral position possible, in an opposite and complementary place to the RV apical lead (Khan et al. 2009). Although there has been work examining the haemodynamic consequences of different lead positions, no study has optimised AV and VV delay at suboptimal lead position and therefore (since different positions may have different optima) we do not know if the position has been compared fairly. Moreover often studies do not report the reproducibility of the selection of the ideal site (Derval et al. 2010), and therefore it is possible that apparent differences between sites are merely chance findings (Pabari et al. 2011). High resolution methods for determining response between different lead sites allow us to explore this question.

1.4 Clues to guide the future direction of research in biventricular pacing from randomised clinical trials

Randomised trials are usually designed to provide definitive answers to clinical questions, but can also be used to guide the direction of future research, and can give us clues to the answers of underlying mechanistic questions. In the trials of CRT the

progressive lifespan gain appears to occur in a non-linear manner suggesting that there is an ongoing therapeutic beneficial effect, rather than a one off peri-implant benefit (J. A Finegold et al. 2013). However, biventricular pacemaker implants have been implanted in patients with a range of ECG characteristics beyond the conventional indication of sinus rhythm and LBBB. In Europe it is estimated that 32% of CRT recipients did not have LBBB nor a pacing indication (Bogale et al. 2012). These may have been implanted in patients with imaging evidence of mechanical dyssynchrony (Bogale et al. 2012; Nijjer et al. 2012). In the EchoCRT trial, patients with narrow QRS were selected for implant based on imaging evidence of mechanical dyssynchrony and mortality was increased by 81% (p=0.02), (Ruschitzka et al. 2013). Potentially this means there is a large population of patients who may be at risk of harm from their biventricular pacing. If this mechanism of harm was implant related, then ongoing pacing should not have an ongoing harmful effect. If this harm is due to ongoing physiological effects of pacing, it means that there may be the opportunity to prolong lifespan in these individuals by switching off biventricular pacing. Analysing the time course of mortality from of biventricular pacing in patients with narrow QRS and non-LBBB morphologies gives us clues as to whether this harm is due to an ongoing physiological effect. If this is the case, the patients could potentially be probed further using high resolution physiological techniques to determine whether there is a benefit to switching off biventricular pacing. I examine the time course of mortality and heart failure hospitalisation of patients from such trials to determine this.

2 Materials and Methods

2.1 Equipment used for measurements

2.1.1 Non-invasive blood pressure measurements

Non-invasive beat-to-beat blood pressures were measured using a Finometer (Finapres Medical Systems, Amsterdam, Netherlands). This is a digital photoplethysmograph which uses an inflatable finger cuff and applies a volume-clamp technique (Penaz 1973) to generate an continuous arterial pressure waveform. A balloon enclosed is enclosed in the semi-rigid cuff and the volume of gas in the balloon is continuously adjusted so that the finger artery is dynamically unloaded and the arterial diameter is kept constant for the duration of measurement. A servo controller compares the arterial diameter with a reference value, the servo set point, which is set a state of near zero transmural pressure. This set point is determined in an automated manner from a pressure-volume diagram of the finger arteries. The set-point can change due to variability of smooth muscle tone in the digital arteries. The device intermittently calibrates to adapt to this, keeping the transmural pressure near zero at all times during measurement. The intra-arterial pressure is measured by assessing the cuff pressure required to exactly counteract the change in intra-arterial pressure (Imholz et al. 1998).

The cuff was applied to the middle phalanx of the middle finger and allowed to calibrate until a consistent pressure trace was obtained. On small number of occasions where an acceptable trace could not be obtained from the middle finger, an alternative finger was used where a suitable trace was obtained. The Finometer automatically calibrates every 10 seconds, extending the period between calibrations as a more consistent trace is obtained. Once a 30 second period of consistent pressure

was seen, calibration was paused and recordings were commenced. The participant were asked to keep their hands still during recordings and the height of the hand was kept constant during recordings.

The analogue outputs from the Finometer were configured for our data acquisition set up. A connection box is provided with the Finometer with four output channels. One of these is configured to select the "finger" signal (finger BP). BNC cables are connected from this connection box to our acquisition system (described below).

Figure 2-1: A Finometer was used for non-invasive beat-to-beat blood pressure measurements

2.1.2 Invasive blood pressure measurements

Invasive arterial blood pressure measurements where required were recorded from sheaths placed in the radial or femoral artery. Pressure was transmitted via fluid filled tubing to a fluid filled column connected to an external pressure transducer. The pressure transducer was secured at a fixed height in the cardiac catheter laboratory operating table to prevent incorrect readings due to variation in the height of the

transducer. Pressure recording were transmitted to the data acquisition system via a Volcano Combomap 6800 Pressure and Flow System (Volcano Corporation, San Diego, CA, USA).

2.1.3 Electrocardiography

Three lead surface ECG measurements were recorded using a Fukuda Denshi DS7100 Monitor (Fukuda Denshi, Tokyo, Japan), with an analogue output. Leads were placed in standard positions (right and left shoulders, and right hip)

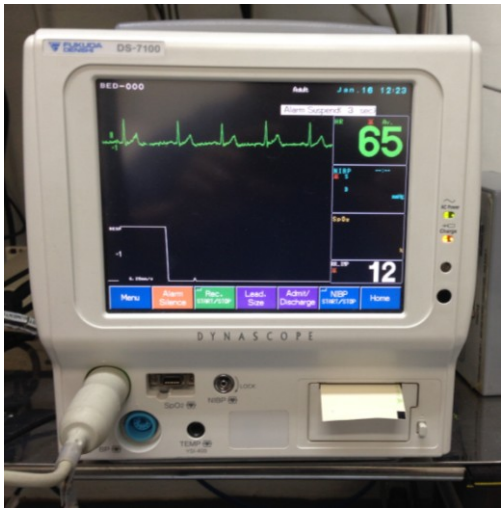

Figure 2-2: Fukuda Denshi DS7100 Monitor

The Fukuda Denshi ECG monitor was used on participants where haemodynamic data was collected.

2.1.4 Pacemakers and pacemaker programmers

Pacemakers manufactured by St Jude Medical (St Paul, MN, USA), Boston Scientific (Natick, MA, USA), and Medtronic (Minneapolis, MN, USA), were used for both the invasive and non-invasive elements of the study. Programmers from all three manufacturers were used with the appropriate software to allow adjustment of pacemaker mode, heart rate, atrioventricular (AV) delay and interventricular (VV) delay: Medtronic's CareLink™ programmer, St Jude Medical's Merlin™ programmer, and Boston Scientific's Latitude™ programmer.

Where only temporary biventricular pacing was required for the protocol pacing was established using quadripolar electrodes (Josephson Curve, Bard Vikings) connected to a pacemaker generator using purpose built pacemaker leads (Figure 2-3). These specially manufactured leads were connected to a Medtronic Insync III CRT pacemaker. These leads allowed electrogram data from the leads to be simultaneously analysed on an electrogram recording system (see 2.1.7).

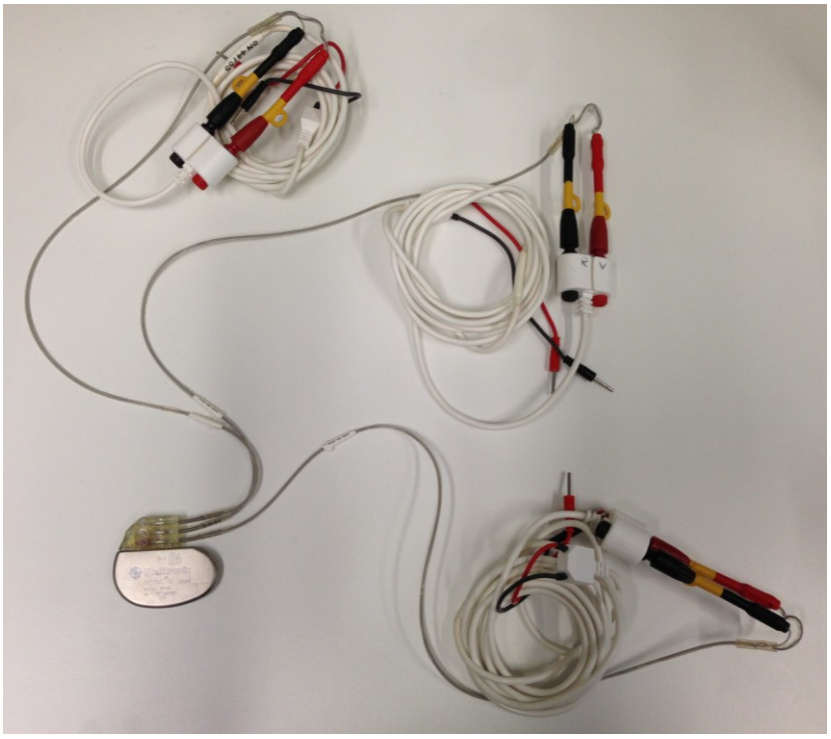

Figure 2-3: Medtronic InSync III CRT-pacemaker with customised pacing leads attaced

Pacing leads were manufactured for the purposes of these research studies to allow temporary biventricular or dual chamber to be established via quadripolar electrodes.

2.1.5 Customised device to mark transition of pacemaker setting

Current pacemakers are not able to conventionally output any changes to an external device except for the devices they program. To allow us to mark on our analysis system when any programming changes had been made to the pacemaker, such as the AV or VV delay, a purpose built transition marker box was built ("toggle box").

When the researcher programmes any changes to the pacemaker, they simultaneously press a button on the transition marker box to allow our analysis system to mark changes in pacemaker settings.

The box maintains a continuous voltage output. The magnitude of the voltage corresponds to a pacemaker setting. For example if a reference AV delay of 120 ms is used (Figure 2-4), a continuous voltage is output at this setting (1.2 V). When the AV delay is changed to 40 ms on the pacemaker programmer, the toggle button is pressed on the transition marker box, and the voltage output then changes to one corresponding to 80 ms (0.8 V).

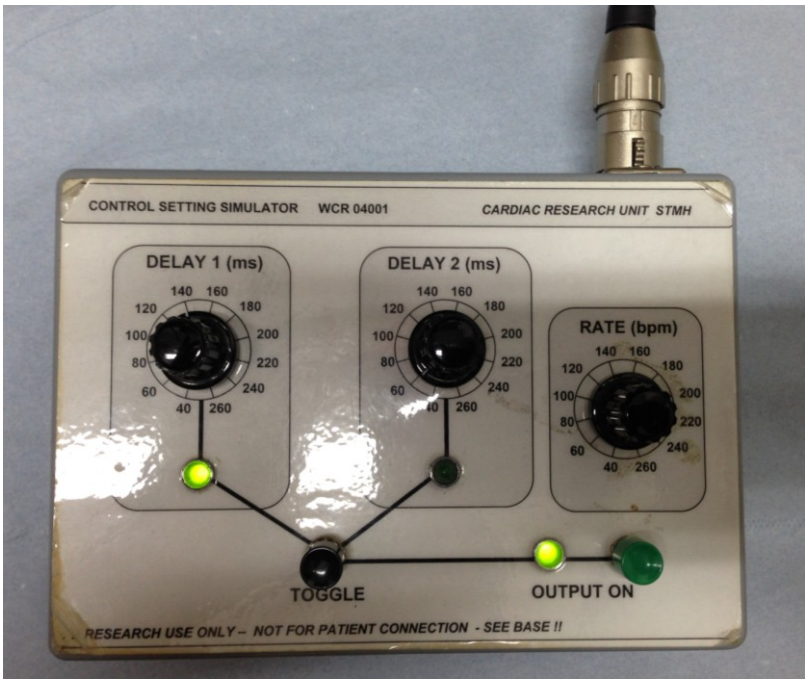

Figure 2-4 Customized transition-marker box

This device was used to indicate the pacemaker setting on the analysis system. Two dials are marked, the reference delay (on the left) and the tested delay (on the right). When the button labelled "Toggle" is pressed, the voltage output will switch between the either the tested or reference delay to the other. The numbers indicate the AV or VV delay being tested.

2.1.6 12 lead ECG measurements

12 lead ECG measurements were printed using a GE MAC 1200 ST ECG machine (GE Healthcare, Buckinghamshire, UK).

2.1.7 Real time 12-lead ECG measurement and intracardiac electrogram measurements

For all invasive studies continuous 12-lead ECG measurements were made using a Bard system for the entire duration of the study (Bard Labsystem Pro, Bard Electrophysiology Division, Lowell, MA). This system was also used to record measurements of intracardiac electrograms where they were required for positioning of pacemaker leads.

2.2 Data acquisition system for blood pressure measurements

A custom designed data acquisition system was used for all haemodynamic measurements. Analog signals were taken from all recording equipment (e.g. the transition box, non-invasive or invasive blood pressure, 3-lead ECG) and digitised and stored on a computer by a hardware signal acquisition system (National Instruments USB 6251 (National Instruments, Austin, TX, USA) (Figure 2-5), and stored as zipped text files that can be retrieved for offline processing. Signals are monitored while recording using a custom display program developed using Labview (National Instruments, Austin, TX, USA) Figure 2-6. The USB 6251 contains a Fast 16 Channel Analogue to Digital Convertor (National Instruments, Austin, TX, USA)) that is set up in the software to sample all signals at 1000 samples per second.

A BNC2090 data acquisition interface box (National Instruments, Austin, TX, USA) is used to allow physical connection of the analogue inputs to the Analogue to Digital Converter. Analogue inputs are connected via BNC cables to the BNC2090. These signals travel from the BNC2090 to the USB6251 via a 68-way cable.

The BNC2090 has a series of labelled channels where the BNC cables are connected. The "finger" output of the Finometer is connected to a channel on the BNC2090.

The connecting cable from the toggle box has three BNC plugs: one (colour coded red), provides a +5V DC power supply to the toggle box, and is plugged into a socket labelled "User 1" on the BNC2090. A short red wire links the "5V" to "User 1" terminals on the BNC2090. The two other BNC cables plug into channels on the BNC2090 (labelled as BoxA and BoxB). BoxA and BoxB can be used for signals which correspond to the AV and VV delay respectively on the recorded data channels. The analogue outputs from the ECG and invasive arterial blood pressure are plugged into separate channels on the BNC2090.

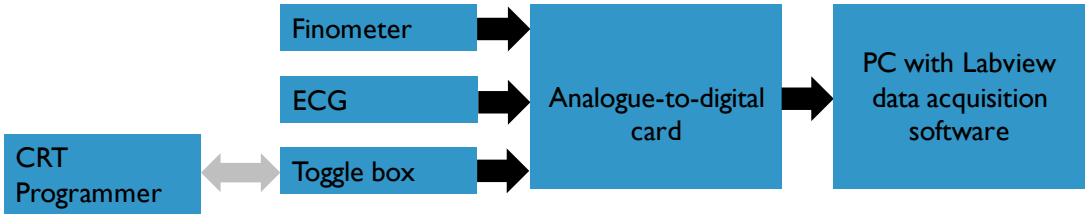

Figure 2-5: Inputs to data acquisition system

Analogue outputs from the Finometer, ECG, and toggle box are fed into an analogue-to-digital card via BNC cables. The digital signals are sent to a PC with the data acquisition software.

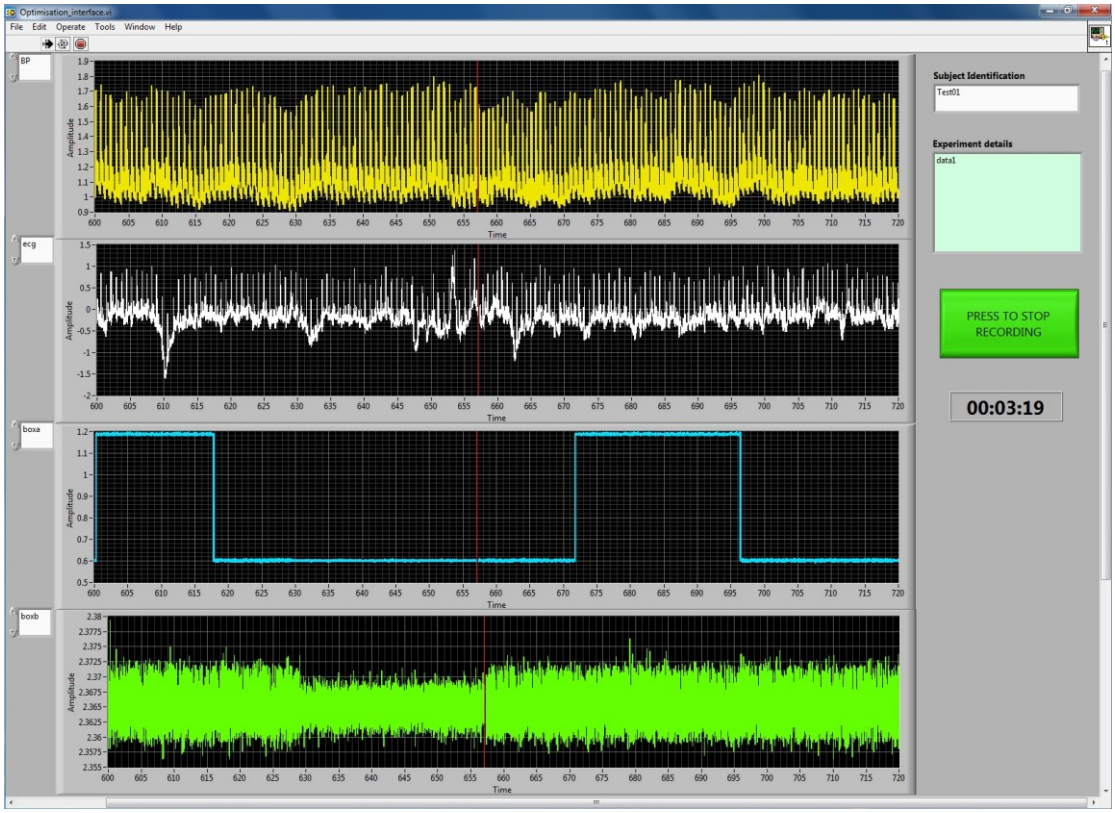

Figure 2-6: Image of real time data acquisition using Labview software

Real time data acquistion is visible on customised software developed using Labview. In this example, the upper panel shows blood pressure recordings, the second panel from the top ECG, and the third panel from the top the output from the toggle box indicating the pacemaker setting. The panels on the right allow the user to start and stop recording measurements and name the appropriate data acquistion files. Data stored from each run of data acquisition was stored in text file format by Labview software.

2.3 Algorithm to measure haemodynamic effects of different pacing configurations

2.3.1 Analysis software

Data analysis was performed with software designed by the group using the Matlab platform (MathWorks, Natick, MA, USA).

2.3.2 Basis for analysis algorithm

The haemodynamic data acquisition protocols are designed to be able to distinguish small differences in haemodynamics reliably in individual patients. There is

considerable beat to beat variability in blood pressure and other haemodynamic variable and therefore when precision is required, it is necessary to perform multiple replicates and take an average to minimise the impact of noise which fall with the square root of the number of replicates.

The basis of this protocol is the observation that when AV delay is changed, there is a resulting change in pressure which is numerically small (of the order of 0.5 to 5 mmHg) by comparison with the natural beat-to-beat variability. Second blood pressure has a tendency to undergo fluctuations that are not only short term (driven by respiration) but also longer term which may be driven by many internal physiological processes which do not necessarily have a predictable or cyclic pattern. Third, the increment in blood pressure after a change in pacemaker setting does not last indefinitely. After a few seconds it partially decays away and is previously described (Manisty et al. 2012) to be the result of peripheral vasodilatation.

The first feature, the smallness of the change in pressure, means that we need to measure it many times to be confident of its value.

The second feature, fluctuations, requires two different methods of handling for the two frequencies. The short term fluctuations can be dealt with by averaging over a series of beats. The long term fluctuations cannot be dealt with by averaging because it is not practical to record for many minutes in a protocol that will require a large number of replications of each transition. Instead we handle the long term fluctuations by measuring the acute increment when a transition is made between a fixed reference setting and the tested setting. The idea is that on some occasions this will occur during a long term down trend in pressure, but on other occasions this will occur during a long term uptrend. If there are sufficient replicates the effects of these background trends will tend to cancel each other out.

The third feature, partial decay of pressure after a short delay, the protocol handles by focusing on the early period before this decay. This is for three reasons. First, over a shorter period there is less time for the long cycle fluctuations to introduce noise into the increment we are measuring and therefore this noise is smaller. Second, over this shorter time period the reflex peripheral vasodilatation has not occurred and therefore any increment is present at its full strength. Third, from purely pragmatic point of view it takes less time to acquire a short duration of recording than a longer one and therefore more replicates can be done in the same time if the replicates are of short duration.

Based on the above considerations, the protocol consists of a series of building blocks that are assembled in stepwise fashion to deliver precision at each level (Figure 2-7). The first level is making a single measurement of the increment between the reference setting and the tested setting. In this protocol this is done by changing the settings between the reference setting and the tested setting (a process which I call a "transition") and measuring the pressure immediately before and immediately after. The average of the seven systolic pressures before the transition is subtracted from the average of the seven systolic pressures immediately after the transition. The reasons for not omitting the first few beats after the transition are previously published (Whinnett et al. 2011).

The next level is to conduct multiple replicates of this increment. In certain protocols, where the greatest level of precision is required, this can be 20 replicates. This is by alternating between the reference setting, to the tested setting for at least 14 beats, and then back to the reference setting for at least 14 beats and then forward to the tested setting for at least 14 beats, etc. By performing 20 such transitions, ten "forwards" and ten "backwards" and remembering to reverse the sign of the increment of the

backward transitions, we obtain 20 measurements of the increment. The average of these 20 can taken as the haemodynamic state of the tested setting relative to the reference setting.

The next level is to test a range of settings. For example VV delays are tested in steps of 20 ms between LV first by 80 ms and RV first by 80 ms. This produces one complete VV delay curve (Figure 2-8).

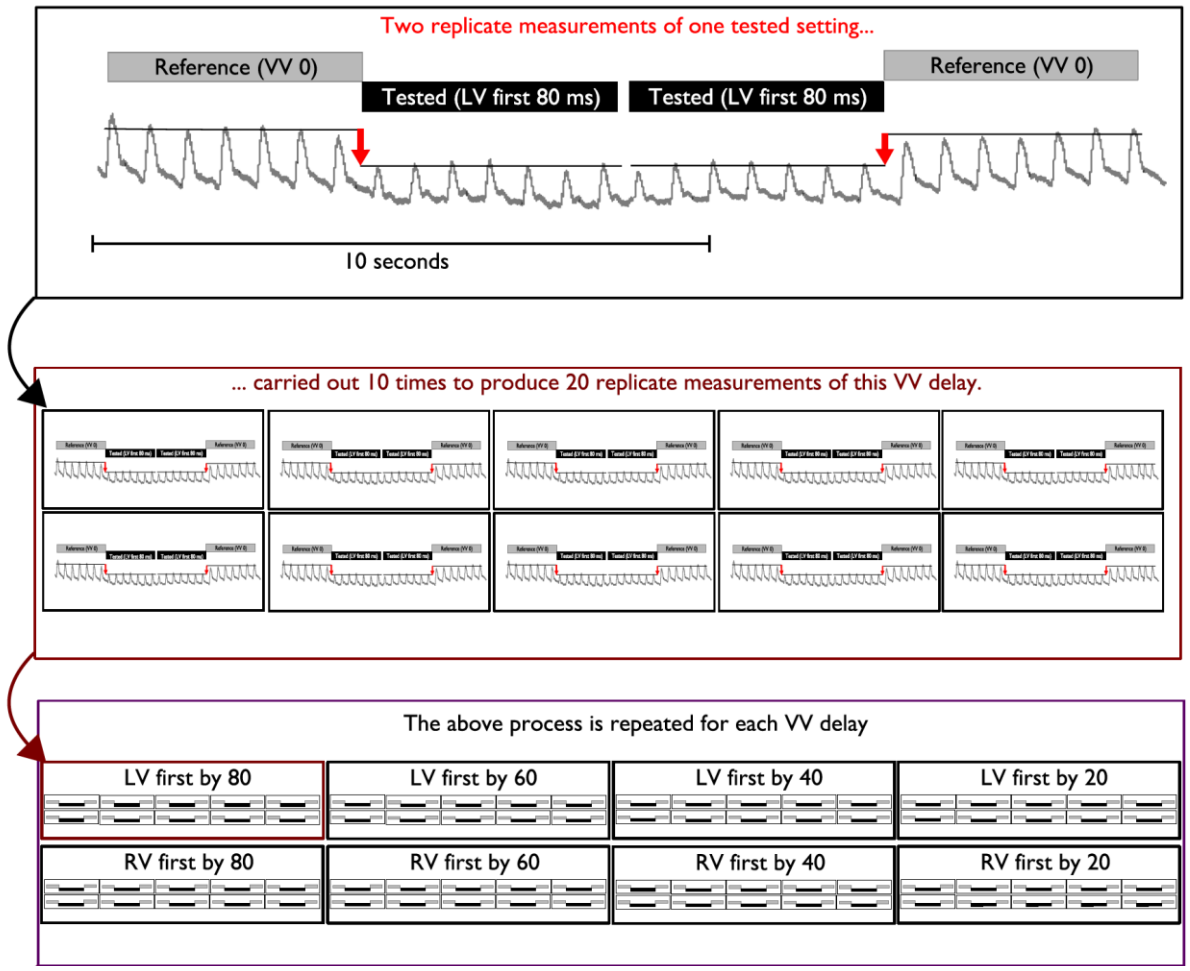

Figure 2-7 Steps involved in haemodynamic protocol

The data acquired during our protocol is illustrated. Relative changes in blood pressure are tested between two settings. This is repeated multiple times, in this example 20 replicates are obtained. The process is repeated for each different pacemaker setting for a given range of values

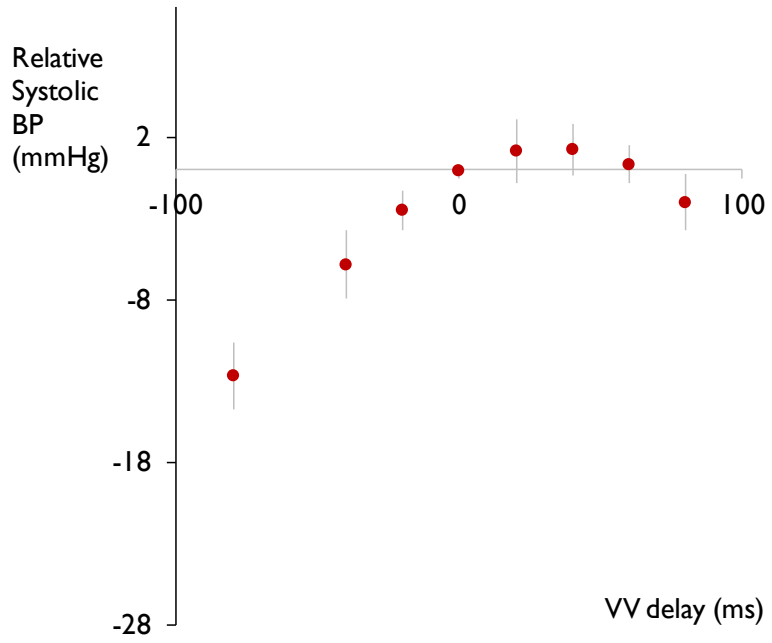

Figure 2-8 Plotting haemodynamic data

The relative systolic BP at each VV delay illustrated in Figure 2-7 is plotted on a graph for further analysis and curve fitting. A negative value indicates that the left ventricle lead paces first, and a positive value that it paces second.

2.3.3 Steps involved during data analysis

A number of steps are required to convert the raw data into results:

(a) Raw data files are generated from Labview in text file format

(b) Text files are converted to Matlab files

(c) Transitions between pacemaker settings are then verified. If the output from the toggle box does not correspond to the change in ECG morphology expected when a pacemaker setting is changed, the transition point is realigned (Figure 2-9).

(d) Processing of blood pressure date to give a relative systolic blood pressure between two different pacemaker settings.

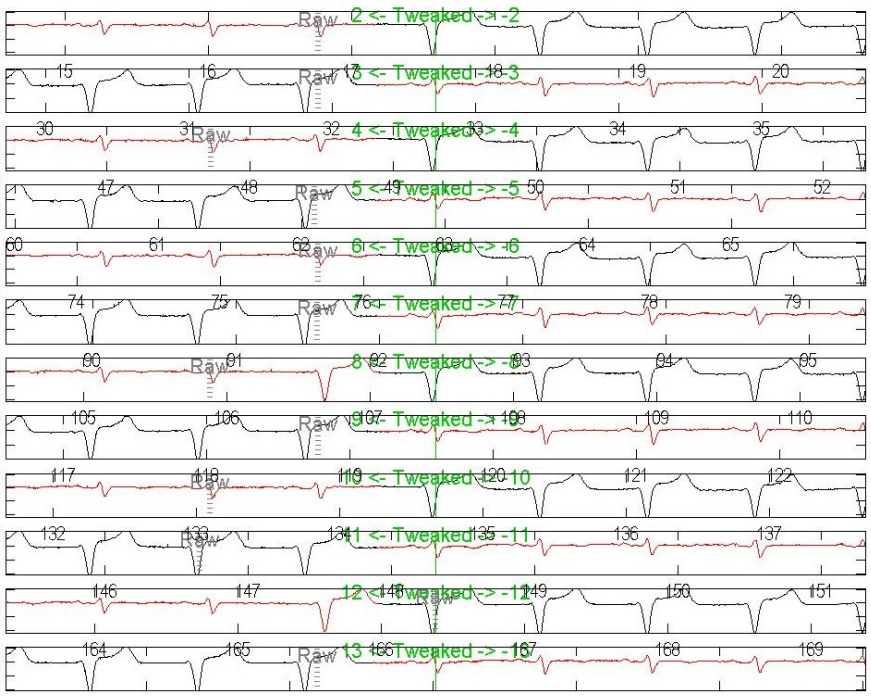

Figure 2-9 ECGs pre and post transition

This is an image of the ECG from transitions between no ventricular pacing and biventricular pacing. The grey lines marked "Raw" represent when the toggle box has been used to mark a change in the pacemaker settings. The green lines mark where the transitions have been tweaked either by an automated method or manually after inspecting the ECGs.

2.3.3.1 Confirmation of data alignment

It was necessary to confirm that output of data from all sources was in real time, and appropriately aligned. This could be checked by artificially introducing a simultaneous artefact on the ECG and blood pressure trace, and ensuring both also occurred at the same time on the analysis program.

2.3.3.2 Marking changes in pacemaker settings

Even though a toggle box was used to identify changes in pacemaker settings, there was often a delay between the transition time indicated by the toggle box, and the actual time the pacemaker programming changes had taken place. During the analysis, the first step was to adjust the transition from this "marked" time to the actual changes in the ECG morphology. The software allowed two methods to adjust

the timing of the transitions, the first automated, and the second manual, requiring visual inspection of ECG morphology by the person performing the analysis.

For the automated method, the ECG detects the centre of the R-wave, and examines the P-QRS complex pre and post. This allows it to analyse the PR interval, and the QRS morphology, both of which will change depending on the change to AV or VV delay introduced. Two successive beats are then compared and the programme marks a change (i.e. a transition) in the morphology when one of these beats differ (Figure 2-10).

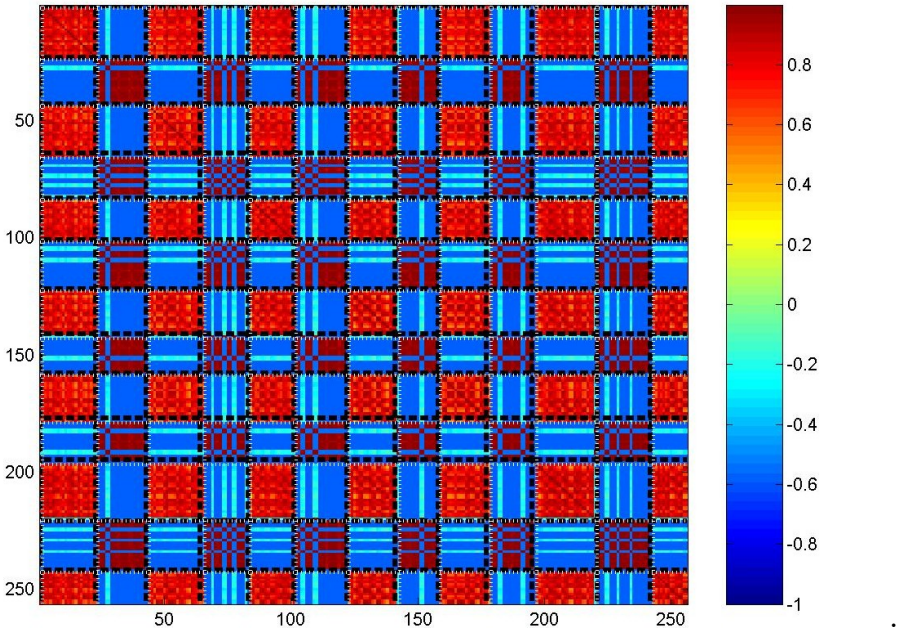

Figure 2-10 Illustration of automated identification of transition points

Two adjacent beats are compared by the algorithm to identify the transition point between pacemaker settings. The algorithm performs a correlation of the the ECG morphologies and the correlation coefficient is converted into a colour (scale illustrated on the right). The black hashed marking represent the transition marked using the toggle box, and the white hashes the transition identfied by the automated analysis. In this example the transitions were between no ventricular pacing and biventricular pacing which is why there is such a distinct change in colour. The axes represent beat number.

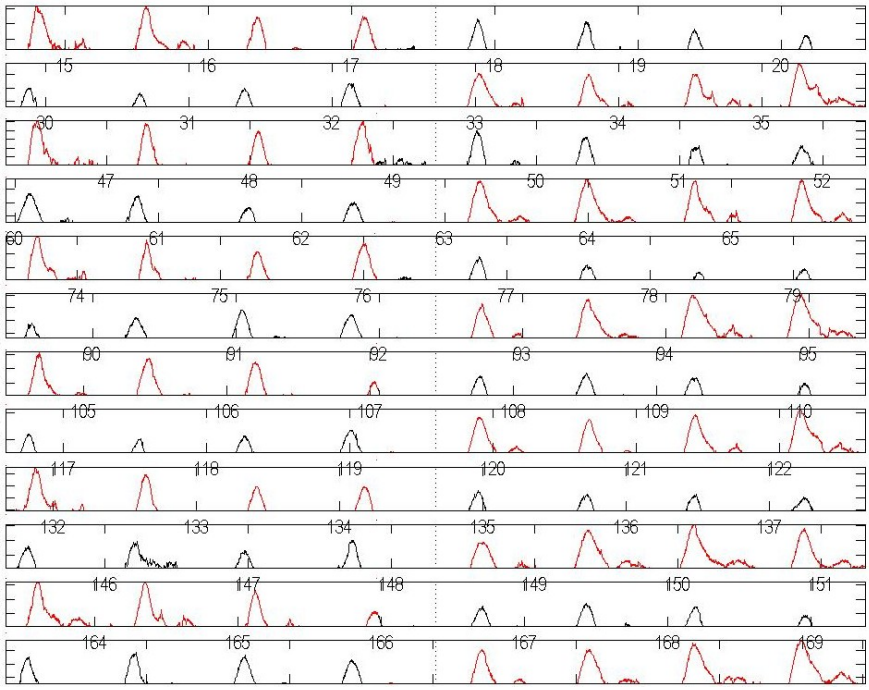

Figure 2-11 Blood pressure peaks pre and post transition

This is an image of the peaks of the blood pressure traces from the acquisition system. The dotted line in the middle represents the transition points.

2.3.3.3 Measurement of haemodynamic changes

After accurate identification of the transition between pacemaker settings, changes in acute haemodynamics can be measured. The software can analyse any number of haemodynamic measurements which have been collected using our acquisition system. Work from our group has suggested that systolic blood pressure has the best properties in terms of efficiency and reproducibility (Whinnett, Davies, et al. 2008). The algorithm will measure relative changes in systolic blood pressure between transitions. The average systolic pressure at the "reference setting" is subtracted from the average systolic blood pressure at the "tested setting" for each individual transition. The number of beats which are averaged can be adapted in the analysis programme, but previous work indicates that one respiratory cycle offers the best properties (Whinnett et al. 2011), and usually this is in the range of 7-8 beats either side of the transition. The number of transitions is determined by the operator

collecting the data. The programme will generate and average for each transition at any given setting. The Matlab programme allows selection of the haemodynamic measurement to be analysed. For the non-invasive experiments with was non-invasive systolic blood pressure. For in the invasive experiments with was invasive systolic blood pressure.

2.3.3.4 Exporting of data for further analysis

For each experiment, where a range of AV or VV delays are tested at a given heart rate, the Matlab programme will export the data into an excel document for further analysis. For each AV or VV delay tested, the average BP change between transitions is exported for each individual transition. These values can be used for curve fitting on any spreadsheet software (Figure 2-8). Microsoft Excel (Microsoft, Redmond, WA, USA) was used for curve fitting in these experiments.

2.4 Data acquisition system for Doppler measurements

A GE Vivid-i echocardiography machine (GE Healthcare, UK) was used for acquisition of Doppler echocardiography measurments of the left ventricular out flow tract (LVOT). Images were acquired using a 1.5-3.6 MHz transducer (3S-RS).

To allow automated measurements of Doppler velocities through the LVOT, a customised data acquisition system was designed with real time images exported to a PC for further processing and analysis.

Using the VGA output, data is exported using video frame grabber (VGA2USB Pro, Epiphan Systems, Canada). Images on the screen of the echo machine are exported with the same colour depth and resolution (800 × 600). The frame grabber converts the analogue VGA signal to a digital RGB images which are provided as a 1D vector of pixel values. Images were acquired at 40 frames per second, which is higher that

the 30Hz refresh rate on the screen and VGA output, so no images were lost during transfer.

It was essential that no settings were changed during acquisition of the Doppler traces such as scaling, gain, or movement of the baseline.

2.5 Automated algorithm to automatically trace around Doppler flow measurements

2.5.1 Creating a single long strip of Doppler images

The images acquired and collected on the PC are then processed using specialised software developed by the group and automated measurements are made of the Doppler traces.

Before automated measurements can be made, it is necessary to reconstruct the Doppler trace into a single continuous trace for each recording. The raw images are transferred in a vast number of frames, and each frame contains a rectangular segments with the Doppler trace (the Doppler region) and other surrounding images from the display on the echo machine. First the surrounding images must be removed. Four different predefined layouts exist for the GE Vivid-i machine. A bank of templates for these layouts together with template matching techniques are used to automatically crop the captured frames to leave the Doppler-region.

Template matching is also used to determine the scale of the axes from the images uploaded. This is done by extracting templates of numbers for the machine with its font, size and colour. After the boundary of the Doppler region is detected, the template matching technique searches for the relevant numbers along the boundaries.

The horizontal axis (zero velocity line) is identified as the maximum pixel value in each row of the Doppler region.

On the GE Vivid-i, the Doppler signal is updated between frames by sweeping the Doppler image using a sliding bar from the left of the screen to the right. Each frame thus contains a mixture of information from the preceding frame and new information. The location of the sliding bar can be calculated by comparing consecutive frames and identifying the segment where the pixel values differ. If a graph is plotted showing the location of the sliding bar against the frame number, a "zigzag" line is produced, with the sharp drops in the zigzag representing when the bar reaches the end of the Doppler region and restarts from the left.

The information from the consecutive frames can then be collated to from a single long Doppler strip.

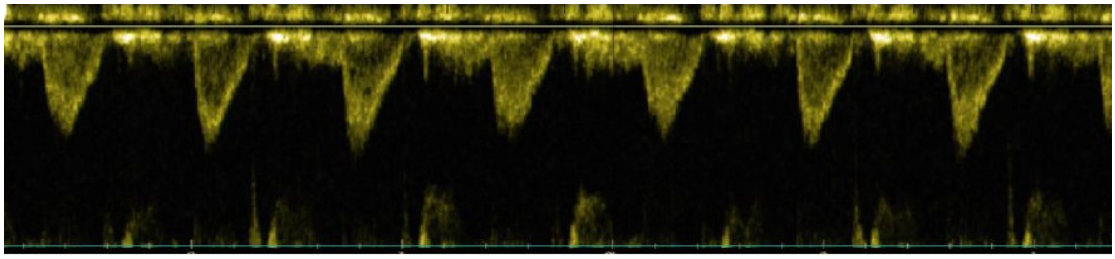

Figure 2-12 Image of a reconstructed Doppler Strip
Image of a reconstructed Doppler strip using this novel piece of software. Adapted from Zolgharni et al. 2014.

2.5.2 Automated tracing of Doppler traces

Manual tracing of long segments of Doppler is labour intensive and vulnerable to observer bias. For this reason, an automated algorithm was developed and validated to allow automated tracing of the Doppler profiles (Zolgharni et al. 2014).

A number of steps are applied to the long Doppler trace to facilitate automated measurement. First an objective thresholding technique is applied to isolate required part of the Doppler trace from background speckle noise and aliasing. The RGB Doppler image acquired is converted into a gray-scale image from a weighted sum of the R, G, and B component (0.299 x R + 0.587 x G + 0.114 x B).

Each pixel will have a different level of intensity. A threshold is used to define above which level of intensity a pixel is converted to white (1), and below which a pixel is converted to black (0). The optimum threshold is chosen as the value where the largest number of pixels turn from white to black. The binary black and white image is then used for further analysis (Figure 2-13).

The binary image usually has elements of noise spread across different parts of the image. To filter these out, connected areas that have fewer than 500 pixels are removed. The maximum velocity profile is then constructed using biggest-gap method (Greenspan et al. 2005).

The images is panned from left to right. Individual columns of the image represent a vector containing black and white pixels. The gaps is defined as a cluster of consecutive black pixels. The pixel at the beginning of a gap is defined as one point on the velocity profile.

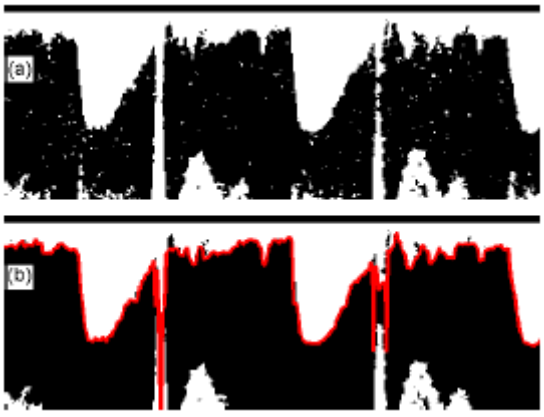

Figure 2-13 Processed binary image of LVOT Doppler

Image of a binary image generated from a LVOT Doppler trace to facilitate automated tracing. Adapted from Zolgharni et al. 2014.

Despite the methods described to eliminate noise, there may yet be some noise spikes on the extracted profile. This technique uses Doppler data to estimate mean cardiac cycle length (previously been validated on a subset of data where ECG data was also available (Zolgharni et al. 2014)). To filter out high frequency noise, a low-pass first order Butterwoth digital filter is applied to the initial velocity profile using the cardiac cycle length as the cut-off frequency. Any frequency 10 times higher than this is filtered out. The processed profile is plotted and superimposed on the original (Figure 2-14). The low pass filter also removes high amplitude outliers and artefacts in the velocity profile to allow individual cardiac cycles to be isolated.

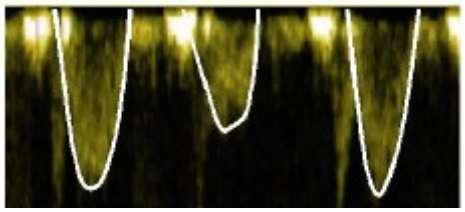

Figure 2-14 A processed profile superimposed on the original Doppler recording

The processed profile used for automated measurements is superimposed on the original reconstructed Doppler recording. Adapted from Zolgharni et al. 2014.

The peak points are then identified on the smoothed velocity curve. To filter out any remaining high amplitude artefacts remaining after the filtering process, a constraint is imposed that any distance between two consecutive peaks should not be smaller than 80% of the cycle length. The peak points are labelled as black dots.

The velocity of each single cardiac cycle was considered to start at the base-point (B1), reach a peak (P), and finish at a base-point (B2). To detect the location of the

base points, the first derivative of the velocity curve is calculated and the local minma either side of the peak is selected. A third order Gaussian model was fitted to the velocity profile to obtain the final LVOT trace. The model is extended beyond B1 and B2 to give the zero-velocity horizontal axis. Curve fitting is performed for each individual heart beat, and the peak and velocity are calculated. The scaling ratios are used to convert pixel units to cm/s and cm (Zolgharni et al. 2014)

Section 1: Challenges of quantifying response and optimisation

3 Meta-analysis of symptomatic response attributable to the pacing component of Cardiac Resynchronisation Therapy

3.1 Abstract

Background

Prognostic benefit from cardiac resynchronisation therapy (CRT) against controls is well established. Symptomatic response rates, however, are controversial and have never been systematically evaluated with standard subtraction of control rates to establish the incremental symptomatic response effect of CRT pacing.

Method and Results

First, my colleague and I identified 150 consecutive CRT papers and assessed researchers' perceptions of the symptomatic response to CRT. The mean quoted response rate was 66%. Only 26 studies acknowledged the existence of response without the device.

Second, I examined actual symptomatic response rates in the randomised trials (CARE-HF, COMPANION, CONTAK-CD, MIRACLE, MIRACLE-ICD, MIRACLE-ICD II, MUSTIC, and REVERSE) totalling 3904 patients. NYHA status improved in 51% of those randomised to CRT versus 35% of controls (incremental effect 16%). This incremental improvement was significantly greater in open studies (with no device for controls) than blinded studies (control arm receiving a device but no CRT, such as a defibrillator or a CRT programmed off), 20% versus 13%, $p<0.001$.

Conclusions

Quoting CRT responder rates in isolation without recognising spontaneous "response", is common but unwise. The incremental symptomatic response rate from CRT pacing is ~16%, much lower than widely reported. This value is similar to that for drugs in heart failure and should not be considered disappointing: they both exert

powerful prognostic benefits. For scientific purposes, e.g. to explore potential improvements, symptomatic benefit from CRT should be quantified, like all other effects, by comparison to control.

3.2 Introduction

Descriptions of the benefits of CRT on survival and hospitalization are rightly always described by comparison to randomised control groups who do not receive CRT. Large clinical trials and meta-analyses have consistently demonstrated prognostic benefits, with clear reductions in mortality (Cleland et al. 2001; Bristow et al. 2004; Higgins et al. 2003; Bertoldi et al. 2011; Adabag et al. 2011), but understanding the symptomatic benefit from this therapy is less straightforward. Many patients symptomatically improve in clinical trials of CRT, even in the non-CRT arm (Linde et al. 2008).This might be due to natural history, placebo effects or being part of a clinical trial.

In this study I set out to determine from the CRT literature whether the conventional scientific approach of subtracting this control-arm improvement rate from the active-arm rate is widely used, and what the incremental symptomatic response attributable to CRT actually is.

This distinction, between observed changes in symptoms with CRT and the net benefit truly attributable to CRT, is important for two reasons:

1. To allow clinicians to provide information to enable patients to give accurate informed consent.

2. To protect researchers, working to improve selection criteria and new methods of delivering CRT, from assuming that responder rates are already high and a small improvement might make it complete. If it is found that commonly-quoted symptom response rates are overstated, the scientific fields of patient selection and

advancement of methods for delivering CRT may be more open than we may assume, and researchers may become less satisfied with achieving symptomatic improvement.

This study is in two parts and was carried out by me with the assistance of a senior house officer (Z Chen). First we analysed the heart failure community's published perception both of what response rates to CRT are, and of how symptomatic response rate should be evaluated: do they recognise the possibility of "spontaneous symptomatic response" to no CRT, i.e. the response rate in the control arm of a randomised controlled trial of CRT where a device is implanted but programmed not to deliver therapy? Second, I conducted a systematic review of randomised, controlled trials to establish a placebo-subtracted symptomatic response rate to CRT that eliminates bias using a range of established markers of heart failure symptoms such as NYHA score, and Minnesota Living with Heart Failure Score. I then assessed whether there is any difference between the symptomatic response rates in the non-CRT arm between blinded trials (where patients have CRT devices implanted which are programmed not to deliver therapy) and open trials (where patients in the non-CRT arm have no device).

3.3 Methods

3.3.1 Assessment of the published perception of the rates of symptomatic improvement to CRT

A Pubmed search was performed by my colleague (Z Chen) according to a protocol designed by me. The search used the terms (MeSH) “cardiac” OR "heart" AND “resynchronization” AND "therapy" OR "therapeutics" 150 consecutive papers in the English language (January 2006 to October 2011) were reviewed in order to gauge the scientific community’s current perception of the symptomatic effects of CRT. From each of these papers we extracted information concerning quoted response rates including the following:

1. Whether symptomatic response or non-response with CRT has been mentioned at any stage in the paper.

2. Whether the symptomatic response with CRT was compared with a control arm response.

3. Whether the authors give a number or word to describe the proportion of symptomatic non-response.

3.3.2 Systematic review of randomised controlled trials to calculate the symptomatic response truly attributable to CRT

3.3.2.1 Selection of trials

I searched the Pubmed database for (MeSH) “Cardiac Resynchronization Therapy” activating the “Randomized Controlled Trials” limit, and analysing papers in English (search performed 10th October 2011). Of the 158 papers listed under this category, only papers which compared a CRT arm with a non-CRT arm were included (total: 61). The non-CRT arm could be either no device (an open comparison study, where it

was clear to both patients and investigators which arm the patient was randomised to) or a CRT device with the LV lead programmed off (blinded comparison study, whether the patients ± investigators were unaware of the group into which the patient had been randomised). Duplicate publications from the same trial were excluded, leaving a total of 12 studies. Of these 12 studies, the RethinQ trial was excluded as the selection criteria for CRT (narrow QRS) was quite different from all the other large trials included (Beshai et al. 2007).

These 11 trials were then screened to search for both baseline and follow up data on different measures of symptomatic response to CRT. These included: NYHA score (Anon 1994), Clinical Composite Score (Packer 2001), six minute walk test, measure peak VO2 on cardiopulmonary exercise testing, and Minnesota Living with Heart Failure Score (MLWHF) (Rector & Cohn 1992). Such data were present in eight of the trials.

3.3.2.2 Analysis of Symptomatic Response

For NYHA Score and Clinical Composite Score which provide categorical variables, the number and proportion of participants who reported an improvement in response was recorded in both of the arms (CRT and non-CRT). For Minnesota Living with Heart Failure Score, peak VO_2 and six minute walk test (which all provide continuous variables), the change in score was noted pre and post CRT. Analysis of results was divided according to the blinding methodology – blinded (CRT implanted in both groups, but switched off in control arm) and open (no CRT implanted in control arm). In COMPANION, the CRT-P arm was compared with the control arm (Bristow et al. 2004).

3.3.2.3 Statistics

For each of the parameters listed above, a weighted average across the clinical trials was calculated for both the CRT arm and the control arm. The difference in response between the two groups is presented as the incremental benefit truly attributable to CRT. A three way contingency table and chi square test was performed to assess for the effect of blinding and CRT response for NYHA class. A Fisher's exact test was performed for Clinical Composite Score. For the continuous variables, data on the standard deviations of the differences in responses were not available for all the trials, precluding calculation of a test statistic. Statistical analyses were performed on SPSS version 16 (IBM, New York).

3.4 Results

3.4.1 Assessment of the published perception of the rates of symptomatic improvement to CRT

Of the 150 publications identified from the Pubmed search 119 mentioned a response rate. Symptomatic response rate was specifically mentioned in 84 (70.6%). Of these, only 26 (21.8%) mentioned this response in comparison to the response in the control arm (Figure 3-1). 6 (23.1%) of these 26 papers did not provide a numerical value for response rate. 2 papers (7.7%) provided values of responses to CRT only and did not mention the numerical value for response rate in the control group. 18 papers (69.2%) provided numerical values for responses to both CRT and control, and statistically compared these response rates. However, in no publication was an absolute difference between response rates in the two groups expressed as a single figure.

44 (37.0%) of the 119 papers that mentioned response rate specifically described the presence of non-responders to CRT. A figure was quoted for the "non-response" in 33 of these papers. Values for non-response rates with CRT given in the papers either gave a single value, minimum and maximum value, or a maximum or minimum value alone (e.g. "up to X% of patients do not respond"). If only the upper or lower limit for non-response was mentioned, averages were calculated for these (Table 3-1). For the studies where a single value for response rate was quoted, the values were averaged across the studies and the mean response rate was calculated to be 66%. Where maximum non-response was quoted, the minimum response rate was calculated to be 65%. Where a range of non-response was quoted, the average response rate range was calculated as 61%-75% For the purpose of this study, where both echocardiographic and clinical responses were quoted, only the clinical non-

response rate was taken. Where papers mentioned response rather than non-response, the mean response rate was 65%.

Table 3-1 Response rates quoted in the literature

	Study	% Non-responders	Based on
Studies that quoted "Up to X%"	K. O'Connor *et al.*	up to 40	does not specify
	M. Pu and WT. Abraham	up to one third	does not specify
	M. Becker *et al.*	up to one third	echo and clinical
	N. Reinsch *et al.*	up to 30	clinical
	M. Sermesant *et al.*	up to 30	echo and clinical
	N.R. Van de Veire *et al.*	up to 30	echo and clinical
	C. Ypenburg *et al.*	up to 50	Echo
	J. Holzmeister and C. Leclercq	up to 35	Clinical
	Mean % non-responders: Up to 35.2	**Minimum response rate: 64.8%**	
Studies that quoted "X%"	J Janoušek *et al.*	18.5	echo and clinical
	M.G. Scheffer *et al.*	20.5	echo and clinical
	A. Auricchio *et al.*	30	does not specify
	S. Kirubakaran *et al.*	30	does not specify
	R. Manzke *et al.*	70	does not specify
	M. Moonen *et al.*	30	does not specify
	N.M. van Hemel and M. Scheffer	30	echo and clinical
	R. Chung *et al.*	30	does not specify
	H. Wiggers *et al.*	30	clinical
	R.J. van Bommel *et al.*	38	echo and clinical
	R. Gradaus *et al.*	30	echo and clinical
	G.B. Bleeker *et al.*	30	clinical
	G.B. Bleeker *et al.*	40	echo
	B.W.L. De Boeck *et al.*	30	clinical
	Q. Zhang *et al.*	46.2	echo
	C. Ypenburg *et al.* Q Zhang *et al.*	30 33	clinical does not specify
	Mean % non-responders: 33.3	**Maximum response rate: 66%**	
Studies that quoted a range	M. Bertini *et al.*	10 to 50	echo
	M. Fox *et al. A1*	11 to 26	clinical
	M. Fox *et al. A2*	40 to 46	echo
	C.M.C. van Campen *et al.*	18 to 50	does not specify
	K. Albouaini *et al.*	20 to 30	does not specify
	A. Manovel *et al.*	20 to 30	does not specify
	E. Liodakis *et al.*	20 to 30	clinical
	E. Liodakis *et al.*	30 to 40	echo
	A. Muxí*et al.*	20 to 30	echo and clinical
	G. Leibundgut *et al.*	25 to 30	does not specify
	S. Buck *et al.*	30 to 40	does not specify
	A.J. Turley *et al.*	30 to 40	clinical
	I.K. Russel and M.J.W. Gotte	30 to 50	does not specify
	J. Holzmeister *et al.*	40 to 50	echo
	B.W.L. De Boeck *et al.*	35 to 40	echo
	Mean % non-responders: 25.3 to 38.8	**Maximum response rate: 74.7%**	

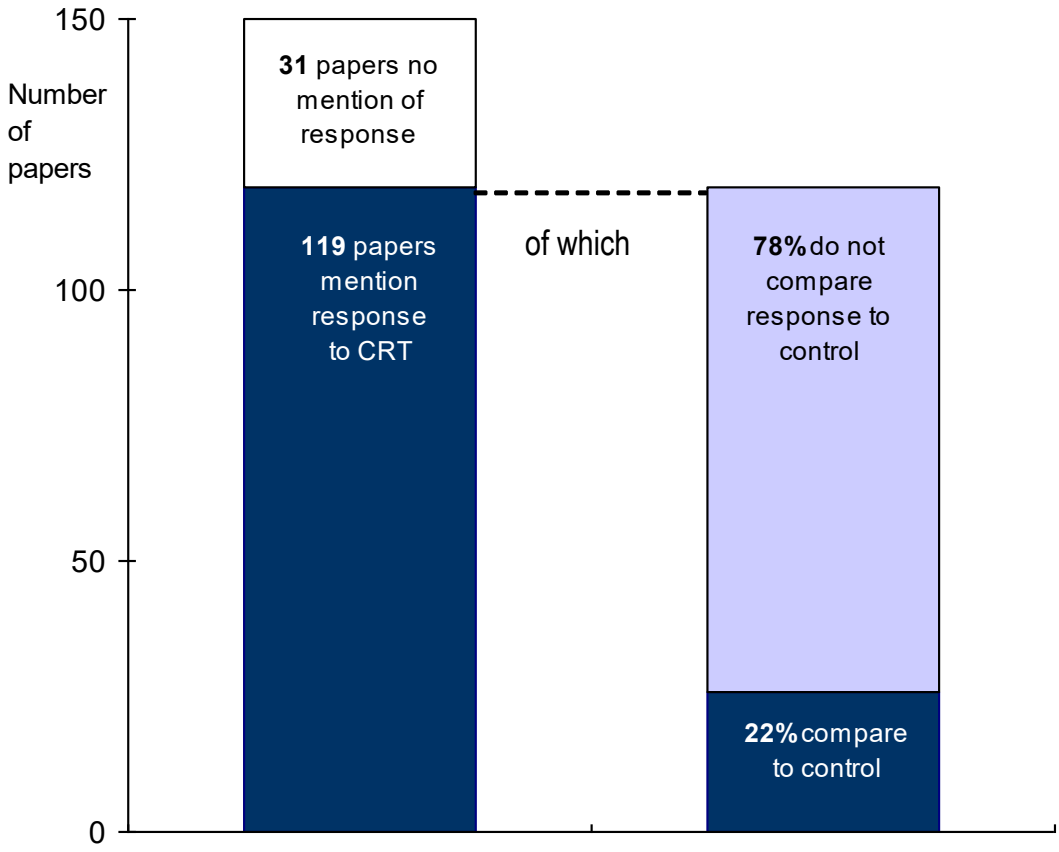

Figure 3-1 Method of analysis of CRT response in the CRT literature

Of the 150 publications identified from the Pubmed search the proportion which refer to response with CRT, and those which compare to control is illustrated.

3.4.2 Systematic review of randomised controlled trials to calculate the genuine symptomatic response truly attributable to CRT

A total of eight trials were eligible for the analysis (Cleland et al. 2005; Bristow et al. 2004; Higgins et al. 2003; Linde et al. 2008; Abraham et al. 2002; Young et al. 2003; Cazeau et al. 2001; Abraham et al. 2004) incorporating 3904 patients (Table 3-2).

Table 3-2 Summary of Trials included

CARE HF: CArdiac REsynchronisation in Heart Failure study (Cleland et al. 2005), Companion: Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (Bristow et al. 2004), Contak CD (Higgins et al. 2003), MIRACLE: Multicenter InSync Randomized Clinical Evaluation (Abraham et al. 2002), MIRACLE ICD (Young et al. 2003), MIRACLE ICD II (Abraham et al. 2004), Mustic: Multisite Stimulation in Cardiomyopathies Trial (Cazeau et al. 2001), REVERSE: REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction Trial (Linde et al. 2008)

Trial	Patients Blinded?	Total Participants		Follow up (months)	Baseline NYHA Class
		CRT	Control		
MIRACLE	Yes	225	228	6	III/IV
MIRACLE ICD	Yes	182	187	6	III/IV
MIRACLE ICD II	Yes	101	85	6	II
REVERSE	Yes	419	191	6	I/II
Mustic	Yes	29	29	3	III
Contak CD	No	245	245	6	II/III/IV
Companion	No	617	308	6	III/IV
CARE HF	No	409	404	3	III/IV

3.4.3 NYHA Response

Of the eight randomised trials, five reported symptomatic response rates using the NYHA classification (Table 3-3). Using a weighted mean across all of the studies, there was an improvement in NYHA class in 51% of participants in the CRT arm, compared with 35% in the control arm (Figure 3-2). This suggests that of a group of 100 patients with CRT devices implanted, 16 would have an improvement in breathlessness as measured by NYHA class resulting purely from cardiac

resynchronisation. A significant difference was detected between the responses seen in the open trials versus the blinded trials ($p<0.001$) with the improvement attributable to CRT greater in the open trials (20%) where the patients in the control arm had no device, versus the blinded trials (13%) where all patients had CRT devices implanted. The absolute increase in NYHA in the CRT arm of the open studies (56%) is numerically higher than the blinded studies (48%). Patients in the blinded studies, which included REVERSE, had milder symptoms at baseline, which might explain their smaller decrement in symptoms. A stratified analysis by baseline symptoms is included in the data supplement.

Table 3-3 Change in NYHA class (%) truly attributable to cardiac resychronisation (CRT minus control) – comparison between open and blinded randomised controlled trials

	Control			CRT			CRT minus control		
Blinded	Worse	Same	Better	Worse	Same	Better	Worse	Same	Better
MIRACLE	4	59	38	2	30	68	-2	-29	30
MIRACLE ICD	5	45	50	3	30	67	-2	-15	17
REVERSE	9	70	20	10	59	31	1	-11	10
Weighted Mean			34			48			13
Open									
Contak CD	17	51	32	13	51	36	-4	0	4
Companion (CRT-P)	62		38	39		61	-23		23
Weighted Mean			36			56			20
Weighted Mean of All Studies			35			51			16

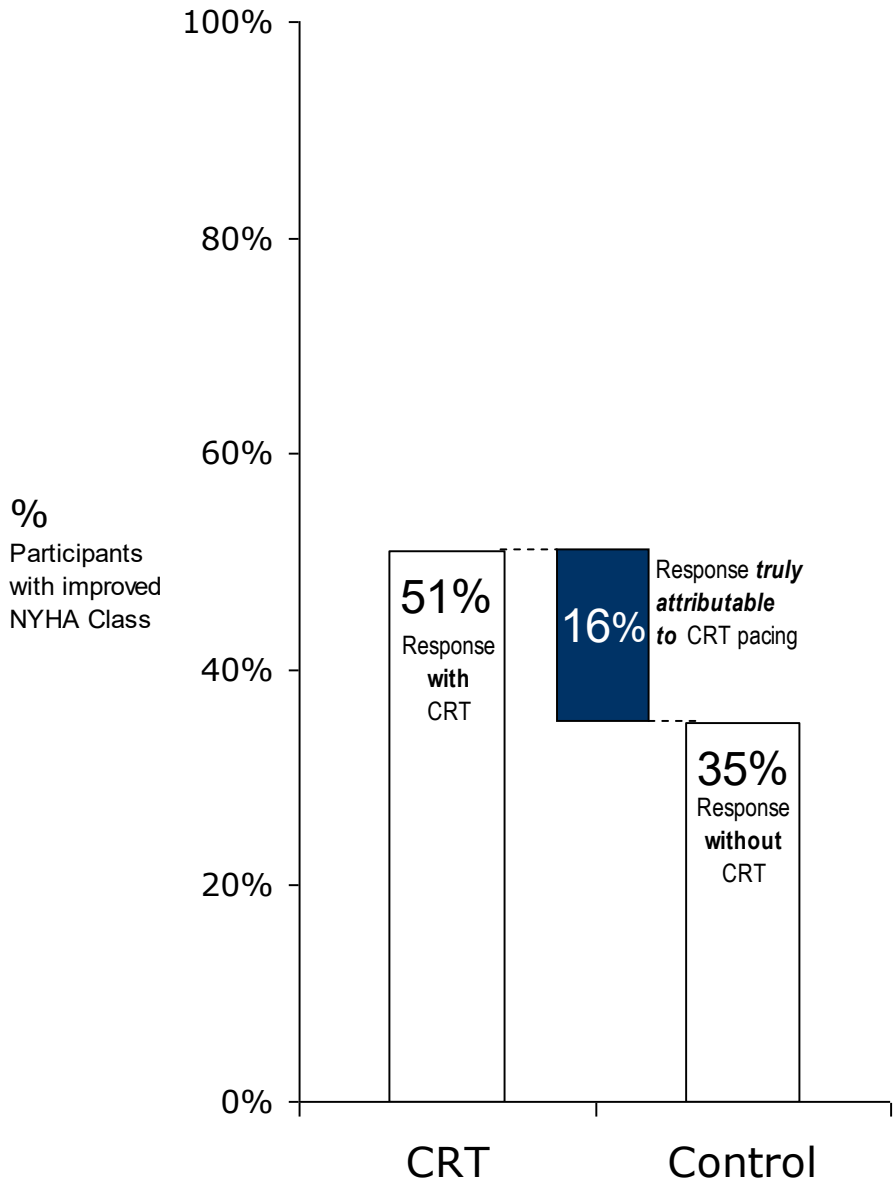

Figure 3-2 Improvement in NYHA Score truly attributable to CRT

The proportion of patients who show an improvement across the treatment and control arms of the trials is illustrated. Only 16% of the improvement can be truly attributed to CRT pacing.

3.4.4 Composite Clinical Score

The clinical composite score has been commonly used as a measure of heart failure response in a range of clinical trials (Packer 2001; Chung et al. 2008; Barosi et al. 2011). The score combines three separate markers of the symptomatic severity of

heart failure: the first is hospitalisation due to heart failure or death, the second is change in NYHA class, and the third is the patient's perception of their symptoms using the Patient Global Assessment score. Based on these measures, the patient can be classified as better, the same, or worse. Improvements in the NYHA score and Global Assessment score categorise the participants in the "better" group. Death, hospitalisation or a fall in the other two measures categorise the participants in the "worse" group. All others come under the "unchanged" category.

The Clinical Composite Score at baseline and follow up was available in three of the trials (Table 3-4). In all three, the patients were blind to the treatment they had received. Across all the groups, a mean of 54% of patients in the CRT arms of the trials had an improvement in the clinical composite score, compared to a 40% improvement in the control arm ($p<0.001$). This suggests that based on this scoring system, 14 patients out of every 100 having CRT devices implanted will have incremental benefit from cardiac resynchronisation (Figure 3-3).

Table 3-4 Response in Clinical Composite Score truly attributable to CRT therapy (CRT minus control)

	Control			CRT			CRT minus Control		
	Worse	Same	Better	Worse	Same	Better	Worse	Same	Better
Trial	%	%	%	%	%	%			
REVERSE	21	39	40	16	30	54	-5	-9	14
MIRACLE ICD	33	24	43	33	15	52	0	-9	9
MIRACLE ICD II	31	34	36	20	22	58	-11	-12	22
Weighted Mean	28	32	40	21	25	54	-7	-7	14

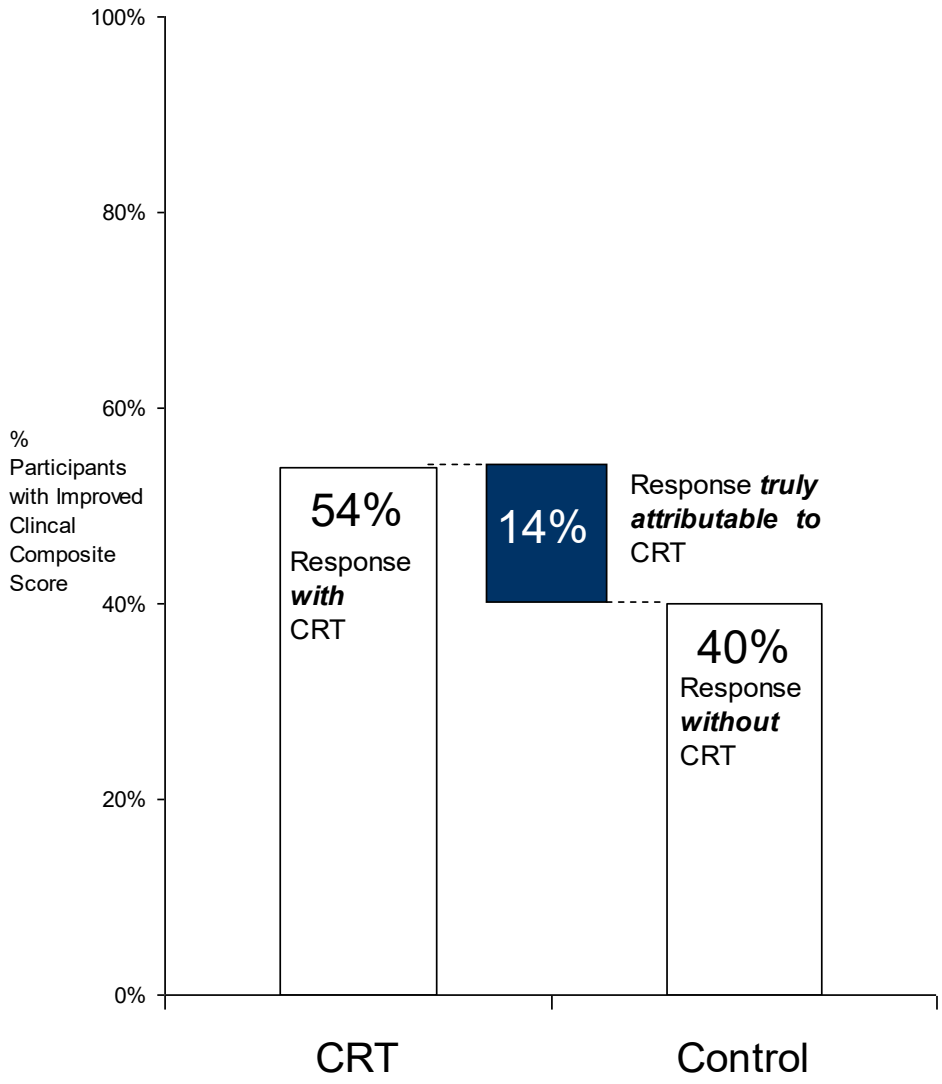

Figure 3-3 Symptomatic Response to CRT (Clinical Composite Score)

The proportion of patients who show an improvement across the treatment and control arms of the trials is illustrated. Only 14% of the improvement can be truly attributed to CRT pacing.

3.4.5 Quality of Life Scores: Minnesota Living with Heart Failure Questionnaire.

Quality of life scores intend to provide a measure of the overall impact of heart failure on the patient's life and can provide an insight into the impact of heart failure symptoms beyond exercise capacity and breathlessness. The Minnesota Score is a widely used marker and was measured at baseline and follow up in seven of the trials.

A score of up to 105 is generated from a series of questions, the higher the score, the worse the estimated effect on quality of life. A 17 point improvement was seen in the MLWHF score with CRT. By deducting the effect seen in the control group, it became apparent that an 11 point improvement in the score is truly attributable to CRT pacing (Table 3-1).

As with change in NYHA status, the incremental effect of CRT pacing (i.e. CRT minus control) was greater in the open than the blinded trials (13.3 versus 7.4). This difference was due to the greater improvement in the score in the control arm of the blinded trials compared to the control arm response of the open trials (9.5 versus 3.9); responses in the CRT arms of the two types of trials were very similar 16.9 versus 17.3). This suggests that there is a measurable placebo effect above and beyond the spontaneous improvement found in the open trials (Figure 3-4).

Table 3-5 Changes in Minnesota Living with Heart Failure Score.

	Minnesota Living with Heart Failure Score (Improvement from baseline)		
	Control	**CRT**	**CRT minus Control**
Blinded			
MIRACLE	9	18	9
MIRACLE ICD	11	17	6
MIRACLE ICD II	10.7	13.3	2.6
Mustic	3.8	17.4	13.6
Weighted Mean	9.5	16.9	7.4
Open			
CARE HF	4.8	14.5	9.7
Companion	12	25	13
Contak CD	-5	7	12
Weighted Mean	3.9	17.3	13.3
Weighted Mean of All Studies	6.0	17.2	11.2

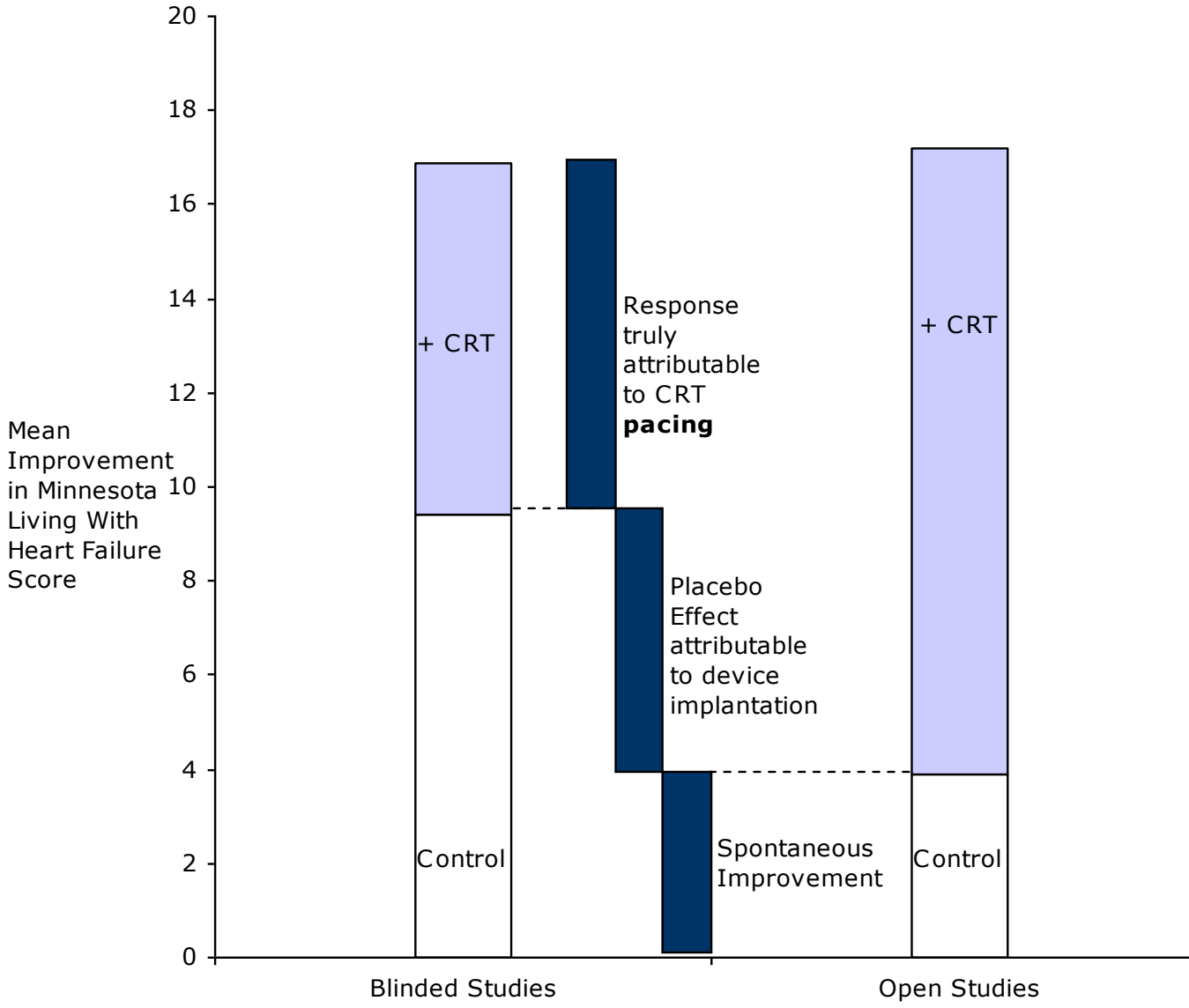

Figure 3-4 Comparison of symptomatic response in Open versus Blinded studies measuring improvement in Minnesota Living with Heart Failure Score

Similar degrees of improvement are seen in the CRT arms of both open and blinded trials. In the blinded trials, a greater improvement is seen in the controls, indicative of a placebo response to device implantation.

3.4.6 Change in Exercise Capacity: improvements in six minute walk distance and Peak VO2 Response truly attributable to CRT

Six of the trials had baseline and follow up data for six minute walk distances, and of these, five had baseline and follow up cardiopulmonary exercise test data (peak VO2) and four were blinded (Table 3-6).

Six minute walk distance improved in both the control and CRT arms of all trials. There was greater incremental effect of CRT arm in the open studies, because of less control arm response than in the blinded studies.

In contrast, although there was an increase in peak VO2 in the CRT arm of all trials, both blind and open, participants in the control arms of both types of trial had minimal response.

Table 3-6 Change in six minute walk and peak VO_2 with CRT

	Follow up Data (Increase from baseline)					
	△ Six minute walk (m)			△ Peak VO_2 (ml/kg/min)		
	Control	**CRT**	**CRT minus Control**	**Control**	**CRT**	**CRT minus Control**
Blinded						
MIRACLE	10	39	29	0.2	1.1	0.9
MIRACLE ICD	52	55	3	0.1	1.1	1
MIRACLE ICD II	33	38	5	0.2	0.5	0.3
MUSTIC	-24	49	73	1.2	2.4	1.2
Weighted Mean	25	45	20	0.3	1.1	0.9
Open						
Companion (CRT-P)	1	40	39	.	.	.
Contak CD	15	35	20	0	0.8	0.8
Weighted Mean	10	38	29	0	0.8	0.8
Weighted Mean of All Studies	18	41	23	0.2	1.0	0.8

Table 3-7 Stratification of results by baseline NYHA Class

1. NYHA Class

Percentage of patients

	Control			CRT			CRT minus control		
NYHA I/II	Worse	Same	Better	Worse	Same	Better	Worse	Same	Better
REVERSE	9	70	20	10	59	31	1	-11	10
Weighted Mean			20			31			10
NYHA III/IV									
MIRACLE	4	59	38	2	30	68	-2	-29	30
MIRACLE ICD	5	45	50	3	30	67	-2	-15	17
Contak CD	17	51	32	13	51	36	-4	0	4
Companion (CRT-P)	62		38	39		61	-23		23
Weighted Mean			39			60			21
Weighted Mean of All Studies			35			51			16

2. Minnesota living with Heart Failure Score

	Minnesota Living with Heart Failure Score (Improvement from baseline)		
	Control	**CRT**	**CRT minus Control**
NYHA I/II			
MIRACLE ICD II	10.7	13.3	2.6
Weighted Mean	10.7	13.3	2.6
NYHA III/IV			
CARE HF	4.8	14.5	9.7
Companion	12	25	13
MIRACLE	9	18	9
MIRACLE ICD	11	17	6
Mustic	3.8	17.4	13.6
Weighted Mean	8.0	19.2	11.2
Weighted Mean of All Studies	8.2	18.9	10.6

3. Six minute walk and Peak VO_2

	Follow up Data (Increase from baseline)					
	Six minute walk (m)			Peak VO_2 (ml/kg/min)		
	Control	**CRT**	**CRT minus Control**	**Control**	**CRT**	**CRT minus Control**
NYHA I/II						
MIRACLE ICD II	33	38	5	0.2	0.5	0.3
Weighted Mean	33	38	5	0.2	0.5	0.3
NYHA III/IV						
MUSTIC	-24	49	73	1.2	2.4	1.2
Companion (CRT-P)	1	40	39	.	.	.
MIRACLE	10	39	29	0.2	1.1	0.9
MIRACLE ICD	52	55	3	0.1	1.1	1
Weighted Mean	17	43	26	0.3	1.3	1.0
Weighted Mean of All Studies	20	43	23	0.3	1.1	0.9

3.5 Discussion

While there is no doubt that CRT improves survival (versus control) and improves symptoms, the symptomatic response rate reflected in the clinical research literature is arguably an overestimation of the incremental effect of CRT pacing itself. The actual incremental symptomatic improvement due to CRT pacing, as documented by large, systematically conducted, externally monitored and meticulously reported clinical trials, is 14-16%. Much of this overestimation is the result of failing to subtract the symptomatic improvement found in the control arm.

Defining response as improvement in NYHA, in these 5 major randomised clinical trials, control arm response was 35%. In their counterparts in the treatment arm who received CRT pacing, the symptomatic response rate was 51%. The presence of CRT pacing therefore increased response rate by 16 absolute percentage points.

3.5.1 Symptomatic response as a goal of CRT

Symptomatic response rates arouse great interest despite the intrinsic difficulties and poor reliability of the methods available for measuring them. They are frequently mentioned in the clinical literature (Figure 3-1) and sessions at scientific conferences are dedicated to discussing ways to reduce non-responder rates. It is conceivable that real world symptomatic response rates are even lower than calculated in this study, given the broadening of the indications for CRT in milder heart failure (Mcmurray et al. 2012). In the trials we studied, 2.7% of subjects were in NYHA I, 21.7% in NYHA II, 67.5% in NYHA III and 8% in NYHA IV. In patients starting with milder symptoms, symptomatic response rate attributable to CRT pacing might be even lower. In the REVERSE Trial and MIRACLE ICD-II trial where patients had milder symptoms to start with (NYHA I-II), symptomatic response rates were even lower

(Table 3-7). The presence of the REVERSE trial may give the impression that the overall improvements in NYHA class are lower in blinded studies than open studies; without REVERSE an opposite effect appears with the weighted percentage improvement in blinded studies increasing to 65% and overall to 60%.
Nevertheless there is no doubt over mortality benefit from CRT, which has been well established by randomised controlled trial *against no CRT* (Cleland et al. 2005). This study does not contradict the excellent survival and hospitalisation advantages conferred by CRT. Nor does it contradict the clear symptomatic benefits: it only suggests that the often-quoted responder rates are 4-fold larger than the incremental effect delivered by CRT pacing. It also highlights the importance of taking into account the study design when relaying conclusions from studies using symptoms as an endpoint.

3.5.2 Association between symptomatic benefits and improvements in markers of functional capacity (peak VO_2 and 6 minute walk test)

Symptomatic improvement is desirable but can arise from sources other than genuine physiological improvement. Comparison of blinded with open studies can be illuminating. For peak VO_2, an objective measurement, the control arm has only one fifth the response of the therapy arm, regardless of study design. For measurements such as six minute walk and MLWHF score where patient's attitudinal state may have a greater role, in open studies again the control arm has only about one fifth the response of the therapy arm, but in blinded studies the control arm has more than half the response of the therapy arm (Figure 3-4). Blinding enhances the response rates in the control arm for these variables.

3.5.3 Mortality versus symptomatic benefits

It is not universally agreed whether CRT should be considered a treatment to reduce the *risks* of an event such as death, or to improve *symptoms* from heart failure. If its primary purpose is event risk reduction, a lack of detectable change in symptoms in an individual should not be perceived as a therapy failure, and individual patients should not be classified into 'responder' and 'non-responder'. Prognostic and symptomatic improvements may not always be concordant: many patients benefit from reduced risk of events or deterioration, without any perceptible immediate symptomatic benefits. While in later disease, the symptomatic goal may be a detectable improvement, in earlier disease the symptomatic goal may be prevention of deterioration: this is impossible to confirm in individuals since no comparator arm is available.

It may not be wise to spend effort describing symptomatic improvement rates in individual patients, or to focus attention and studies on 'non-responders', since the great majority of response has nothing to do with CRT pacing.
Comparison to a control arm is already standard for discussion of death and hospitalization benefits of CRT. In CARE HF, mortality was 20% in the treatment arm was versus 29.7% in the control arm: 10 deaths prevented per 100 devices implanted. This large reduction in mortality compares very favourably with many cardiovascular treatments.

3.5.4 Does it matter whether the effect is caused by CRT pacing or not?

In an individual patient, it is not possible to tell in normal clinical practice, which of the three explanations (actual benefit of CRT pacing, placebo effect or spontaneous improvement/variation) is the cause of an observed improvement in heart failure

symptoms, just as it cannot be told for drugs. If a patient believes their CRT implant has improved symptoms, it may be good medical practice to allow that belief to stand. In scientific fora or scientific journals, however, we should avoid basing reasoning on effect sizes that include an extraneous added component (Nijjer et al. 2012), because (for example) it reduces our ability to compare two effect sizes, and thereby recognise subtle improvements in strategy**.** There are also costs to patients, health services and to research, of working from erroneous effect sizes of CRT pacing. Long term complications risk from implanting CRT devices is not trivial, with rates quoted between 4% and 28% (Daubert et al. 2012; Brignole et al. 2013a). For heart failure physicians to make the decision to offer CRT, and for patients to make an informed decision to proceed, they need reliable information on the actual effect of CRT pacing (Ioannidis 2005).

3.5.5 Comparison of the symptomatic benefits of CRT with other heart failure treatments

Despite the symptomatic response rates attributable to CRT being significantly lower than those commonly quoted, the number needed to treat for CRT would be ~6. In the context other recent innovations in cardiovascular medicine (Wallentin et al. 2009; Mehran et al. 2009), CRT compares favourably. It is greater than that of beta blockers or aldosterone antagonists and second only to ACE inhibitors (Table 3-8).

Table 3-8 Symptomatic improvement with pharmacological therapy after deducting the effect in the placebo arm (%)

	Placebo			Drug			Drug minus Placebo		
	Worse	Same	Better	Worse	Same	Better	Worse	Same	Better
ACE inhibitors	30	41	29	12	37	52	-20	-3	**23**
β-blockers	14	42	45	9	32	59	-12	-4	**10**
Aldosterone Antagonists	44	24	32	32	25	37	-11	0	**6**

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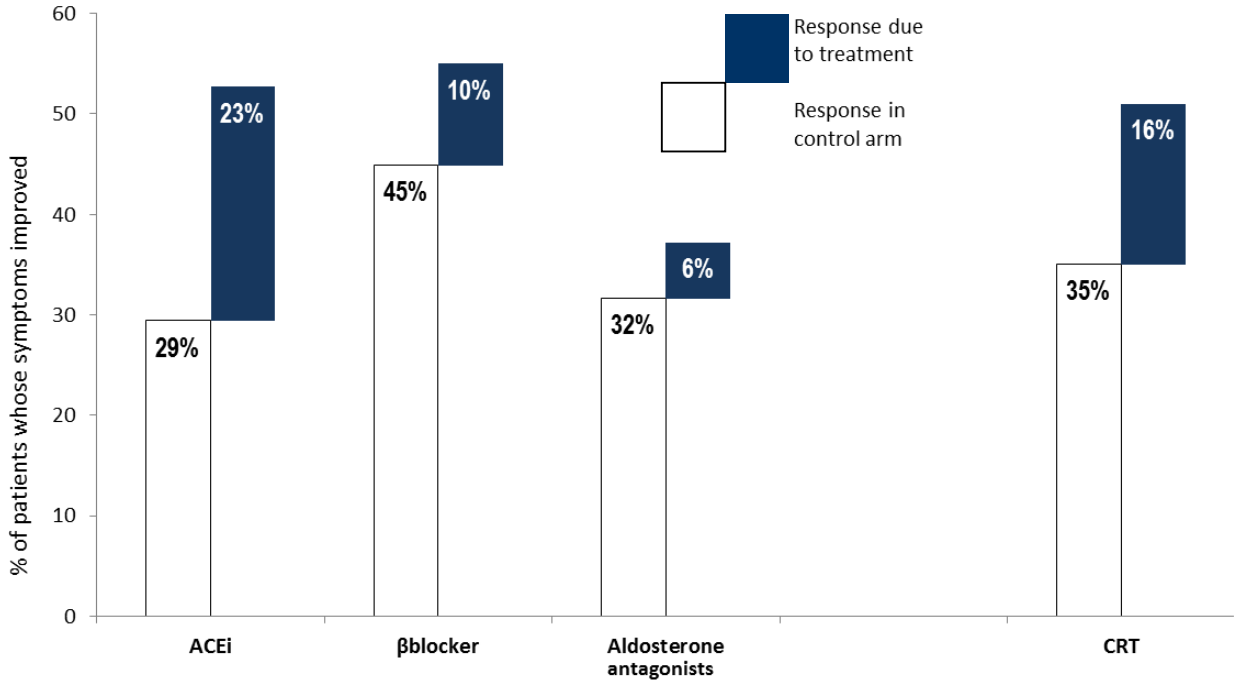


Figure 3-5 Symptomatic improvement with pharmacological therapy after deducting the effect in the placebo arm, compared to CRT

Symptomatic improvement with pharmacological therapy after deducting the effect in the placebo arm, compared to CRT. The proportion of patients who show a control arm subtracted symptomatic response to ACE inhibitor, Aldosterone antagonist, and beta blocker therapy for heart failure is compared to CRT

3.5.6 Distinction between individual and group-mean effects

Reliably assessing changes is vastly more difficult for individuals than for group mean effects. Averaged across a population, spontaneous changes within individuals (which can be in either direction) tend to average out, so that the underlying treatment effect becomes more evident. Clinical trials show benefits as a population average, not only for measurements, but also for hard endpoints since event rates too can be considered to be averages counting 1 for event and 0 for no event (Muntwyler et al. 2002).

However we should not assume we can usefully quantify the effect of CRT in individual patients with routine approaches (Kommuri et al. 2012). Assessing symptomatic effects in individuals in the conventional way is mostly unreliable, because previous status is an unsound control. Reverse remodelling documented by reductions in LV volumes has consistently shown an association with improvements in mortality, more consistently than other echocardiographic parameters across populations (Foley et al. 2009; Verhaert et al. 2010; Ypenburg et al. 2009). However, using these for *individualised* response prediction is difficult because of the unavoidable effect of chance (Nijjer et al. 2012; Shun-Shin & Francis 2012). When analysing any change in a continuous variable such as a chamber dimension on an echocardiogram, if the intervention were to have no effect there remains a 50% chance that when the measurement is repeated, it will be higher; and likewise a 50% chance that it will be lower.

If individualised response quantification is needed for research purposes it could instead be achieved by measuring a physiological marker with the device on and off, with the intra-individual error bar made as small as is needed by repeating the process enough times (Bogaard et al. 2010; Stegemann & Francis 2012) to quench the effect of noise. Just as the presence of symptomatic response does not signify that the pacing is having any useful effect, the lack of symptomatic response does not signify that the pacing is not having any useful effect. Patients who do not describe symptomatic response may still receive a prognostic benefit and should not be denied a treatment which offers this (Patwala et al. 2009).

This analysis has highlighted that markers of symptom response are affected by very many more phenomena than just biventricular pacing itself. Using symptomatic response, in a cohort without a control group, and without assessing differential response with pacing on and off, biases us to substantial overestimation of the pacing

effect on symptoms. Cognitive and psychological status may influence this bias. If it is purely desired to increase symptomatic response, as distinct from increasing the physiological benefits that lead to symptomatic response, future research might focus on interventions that are explicitly psychological.

3.5.7 Clinical implications

The widely perceived rate of symptomatic response rate to biventricular pacing is shown by the randomised controlled trials to be an overestimate of the CRT pacing effect itself. Even in trial populations who may be more optimistic than the general heart failure population, and even counting all causes of improvement in symptoms (spontaneous, placebo, and pacing-mediated):

- Only half report a symptomatic improvement;
- Of that half, two thirds would have reported improvement without pacing and only one third (~16% of all recipients) are reporting it specifically because of pacing.

Discussing this openly might be uncomfortable but is a scientific starting point to developing better methods of judging which individuals are receiving advantage from pacing itself (Figure 3-6).

Multiple randomised controlled trials, in which individual variability is damped down by averaging, have demonstrated beyond doubt substantial symptomatic and survival improvements with CRT across groups of patients: clinicians can continue with confidence to recommend CRT implantation in the same way that they do drug therapy. However, symptomatic change should not necessarily be the focus of individual consultations.

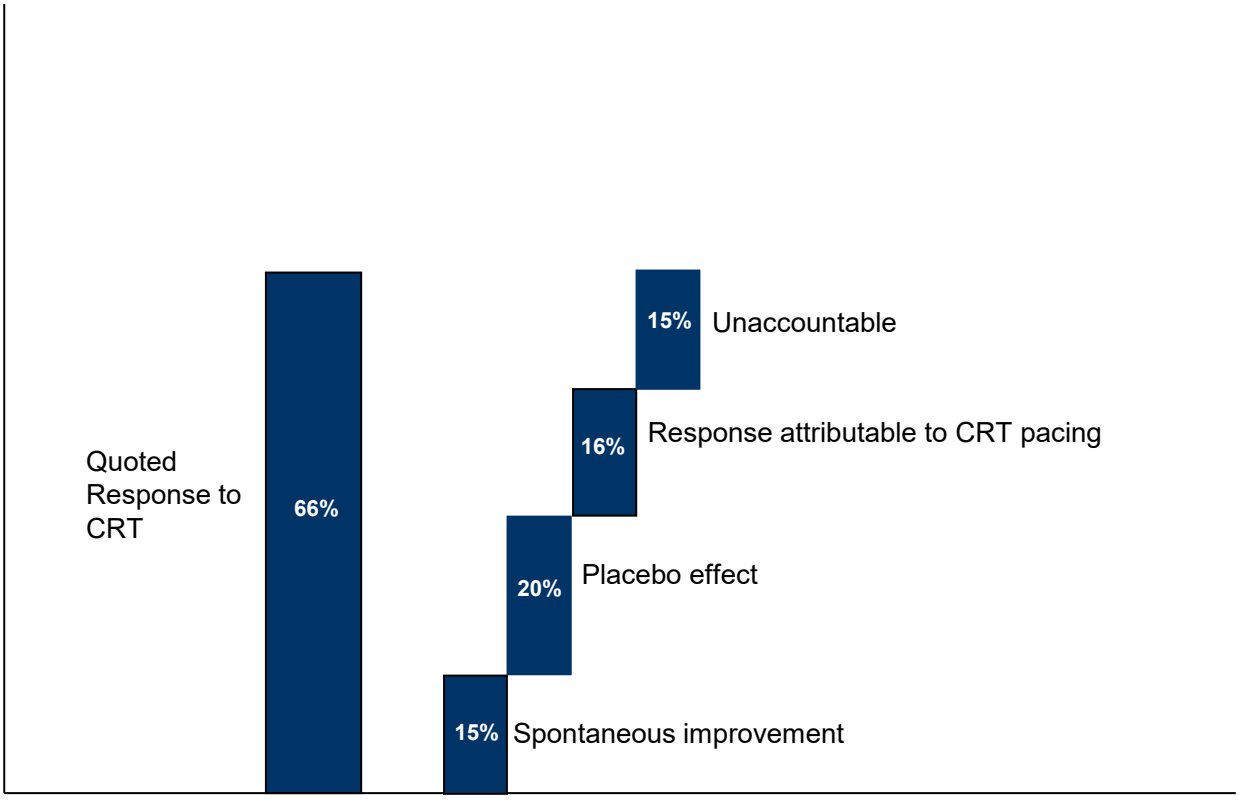


Figure 3-6 An example schematic to explain the contributors to the widely-recited 66% response rate to CRT

This graph illustrates how the overall symptomatic response to CRT could be divided. The proportion due to the physiological effects of pacing could be clearly defined, and the role of spontaneous improvement, and placebo (approximated from calculations using Minnesota Living with Heart Failure Score) could be defined.

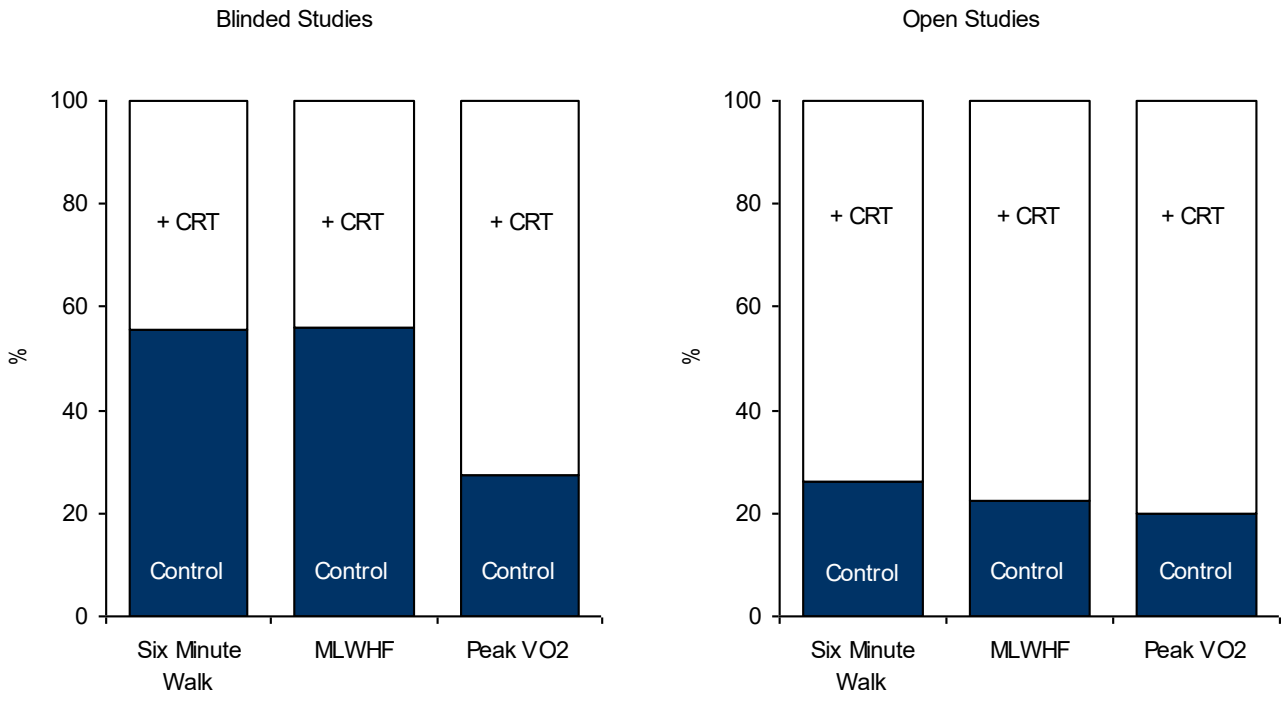


Figure 3-7 Comparison of symptomatic response in Open versus Blinded studies. Comparison of symptomatic response in Open versus Blinded studies. Improvement in control arms as a proportion of the CRT arm response is illustrated using Peak VO2, MLWHF Score, and Six minute walk distance. Open and Blinded studies are compared.

3.5.8 Study Limitations

We collated data from the large, carefully-conducted clinical trials which reported it. However, some recent trials, such as RAFT and MADIT CRT, did not show these data (Goldenberg et al. 2011; Tang et al. 2010). The trials in this systematic review used different methods to monitor symptomatic response. NYHA data is not available for all the trials listed here, and Clinical Composite Score is only present for four of the trials for example.

We cannot exclude changes in symptoms smaller than the resolution of the methods: NYHA class, by definition, is a crude measure of symptom response. While another scale with more gradations might detect smaller improvements in symptoms caused

by CRT, it would similarly detect smaller fluctuations arising for reasons other than the CRT. It is this presence of intercurrent variation in clinical state, and not failure of any individual index, that is the obstruction to useful determination of response to CRT in individuals. All of the markers of symptom response used in this study could all be classified as "soft end-points" which are very much influenced by the opinions of individual patients and physicians. The greater spontaneous improvement in the control arms of the blinded studies versus the open studies demonstrates this (Figure 3-4). We hope our study will stimulate the development of more reliable markers of response (Stegemann & Francis 2012) and more open discussion of variability over time and spontaneous improvement.

Our study examines a range of different methods for analysing symptom response. NYHA class and CCS are categorical variables, while changes in MLWHF score, and six minute walk distance continuous. For any continuous measured physiological variable, raw response rate with doing nothing is ~50%, because the value will not be the same the second time, and approximately half the time will be a little higher, and half the time a little lower.

In addition, the time point at which response rate is said to be two-thirds is not usually stated, but the only reliable sources of symptomatic response rates *to* CRT pacing itself – the controlled trials – reported at up to 6 months which was the reason we conducted our analysis at that time point. Symptoms may continue to improve over a longer period of time. Due to the success of CRT, many of the individuals in the control arms of these studies went on to receive CRT which prevents us from calculating a long-term control-subtracted response rate (Cleland et al. 2012). Available data regarding long term evolution of symptoms is only from observational data where it appears that non-control-subtracted long term symptom response is good (Bogale et al. 2012), but these results should be interpreted in the light of the

shorter-term data which are that symptomatic response in the control arm can be closer to that of the active arm than commonly realised.

Biventricular pacemakers are now commonly implanted in patients older than those in the trials analysed here (Bogale et al. 2012). There are no control-subtracted symptom data sub-stratified by age. However, the uncontrolled observational data in older patients suggest that symptom response is no different than in their younger counterparts (Verbrugge et al. 2013) and there is no reason to believe that age affects the distribution of the components contributing to observed response rate.

Patients with atrial fibrillation represent almost 1 in 5 patients with biventricular pacemakers (Bogale et al. 2012) and this is a group we have not studied closely in this analysis. However, data on this group of patients from randomised controlled studies is limited, with studies that have been very small (Leclercq et al. 2002), or based on subgroup analysis of larger trials where the study has not been specifically powered to address the question (Tang et al. 2010).

3.5.9 Conclusions

Symptomatic response rate to the pacing element of CRT is distinctly less than the two-thirds currently perceived by the scientific community. Symptomatic improvement *with* CRT in the clinical trial setting is 51%-54% depending on the measure used. Once the effect of spontaneous improvement is subtracted, the symptomatic improvement rate truly *attributable to* CRT pacing is only 14%-16%.

There are signs of a placebo effect in symptom endpoints: controls in blinded trials show improvements more nearly matching their CRT counterparts, than do controls in unblinded trials.

This analysis is not designed to detract from the clinical benefits or accomplishments of CRT as a discipline, or CRT research in general. It is designed only to analyze the

components of reported rates of CRT response, and scientifically to put the pacing-mediated component into the context of response rates with other therapeutic modalities that have been similarly assessed. The ultimate purpose is to provide clinicians with information that can be comparable between device and drug therapy, and to provide readers and researchers with a reliable frame of reference.

3.6 Contributions

This chapter arise from a study conceptualised by myself with my supervisor. The data extraction was carried out by myself and a colleague, and our roles are indicated in the methods section. The analysis was conducted entirely by myself under the supervision of my supervisor. Five consultants including my supervisor, as well as anonymous peer reviewers, guided me in the development of the discussion. The text of this chapter is published as "Sohaib SM, Chen Z, Whinnett ZI, Bouri S, Dickstein K, Linde C, Hayes DL, Manisty CH, Francis DP. Meta-analysis of symptomatic response attributable to the pacing component of cardiac resynchronization therapy. *Eur J Heart Fail*. 2013;15(12):1419-28."

4 Cardiac Resynchronisation Therapy Optimisation Strategies: Systematic classification, detailed analysis, minimum standards and a roadmap for development and testing

4.1 Abstract

In this chapter I worked with an international group of CRT specialists to write a comprehensive classification system for present and future schemes for optimising CRT. This system is neutral to the measurement technology used, but focuses on little-discussed quantitative physiological requirements. I then present a rational roadmap for reliable cost-effective development and evaluation of schemes. A widely recommended approach for AV optimisation is to visually select the ideal pattern of transmitral Doppler flow. Alternatively, one could measure a variable (such as Doppler velocity time integral) and "pick the highest". More complex would be to make measurements across a range of settings and "fit a curve".

This chapter provide clinicians with a critical approach to address any recommendations presented to them, as they may be many, indistinct and conflicting. I present a neutral scientific analysis of each scheme, and equip the reader with simple tools for critical evaluation. Optimisation protocols should deliver: (a) singularity, with only one region of optimality rather than several; (b) blinded test-retest reproducibility; (c) plausibility; (d) concordance between independent methods; (e) transparency, with all steps open to scrutiny. This simple information is still not available for many optimisation schemes.

Clinicians developing the habit of asking about each property in turn will find it easier to winnow down the broad range of protocols currently promoted. Expectation of a sophisticated enquiry from the clinical community will encourage optimisation protocol-designers to focus on testing early (and cheaply) the basic properties that are vital for any chance of long term efficacy.

4.2 Introduction

Clinicians rightly look for large endpoint trials to guide therapeutic choices. While for dichotomous choices with large effects (such as implanting a device versus not) this has been effective, for therapeutic decisions with more numerous choices and likely smaller effects this approach in isolation may be inefficient. The process of optimizing atrioventricular (AV) and interventricular (VV) delay of biventricular pacing (cardiac resynchronisation therapy, CRT) devices is an example. Well-conducted bias-resistant long-term trials are expensive and therefore few (Auger et al. 2013). If the optimisation methods evaluated in them have not gone through a series of screening steps, the substantial investment may become allocated to strategies that are mathematically or physiologically implausible.

In this report I lay out a rational pathway for development and testing of optimisation protocols. This is useful both to researchers and to clinicians not considering themselves researchers. I list key questions to ask of strategies being developed, to encourage early recognition of some strategies that have no chance of ultimate effectiveness.

It does not instruct clinicians on what approach should be used to optimize CRT, because a reliable answer is not yet available. Instead it provides clinicians with questions which may enable them to reject many methods currently proposed to them, by finding the answers to be unsatisfactory or unavailable, or even in some cases just by careful consideration of the quantities involved. The same logical sequence of

questions should also be followed by researchers developing a protocol, to prevent waste of research resources.

Small studies have consistently shown acute hemodynamic benefit of atrioventricular (AV) and interventricular (VV) delay optimisation (Auricchio et al. 1999; Z I Whinnett et al. 2006). However, evidence on the long-term benefit of cardiac resynchronisation therapy (CRT) optimisation from large clinical trials has focussed on a few methods and none has been convincingly positive. Guidelines therefore do not provide direction on how to program CRT (Brignole et al. 2013a; Daubert et al. 2012)

Many different variables can be measured to guide the programming for biventricular pacing, ranging from echocardiographic guidance based on diastolic or systolic haemodynamics, to electrogram guidance, as well as blood pressure and its derivatives(Houthuizen et al. 2011). In some cases, even after deciding which variable to monitor during optimisation, different protocols may be used to select the best pacemaker setting for that variable. This review systematically classifies the broad strategies for optimisation, provides detailed descriptions of the individual methods, and for each provides a practical perspective (Table 4-1).

Table 4-1 Common strengths and weakness of different approaches to optimisation

Approach	Common Strengths	Common Weaknesses
1: Spot the Pattern	– Easy to describe – Low cost	– Potentially susceptible to multiple sources of variability (inter and intraobserver, in addition to biological)
2 and 3: Pick the Highest or Lowest	– Usually requires maximisation of a relevant physiological parameter – Averaging of beats allows effects of variability to be quantified, and minimised.	– Very large numbers of beats need to be collected to adequately reduce the effects of noise
4: Predict the Optimum	– Time efficient method for the operator – Potentially highly reproducible due to automation	– No direct measurement of physiologic effect – Substantially conflicting algorithms suggests the majority of these must be wrong – Validation and clinical studies have been susceptible to pitfalls in evaluating optimisation technology
5: Fit a curve	– Usually requires maximisation of a relevant physiological parameter – Data far from the optimum can be used to identify the optimum – Optima between two tested settings can be identified	– Requires curve fitting which is not traditional medical practice
6: Find the inflection	– Potentially highly reproducible – Large variety of possible markers	– No maximisation of a physiological parameter – Large variety of possible markers

I then describe a series of rational steps that should be performed by any investigator designing and evaluating an optimisation protocol (Table 4-2). Clinicians, when faced with a proposed optimisation protocol, might apply these as a sequential checklist of properties, which would help avoid fruitless endeavour.

Table 4-2 Consensus Recommendation for Evaluation of Optimisation Technology

	Feature	Implications & Pitfalls for Clinical Trial & Clinical Study Design
Step 1: Singularity	The optimisation scheme should provide, one small region for the optimum.	Pre-requisite for a clinical trial
Step 2: Reproducibility	The scheme should pick almost the same value when the entire optimisation acquisition and analysis process is repeated, with blinding.	Pre-requisite for a clinical trial
Step 3: Plausibility	Values selected by the scheme should be physiologically realistic.	Advisable if a clinical trial is to have some chance of success.
Successful "SRP" (Single, Reproducible, Plausible) behaviour		
Step 4: Clustering	Does the optimisation scheme under assessment choose values similar to another scheme with adequate "SRP"?	Test for agreement with the *pacemaker setting* chosen by another SRP passed scheme. (Do not waste time correlating the physiological measures at the two settings)
Step 5: Cluster selection	A scheme with adequate "SRP" may consistently agree with certain schemes but not others.	If there is more than one cluster, each is likely to be preferentially optimising one aspect of physiology at the expense of another: pick the cluster maximising the most desirable physiological features (pressure and flow).
Step 6: Scheme selection	From the chosen cluster of "SRP" schemes, which scheme is most practical?	An outcomes trial could be realistically designed at this stage. The control arm could be nominal settings or any irreproducible scheme (since both give some chance of accidentally giving the optimum).

4.3 Approach 1: Spot the pattern

Example: Mitral inflow pattern (Ritter et al. 1999)
Also applicable to: TDI VV optimisation (Vidal et al. 2007)

This may be the earliest form of physiological AV optimisation, preceding even the advent of biventricular pacing. Across the range of different AV delays, the clinician chooses the setting which gives the qualitatively most desirable pattern using the measurement tool. The paradigm case is Doppler interrogation of mitral valve inflow (Houthuizen et al. 2011). The preferred Doppler pattern is separation of the E wave and A wave on Doppler without truncation of the A wave. This test is performed in the supine, resting patient.

4.3.1 Protocol

Pulsed-wave Doppler is used to measure transmitral flow during diastole. The pattern is recorded at each tested AV delay. There is no guidance on the number of beats to be recorded at each setting. Publications describing the technique typically show just one beat. At each AV delay, the pattern is noted (Figure 4-1). Adequate separation of the E and A wave should allow selection of an AV delay which maximises LV filling in diastole. With a long AV delay, there is fusion of the E and A wave, with a short AV delay there is truncation of the A wave. Different protocols have been described to select the optimal AV delay. One algorithm described by Ritter et al (Ritter et al. 1999). estimates this AV delay by assessing time from the onset of the QRS to the end of the A wave at a long and short AV delay, and using these figures predicts the optimal AV delay. The algorithm was originally developed for optimising AV intervals during RV pacing with AV block, but has been widely adopted for CRT optimisation. Another approach, the “iterative method”, starts with a long AV delay, and shortens it in 20 ms intervals until there is A wave truncation, and subsequently extends it in 10 ms increments until a desirable pattern is obtained (Cleland et al.

2001). Another variant of this approach is where a long AV delay is programmed, and the time from the end of the A wave to the onset of systolic mitral regurgitation is deducted to calculate the optimal AV delay (Meluzín et al. 2004).

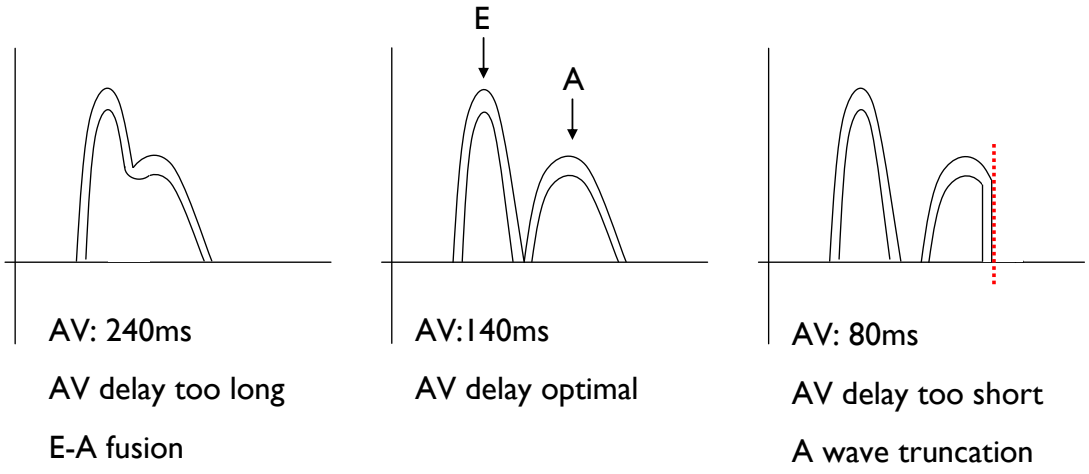


Figure 4-1 Iterative optimisation: protocol

Illustrative example of pattern changes to identify during iterative optimisation.

Figure 4-2 shows this method in a patient, at three different AV delays: 80ms, 120ms, and 160ms. It shows more than one beat at each AV delay, so that beat-to-beat variability is obvious. While cartoons (Figure 4-1) – or example cases commonly used in teaching – may have obvious, dramatic differences between settings, accentuated by selective display of convincingly different profiles (and not showing between-beat variability), in unselected case series the differences between settings are often more subtle (Jones et al. 2014). Despite this, the protocol described above is typically recommended for selecting the optimal programmed settings.

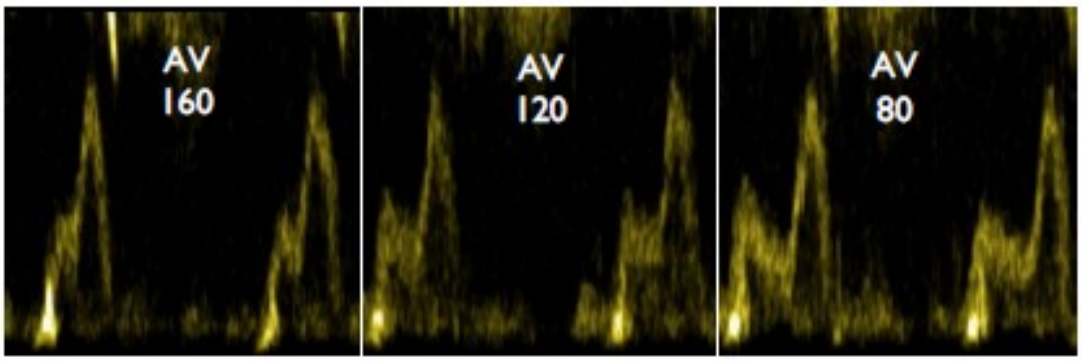


Figure 4-2 Iterative optimisation: clinician's perspective

Real world data: Pulsed wave Doppler traces of mitral valve inflow at three different AV delays.

A clinician with only the information above and an echocardiography machine can easily test the iterative scheme by a series of quick, low-cost explorations:

Exploration 1. Have two independent staff members conduct separate optimisations on the same handful of patients, blinded to each others' findings. Is the optimal AV delay very similar (to within 10 or 20 ms) between these two sessions? Time can be saved by having the sessions in immediate succession, but independent data must be collected: re-reading the same scans is not relevant at this stage. If this test-retest reproducibility is strong, the method is at least internally valid. If test-retest reproducibility is weak, then the further explorations below can identify why.

Exploration 2. Eliminate acquisition variability by using a single set of acquired images. Do two mutually blinded reporters reviewing the same images consistently agree on the optimum? If they do, then biological (or equipment) variability between sessions is the explanation for lack of reproducibility. If they do not agree, then either the protocol instructions are being understood differently by different operators, or the protocol is not really an algorithm. A third exploration is required to separate these possibilities.

Exploration 3. Eliminate variability of acquisition and of reporters' understanding of the protocol: does the same reporter being re-shown the same images on a second occasion, consistently select the same optimum? If not, the protocol is not ready for use in clinical practice or in research and should be revised until it is able to achieve this.

Two large studies (InSync-III completed in 2005 (León et al. 2005), SMART-AV completed in 2010 (Ellenbogen et al. 2010)) appear to have collected formal test-retest reproducibility of the optimum using a "pick the pattern" strategy, but the results are unpublished. Explorations 2 and 3 for transmitral Doppler (Raphael et al. 2013) suggests that between-observer and even within-observer, same-image agreement is already poor (kappa = 0.23) and therefore test-retest reproducibility (which must additionally include biological variation) must be worse.

4.4 Approach 2: Pick the highest

Example: LVOT VTI
Also applicable to: Impedance cardiography(Khan et al. 2011)**, Invasive dP/dtmax**(Auricchio et al. 1999)**, Mitral inflow E-A VTI** (Jansen et al. 2006)**, Mitral inflow E-A duration** (Jansen et al. 2006)**, Cardiac Output** (Berberian et al. 2005; Wang et al. 2011)**, Stroke Volume**(Dizon et al. 2010)**.**

Moving beyond qualitative pattern recognition, another approach is to quantify some variable describing the effectiveness of cardiac function, and then pick the pacemaker setting that maximises this variable. This could be applied to a range of physiological measures that can be quantified invasively during the time of device implant, or non-invasively using echocardiography, impedance cardiography, or non-invasive blood pressure measurements. Such measures include peak blood flow, stroke volume, stroke distance (velocity-time integral), arterial or ventricular pressure, ventricular dP/dtmax, and bio-impedance. This category encompasses many different variables where the same overall approach is used to pick the optimum, but each of these have

very different signal to noise characteristics, and protocols vary in using a single measurement at each AV delay, repeated measurements, or comparison to a reference state. "Pick-the-highest" schemes can be used for either AV or VV optimisation. The example protocol given here is for AV optimisation using stroke volume (LVOT VTI) measured by Doppler echocardiography.

4.4.1 Protocol

LVOT VTI can be used for AV optimisation, and is often recommended for VV optimisation (Waggoner et al. 2008; Dizon et al. 2010). At each pacemaker setting, a sample of pulsed wave Doppler images is acquired from the LVOT, while keeping the probe position constant between settings. It is often recommended to average the VTIs of 3 beats, although articles describing the technique commonly show the process being carried out on a single beat per setting (Waggoner et al. 2008) . Increments of 20ms in the AV delay are commonly recommended. The AV delay setting which yields the highest VTI is selected as the optimum. The same approach is used for VV optimisation

4.4.2 Clinician's Perspective

The clinical data from one patient in Figure 4-3 illustrates several features that are rarely highlighted. First, differences between VTIs at the same setting are not trivial. Second, if only one beat had been measured at each setting, the selection of the optimum would be largely a matter of chance. Third, on any one single-beat dataset, the pattern of VTI against AV delay has not a single peak, but several alternating local maxima and minima (Pabari et al. 2011).

Variability is not peculiar to Doppler: it is present in all physiological variables. In some cases it is almost exactly concordant in simultaneous measurements from sensors using different physical principles from different sites in the body (Kyriacou,

Pabari, Whinnett, et al. 2012), which suggests that it is not caused by equipment or operator error, but instead genuine biological variation between beats. It is preferable to test AV delays in random order rather than sweeping, for example, from short to long. Otherwise, a trend in state of the patient, either towards more relaxed or more agitated, during the study might cause a progressive trend in heart rate, sympathetic and vagal tone and thereby introduce a systematic bias in the optimum calculated.

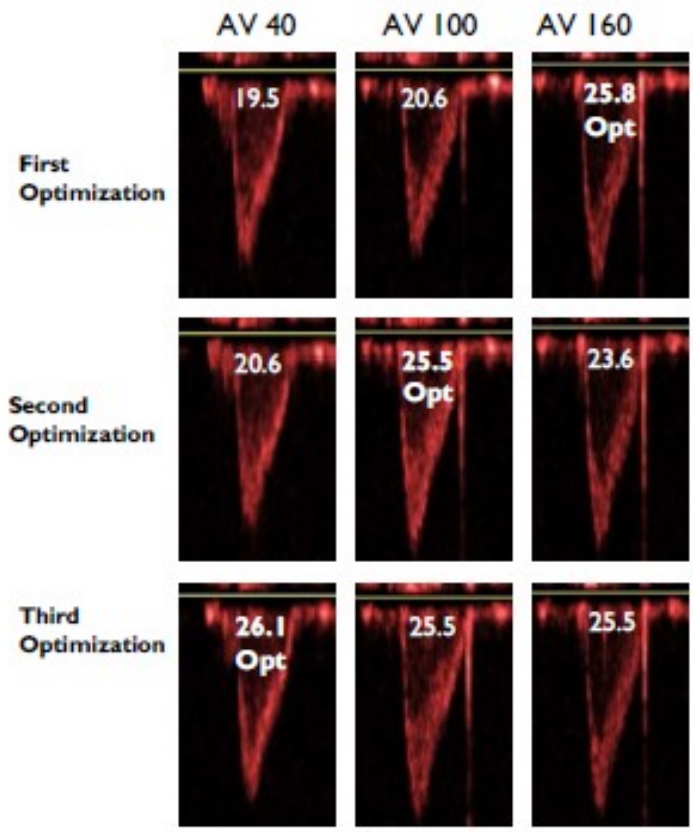


Figure 4-3 LVOT VTI based AV optimisation

The VTI is calculated at a range of AV delays. 40ms, 100ms, and 160ms are presented here. This is repeated three times.

Quantitative approaches such as “pick the highest” permit more advanced analysis of the optimum and of its reliability because at each AV delay, there is a number, and not just an image. Numbers can be averaged across beats, to reduce the influence of biological variability.

Moreover, the degree of variability can be quantified and discussed openly. Where protocols recommend more than one beat be acquired and averaged, they are either vague regarding how many are needed, or specify a number such as 3, without showing how it is derived.

Determination of the number of beats required is a straightforward within-patient sample-size calculation (Francis 2013b) that readers should try themselves – having made a few pilot measurements in their own laboratories, because published claims in this field are not always representative of real life. Physiological responses associated with changes in AV delay are generally approximately parabolic in a region near the optimum(Auricchio et al. 1999; Z I Whinnett et al. 2006; van Geldorp et al. 2011; Quinn et al. 2009), whose curvature is easily described by the coefficient of x2 when fitted to a 2nd order polynomial. Biological variability is assessed by recording several beats at the same setting, over a period of time (rather than only immediately adjacent beats which will be artificially similar), and calculating the standard deviation of the measurements to quantify their scatter. The clinician will need to decide what margin of error is acceptable in determining the optimum: ± margin ms. From these three values, the number of repeated measurements per setting required to identify the optimum, achieving 95% confidence interval that it is within ± margin ms of the true optimum, can be calculated by the formula (Francis 2013b):

$$replicates = 2\frac{(scatter/curvature)^2}{margin^4}$$

Equation 1: Number of replicates required to identify the optimum with defined 95% confidence interval

The greater the scatter, the more repeated measurements are required. The shallower the curvature, the more measurements are required. The more precision that is required, the more replication of measurements are needed. To achieve a margin of

error of ±20 ms, with typical scatter of 5% and curvature (Francis 2013b; Turcott et al. 2010)of 0.44%/(20ms)^2 the number of beats required per setting is ~260. For stroke volume, based on VTI, a curvature of 1.6ml/(40ms)^2 i.e. 0.001 ml/ms^2 and scatter of approximately 6ml have been reported,(Francis 2013b) so the number of replicates required is $2\times(6/0.001)^2/204 \approx 450$ per setting. For non-invasive beat-to-beat blood pressure increment assessed as a 10-beat average, a curvature of 1194 mmHg/s^2 and scatter of 3.9mmHg are reported (Z I Whinnett et al. 2006), indicating $2\times(3.9/1194)^2/(0.02)^4 \approx 130$ per setting. Invasive measures such as left ventricular dp/dt_{max} are also in use. Pressure measurements can easily be made fully automatic, eliminating interpretation variability, and do not critically depend on stable positioning of sensors, but do not eliminate natural biological variability from respiration and other sources, which should be quantified in the protocol-planning phase, in order to determine how many replicates are needed.

To determine the number of repeat measurements that are required, the likely true physiological difference between the two different tested settings is required (for example 2-3%), as well as the variability of measurements being taken (noise, or scatter, for example 5-10%) (Francis 2013b). To be 90% certain that the correct setting has been chosen, the number of beats required can be calculated (Francis 2013b), which can easily be over one hundred times larger than the three beats usually advised.

4.5 Approach 3: Pick the lowest

Example: Minimising dyssynchrony using echocardiography (Sonne et al. 2012)
Also applicable to: Myocardial Performance index(Porciani et al. 2005)

Minimizing an undesirable characteristic is an alternative to maximizing a desirable one. Mathematically the processes are equivalent. This can be applied to markers of dyssynchrony. For those who believe that the principal mode of action is to correct

inter and intraventricular dyssynchrony, this is a logical method for optimisation. However, unlike the other methods which are described here, there are relatively few examples of its use in the scientific literature. This approach has the same formula as Approach 3 for calculating the number of replicates needed which, because of the greater variability can become very large.

Minimising the ratio of the isovolumic times to the ejection times (the myocardial performance index) has also been described (Porciani et al. 2005).

4.6 Approach 4: Predict-the-optimum

Examples: The Electrogram methods: QuickOpt™, SmartDelay™, Adaptive CRT™

Biventricular pacing is implemented by electrophysiologists using devices with a prominent capacity for recording electrograms, and therefore it is not surprising that a variety of algorithms have been proposed to use information related to electrical activation, either from these intracardiac electrograms, or the surface ECG to predict which AV and/or VV delay will deliver the greatest physiological effect (Bertini et al. 2008). These proposed algorithms differ substantially in their proposed AV or VV optima, which implies that for most of them the claim they recommend the optimum AV or VV delay must be incorrect (see below). Algorithms based on the surface ECG target the settings which deliver the narrowest QRS complex (Bertini et al. 2008), device based algorithms employ different elaborate formulae to predict the best setting for the AV or VV delay.

4.6.1 Protocol: QuickOpt™

The QuickOptTM method recommends values for both AV and VV delay (Anselmino et al. 2009; Abraham et al. 2010; Abraham & et al 2010; Baker et al. 2007). For sensed AV delay, the device analyses the duration of the atrial intracardiac

electrogram and adds either 60 ms (if electrogram duration <100 ms) or 30 ms (if electrogram duration >100 ms). This is a zigzag relationship (Figure 4-4), meaning for example that, counter intuitively, all patients with atrial electrogram durations between 100 and 128 ms receive shorter recommended AV delays than those with the shorter electrogram duration of 99 ms. Another counterintuitive feature is that every patient in the region of 70 to 129 ms receives an AV delay recommendation identical to that of some patients that are exactly 30 ms away but different from that of all patients with electrogram durations which are closer.

Why a zigzag relationship is thought to be biologically plausible has never been explained, nor has the data which originated the particular values 100, 60, and 30 ms been made public.

The QuickOpt™ VV delay is calculated using the following method (Baker et al. 2007):

QuickOptTM VV is defined as the average of two quantities:

- Time delay from RV sensing to LV sensing
- Tow much longer an LV paced activation takes to reach the RV, (Conduction time left to right) than an RV paced activation takes to reach the LV (conduction time right to left) (a manifestation of directionally sensitive conduction velocity)

For example if during sensing the RV senses 90 ms before the LV, then the first quantity is +90 ms. Then if LV pacing takes 110 ms to activate the RV, and RV pacing takes 108 ms to activate the LV, then the second quantity is 2 ms. In this example the QuickOptTM VV formula would give 90ms – 2ms = 88 ms, multiplied by 0.5 = 44 ms.

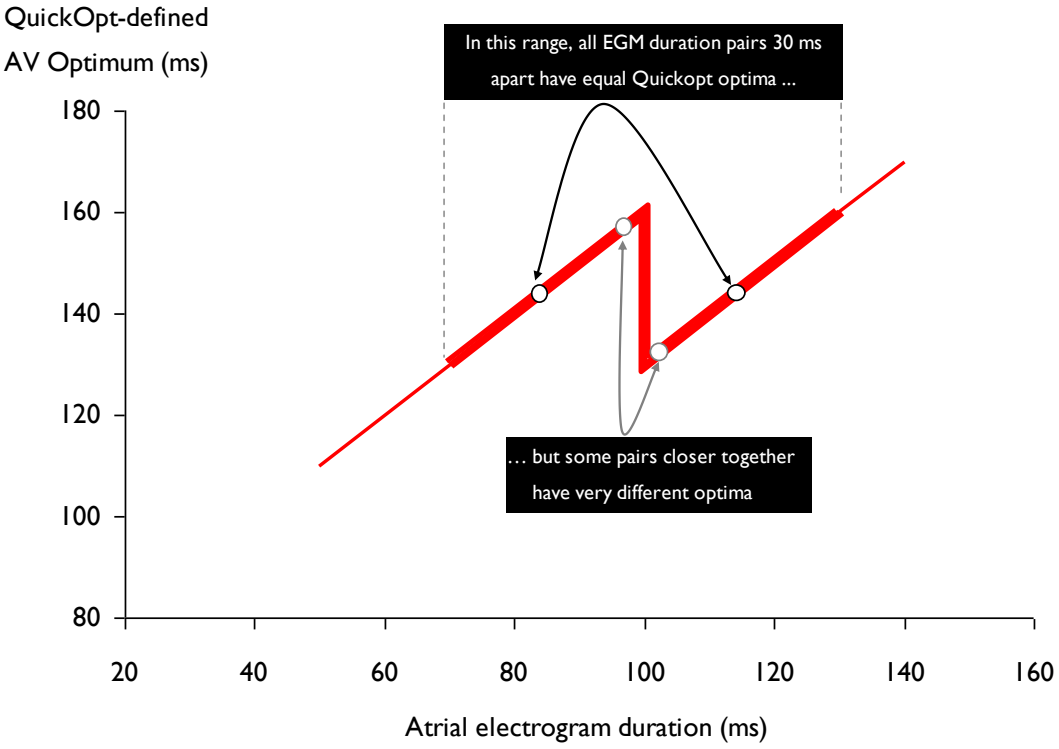


Figure 4-4 Graphical representation of QuickOpt™ AV delay

Optimum AV for the underlying atrial EGM duration is plotted

4.6.2 Protocol: Expert Ease for Heart Failure + (EEHF+)™ & SmartDelay™

EEHF+™ (Boston Scientific, Minnesota, USA) calculates the AV optimum from the intrinsic sensed and paced AV intervals, QRS duration, and a series of 6 constants, two of which are chosen based on the position of the LV lead (Gold et al. 2007):

Sensed AV optimum = a constant × QRS + another constant × Sensed AV interval + another constant depending on lead position

Paced AV optimum = another constant × QRS + another constant × Sensed AV interval + a different constant depending on lead position

SmartDelay™ (Boston Scientific, Minnesota, USA) appears to be a modification of the EEHF+ formula (Gold et al. 2007), both of which are said to be derived from the PATH-CHF data in a way that appears not to be publically described. It was used in the SMART-AV trial (Ellenbogen et al. 2010). The SmartDelay™ algorithm makes recommendations for both sensed and paced AV delays. If the LV lead position is not stored, an automated guess of the position is made using the RV sense to LV sense interval. If the LV sensed electrogram is >40ms after the RV, the assumption is the LV lead is considered to be in a conventional free wall position, otherwise a more anterior position. Depending on the A-LV time and the A-RV time, and the lead position, the SmartDelay™ may also choose to pace only the LV or both LV and RV. An electrogram-based optimisation scheme from this manufacturer was used in the COMPANION Trial (Bristow et al. 2004).

4.6.3 Protocol: Adaptive CRT™

Adaptive CRT™ (Medtronic, Minnesota, USA) is a third electrogram based method (Krum et al. 2012).

Initially a set of baseline intervals is measured by the device.

A-RVs: atrial sensing (As) or pacing (Ap) to RV sensing

A-Pend: P-wave conduction interval determined as the time from atrial sensing (As) or pacing (Ap) to the end of the P wave in the far-field electrogram

RVs-QRSend: the QRS conduction interval, determined as the time from RV sensing to the end of the QRS complex in the far-field electrogram

A-Pend and A-RVs are quantified in the atrial sensed state and separately in the atrial paced state. The algorithm dichotomises patients into normal AV conduction versus

abnormal AV conduction (As-RVs >200ms, or Ap-RVs>250ms)(Krum et al. 2012; D. Birnie et al. 2013). The recommended AV delays are then defined in the following way.

If AV conduction is normal and heart rate is below 100 beats/min, LV-only pacing is delivered with AV delay calculated from As-RVs as below:

AV optimum = 70% of A→ RVs if A→ RVs > 133.3 ms

or (A→ RVs − 40 ms) if A→ RVs < 133.3 ms(Khaykin et al. 2011)

In the other cases, i.e. either AV conduction is abnormal or heart rate exceeds 100 beats/min, the algorithm jumps to two different formulae:

For sensed:

Adaptive CRT AV = the smaller of: As→ Pend + 40 ms and A→ RVs−50 ms.

For paced:

Adaptive CRT AV = the smaller of: Ap→ Pend + 30 ms and A→ RVs−50 ms(Jones et al. 2010)

The Adaptive CRT VV delay recommendation is calculated from the intrinsic A-RVs and RVs-QRSend intervals by a process which appears to be still confidential, although it is disclosed that shorter intervals lead to the time of RV pacing to be progressively more delayed (Krum et al. 2012). Although the VV algorithm itself has not been publicly been disclosed, it is believed to delay the right or left ventricular lead by a maximum of 20 ms for all patients in whom the native QRS width is greater

≥80 ms. Again, the nature, physiological justification, and clinical derivation and supporting data, appear to be secrets.

4.6.4 Clinician's Perspective:

This approach shares the advantage with programming nominal settings, of being instant, potentially highly reproducible, and effortless, but has the extra advantage of allowing the clinicians to claim to "have carried out an optimisation". However, these electrogram-based algorithms, and various surface-ECG-based algorithms, fall short of what can reasonably be described as an optimisation.

First, the clinician does not establish directly in the individual patient that the AV or VV setting programmed is delivering the greatest physiological effect: instead the clinician must trust that the algorithmic predicts the correct setting. Second, the three methods give contradictory recommendations as can be seen from their formulae. Third, some of the formulae stretch credulity to its limit. For example, the zigzag shape of Figure 4-4 implies a rare phenomenon: a biological response curve with not only a sharp discontinuity, but a double switchback.

A clinician choosing to trust this prediction approach, without themselves making measurements of cardiac function, are implicitly hoping that (a) electrogram data indeed contain all the required information to identify a physiological optimum, (b) of the 4 mutually contradictory electrogram formulae, only 3 are incorrect while 1 is correct (d) the clinician has happened to choose a manufacturer who happens to have the only correct formula.

The secrecy around their origin or even their true nature gives little reason for such trust. Clinicians hoping to gain confidence from the studies used to validate the formulae may be disappointed. They fall into four families:

4.6.5 Agreeing with methods that do not agree with themselves.

Some of the electrogram methods were reported to give the same optima as Approach 1 (spot the pattern) using transmitral Doppler, or Approach 2 (pick the highest) with aortic VTI or left ventricular dP/dt. The weak point in this chain of reasoning is that bias-resistant, independent assessments of the test-retest reproducibility of methods in Approach 1 and Approach 2 are rather scarce, which make them uncertain gold standards (Ritter et al. 1999; Waggoner et al. 2008). A method under test cannot reliably agree with a reference standard that does not agree with itself.

4.6.6 Studies whose results show the opposite of the reported conclusions

Some electrogram methods have been shown to give VTI values that correlate with the highest VTI achievable across patients, but this only shows that VTI varies between patients much more than it varies between AV delays (Francis et al. 1999). Indeed the strength of the correlation would become 1 if optimisation had no effect at all (in a noise-free measurement). Strong correlations can indicate simply the smallness of the effect of changing the pacemaker setting (Figure 4-8 and Figure 4-9), and therefore that the analysis is irrelevant.

4.6.7 Agreement with physiological optima poor

When the electrogram optima are directly compared to the physiological optima, correlation has been found to be poor (van Gelder et al. 2008).

4.6.8 Clinical endpoint impact has been neutral

The Adaptive CRT™ methods showed non-inferiority in outcome measures to echo based methods for optimisation (spot the pattern for AV, pick the highest for VV) (Martin et al. 2012). Non-inferiority in outcome measures does not guarantee that either is an effective optimisation technique. It may signify that both might be similarly inadequate at optimizing, or both similarly adequate.

A simple test of the plausibility of the predict-the-optimum methods is that they should agree with each other, but this is difficult to confirm because they are implemented on different pacemakers. An alternative is to compare their formulae, but these – when disclosed – appear to be substantially different. Independent studies with blinded, bias-resistant design (see Pitfalls section), showing in individual patients the spectrum of differences in measures of cardiac function between AV programmed to nominal and to predicted optimum, are needed to underpin these methods.

4.7 Approach 5: Fit a curve.

Example: Finger photoplethysmography (Z I Whinnett et al. 2006)
Also applicable to (potentially): all the pick the highest approaches.

The concept of an "optimum" AV delay implies that there is a region on the spectrum of AV delay where cardiac function is good, and when AV delay is changed in either direction function becomes progressively worse. Biological relationships of this nature are typically curved, with small departures from the peak having only small effects on the physiological variable, but progressively larger departures having effects that grow proportionally to the approximately the square of distance. Such curved relationships to a first approximation can be described by a parabola, which can be fitted to observed data using any standard spreadsheet software. This "fit a curve" approach (Zachary I Whinnett et al. 2006; Z I Whinnett et al. 2006) can be used for any physiological measurement that the clinician wishes to maximise, such as blood pressure, aortic VTI, or impedance cardiography. Invasive measurements were used with this approach in the early trials of CRT (Auricchio et al. 1999; Auricchio, Ding, et al. 2002; Butter, a. Auricchio, et al. 2001). It can be used as a direct replacement for the pick-the-highest approach. Two settings such as AV and VV delay could even be optimized simultaneously by testing a grid of combinations

and plotting the surface of haemodynamic response, so that the peak of the resulting dome indicates the optimum combination of AV and VV delays (Z I Whinnett et al. 2006; Quinn et al. 2009; Berberian et al. 2005).

4.7.1 Protocol

Figure 4-5 shows an example of an AV optimisation using non-invasive blood pressure monitoring (Zachary I Whinnett et al. 2006).

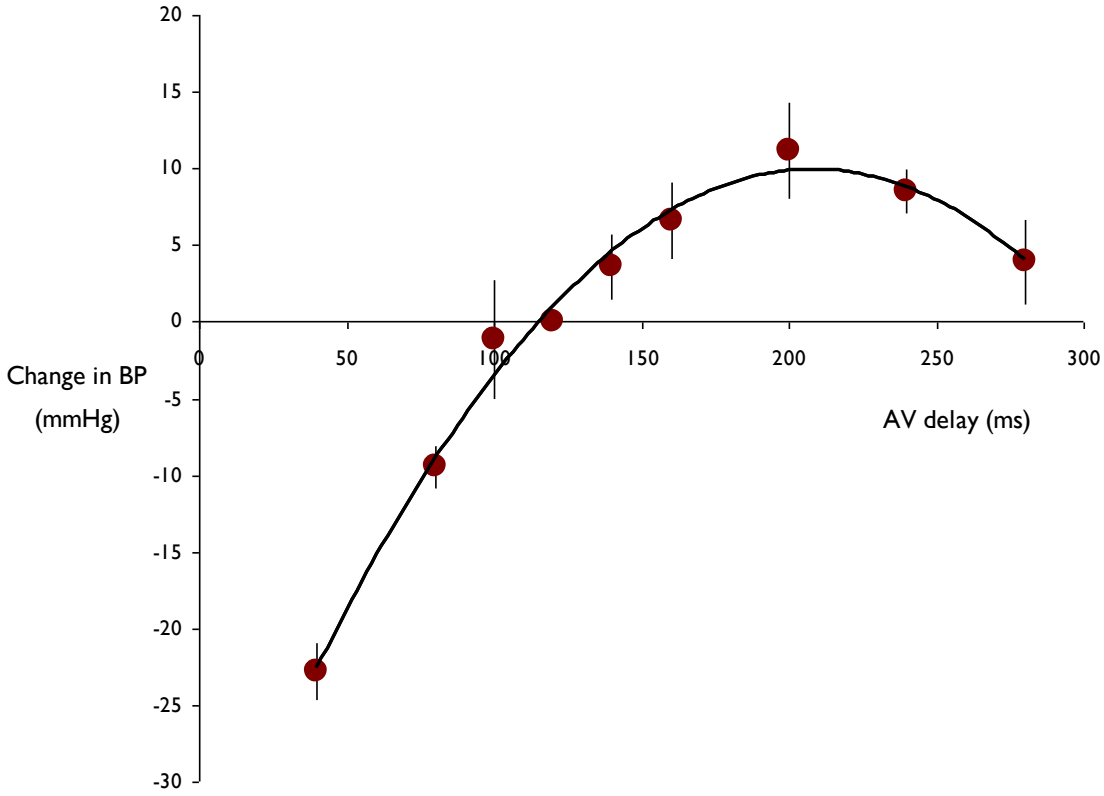


Figure 4-5 Non-Invasive BP Optimisation

Changes in beat to beat blood pressure are averaged before and after a transition between a reference and tested AV delay and used to construct an optimisation curve. The peak of curve identifies the optimum.

The protocol begins like pick-the-highest, but then involves fitting a curve, which may be a simple parabola or require a more complex shape (van Geldorp et al. 2011; Turcott et al. 2010; Bogaard et al. 2010) if very long AV delays are covered that take physiology into a plateau region. Instead of picking the setting which gives the

highest measurement, the peak of the curve is calculated, which may be in between two tested settings. The confidence interval of the optimum can also be estimated (Francis 2011).

Raw datasets that show multiple peaks and troughs (Figure 4-10) are treated by the curve-fitting approach to be uninformative noise. This is in contrast to a naïve interpretation that every difference between measurements at two settings represents biologically important differences between the settings. A second undesirable result is a parabola oriented upside down since, in such a dataset, noise has overwhelmed signal. While such an individual dataset can easily be rejected, if this happens often it should be remembered that in an equal number of cases noise will have overwhelmed signal, but by chance the resulting parabola happened to be oriented in the expected direction (Figure 4-10) (J. A. Finegold et al. 2013).

Uninformative data sets can be exposed either by repeating the optimisation and showing no relationship between successive results, or by calculating the confidence interval of the optimum and finding it to be unacceptably broad (Turcott et al. 2010; Francis 2011). Optimisations of AV and/or VV delay can be presented with a 95% confidence interval of the optimum, to give the reader an idea of the degree of precision achieved. Curve-fitting allows this to be established from a single optimisation (Zachary I Whinnett et al. 2006), from the variability between replicate physiological measurements (expressed by their standard deviation or "scatter") and the curvature of the response (Francis 2013b). The curvature is expressed in physiological units of response (e.g. mmHg, mmHg/s, ml, or %EF) per ms2, if the AV or VV delay is measured in ms. Curvature is the quadratic coefficient (the coefficient of x2) in the curve that fits response to AV or VV delay as shown in Figure 4-5. If the dataset is width ms wide, and it is desired to know the optimum to with a standard

error of precision ms, and the dataset can be positioned to straddle the optimum approximately centrally, then the total number of individual measurements required (number of settings × number of replicates) can be planned by the following formula (Francis 2011):

$$\text{Total number of measurements required} \approx 3 \left(\frac{Scatter}{Width \times Precision \times Curvature} \right)^2$$

Equation 2: Calculating the number of measurements required for calculating the AV optimum with a defined precision using curve fitting

This can be demonstrated with reported values for pressure (Francis 2011). Taking each sample as a ten beat average, where scatter is 3.9mmHg, a range (width) of 160ms of AV delays is tested (i.e. 80-240ms), curvature 1194mmHg/s2, with a 95% confidence interval of ±10ms, i.e. a standard error of 5 ms to identify a programmable AV delay. Using these values, a minimum of 50 measurements is required. If the scatter is doubled in this example, the number of measurements required will increase four-fold to 200.

4.7.2 Clinician's Perspective:

This approach has much in common with pick-the-highest. It differs only in fitting a curve to identify the optimum, which if conducted on paper alone makes it slightly more complicated. If the measurements are being documented electronically then curve fitting requires no additional effort.

Fit-a-curve and pick-the-highest have never been tested head to head for their ability to identify the optimum reliably (i.e. with good test-retest reproducibility). It is possible that they may behave differently in response to changes in protocol. For example, testing additional settings under the pick-the-highest approach might

increase the chance of picking the wrong setting (because there are more wrong settings)(Francis 2013b), but under the fit-a-curve approach might decrease the chance of picking the wrong settings (because additional data would improve the precision of determination of the optimum)(Francis 2011).

There are some theoretical advantages of fit-a-curve. First, it can interpolate optima in between tested settings. Second, it automatically identifies some datasets that have too little signal for the amount of noise, so that an extended dataset can be acquired. Third, the habit of formally measuring the curvature (and biological noise) may assist in protocol planning. Finally, the estimated location of the optimum is based on the entire ensemble of data so that measurements at settings far from the optimum (where signal is larger) can contribute to its localisation.

Although fit-a-curve is sometimes used in research optimisations (Zachary I Whinnett et al. 2006; Z I Whinnett et al. 2006; Turcott et al. 2010), it is not standard clinical practice.

4.8 Approach 6: Find the inflection

Example: Peak endocardial acceleration (Ritter et al. 1999; Ritter et al. 2012)

More recently a family of approaches have been introduced which involve measuring a variable whose response to changes in settings is sigmoidal, with a plateau of low values at one set of extreme settings, and a plateau of high values at the other extreme, and progressive changes in the intermediate zone. Often the point of inflection is defined as the optimum, as is the case for the SonR™ method (Sorin Biomedical, Milan, IT), which uses a heart sound sensor in the lead tip (Ritter et al. 2012) (Figure 4-6). It is not entirely clear why this middle value of heart sound should be considered desirable for cardiac resynchronisation.

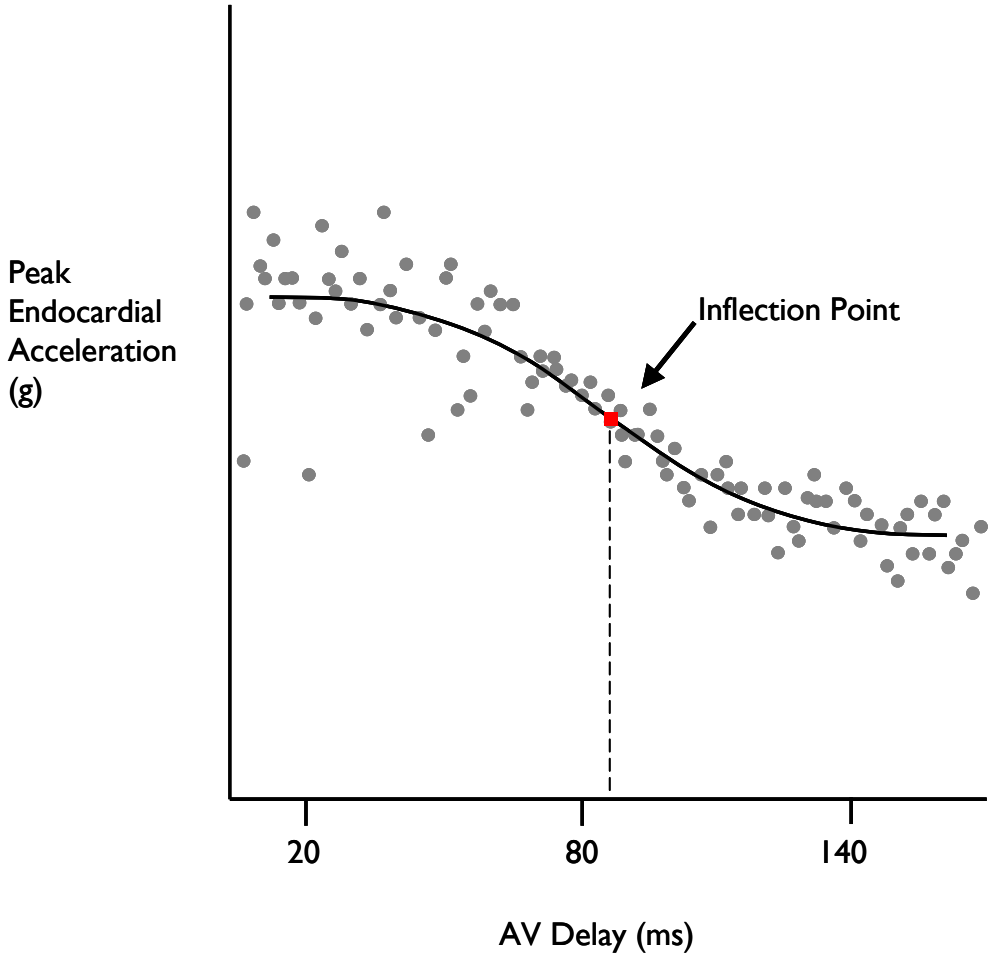


Figure 4-6 SonR™ AV optimisation

SonR™ AV optimisation measurements from data presented on a Sorin device programmer screen. Adapted from Ritter et al (Ritter et al. 2012)

Difficulty with these inflection based schemes is that any variable which has a plateau of low values at one extreme of AV delay, and a plateau of high values at the other extreme, will have a point of inflection in between, but this gives no reassurance that this setting has any desirable physiological characteristics. For different variables in the same patient, this inflection point might easily occur at different AV delays which undermine the belief that the inflection point of any particular variable is "the" optimum.

A thought experiment illustrates the difficulty in putting one's trust in an inflection-based scheme. Figure 4-7 shows a family of inflection schemes each of which measures one variable that has one plateau level at one extreme, a different plateau level at the other extreme, and a progressive change in between. In each case there will be a mathematically discoverable point of inflection, but the different points of inflection have no reason to agree. That the point of inflection on a single variable is reproducible, therefore, does not give reassurance that cardiac function is maximal at that setting.

In some circumstances, it may be rational to seek the halfway point between two plateaus of a measured variable. For example if it is desired to have the ventricle half captured by pacing, and half activated natively, then it may be rational to seek the AV delay setting that gives a vectorcardiogram halfway between its fully paced and fully native states. Such concepts have been tested against separate haemodynamic measurements (Verbeek et al. 2006; van Deursen et al. 2012).

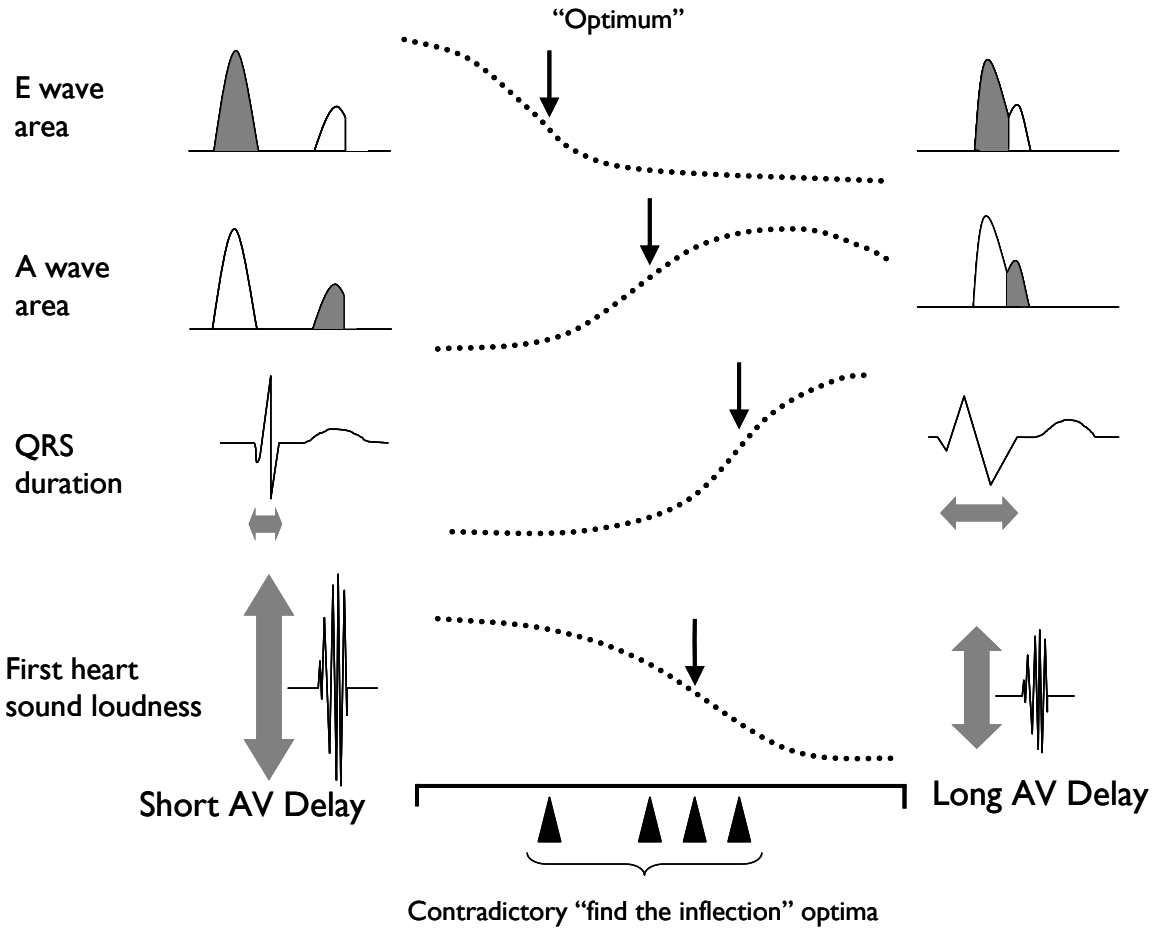


Figure 4-7 The challenge for find-the-inflection is in the wide variety of possible variables

Many variables have the property of having a plateau at each extreme of AV delay with progressive changes in between. Transmitral E wave VTI (or duration), in the first panel, is large for short AV and remains large until the AV becomes so long that the E wave fuses with the A wave. Conversely the A wave, in the second panel is small for short AV but progressively increases until E-A fusion occurs at long AV delays. QRS complexes may have one configuration across a range of short AV delays which give full capture and another configuration when programmed AV delay is too long to capture. Accordingly QRS duration (third panel) is likely to form a plateau for short AV delays, and another for long AV delays with progressive changes in between as fusion evolves. The first heart sound (fourth panel) is loud at a short AV delay and soft at a long AV delay, with progressive changes in between. All of these variables must have a point of inflection, but there is no reason why there should be any correspondence between them or between any of them and overall cardiac function. An infinite list of such variables could be concocted, so that if inflection was accepted as a means of optimisation, almost any AV delay could be justified as an optimum in any patient.

4.9 Recommendation for an efficient approach for evaluating optimisation protocols

4.9.1 Need for a new approach

Clinical trials remain the gold standard to test the efficacy of a therapeutic intervention. However, it is unrealistic to skip directly to endpoint clinical trials for all potential optimisation schemes because the cost of these is very large and therefore the number of methods that can be tested adequately is very small. Negative trials of unreliable methods may create an impression that it does not matter what AV or VV delay settings are programmed. However, there are many possible interpretations:

(a) Choice of AV and VV settings other than nominal really has no effect. If all settings are just as effective as nominal, then all settings must be just as effective as each other. If CRT really does work equally well regardless of programming, then the belief that it works by a sophisticated synchronization effect is false.

(b) AV and VV delay do matter, but the effect of the choice of these is much smaller than the effect of switching on CRT with any setting because the baseline unresynchronized state is so far below optimal that any AV / VV combination in the reasonable zone is better than no CRT, but not much different from each other. A more sensitive marker of function, than clinical outcomes, might be able to detect it.

(c) AV and VV delay might matter for some patients, but have little or no impact on most patients. While this hypothesis is easy to propose, it is difficult to test unless there are reproducible measures of response within individual patients, which are only just emerging now (Bogaard et al. 2012; Stegemann & Francis 2012). There is some evidence from the SMART AV trial that optimisation using that one particular "predict the optimum" approach works more effectively in individuals who have a long Q-LV time (Gold et al. 2013).

(d) AV and VV delay may matter, and a particular method might in principle give an unbiased assessment of the optimum combination but with a great deal of random noise, i.e. irreproducibility due to a poor signal to noise ratio. This can be introduced by biological sources of beat to beat variability such as respiratory variation, which is why some attempts are made to reduce this by ensuring measurements are made in the same phase of respiration. A large number of estimates of the optimum for one patient would yield results whose average accurately defined the optimum but whose individual values might be widely scattered and therefore erroneous. Protocols that use too few replicates might be like this, often inadvertently recommending a random setting. Additionally, optimal device settings may change with physiologic state, posture, heart rate and type of activity; but answering such questions can only begin once reproducible optimisation is available.

(e) The particular method might include an element of bias which is specific to each patient (as well as noise). For example, in Patient 1 the average of very many obtained optima might be 40 ms shorter than the true optimum while in Patient 2 the obtained optimum might average 50 ms longer than the true optimum. In this case, then no amount of averaging will resolve or even expose this: comparison with other candidate optimisation schemes is essential.

(f) The candidate optimisation method might contain no information at all. In a thought experiment, an example might be random selection amongst the range of plausible values. In this case, failure of an endpoint trial is guaranteed but casts no light on the concept of optimisation other than that this candidate method is not it.

4.9.2 Pitfalls to avoid when evaluating optimisation methods

New protocols for optimisation typically undergo clinical testing. There are several common errors that research planners can easily fall into, which can create artificially large appearances of the efficacy of optimisation. Clinical readers should watch out for, and disregard, reports based on these types of fallacious reasoning.

4.9.2.1 Mistaking noise for benefit

The biggest trap is to misinterpret random variability in measurements as evidence of having delivered benefit. The "pick the highest" approach is particularly vulnerable. Natural biological variation will ensure there is always a highest value (even if changes in AV delay have no underlying effect). This will always be higher than (or equal to) the value at nominal settings. Across a group of patients, this will produce a highly statistically significant, but spurious, p value. The p-value is only identifying, correctly, that the protocol is deliberately picking the highest value: it tells us nothing about whether the observed increment is noise or not. Figure 4-8 explains this problem.

Avoiding this bias is easy and quick. Once the measurements at the various settings have been made, the setting with the highest value is defined as the proposed optimum. Re-measurements are then made for just the reference and the proposed optimum setting, by a blinded observer. The increment now seen between reference and pre-defined optimum in these re-measured values represents an unbiased quantification of the effect of optimisation.

Within-patient distribution		**Between-patient distribution**	
Enter the within-patient spread		Enter smallest plausible value	**100**
between settings (standard deviation)	**25**	Enter largest plausible value	**900**

Press F9 to re-run simulation

	VTI measured at various AV delays											Apparent VTI optimum			Apparent
	40	60	80	100	**120**	140	160	180	200	220	240	AV delay with highest VTI	**VTI** at that AV	**VTI** at 120 ms	VTI increment from optimization
Pat 1	229	223	260	235	**241**	212	273	194	223	225	211	160	273	241	+33
Pat 2	747	665	696	759	**707**	710	693	697	683	720	710	100	759	707	+53
Pat 3	479	541	546	539	**578**	536	490	514	518	497	536	120	578	578	0
Pat 4	647	635	578	594	**603**	595	616	597	609	614	603	40	647	603	+44
Pat 5	801	735	764	807	**773**	754	744	761	790	782	754	100	807	773	+34
Pat 6	153	120	123	119	**118**	163	141	118	116	100	120	140	163	118	+45
Pat 7	180	174	170	155	**186**	176	148	154	143	158	169	120	186	186	0
Pat 8	431	433	429	375	**430**	390	418	387	418	400	376	60	433	430	+2
Pat 9	375	342	335	280	**294**	282	317	320	285	299	270	40	375	294	+80
Pat 10	111	132	74	117	**122**	144	119	142	97	122	133	140	144	122	+22
Pat 11	840	894	849	803	**865**	862	846	828	854	838	793	60	894	865	+29
Pat 12	779	811	739	772	**728**	772	765	787	784	813	812	220	813	728	+84
Pat 13	565	585	540	598	**548**	564	554	570	599	601	562	220	601	548	+53
Pat 14	200	183	191	196	**187**	186	160	163	183	196	171	40	200	187	+13
Pat 15	148	128	150	196	**165**	151	142	161	100	116	157	100	196	165	+31

Mean increment in VTI	+35
SD of increment in VTI	26
p =	**0.00014**

Figure 4-8 Simulation to demonstrate how noise can be mistaken for benefit during optimisation.

The variable in this simulation could be substituted with any which is under consideration for an optimisation protocol. A standard deviation to indicate the variability of the parameter within an individual is entered, following by the maximum and minimum plausible difference in values between two individuals. Noise is easily mistaken for benefit by simply picking the highest value without consideration of underlying variability, and a false impression of statistical significance is given when averaged across a group of individuals.

4.9.2.2 Mistaking large between-patient difference for information about optimisation reliability.

A second common trap is to mistake a high correlation between $VTI_{AVdelay1}$ and $VTI_{AVdelay2}$ across patients as evidence of successful optimisation. Such correlations are always high when the between-patient difference in VTI is much larger than the between-setting difference, even if the proposed optimisation scheme is simply

randomly selecting a setting. Figure 4-9 shows this error in detail. Researchers should correlate not VTIs, but AV delays.

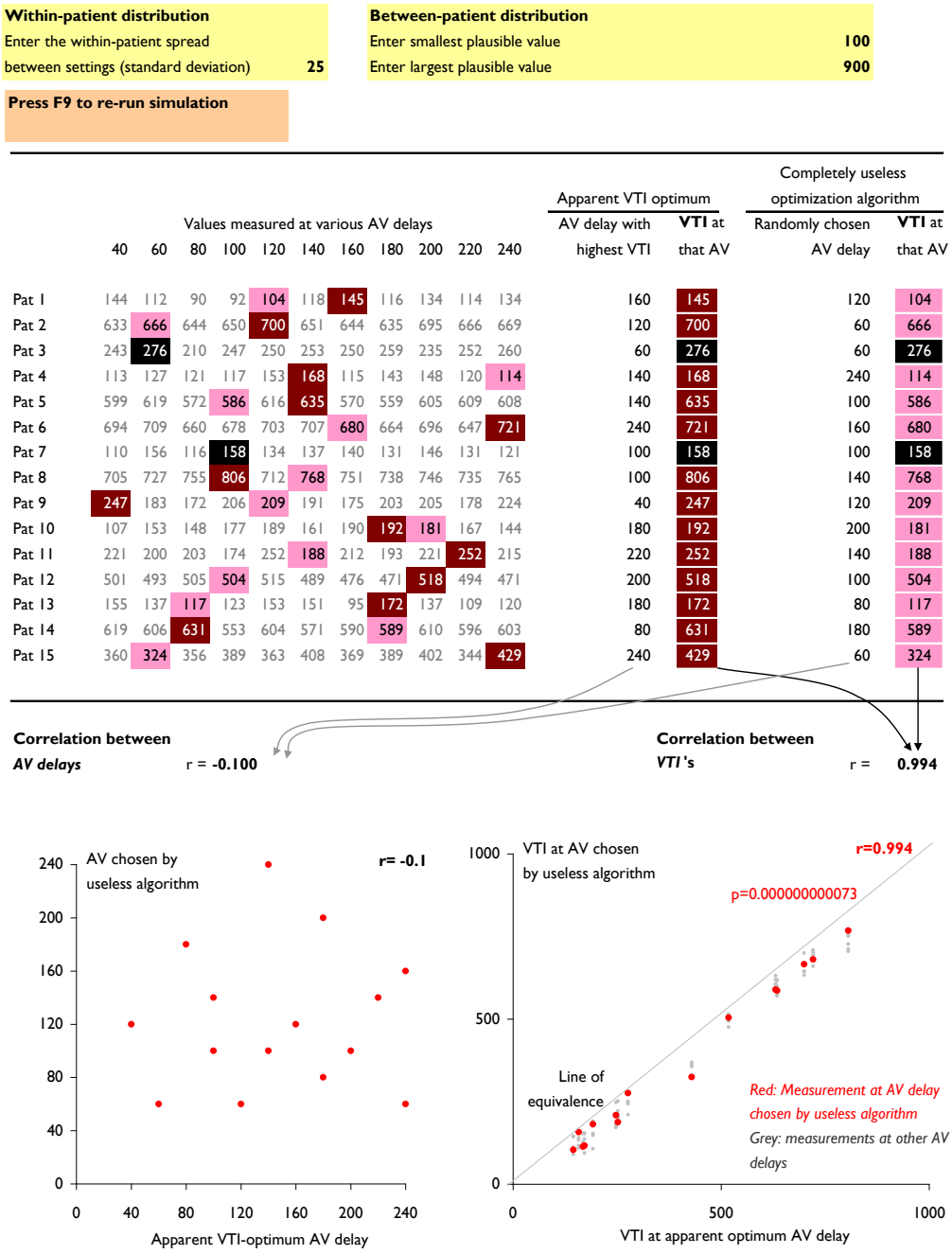


Figure 4-9 How between-patient difference can be mistaken for optimisation reliability

A second common error demonstrated in this simulation is to evaluate the optimum by constructing a correlation of a single parameter with itself (e.g. LVOT VTI), by plotting the parameter measured at the optimum on the x axis (e.g. LVOT VTI at the selected optimum using the LVOT VTI pick the highest method), and the same parameter measured when using an optimum selected using our new optimisation method on the y axis (e.g. the LVOT VTI at the optimum selected by a newly developed electrogram method). This will always

demonstrate a strong positive correlation because variation in LVOT VTI between subjects is greater than variation within an individual. When instead the key information, the AV delays selected by the two algorithms, is compared (lower left panel) using the same data, there is no clear correlation between the two methods.

4.9.3 Roadmap for way forward in developing and evaluating optimisation protocols

We should avoid repeating the considerable expense of clinical trial such as SMART-AV (Ellenbogen et al. 2010) and FREEDOM (Abraham et al. 2010) that despite meticulous conduct showed no objective endpoint benefit. Commercial pressure to move directly to endpoint trials, without opening the physiology of the confidential methods to normal scientific discourse, may be partly to blame.

In SMART-AV, the blinded test-retest reproducibility of iterative Doppler optimisation appears not to have been formally explored, the justification for the SmartDelay™ formula was not open to scientific enquiry, and whether it even acutely optimized cardiac function appears never to have been independently tested.

We should only embark on large clinical trials when we have actively chosen optimisation schemes that consistently withstand open scientific critique in reliably-measured physiological studies under blinded scientific conditions.

It may be tempting to recommend limiting optimisation to patients who appear to have not responded to CRT with nominal programming (Brignole et al. 2013b), but this has two undesirable consequences. First, patients whose physiology is such that there is no possibility of improvement by CRT, might be obliged to undergo unnecessary additional clinical manipulations. Second, patients who are fortunate enough to have a partial physiological response, or an optimistic outlook that biases them to report symptomatic improvement, would be denied the opportunity for further

physiological benefit. It would be better to develop a reliable understanding of the physiology of optimisation based on reproducible physiological methods, and only then make a judgement on how the provision of optimisation should be restricted.

Evaluating optimisation schemes should begin with quick, inexpensive experiments that can be used to improve basic protocol properties such as reproducibility, and to abandon avenues of optimisation that never fulfil rudimentary requirements of a decision-making algorithm. Progressively more elaborate experiments can then be carried out, on progressively fewer optimisation algorithms. A small number of algorithms with strong internal validity will survive. If they all give concordant optima, then the clinician is free to choose whichever is most convenient. If they give discordant optima (beyond their own test-retest variability) then they will likely form a small number of clusters, with each cluster optimizing one aspect of physiology at the expense of another. In that case the clinician can then choose which aspect of physiology (such as pressure, flow, intensity of heart sounds, etc) should take priority. If there is dispute, an endpoint trial could be carried out. This selection process can be described by a series of steps that each optimisation scheme can be taken through, beginning with simple tests that can be done in a few minutes in one or two patients (Table 4-2).

4.9.4 Step 1: Singular?

The most basic requirement is that an optimisation scheme identifies a single region on the AV or VV delay spectrum as optimal (Figure 4-10, panel a). It is acceptable for multiple settings to be considered equally optimal, but only if they are adjacent, and with the recognition that the precision of the optimisation is poorer (otherwise an optimisation scheme that reports for every patient that the optimum lies in the range AV 40ms to 300ms, would be considered perfect). It should not be expected for non-

adjacent settings to be optimal, with intervening non-optimal settings. The optimal setting or range of settings should therefore be singular.

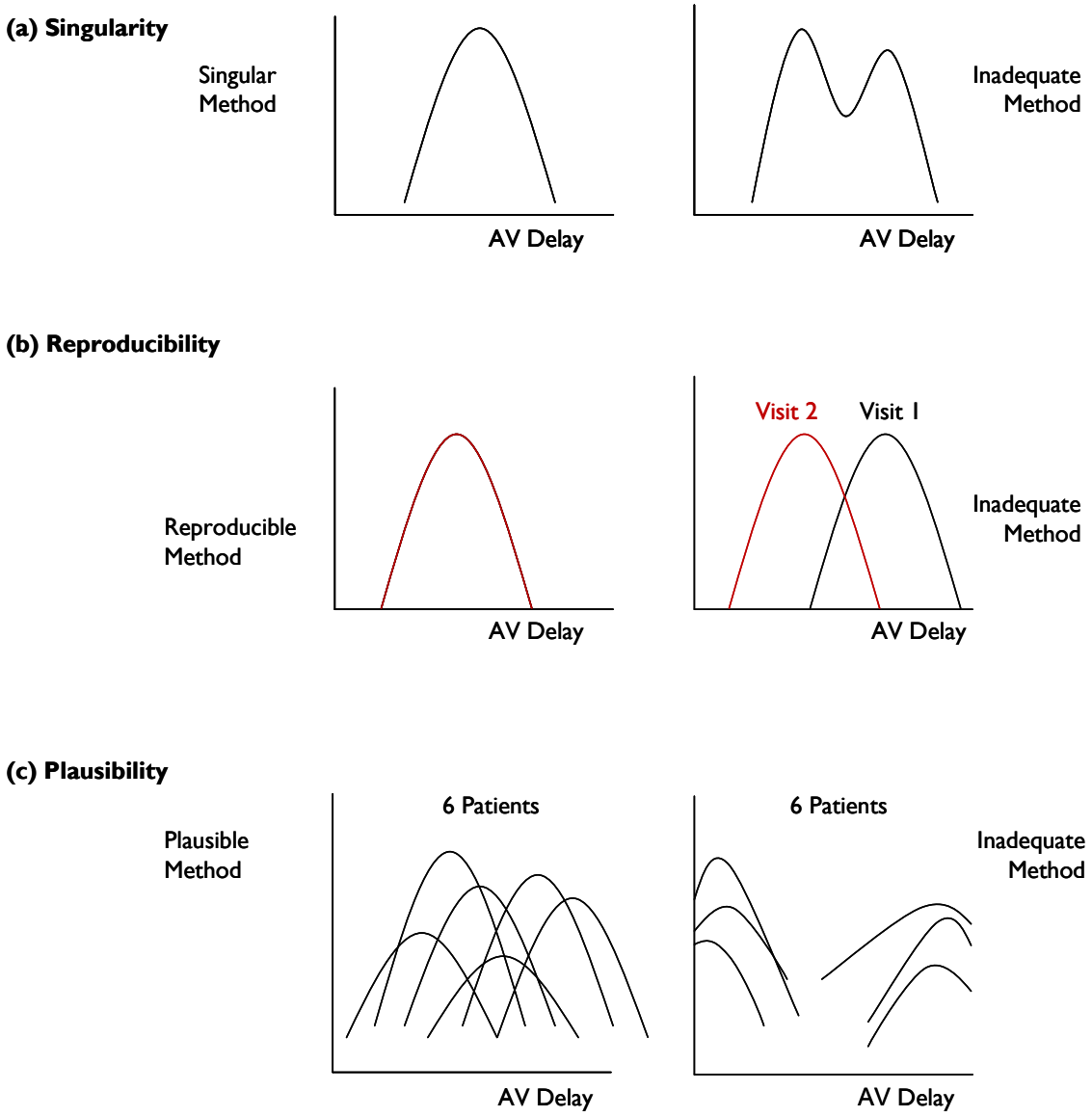


Figure 4-10 Ideal features of an optimisation scheme

Optimisation schemes should be (a) singular, (b) reproducible, (c) plausible.

4.9.5 Step 2: Reproducible?

Singular schemes can then be tested for reproducibility. (Schemes which give non-singular optima or a very broad optimum range in individual patients can be discarded before this stage). If the same patient were to undergo a separate optimisation in the same physical state, by staff blinded to the original findings, the second optimum AV or VV delay should be nearly the same as the first (Figure 4-10: panel b). The investigators should not give in to the normal clinical temptation to peek at the previous value (J. A. Finegold et al. 2013), because doing this destroys the value of the experiment. If the optimum value changes between datasets acquired in the same clinical state, then either the optimum is truly changing (in which case there is no point carrying out optimisation) or the optimisation scheme is unreliable.

The simplest description of the reproducibility of the optimum is the standard deviation of differences between successive AV or VV delay optima. A more advanced description (to prevent an optimisation scheme appearing to be perfect by simply reporting an identical value across all patients) is the intra-class correlation coefficient of the optima across patients.

4.9.6 Step 3: Is the value plausible?

Singularity and reproducibility alone do not give reassurance that optima are physiological. For example, defining the optimum AV delay in milliseconds as the patient's height in centimetres is singular and reproducible, but biologically implausible. Likewise a scheme that always defined the optimum VV delay in females as RV-first by 60 ms, and males as LV first by 80 ms would also be singular and reproducible, but not biologically plausible (Figure 4-10, panel c).

In the examples above, implausibility is immediately evident, but in other cases it may be contentious. For example, a scheme may recommend that on the transmitral

Doppler, the area under the curve of the A wave (including any overlapping E wave) should be measured, and that the optimum is not the setting that minimised it (e.g. AV 0) or that maximised it (AV so long as to cause intrinsic conduction), but the setting which is half-way in between, or at the point of inflection. Many variants of such schemes could be proposed using the numerous available variables, producing a spectrum of contradictory optima (Figure 4-7).

Any scheme which consistently chooses an extremely long or short AV delay is implausible, but equally a scheme which arbitrarily chooses a value a fixed portion between the two extremes could also be doubted.

Plotting the distribution of optima obtained may give an additional clue to plausibility, since (for example) simultaneous atrial and ventricular activation, can be detected as implausible (Kyriacou et al. 2013).

If a singular, reproducible scheme passes the step of plausibility, it can be admitted to the "elite" of schemes, which can then be tested for clustering. Schemes that are non-singular, irreproducible or implausible, need not go forward for testing for clustering because this would be a waste of resources (including patient time).

4.9.7 Step 4: Clustering of schemes

Singular, reproducible, and plausible optimisation schemes are still not yet necessarily ready for large-scale trialling. There are simple, cheap tests that can still winnow out unsuitable methods.

Since they all claim to have identified "the" optimum, they should all report the same setting (Figure 4-11). Each scheme will have an error bar in its determination of the optimum, which is known from the test-retest reproducibility studies (Step 2) and

therefore the only discrepancy beyond this need be considered significant disagreement.

The schemes will fall into one or more clusters. For example, schemes that aim to maximise systemic arterial blood pressure will tend to identify the same optimum regardless of how pressure is measured. Meanwhile, if there were several schemes that (for example) maximised peak velocity of the tricuspid valve, they would tend to identify the same optimum, and this optimum may be rather different from that obtained by the arterial-pressure-maximising schemes. Optima based on intracardiac measurements need not necessarily agree with each other, since there are many potential variables, and maximization of one may be at the expense of another. Outside of the heart, however, there are fewer opportunities for biventricular pacing to manipulate different variables discordantly, since the heart ejects its stroke volume and the observed pressure is the consequence of this, and all extracardiac variable arise from pressure or flow or both. Measures such as systemic pressure, cardiac output, and cardiac power output might therefore have mutually consistent optima (Manisty et al. 2012; Rubinstein et al. 2012).

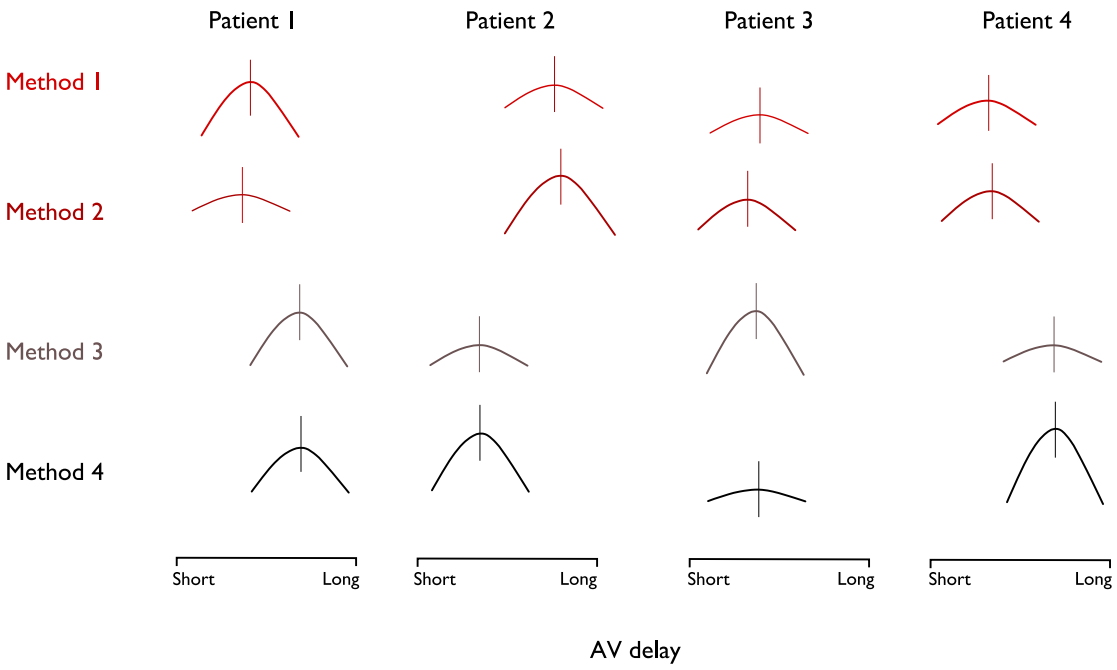


Figure 4-11 Identifying "clusters" of concordant schemes

In this sketch, one patient undergoes optimisation by 4 schemes, and the results are two clusters. One cluster is schemes 1 and 2: they agree with each other in this patient. A separate cluster is schemes 3 and 4: they agree with each other (but not with schemes 1 and 2). This is reproduced in three further patients.

4.9.8 Step 5: Choosing a cluster

It is not known whether there will be only one cluster of optimisation schemes, or several separate clusters. If there are separate clusters of schemes, clinicians should select which cluster represents the variables they believe should be maximised at the expense of the variables in the other clusters. It may be that the choice is obvious. If not, an endpoint trial would at that point be justified, and could confidently be carried out between two very reliable schemes in separate clusters (i.e. schemes that disagree with each other but are each individually singular, reproducible, and plausible).

4.9.9 Step 6: Choosing an optimisation scheme

After these 5 stages, there will be a single cluster of optimisation schemes, each individually being singular, reproducible, and plausible. Each scheme would in effect be already validated against all the others in that cluster. Since all schemes in the

cluster reported the same optimum, any could be chosen for clinical use, perhaps based on cost or convenience.

No endpoint trials would be carried out until this stage, unless at stage 5 a trial was needed to decide which cluster to reject. An endpoint trial could now be rationally planned. If several important physiological variables were consistently maximised simultaneously by an optimisation scheme, then choosing a scheme from a contradictory cluster would be deliberately choosing to depress several physiological variables below their maximum, which would need careful justification. Identifying these clusters might therefore permit elimination of many schemes before having to conduct long term studies.

Application of these steps would arrive automatically at one or more mutually consistent suitable optimisation methods before any single major expenditure on endpoint trials. Steps 1 to 5 are inexpensive, and could be carried out in multiple independent environments, with results only being considered verified when independent studies concur.

Identifying "clusters" of concordant schemes: In this sketch, one patient undergoes optimisation by 4 schemes, and the results are two clusters. One cluster is schemes 1 and 2: they agree with each other in this patient. A separate cluster is schemes 3 and 4: they agree with each other (but not with schemes 1 and 2). This is reproduced in three further patients.

4.10 Conclusion

Clinicians planning to actually carry out optimisation must select amongst the five optimisation strategies recommended (spot-the-pattern, pick the highest or lowest, predict the optimum, fit a curve, find–the-inflection) and the range of measured

variables recommended. Published protocols and even guideline recommendations cannot necessarily be trusted because study authors may inadvertently exaggerate the utility of their locally-favoured methods, and guideline preparation does not involve checking whether protocols are reliable, plausible, or even possible (Brignole et al. 2013a; Daubert et al. 2012). In the absence of trustworthy protocols, clinicians may feel forced to fall back on arbitrary processes for conducting optimisation, but it is difficult to recommend this since such adjustment might just as easily make physiology worse as better. Readers of this document now have a rational process for selecting between optimisation schemes, based on actually trying them exactly as described in a handful of patients. First, does the method give a single optimum? Second, is the optimum genuinely reproducible on an "other day, other hands, other eyes" basis? Third, are the optima plausible? Fourth, does the optimum cluster (Brignole et al. 2013a) with other singular, reproducible, and plausible methods? Finally, the clinician should choose the cluster including the variables most confidently believed to be signs of better cardiovascular outcomes, and from that cluster select a variable that can deliver an optimum of clinically satisfactory precision.

If ultimately an approach to maximize a physiological marker is taken, fitting a curve does allow comprehensive use of the acquired data, but even still sufficient time must be allocated to achieve a narrow confidence interval, otherwise the optimisation protocol may make up to half of patients worse.

4.11 Contributions

This chapter arose from a review conceptualised by myself with my supervisors. We invited an international panel of experts in the field of CRT to provide opinions and

help develop the guideline recommendations. The writing of the text and construction of all the Figures was conducted primarily by myself under the supervision of my supervisor. The text of this chapter is published as "Sohaib SM, Whinnett ZI, Ellenbogen KA, Stellbrink C, Quinn TA, Bogaard MD, Bordachar P, van Gelder BM, van Geldorp IE, Linde C, Meine M, Prinzen FW, Turcott RG, Spotnitz HM, Wichterle D, Francis DP. Cardiac resynchronisation therapy optimisation strategies: systematic classification, detailed analysis, minimum standards and a roadmap for development and testing. *Int J Cardiol*. 2013;170(2):118-31."

Section 2: High resolution methods to probe the current methods

5 Validation of multiple electrogram based AV Delay Optimisation Schemes by cross-comparison and by pressure based optimisation

5.1 Abstract

Background

Manufacturers have each implemented different electrogram-based automatic algorithms for programming AV delay in CRT devices with the intention of maximising cardiac function. Whether the different algorithms agree has never been formally tested. In this study we quantified the agreement between the electrogram-based algorithms and their agreement with high-precision haemodynamic optimisation using non-invasive assessment of arterial pressure.

Method & Results

Because the QuickOpt™ algorithm can only be carried out with St Jude devices, this study could only enrol St Jude device recipients. Twenty-six patients underwent measurements of electrogram features required for calculation of the electrogram based AV delay optimum as defined by QuickOpt™ (St Jude Medical), AdaptivCRT™ (Medtronic), and ExpertEase for Heart Failure +™ (EEHF+™, Boston Scientific). All also underwent haemodynamic AV delay optimisation.

For sensed AV delay, agreement between the haemodynamic optimum and electrogram based optima was poor (versus QuickOpt™ R^2=0.00, p=0.93; versus AdaptivCRT™ R^2= 0.03 p=0.42; versus EEHF+™ R^2=0.09 p=0.14). The different electrogram based optima were also generally mutually contradictory (QuickOpt™ versus EEHF+™ R^2=0.00, p=0.76; QuickOpt™ versus AdaptivCRT™ R^2=0.02, p=0.51). One pair of electrogram based optima, AdaptivCRT™ versus EEHF+™, did show a significant correlation (R^2=0.63, p<0.001) but this was because both their formulae shared an electrogram variable. Even still AdaptivCRT™ recommended an

AV delay on average 21ms longer (p=0.049) than EEHF+^{TM}. Paced AV delay recommendations showed the same pattern.

Conclusion

Different manufacturers' electrogram methods are substantially contradictory. None has impressive agreement with a reproducible method for haemodynamic AV delay optimisation. These data warrant further, independent, exploration since manufacturer electrogram methods are widely used by clinicians who might be assuming that they maximise cardiac function.

5.2 Introduction

Automated electrogram-based methods for atrioventricular (AV) delay optimisation offer the potential for rapid, reproducible selection of AV delay in biventricular pacemakers. However, different manufacturers have implemented different algorithms for selecting AV delay (Sohaib, Whinnett, et al. 2013). If these algorithms are indeed identifying the setting that provides the best cardiac function, then

(a) for any individual patient, the different manufacturer algorithms should agree on the choice of AV delay, and

(b) the electrical algorithms should also agree with the optimum identified by a physiological method that specifies the optimum with high precision and reproducibility.

These experiments do not appear to have been published in the literature.

It is essential that any correlation plots show on both axes AV delay and not cardiac output or other measures of cardiac function (Stegemann & Francis 2012; Sohaib, Whinnett, et al. 2013). This is because different patients will have very different values of (for example) cardiac output and the effects of AV delay adjustment are relatively small. Therefore any correlation plot of cardiac output at AV delay obtained by one versus another method, i.e. with each point representing one patient, will automatically show a strong correlation. The strength of that correlation gives no information on whether the two methods are consistent in suggested AV delays (Stegemann & Francis 2012).

Currently available electrogram algorithms include QuickOpt™ by St Jude Medical (Anselmino et al. 2009; Abraham et al. 2010; Baker et al. 2007), AdaptivCRT™ by Medtronic (Krum et al. 2012; D. Birnie et al. 2013; Khaykin et al. 2011; Jones et al. 2010), and a series of algorithms by Boston Scientific. The Boston Scientific algorithms began with the method used in the COMPANION Trial (Bristow et al. 2004) which appears not to have been published. The second was ExpertEase for Heart Failure Plus (EEHF+™)(Gold et al. 2007). The third is SmartDelay™ (Ellenbogen et al. 2010) which is present on current devices.

Many of these methods are said to have been developed using echocardiographic methods for AV delay optimisation (Anselmino et al. 2009; Khaykin et al. 2011; Jones et al. 2010; Baker et al. 2007). Unfortunately those echocardiographic methods for optimisation in themselves are an uncertain gold standard (Jones et al. 2014; Raphael et al. 2013), for example, not having a good track record of blinded test-retest reproducibility in independent hands. Thus it may be unwise to assume that a belief that two electrogram methods each agree with echocardiographic optimisation means that the two electrogram methods agree with each other.

Many physiological methods are available to maximise cardiac function (Sohaib, Whinnett, et al. 2013). Non-invasive blood pressure based optimisation has the advantage of not requiring invasive catheters and therefore being able to take enough time to make the numerous measurements (Francis 2011; Francis 2013b) that are required to identify genuine effect of AV delay changes in the milieu of unavoidable biological noise. Performing multiple replications and using automated software to

accumulate and plot the results permits a haemodynamic optimum to be identified with high precision and test-retest reproducibility (Zachary I Whinnett et al. 2006).

In this study in a series of patients with CRT, I conducted in each patient electrogram based optimisation of AV delay by several different manufacturer methods and using non-invasive pressure based optimisation.

5.3 Methods

Patients undergoing haemodynamic AV delay optimisation were recruited as a sub-study of the British Randomised Controlled Trial of AV and VV Optimisation (BRAVO, NCT01258829). The inclusion criteria and study protocol have previously been published (Whinnett et al. 2014). Only patients in sinus rhythm with a preserved AV conduction could be included to allow evaluation of the algorithms.

5.3.1 Algorithms evaluated

I only studied electrogram algorithms which are suitable for scientific discussion, i.e. those whose steps are publically available and citable. Fully documented algorithms were available for QuickOpt™ (Baker et al. 2007), AdaptivCRT™ (Martin et al. 2012), and Expert Ease for Heart Failure+™ (EEHF+™) (Gold et al. 2007). A representative of Boston Scientific kindly offered to let us see the algorithm of SmartDelay™ but had to impose the condition that we would not reveal its details. We declined this offer.

I wanted to cover electrogram based algorithms from several manufacturers. Inclusion of the QuickOpt™ algorithm imposed a constraint because one of its necessary measurements (atrial electrogram duration) is only available on devices by St Jude Medical. Fortunately all the measurements necessary for all the other electrogram methods can be made from parameters reported by St Jude Medical devices. For this reason only, this substudy involves only patients with St Jude Medical devices. The BRAVO trial is funded entirely by the British Heart Foundation charity and enrolled patients with devices from any manufacturer. Neither the BRAVO trial nor this electrogram substudy has any connection with any device manufacturer.

5.3.2 Electrogram Recordings

For each patient, device electrogram tracings were printed out at 50mm/s sweep speed and included a surface 3 lead ECG strip. At least 10 beats of the patient's normal sinus rhythm were printed (with atrium and ventricle sensed). A further 10 beats were recorded with atrial pacing and intrinsically AV conducted rhythm (atrium paced, ventricle sensed). For this, atrial pacing rate was set 5 to10 beats above the spontaneous sinus nodal rate. Measurements were averaged from at least five beats per patient.

5.3.3 QuickOpt™

The QuickOpt™ algorithm uses the zig-zag formula (Sohaib, Whinnett, et al. 2013) based on the duration of the atrial electrogram duration as follows (Baker et al. 2007):

Sensed AV Optimum =atrial EGM duration + 60 ms (if EGM duration <100 ms)

atrial EGM duration + 30 ms (if EGM duration >100 ms)

Paced AV Optimum = Sensed AV + 50 ms

We obtained the QuickOpt™ AV optimum directly as reported by the device.

5.3.4 AdaptivCRT™

The AdaptivCRT™ algorithm uses the AV interval detected by the device and a method which calculates the time from atrial sensing (or pacing) to the end of the P wave (Martin et al. 2012).

During atrial sensing, if the heart rate is less than 100 bpm, and if there is a normal PR interval (<200 sensed, <250 paced), only the LV is paced and the AV optimum is calculated based on the time delay between atrial sensing and right ventricular sensing as follows:

Sensed AV Optimum = 70% of $A_s \rightarrow RV_s$ (if $A_s \rightarrow RV_s > 133.3$ ms)

Sensed AV Optimum = $A_s \rightarrow RV_s - 40$ ms (if $A_s \rightarrow RV_s < 133.3$ ms)

where $A_s \rightarrow RV_s$ is atrial sensing to RV sensing (Khaykin et al. 2011).

If the heart rate is above 100 bpm, the PR interval is long, or during any atrial pacing:

Sensed AV Optimum = the smaller of: $A_s \rightarrow P_{end} + 40$ ms and $A_s \rightarrow RV_s - 50$ ms.

Paced AV Optimum = the smaller of: $A_p \rightarrow P_{end} + 30$ ms and $A_p \rightarrow RV_s - 50$ ms

$A_p \rightarrow RV_s$ is atrial pacing to RV sensing. $A \rightarrow P_{end}$ is the P-wave conduction interval determined as the time from atrial sensing (A_s) or pacing (A_p) to the end of the P wave in the far-field electrogram (calculated from the surface ECG in the original studies where this algorithm was developed (Figure 5-1) (Jones et al. 2010).

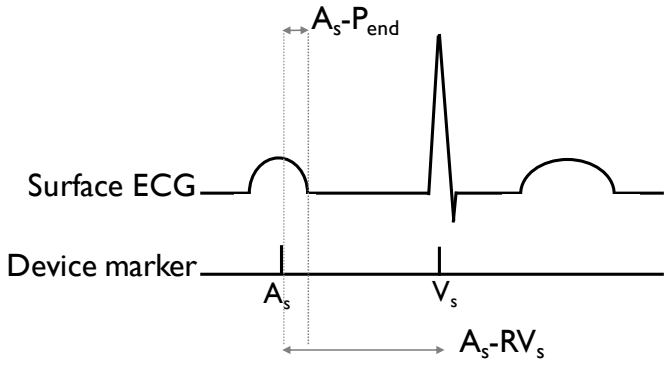


Figure 5-1 Method for calculating A-P_{end}

In this study, the method illustrated above was used to calculate As-Pend and Ap-Pend. This is the difference between the device marker for atrial sensing, and the end of the P wave on the surface ECG (Jones et al. 2010) For Ap-Pend this was calculated as the device marker for atrial pacing and the end of the paced P wave on the surface ECG. As →RVs is atrial sensing to RV sensing

5.3.5 Expert Ease for Heart Failure+™

The EEHF+™ algorithm uses the surface QRS duration (QRS_d) and the AV interval detected by the device to calculate the AV delay optimum. It does this separately for the atrially paced AV delay and the atrially sensed AV delay.

Sensed AV Optimum = $K1 \times QRS_d + K2 \times$ Sensed AV interval + K3

Paced AV Optimum = K1 × QRS_d + K2 × Paced AV interval + K3

where K1, K2, and K3 are constants dependent on lead position. When the LV lead is in a conventional position on the free wall of the LV, and biventricular pacing is instituted, the following constants are used: K1=-0.728, K2=0.757, and K3=71.3 (Gold et al. 2007). When the LV lead is pacing the anterior wall, a different set of constants is used during biventricular pacing (K1=-0.835, K2=1.041, and K3=49. For the purposes of this study, the QRS duration was calculated from a 12 lead ECG, and the AV intervals were measured on the device electrogram printouts. We requested information on lead position from the referring clinician.

5.3.6 Haemodynamic Optimisation

All patient underwent haemodynamic optimisation using non-invasive systolic blood pressure as previously described (Whinnett et al. 2014). In brief, this consisted of repeated alternations in AV delay between a reference AV delay (120 ms) and each tested delay. Non-invasive blood pressure monitoring (Finapres Medical Systems, Amsterdam, Netherlands) was carried out continuously and the change in blood pressure was defined as the increment from the 8 beats immediately prior to transition to the 8 beats immediately after transition. This method of quantifying the direct physiological effect of altering AV delay was chosen because we have found it to have suitable test-retest reproducibility (Z I Whinnett et al. 2006).

5.3.7 Statistical analysis

Statistical analyses were performed on R 3.0.2. Data are presented as mean ±standard deviation (SD). Statistical comparisons were made using one-way analysis of variance (ANOVA) for comparison of the groups. Post-hoc testing was performed if the ANOVA was significant. All tests were two-tailed and $P<0.05$ was considered significant. Correlation between each method of AV optimisation was tested using Pearson's product moment correlation coefficient.

5.4 Results

During the study period 26 patients met the eligibility criteria. Their clinical characteristics are defined in Table 5-1. For EEHF+^{TM} algorithm, the formulae are different between a laterally and anteriorly positioned leads. Of the 26 patients, lead position information was available on 22 and declared to be lateral rather than anterior in the majority (21/22, 95%). For the remaining four patients, the formula for the lateral position was used on the grounds that this was the most common position in the other patients, for whom data were available.

5.4.1 Group means of AV delay optima

The mean AV delay optima were different between the different algorithms in the same group of 25 patients ($p < 0.001$ for atrial pacing, and $p<0.001$ for atrial sensing, by one way ANOVA). Subsequent post-hoc pairwise comparisons found that QuickOpt^{TM} on average reports AV delay optima that are significantly lower than AdaptivCRT^{TM} during atrial sensing ($p<0.01$) and the haemodynamic method during both atrial sensing ($p<0.01$) and atrial pacing ($p<0.01$) (Table 5-2). The optima from EEHF+^{TM} were significantly shorter that the haemodynamic optimum during both atrial sensing ($p<0.01$) and pacing ($p<0.01$) and slightly but statistically significantly shorter than those of AdaptivCRT^{TM} during atrial sensing ($p=0.049$). The optima for AdaptivCRT^{TM} were significantly shorter than the haemodynamic optimum during atrial pacing ($p<0.01$). The other pairwise comparisons at the group level were not statistically significant.

Table 5-1 Patient Characteristics

Patient characteristics are described above. ACE - angiotensin converting enzyme, ARB - angiotensin receptor blocker, LBBB - left bundle branch block, LV EDD - left ventricle end diastolic dimension, MRA - mineralocorticoid receptor antagonist, NYHA - New York Heart Association.

ECG Morphology	
LBBB	21
Non-LBBB	5
Beta blocker	23
ACE inhibitor / ARB	24
MRA	20
Diuretic	20
NYHA	
II	24
III	2
CRT-D	24
CRT-P	2
Ischaemic	18
QRS duration (ms)	163 ± 30
LVEDD (mm)	6.0 ± 0.9

Table 5-2 Average values for AV delay optima

The mean AV delay optimum calculated using each different method is listed (±SD)

	Sensed	Paced
QuickOpt	114 ± 17	163 ± 16
Adaptive CRT	143 ± 30	180 ± 36
EEHF +	122 ± 46	162 ± 45
Haemodynamic	152 ± 46	212 ± 35

5.4.2 Agreement between electrogram based optimisation schemes

The more relevant question is not whether the different algorithms recommend a similar mean AV delay across the group of patients, but whether for individual patients the different algorithms agree. Mutual agreement on optimum AV delay for

any pair of electrogram methods was generally poor, as shown in Figure 5-2 and Figure 5-3. For example, the R^2 values between the QuickOpt™ AV delay optimum and other methods were against AdaptivCRT™ 0.02 (p=0.51) sensed and 0.08 (p=0.15) paced, against EEHF+™ 0.00 (p=0.76) sensed and 0.01 (p=0.73) paced.

The exceptional pair was AdaptivCRT™ and EEHF+™ (sensed: R^2=0.63, p<0.001; paced: R^2=0.46, p<0.001). Nevertheless, even at the group level, there was a systematic difference between the mean AV delay optima selected by the two methods, with the AdaptivCRT™ AV delay optimum longer by an average of 21 ms than EEHF+™ during atrial sensing (p=0.049) and also 18 ms longer during atrial pacing (p=0.18) as shown in Figure 5-2 and Figure 5-3.

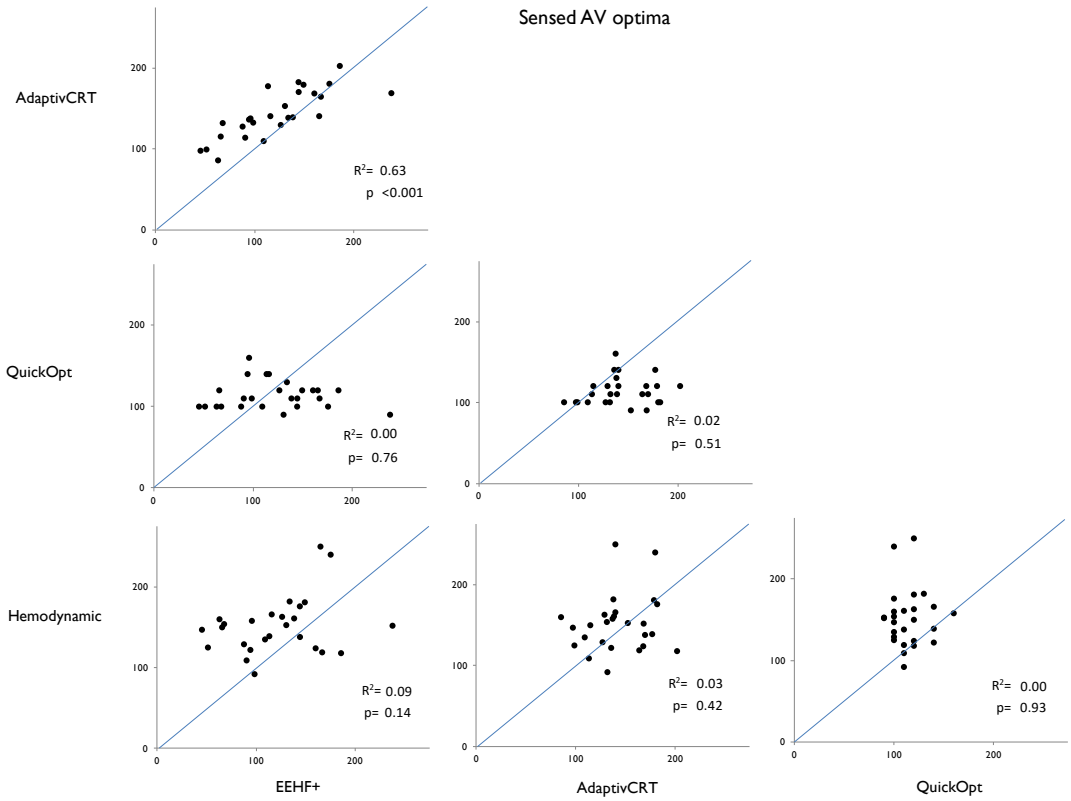


Figure 5-2 AV delay optima during atrial sensing

AV delay optima (ms) selected using the different electrogram based optimisation schemes are compared to each other and to the AV delay optimum selected by non-invasive haemodynamic optimisation.

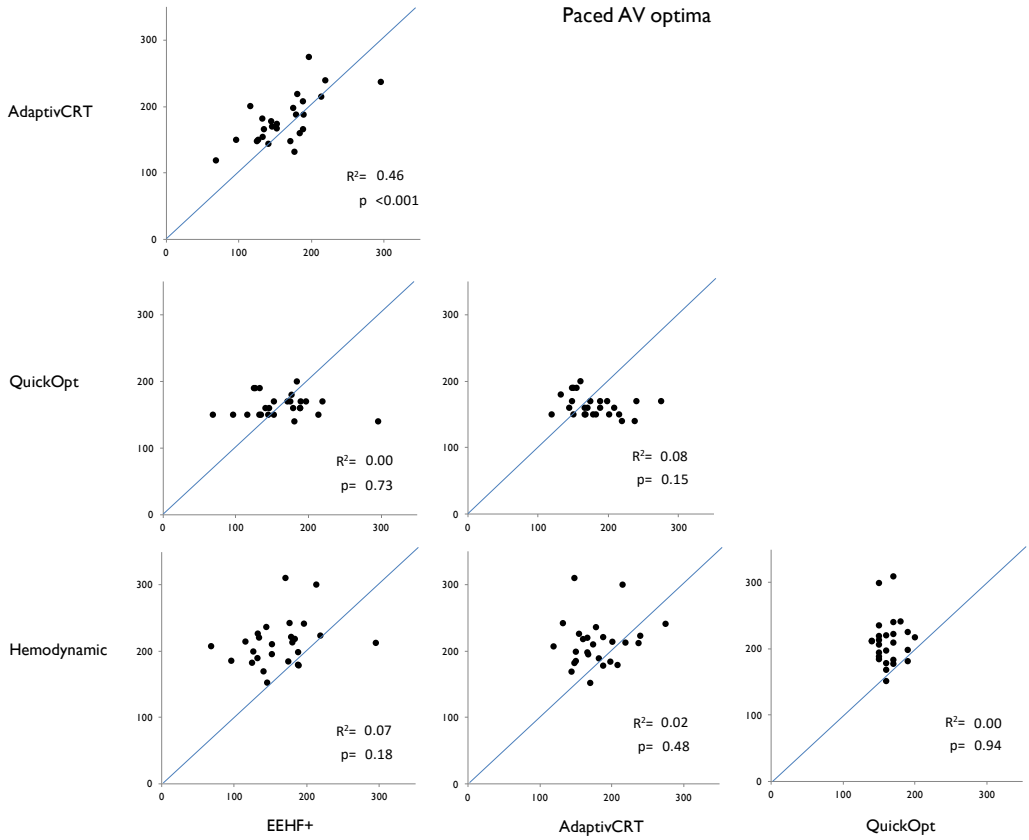


Figure 5-3 AV delay optima during atrial pacing

AV delay optima (ms) selected using the different electrogram based optimisation schemes are compared to each other and to the AV delay optimum selected by non-invasive haemodynamic optimisation.

5.4.3 Agreement between electrogram optima and haemodynamic optima

Agreement between the haemodynamic optima and electrogram optima was poor. This was the case for both sensed and paced AV delay optima (Figure 5-2 and Figure 5-3, respectively). This appeared to be poorest with the QuickOpt™ algorithm (sensed: R^2<0.00, paced: R^2<0.00) but was also poor with AdaptivCRT™ (sensed: R^2=0.03, paced: R^2=0.02) and EEHF+™ (sensed: R^2=0.09, paced: R^2=0.07).

5.5 Discussion

This seems to be the first study to report the different AV delay optima recommended by multiple electrogram methods in the same individuals. The agreement between different algorithms on the choice of AV delay is poor. Even at the group level, there are differences in mean AV delay recommended, with some schemes picking longer AV delay optima than others. More importantly, at the individual patient level, there is for most manufacturers no correlation between the AV delay optima recommended by their algorithms, and for all the tested manufacturer algorithms no correlation between the AV delay optima recommended and the AV delay that produces maximum increment in systolic blood pressure relative to the reference AV delay.

5.5.1 Features of published equations to explain differences in optima

Inspection of the details of the algorithms shows reasons for them to disagree. The QuickOpt™ algorithm has a surprising feature that patients with very different atrial electrogram durations are mapped onto the same recommended AV delay. Meanwhile, a small step up in the electrogram duration from 99 to 101 ms causes a large drop in the AV delay optimum selected. This "zig-zag" relationship between electrogram duration and the QuickOpt™ AV delay optimum is shown in Figure 5-4.

The reason that the EEHF+™ and AdaptivCRT™ algorithms correlate much better than other pairs is that both use similar inputs. Each of these two algorithms has a family of formulae used in different situations but all the formulae are (or are composed of segments that are) linear functions of the time between atrial sensing and RV sensing.

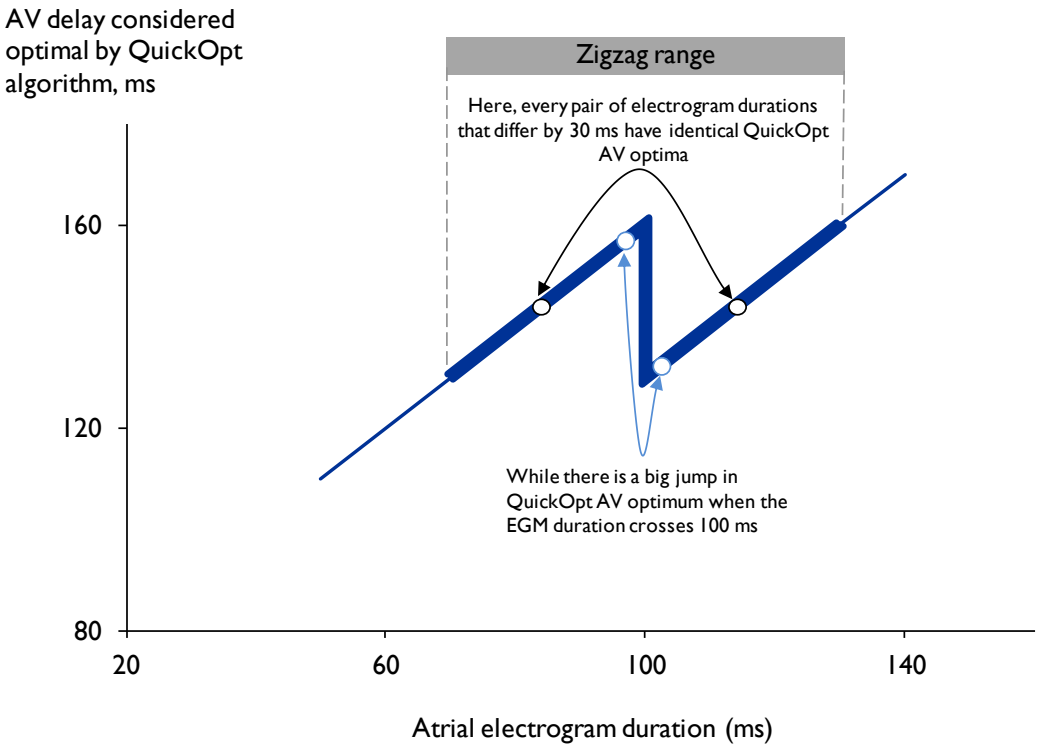


Figure 5-4 Understanding the distribution of QuickOptTM AV delay optima
Application of the QuickOpt™ formula (Baker et al. 2007) for calculating an AV delay optimum. Drawn from published QuickOpt™ formulae. Concept of plotting formulae graphically adapted from Sohaib et al., International Journal of Cardiology 2013 (Sohaib, Whinnett, et al. 2013).

5.5.2 Choosing an algorithm

If the different manufacturer algorithms gave similar values for individual patients as would be expected if they are all identified by optimal cardiac function, then any algorithm could be used in place of another. However, all the algorithms we tested gave mutually contradictory recommendations for AV delay programming. Therefore, of the three algorithms, at least two must be failing to identify an optimum reliably.

Moreover, unfortunately none of the three identify the AV delay that leads to the greatest blood pressure response in our experiment. It is not clear whether there have been blinded studies to test whether the electrogram algorithms consistently identify

the same AV delays as a reproducible haemodynamic algorithm that maximises pressure or flow.

The electrogram methods are sometimes described as recommending the same AV delay as the iterative process of identifying the qualitatively optimal appearance of transmitral Doppler as AV delay is adjusted. However, it is rarely specified whether the operator examining the Doppler trace is blinded to the electrogram recommendation. Second, there are no blinded data confirming whether the qualitatively optimal shape of transmitral Doppler trace maximised blood pressure or even flow. Third, no protocol for this iterative transmitral Doppler optimisation has been found to be reproducible between test and retest by mutually blinded operators. Fourth, it is not possible for the three electrogram methods to all agree with transmitral Doppler as the three electrogram methods disagree with each other.

Nevertheless, at least two of the electrogram algorithms have undergone substantial randomised controlled trials against no optimisation or against a protocol of optimisation of the Doppler pattern which itself may have suboptimal reproducibility (Raphael et al. 2013). Long term outcomes of QuickOpt™ optimisation were evaluated against fixed nominal settings in the FREEDOM trial (n = 1580) and did not show superiority over nominal (Abraham et al. 2010).

AdaptivCRT™ has been evaluated against iterative transmitral Doppler pattern optimisation and met the criteria for non-inferiority (Martin et al. 2012).

EEHF+™ itself appears not to have undergone such large scale randomised comparison against an alternative, but it may be very similar to the same manufacturer's SmartDelay™ algorithm which has. The SMART-AV Trial compared SmartDelay™ with two other arms, fixed nominal settings and iterative transmitral Doppler pattern optimisation. There was no significant difference between groups in

primary outcome (Ellenbogen et al. 2010). Unfortunately the detailed SmartDelay™ algorithm is not publically available. Although it has been kindly offered to us by the manufacturer on a confidential basis, we chose not to receive it if we could not publish it for others to see.

There are trials (Bristow et al. 2004; Moss et al. 2009) which have implemented an electrical algorithm uniformly within the CRT recipients. However, these trials were designed to test CRT against no CRT, and therefore they give no information on whether the electrical algorithm for selecting AV delay is making a contribution.

5.5.3 Limitations

We only studied AV delay optimisation in this study and not VV optimisation. For QuickOpt™ and AdaptivCRT™, which have VV optimisation options, we therefore do not know the level of mutual agreement. For EEHF+™ there is no VV optimisation option and therefore for patients with those devices clinicians might be choosing to leave the VV delay at the default of zero. My other work (Chapter 7) has found that while AV delay has a relatively large effect on haemodynamics, VV delay has a much smaller effect (if it is altered while keeping the time to the first ventricular stimulation constant).

We chose to only conduct experiments whose methods we could describe fully without risk of legal challenge. Therefore we were unable to test SmartDelay™ or any other algorithm whose details are undisclosed or only available confidentially.

For AdaptivCRT™ we used the surface ECG to calculate the A-Pend. This was the approach used by the literature describing the development of the AdaptivCRT™ algorithm. However, the automated algorithm in the implanted device does not have

the true surface ECG and substitutes an equivalent derived from far field signals available to the device (Medtronic 2013).

Our study only addressed electrical algorithms and therefore did not cover the SonR^{TM} method which defines the AV delay optimum as the value which produces a middling level of the first heart sound (Ritter et al. 2012).

5.5.4 Clinical implications

Clinicians using device based electrogram schemes to select AV delay should be aware that the AV delays recommended by the three manufacturer algorithms are different. Even where they correlated there is an offset between them. None of the three we were able to test seem to select the AV delay that causes the heart to produce the most pressure. The formula used by a fourth algorithm, SmartDelay^{TM}, cannot currently be published openly.

5.5.5 Conclusions

Different manufacturers' electrogram methods are substantially contradictory. None has impressive agreement with a reproducible method for haemodynamic AV delay optimisation. It would be advantageous for future studies deriving electrical optimisation algorithms to test them under controlled scientific conditions to establish whether they identify the same values as each other, and the same values as a non-electrical confirmation of maximisation of cardiac function. At an even simpler level, the formulae being applied to patients should be made available for their clinicians to read without being bound to secrecy.

6 Evidence that breath-holding may not be necessary for Doppler measurements of the left ventricular outflow tract

6.1 Abstract

Background

Conventions vary on whether measurements of left ventricular outflow tract (LVOT) waveforms should be measured with breath-hold. Breath-holding requires coordination between operator and patient, is sometimes difficult, and limits duration of continuous measurements. I investigated the effect of breath-holding on LVOT velocity-time integral (VTI) and peak velocity.

Methods

In 36 patients (mean age 63±18.9), LVOT Doppler traces were recorded during 30 seconds of free breathing and two 15-second periods of held end-expiration. Peak velocity and VTI were measured by a validated algorithm.

Results

For peak velocity, there was no difference between breath-holding (98±22cm/s) and free breathing (102±24cm/s; p=0.08). The variability, quantified as the beat-to-beat standard deviation within individual patients, was equivalent between breath-hold (7±6cm/s) and free breathing (7±4cm/s, p=0.41). There was no tendency for measurements to decrease during the 15 seconds of breath-hold (mean regression slope −0.28cm/s/beat, p=0.27) or 15 seconds of free breathing (mean regression slope: −0.21cm/s/beat, p=0.08).

For VTI, breath-holding averaged 20±5 cm and free breathing slightly higher at 22±5cm, p=0.02. Variability was 2±1cm with breath-holding and 2±1cm with free breathing, p=0.45. There was no tendency to measurements to decrease during the recordings (mean regression slopes −0.11 ± 0.12cm/beat, p=0.08, and −0.04±0.05cm/beat, p=0.19 respectively).

Conclusion

Protocols may not require breath-holding for Doppler measurements of LVOT velocity. Breath-holding imposes additional burden on patients, does not improve reproducibility, and may slightly reduce VTI. If improvement is required, averaging more measurements (easier with free breathing) may be the best approach to improving precision.

6.2 Introduction

Doppler measures of transvalvular blood flow in the heart are crucial markers in diagnosis and follow up of many cardiac diseases, both in clinical practice and in research protocols. They are part of guideline protocols for optimisation of AV and VV delay in cardiac resynchronisation therapy pacemakers.(Gorcsan et al. 2008) There are recommendations to average at least 3 beats in sinus rhythm or 5 beats in atrial fibrillation should be averaged.(Baumgartner et al. 2009) Studies use a variety of approaches, with some (Jansen et al. 2006; Thomas et al. 2009) using a breath-holding protocol and some not. (Dubin et al. 1990; Hardt et al. 2007; Riedlbauchová et al. 2005)

Breath-holding can be difficult for some patients to understand and comply with, especially when patients are breathless or otherwise distressed. There is an additional problem for clinicians or researchers who wish to make serial measurements of long sequences of successive beats, for example to detect the dynamic effect of an intervention over several seconds (Manisty et al. 2012). A requirement for breath-holding indirectly limits the number of successive beats that can be measured because prolonged breath holding can be uncomfortable and, if sustained, the voluntary effort necessary may itself create physiological fluctuations.

In this study with the assistance of a medical student (S Tai) I compare the test-retest variability of LVOT measurements under breath-holding versus free breathing. To help our study resist bias we use a validated, vendor-independent, automated algorithm (Zolgharni et al. 2014). This traces Doppler envelopes without human

intervention, minimising the possibility that we may through manually choosing heart beats inadvertently displace our results one way or another.(Francis 2013a)

6.3 Methods

6.3.1 Study Participants

36 consecutive patients who arrived at the echocardiography department at St. Mary's Hospital for echocardiograms scheduled for clinical reasons. All patients provided informed consent. The study was approved by a local ethics committee.

6.3.2 Echocardiography

Transthoracic pulsed wave (PW) LVOT Doppler flow velocities were recorded from the apical 5-chamber view, with the patient in the left lateral decubitus position using a Vivid I (GE, Fairfield, CT, USA) with a 1.5-3.6MHz transducer and simultaneous 3-lead electrocardiogram (ECG) acquisition.

All echocardiograms were obtained by or under the direct supervision of an individual with British Society of Echocardiography (BSE) accreditation. The ECG settings were adjusted such that QRS complexes were positive, with distinct R waves for accurate QRS detection via the automated algorithm.

One 30-second recording of consecutive cardiac cycles during free breathing, and the two 15-second recordings of consecutive cardiac cycles during end-expiration breath-hold were sequentially obtained from each patient (Figure 6-1). During each recording, echocardiographers were instructed to maintain a fixed probe position, sample volume position and all other technical settings.

Data was exported via a standard image acquisition tool (Epiphan, VGA2USB Pro™) to a PC running validated image-analysis software. Full details of its design are given in a previous publication (Zolgharni et al. 2014).

Figure 6-1 Prolonged pulsed wave Doppler recordings of LVOT velocity

These data were acquired by a standard echocardiograph connected to our equipment (full details in the experimental methods 2.5) which captures echocardiograph output, automatically concatenates it to produce Doppler strips of any required length, and then automatically traces Doppler envelopes without user intervention. The red lines are the traces drawn automatically whose peaks and areas-under-curve are exported for statistical analysis.

6.3.3 Statistics

Distributions were summarized using means and standard deviations. The impact of free breathing as compared to breath-holding on the individual mean peak velocity and VTI results was assessed using paired t-tests. The F-test was used to assess the effect on within-patient standard deviations. Bland-Altman plots and Limits of Agreement were calculated comparing free breathing and breath-hold. Intra-class correlation coefficients were calculated. To assess the stability of beat-to-beat peak velocity and VTI over time during free breathing and breath-hold, the percentage difference of each beat's VTI and peak velocities from patient's mean was plotted

against beat number. Regression coefficients were calculated for each patient, and t-tests were used to assess for a significant rise or fall in values within each time-period.

To assess the stability of beat-to-beat variability over time during free breathing and breath-hold each period was divided up into 7.5s intervals. For each patient the coefficient of variation within each period was calculated. Differences between these periods were compared using paired t-tests.

6.4 Results

15 male and 21 female patients, aged 27 to 95 years (63±18.9) were recruited. Of these 36 patients, 1 patient (male, age 95) consented but was unable to comply with a request to hold his breath. Therefore, 35 patients were studied. Individual beat measurements are demonstrated for all patients demonstrated for each breath-hold manoeuvre (Figure 6-2, Figure 6-3, Figure 6-4).

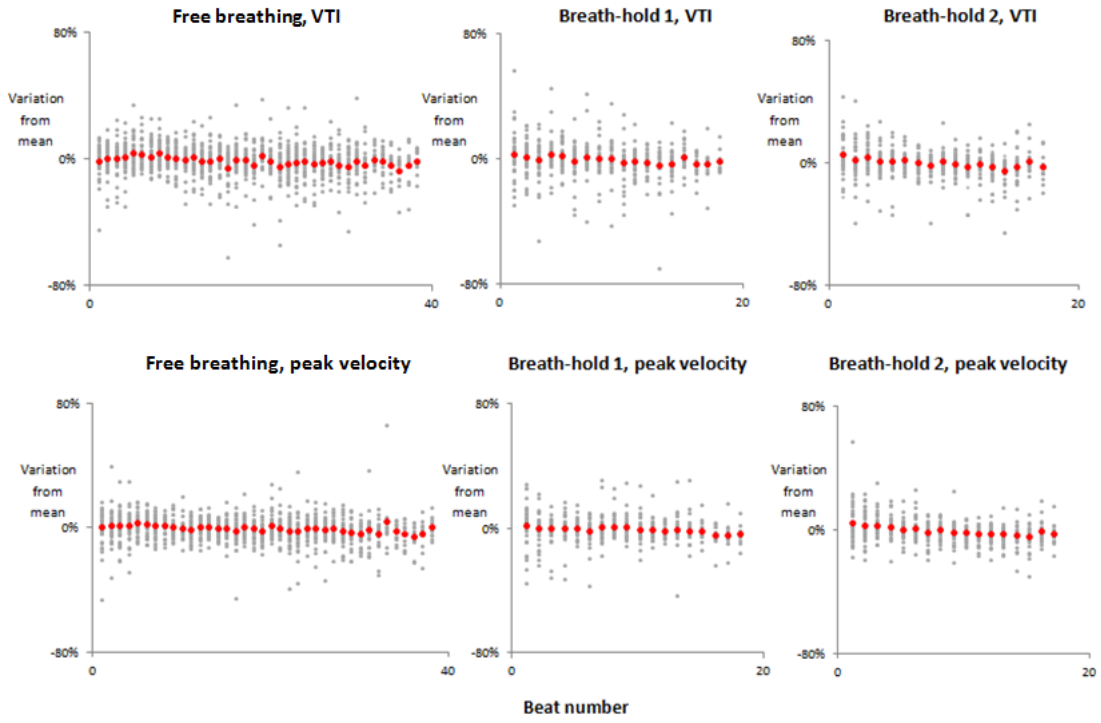


Figure 6-2 Scatter plots showing percentage difference from mean VTI and peak velocities for the individual beats of every patient during free breathing and breath-hold

Each grey dot represents the measurement for a single beat in a single patient. Each red dot represents the mean percentage difference between the mean reading for each patient and each particular beat averaged across all patients. Data are shown for each beat number for which there are data for 10 patients or more.

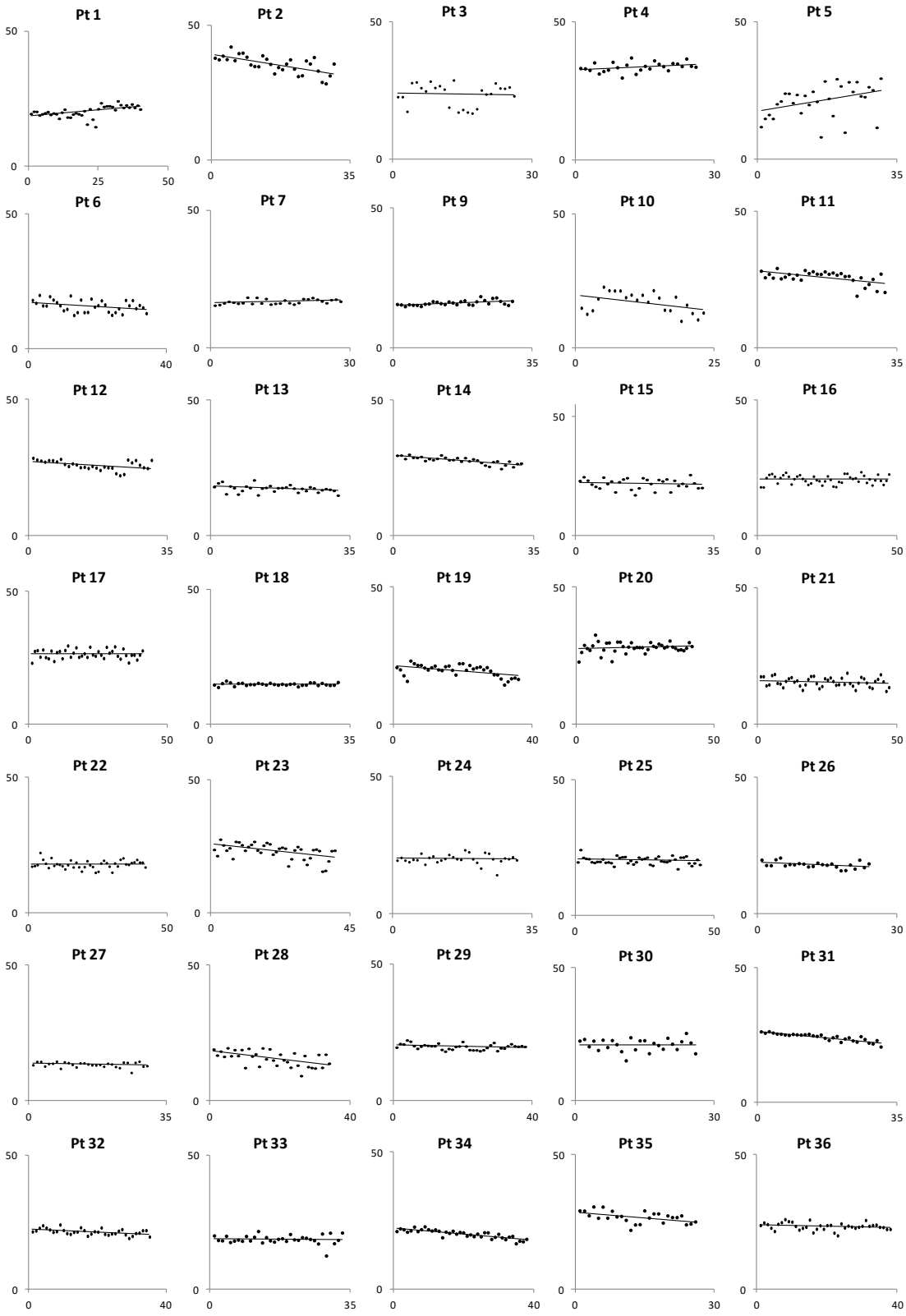


Figure 6-3 Individual data in free breathing for every beat in every patient

Each panel represents one patient. Each data point represents the VTI for one beat. In each panel the horizontal axis is time in seconds and the vertical axis is stroke distance in cm. A regression line is plotted for each patient to give a visual impression of the average rate of change during the recording.

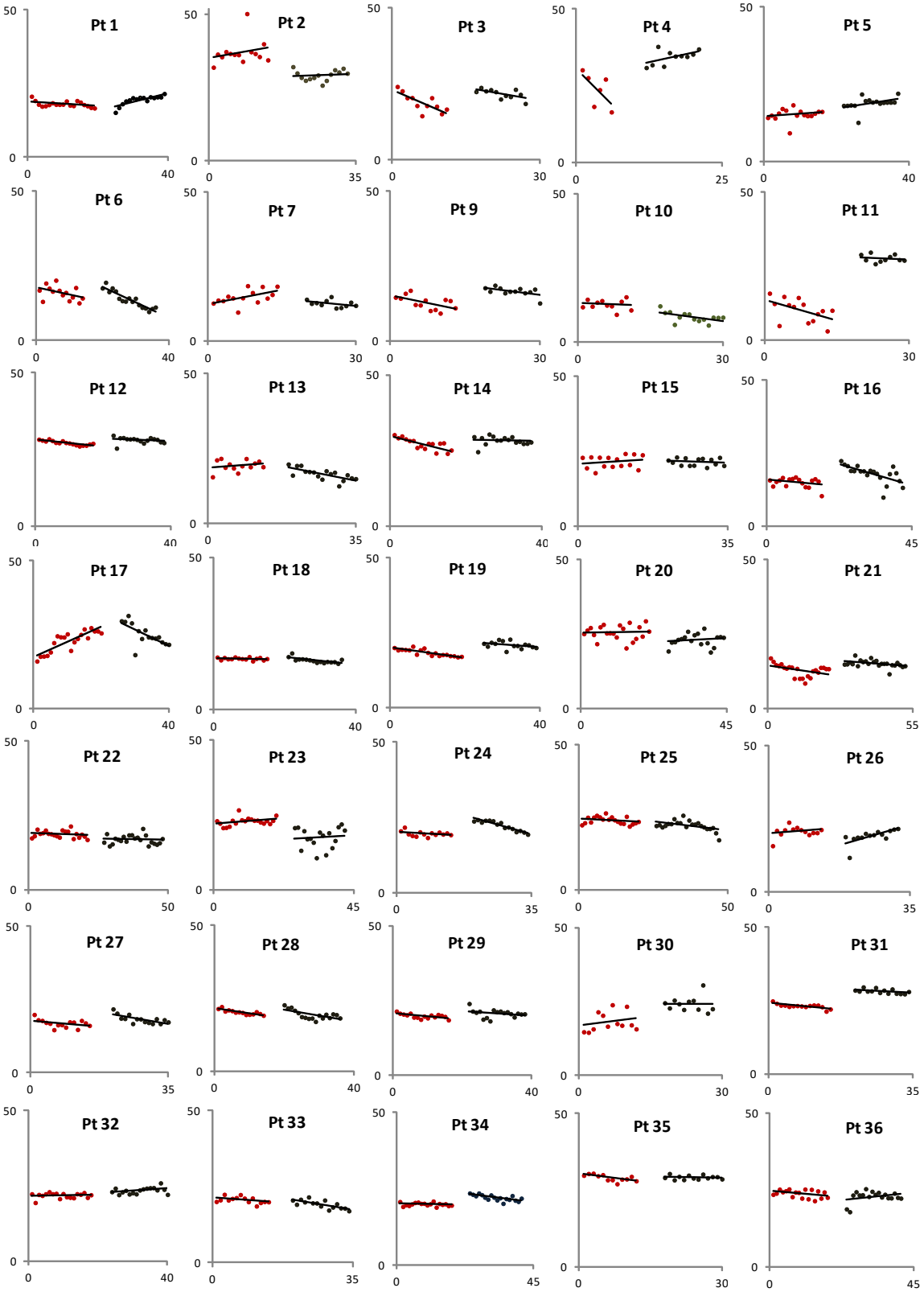


Figure 6-4 Individual data during breath holding for every beat in every patient

Each panel represents the two breath holds of one patient. Each data point represents the VTI for one beat. In each panel the horizontal axis is time in seconds and the vertical axis is stroke distance in cm. A regression line is plotted for each breath hold to give a visual impression of the average rate of change during the breath hold.

6.4.1 Effects of breath holding on peak velocity values and mean VTI

We had pre-specified that the analysis comparing free breathing and breath-hold would use the first 15s of free breathing and the first 15 second breath hold. In this analysis peak velocity during breath-holding was not different to free breathing : 98±22 cm/s versus 102±24 respectively (p=0.08, Table 6-1**)**. VTI was slightly lower during the first breath hold attempt (breath hold 20±5 cm versus free breathing 22±5 cm, p=0.02, Table 6-2).

We wanted to conduct a post hoc analysis using the second set of breath hold data. However, in light of the analysis described below that showed that recordings during the second 15 seconds of free breathing were more vulnerable to downward drift of values (perhaps because of inadvertent loss of ideal probe positioning) we decided to compare this against the *first* 15 seconds of free breathing. In this analysis peak velocity was not significantly different between breath-hold and free breathing (102±24 cm/s versus 101±23 cm/s respectively, p=0.60). Nor was VTI (21±5 cm versus 22±5 cm respectively, p=0.29).

There was no difference in test-retest variability between free breathing and breath hold, as defined by the intra-class correlation coefficient (Table 6-3). Bland Altman plots are shown in Figure 6-5.

Table 6-1 Assessing magnitude of peak velocity measurements during recordings of free breathing versus breath-hold

	Absolute values		Variability	
	Mean, cm/s	*P* *(versus 15s free breathing)*	Within patient SD, cm/s (mean ± SD)	*P* *(versus 15s free breathing)*
Free Breathing (15s)	102±24		7±4	
Free Breathing (30s)	101±23		8±4	
First breath-hold	98±22	*0.08*	7±6	*0.41*
Second breath-hold	101±23	*0.6*	7±4	*0.63*

Table 6-2 Assessing magnitude of VTI measurements during recordings of free breathing versus breath-hold

	Absolute values		Variability	
	Mean, cm	*P* *(versus 15s free breathing)*	Within patient SD, cm (mean ± SD)	*P* *(versus 15s free breathing)*
Free Breathing (15s)	22±5		2±1	
Free Breathing (30s)	21±5		2±1	
First breath-hold	20±5	*0.02*	2±1	*0.45*
Second breath-hold	21±5	*0.29*	2±1	*0.91*

Table 6-3 Intra-class correlation (ICC) of mean VTI and peak velocity between the various respiratory manoeuvres

	Mean VTI	Mean peak velocity
Free breathing versus first breath-hold (15s)	0.84	0.88
Free breathing versus second breath-hold (15s)	0.92	0.91
First breath-hold versus second breath-hold	0.82	0.86

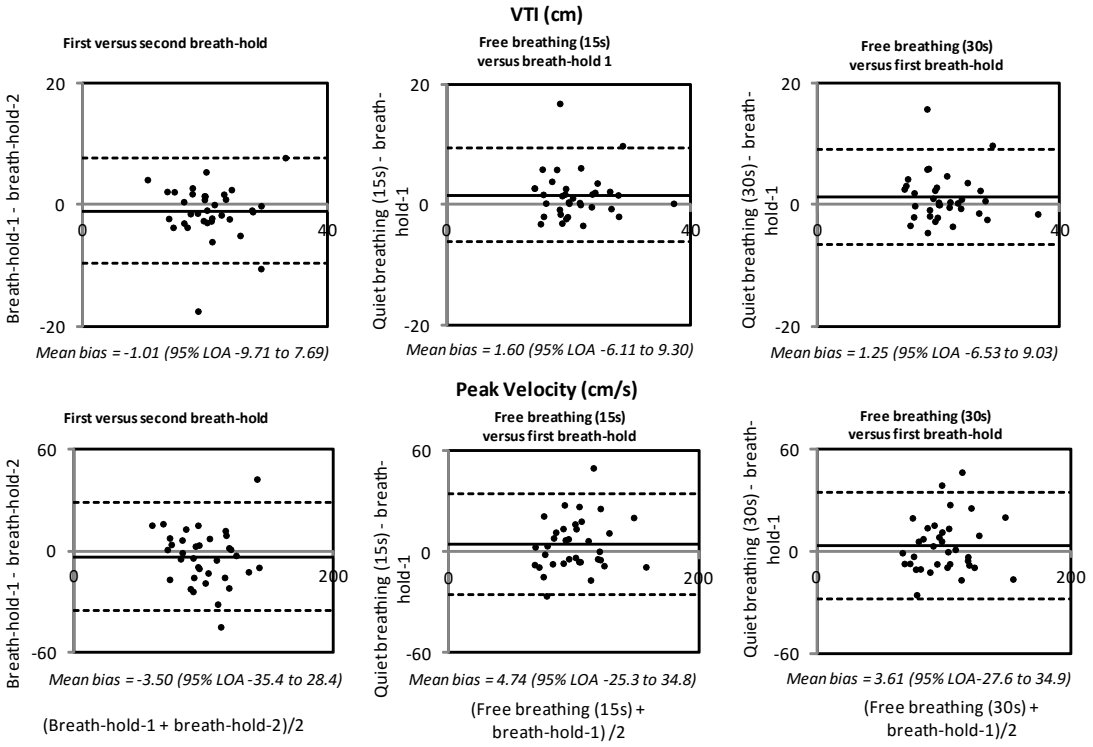


Figure 6-5 Bland Altman plots to assess agreement between peak velocity and VTI measurements during free breathing and breath holds

The upper panels show Bland Altman plots for VTI, the lower panels for peak velocity. The panel on the left compares replicate 15 second breath-holds. The middle panel compares 15 seconds of free breathing with breath-hold, the panel on the right compares 30 seconds of free breathing with a breath hold.

6.4.2 Effect of breathing on variability

Free breathing and breath hold did not differ in the beat-to-beat scatter of VTI measurements, or in the beat-to-beat scatter of peak velocity, across all patients (Table 6-1**,** Table 6-2). We also conducted this analysis for each individual patient in isolation, and the results are shown in the appendix.

The first and second 15-second halves of the free breathing period showed reproducible values of VTI (ICC=0.97), and of peak velocity (ICC=0.97). The two breath hold periods also had good reproducibility, both for VTI (ICC = 0.84) and for peak velocity (ICC = 0.86).

6.4.3 Temporal changes in blood flow velocity with free breathing and breath holding

There was no consistent increase or decline during the equivalent first 15 s of free breathing for VTI (mean regression coefficient: −0.04cm/beat, p=0.19) or peak velocity (mean regression coefficient −0.21cm/s/beat, p=0.08). However, over a 30 s period of free breathing, on average, there was a tendency for the regression coefficients to be predominantly negative for both VTI (Mean regression coefficient −0.04 cm/beat, p=0.01) and peak velocity (mean regression coefficient −0.17 cm/s/beat, p=0.03). During the first breath-hold there was no tendency for measurements to increase or decrease during the period of the 15 s recording for VTI (mean regression coefficient −0.11 cm/beat, p=0.08) nor peak velocity (mean regression coefficient −0.28 cm/s/beat, p=0.27).

6.4.4 Temporal changes in beat to beat variability with free breathing and breath holding

Beat-to-beat variability is considerable (Figure 2 and data supplement), where the mean coefficient of variation per 7.5-second intervals varies from 7% to 9% for VTI and from 5% to 7% for peak velocity. There was no tendency for this variability to progressively increase or decrease during the recording (Figure 6-6).

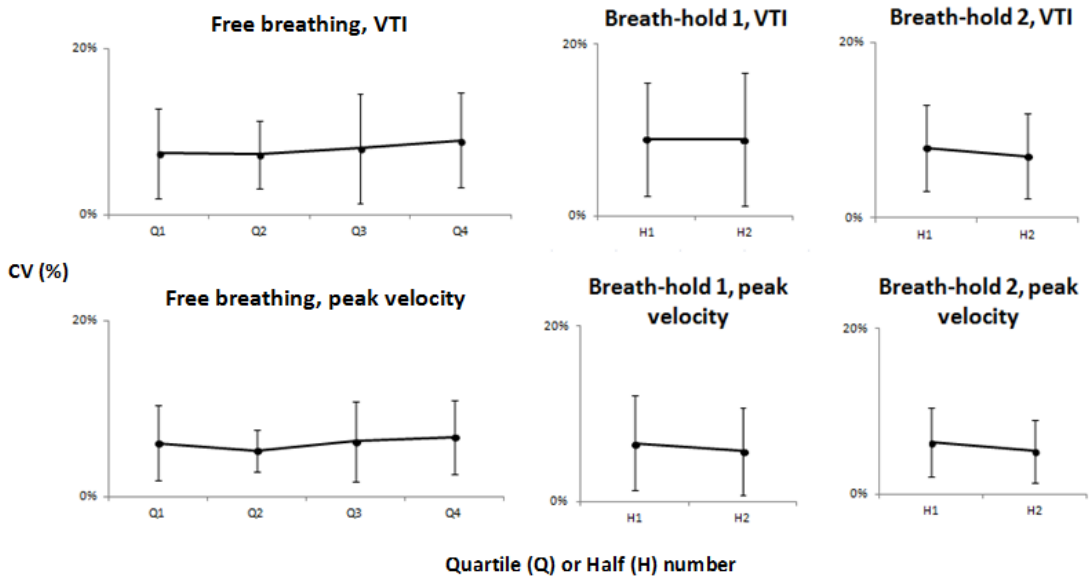


Figure 6-6 Coefficient of variation (CV) during recordings

For each patient and coefficient of variation of VTI, defined as SD/mean, is calculated for each 7.5s epoch within the recording. There are four such epochs (labelled Q1 to Q4 since they are the four quarters) in the 30 second free breathing recordings. There are two such epochs (labelled H1 and H2 since they are the two halves) in the 15 second breath hold recordings. Across all patients the mean (dot) and standard deviation (error bar) of the coefficients of variation are shown. The upper panels show data for VTI and the lower panels data for peak velocity.

6.5 Discussion

Although breathing contributes to beat-to-beat variability, even though breathing is removed, there is no substantial decrease in the amount of beat-to-beat variability. This means we should consider carefully whether it is worthwhile for protocols to require breath-holding.

6.5.1 Contribution of breathing to variability

Intracardiac blood flow is known to fluctuate with inspiration and expiration (Ruskin et al. 1973; Ginghina et al. 2009; Andersen & Vik-Mo 1984; Leeman et al. 1988; Guz et al. 1987) In addition, breathing causes movement of the heart and chest wall (Fenichel 1976; Wade 1954). These can alter beam angulation (Gill 1985) and the

position of scanner sample volume relative to the heart, both of which could affect the observed Doppler velocity (Zhou et al. 1995). These phenomena certainly affect Doppler measurements during breathing (Zoghbi et al. 1986; Zoghbi et al. 1990; Meijboom et al. 1987). Our study does not contradict this concept; it merely quantifies the existence of an even bigger contributor to variability.

This study showed considerable variability with both free breathing and breath-holding, likely due to true biological beat-to-beat variability given that automated tracing eliminated tracing variability, and that the probe position, technical settings, and operator were constant throughout the recording (Saul 1990). If these data are confirmed by others, then the next step in improving the reproducibility of Doppler measurements might be increasing the total duration of the recording (in free breathing) rather than requiring the patient to hold their breath (Meijboom et al. 1987; Greenspan et al. 2005). Durations longer than 15 seconds may best be delivered as two or more separate recordings of 15 seconds because our data suggest values beyond 15 seconds tend to be slightly lower, perhaps because it is sometimes difficult to maintain probe position in exactly the same relationship to the LVOT for prolonged periods.

6.5.2 Causes of beat-to-beat variability

Breathing is not the only source of beat-to-beat variability observed in free breathing. Heart rate varies naturally for many reasons, which may also contribute. Although a prominent source of this is respiratory, there are longer time-scale biological fluctuations too (Saul 1990; Woo et al. 1992). Fluctuation in R-R intervals, as well as the fluctuating sympathetic and parasympathetic signals that drive them, cause fluctuations in preload and afterload, which contribute to fluctuations in stroke

volume.

Prolonged breath-holding may itself cause disturbances because the patient has to use voluntary control of muscles against the involuntary neuromuscular circuitry that would otherwise run natural respiratory cycles (Elisberg et al. 1953; Lin et al. 1983).

Stress and any fluctuation in respiratory gases caused by breath holding may also increase sympathetic outflow. In particular the patient may respond to a request for a prolonged breath hold by performing a partial Valsalva manoeuvre.

6.5.3 Calculating the required number of beats in a clinical protocol

With beat-to-beat variability recognized to be significant regardless of whether the patient is breathing naturally or in a breath hold, how many beats should we measure to minimise variability sufficiently?

Current guidelines on measuring LVOT VTI and peak velocity in clinical practice vary: the American Society of Echocardiography recommends averaging 3 to 5 cardiac cycles in sinus rhythm and 5 to 10 cycles in atrial fibrillation (Quiñones et al. 2002) while the European Society of Echocardiography proposes averaging 2 to 3 cycles in sinus rhythm and 3 to 5 cycles in atrial fibrillation (Lancellotti et al. 2010).

Further research may be needed to guide application of these numbers, because some questions appear to be left open. First, the reader has to guess how to choose between the values in the range. Second, the ranges are different in different time-zones. Third, there appears to be no accompanying explanation for how those numbers were calculated. Fourth, it is not clear what level of reproducibility these numbers are designed to deliver.

A study of M-mode echocardiography showed that averaging over 5 cardiac cycles rather than selecting just one reduced variability by about half (Pollick et al. 1983). This improvement in variability occurred with both standard dimensions (95% CI = 6-32%) and rates of change (95% CI = 23-63%). For transmitral Doppler, beat-to- beat variability during free breathing is relatively large at a standard deviation of 14.5%. As expected, averaging beats reduced the standard error of the mean, to 8.4% at 3 beats and 4.6% at 10 beats. Applying breath-hold achieved halving of these variabilities, being 7.7%, 4.5%, and 2.4% respectively (Meijboom et al. 1987). The trans-aortic velocities in our present study showed less variability than this, and no tendency for the breath holds to significantly reduce variability. One explanation for this could be the nature of LVOT velocities which are monophasic and whose Doppler measurement may be less susceptible to angle artifact attenuating Doppler measurements due to respiratory movements.

Two other studies have also specifically tried to quantify the number of beats required to make an accurate measurements. One showed that while averaging 3 cycles significantly decreased variability compared to using a single cycle, variability (%CV) was still high at around 70%. Instead, at least 20 cycles were required before any further reduction in variability became significant (Kurmanavichius et al. 1989).

This study goes further by defining the coefficient of variation for both LVOT VTI and peak velocity over a long recording. The number of beats required will depend on why the measurement is being performed, and the confidence interval which is required of the measurement. Pragmatically using a coefficient of variation of 7.5% based on the range of measurements acquired in this study for VTI, the number of beats required to be averaged for a desired confidence interval is shown in Table 6-4.

In a published example of CRT, where stroke volume was estimated from LVOT VTI, a 12% increase was seen between a haemodynamically adverse AV delay of 80 ms to the AV optimum in an example of a typical patient (van Geldorp et al. 2011). Using three beats during an optimisation protocol would give a 95% confidence interval of ±9%, more than covering spectrum of moving from and adverse AV delay to the AV optimum.

Table 6-4 Calculating the number of beats to be measured to measure LVOT VTI with a desired confidence interval

Desired 95% Confidence interval	*Necessary SEM*	*Between beat variability of LVOT VTI (Coefficient of variation)*	***Number of beats to be averaged***
± 10%	5%	7.5%	**2**
± 5%	2.5%	7.5%	**9**
± 2%	1%	7.5%	**56**
± 1%	0.5%	7.5%	**225**
± 0.3%	0.15%	7.5%	**2500**
± 0.15%	0.08%	7.5%	**10000**

6.5.4 Limitations

Our study did not address true test-retest reproducibility which is crucial for assessing long term effects of therapies. Instead, it addressed only variability during recordings at one session. When a patient attends for a new scan, the probe may be in a subtly different position and this is likely to increase the variability between the baseline and follow up measurements. Our study design does not address that question but rather focuses on a particular element of variability.

Our study did not directly monitor breathing so we cannot confirm that the oscillations occurring in blood pressure at approximately respiratory frequency are indeed caused by breathing.

Our study did not randomize the order between free breathing and breath holding recordings. There is therefore potential for bias if the greater familiarity of the patients with the equipment a few minutes later may have caused their physiology to be different on the second recording which was breath holding.

6.5.5 Conclusions

When averaged over several beats, Doppler assessment of LVOT velocity made during free breathing are as consistent as measurements made during breath hold. Clinical and research protocols may be benefit from being modified to no longer require breath holding for these measurements. This would make the protocol easier to implement and make it easier for the patient to participate. We hope this study will stimulate other studies checking this finding and perhaps testing other elements of echocardiographic protocols in a similar manner.

6.6 Contributions

This chapter arise from a study conceptualised by myself with my supervisors. I supervised a BSc student (Sarah Tai) who helped with collection of the data and processing of the data using the automated algorithm.

Section 3: Resolving controversies using high resolution physiology

7 Evidence that conflict regarding size of haemodynamic response to VV delay optimisation of CRT may arise from differences in how AV delay is kept constant

7.1 Abstract

Background

Whether adjusting interventricular (VV) delay changes haemodynamic efficacy of cardiac resynchronisation therapy (CRT) is controversial, with conflicting results. No study has addressed whether the convention for keeping AV delay constant during VV optimisation might explain these discrepancies.

Method & Results

22 patients in sinus rhythm with existing CRT-P/D underwent VV optimisation using non-invasive systolic blood pressure. VV optimisation was performed with four methods for keeping the AV delay constant: (a) atrium to left ventricle delay (A-LV) kept constant, (b) A-RV delay kept constant, (c) time to the first-activated ventricle kept constant, (d) time to the second-activated ventricle kept constant. In 11 patients this was performed with AV delay 120ms, and in 11 at AV-optimum.

At AV 120ms, time to the first ventricular lead (left or right) was the overwhelming determinant of haemodynamics (13.75mmHg at +/- 80ms, $p<0.001$) with no significant effect of time to second lead (0.47mmHg, $p=0.50$), $p<0.001$ for difference. At AV-optimum, time to first ventricular lead again had a larger effect (5.03mmHg, $p<0.001$) than time to second (2.92mmHg, $p=0.001$), $p=0.02$ for difference.

Conclusion

Time to first ventricular activation is the overwhelming determinant of circulatory function, regardless of whether this is the left or right ventricular lead. If this is kept constant, the effect of changing time to the second ventricle is small or nil, and is not beneficial. In practice it may be advisable to leave VV delay at zero. Specifying how AV delay is kept fixed might make future VV delay research more enlightening.

7.2 Introduction

The advent of CRT marked a step change improvement in the care of eligible heart failure patients, providing a powerful reduction in morbidity and mortality (Daubert et al. 2012). CRT permits the clinician to adjust the relative timing of left and right ventricular leads, i.e. the interventricular (VV) delay. Some investigators have reported a large haemodynamic effect of VV delay adjustment, sometimes matching the size of the effect of AV delay adjustment (Bogaard et al. 2010; Lim et al. 2008; Vernooy et al. 2007) while others have reported a substantially smaller effect (Z I Whinnett et al. 2006).

In this study I explore whether this discrepancy between groups could be explained by differences in convention on how exactly AV delay is kept constant while VV delay is adjusted.

Traditionally, optimisation of pacemaker timing is divided into AV optimisation and VV optimisation. The reality is that the two are intertwined, and how the two are related is rarely discussed in detail in studies of VV optimisation. When an offset is introduced between the right ventricle (RV) and left ventricle (LV) in a VV optimisation, not only is there an adjustment of the timing between the ventricles , but there will also be an obligatory change in an element of the AV delay: *either* the atrium and the RV (A-RV) *or* the timing between the atrium and LV (A-LV). Depending on how the protocol is planned, either A-RV or A-LV must change during VV delay optimisation despite the intention to keep AV delay constant (Figure 1).

Unfortunately, this matter initially seems minor and accordingly has not received focused attention in the many studies of VV optimisation. Consequently, studies have differed in their approaches for fixing the AV delay while varying VV delay (Auger et al. 2013; León et al. 2005; Bogaard et al. 2010). For example, in some studies the A-

LV timing was kept constant at the AV optimum, and VV adjustment was done solely by changing A-RV timing (Bogaard et al. 2010; León et al. 2005). The reverse is also described with A-RV kept constant (Rao et al. 2007).

In another common approach, the time between atrium and first paced ventricle is kept constant and VV adjustment was done by varying the time to the second ventricle (Ritter et al. 2012; Boriani et al. 2006); which ventricle is first and which is second depends on the sign of the interventricular delay, e.g. an AV delay of 120ms and an interventricular delay of 40ms (LV first) would mean the A-LV is 120ms and the A-RV 160ms, while in contrast an interventricular delay of 40ms (RV first) would mean the A-LV is 160ms and the A-RV is 120ms.

Many authors, including our group in the past (Bogaard et al. 2010; Z I Whinnett et al. 2006), did not consider the distinction important and therefore did not report their choice of convention (Z I Whinnett et al. 2006).

It is not known, whether the choice of convention for keeping AV delay constant determines the magnitude of the hemodynamic response to adjusting VV delay (Bogaard et al. 2013; Vernooy et al. 2007).

This study explores the effect of different choices of what is kept constant during a VV optimisation. We do this by presenting data showing VV optimisations by each of four possible conventions:

- Keeping A-RV constant and adjusting the A-LV;
- Keeping A-LV constant and adjusting the A-RV;

- Keeping time from atrium to the first paced ventricle constant (LV or RV) and adjusting the time to the second ventricle (one of the more commonly reported approaches to VV optimisation);
- Keeping the time to the second ventricle constant while adjusting time to the first ventricle.

7.3 Methods

7.3.1 Study Participants

Twenty-four patients in sinus rhythm with a previously implanted biventricular pacemaker or defibrillator were enrolled from a single centre. Two of the enrolled patients were unable to undergo the protocol due to the onset of diaphragmatic capture in one, and occurrence of frequent ventricular salvos in the other. The remaining 22 patients were able to undergo the protocol. All results for all of these patients are shown.

All 24 patients provided written consent. All procedures and protocols received prior approval from the local research ethics committee and comply with the Declaration of Helsinki.

7.3.2 VV Optimisation Protocol

After the first 11 patients data were analysed it was evident that there was a consistent pattern but internal review threw up the concern that the fixed AV delay used, although a common factory nominal value, was likely to be shorter than most patients physiological optima. It was therefore decided to collect data from a further 11 patients but use for each patient an AV delay identified individually as haemodynamically optimal. No patients had the protocol run at two AV delays because this would require a very lengthy recording session.

For the first 11, VV delay was optimized with AV delay kept constant at a nominal value of 120ms (using four different conventions for keeping AV delay constant). For the second 11, we first performed AV delay optimisation and then conducted the study keeping AV delay fixed at the patients individual AV delay optimum.

The VV optimisation protocol (Z I Whinnett et al. 2006) consisted of alternations in VV delay between zero ms and the tested delay (20ms increments between -80 and

80ms) on a repeated basis for each tested delay. Non-invasive blood pressure monitoring (Finapres Medical Systems, Amsterdam, Netherlands) was carried out continuously and the change in blood pressure was defined as the increment from the 7 beats immediately before transition to the 7 beats immediately after. I took several steps to minimize the impact of inherent beat–to-beat variability on our results. First, the study was performed at an atrial paced rate of 90-100 bpm to maximise the signal-to-noise ratio (Zachary I Whinnett et al. 2006). Each transition in each patient was repeated 16-20 times so that the effect size could be quantified with a small standard error within that individual (Pabari et al. 2011). Our laboratory has focused on systolic blood pressure because it is simple, can be measured invasively or non invasively, and had the best combination of characteristics in a previous study of efficiency and reproducibility (Whinnett, Davies, et al. 2008). VV optimisation was performed using four different conventions for how AV delay is kept constant (Figure 7-1):

1. **VV optimisation with constant A-LV**: Adjusting delay between the LV and RV while keeping the timing from the atrial lead to the LV lead is constant (120ms for the first 11 patients, or the AV optimum for the second 11).

2. **VV optimisation with constant A-RV**: Adjusting delay between the LV and RV ensuring that the timing from the atrial lead to the RV lead is constant (120ms or AV optimum).

3. **VV optimisation by only lengthening**: Keeping the delay from the atrium to the first ventricular lead constant (at 120ms or AV optimum) while delaying either the LV or the RV lead.

4. **VV optimisation by only shortening**: Keeping the delay from the atrium to the second ventricular lead constant (at 120ms or AV optimum) while activating

either the LV or RV lead earlier. This has never been proposed as a convention for optimisation, but we included it for analytical completeness.

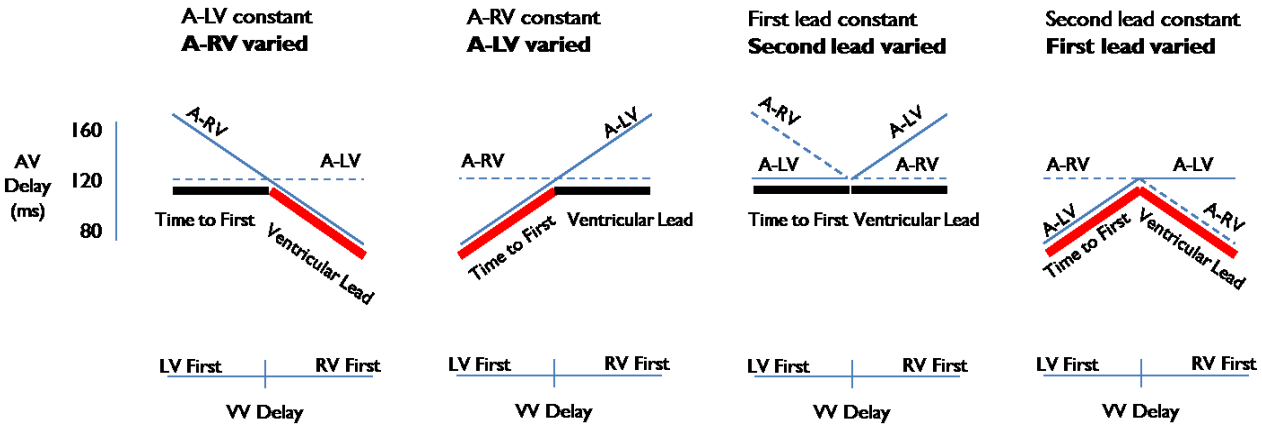


Figure 7-1 Four conventions for VV optimisation

This sketch conceptualises the four different potential conventions for what aspect of AV delay is kept constant during VV optimisation (Time from atrial activation to ventricular activation). On the vertical axis, change in relevant AV delay is represented (this could be to the LV, RV, or first, or second ventricle paced). The horizontal axis represents VV delay, with LV paced first to the left and RV paced to the right. The left panel shows the A-LV being kept constant while the A-RV is varied. The second panel (Boston Scientific convention) shows the converse. The third panel (Medtronic and St Jude Medical convention) shows the time to the first ventricular lead kept constant. The right panel shows the time to the second ventricular lead kept constant which is unlikely to be clinically meaningful, but is presented for completeness.

In this report, when describing VV delay, positive represents RV first, and negative represents LV first.

The second group of 11 patients underwent the preparatory step of AV optimisation so that the fixed AV delay used for them would be their own individual AV optimum. The AV optimisation process was by our standard protocol (Zachary I Whinnett et al. 2006).

Due to differences in terminology between the different manufacturers, two different protocols are required to allow the A-LV or A-RV time to be kept constant.

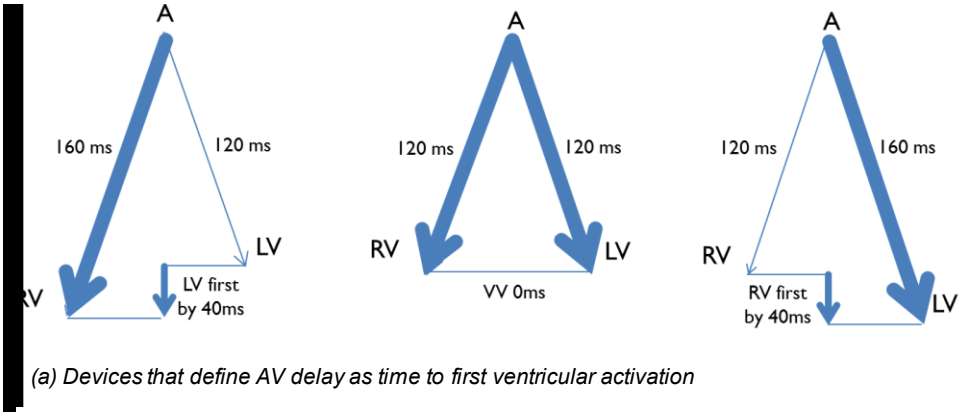
7.3.3 Differences in programming VV delay between manufacturer

7.3.3.1 Devices that define AV delay as time to RV activation:

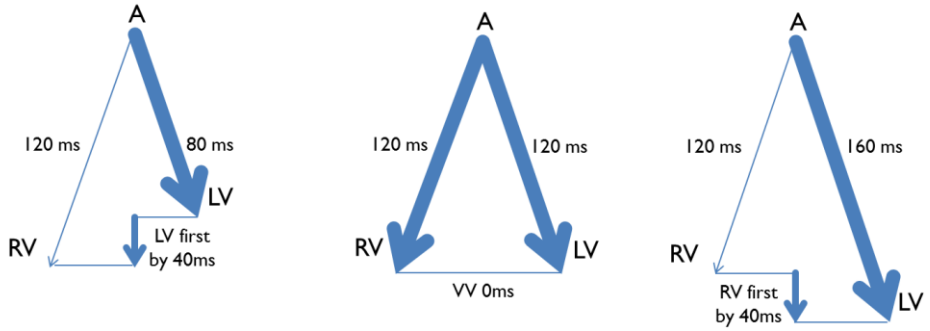
In devices manufactured by Boston Scientific™, programmed AV delay represents the delay between the atrial and RV leads (Figure 7-2). Therefore, for example, when our protocol required us to keep A-RV constant at 120ms and pre-excite the LV by 40ms (i.e. A-LV time of 80 ms), we programmed AV delay to 120ms and LV offset of -40ms. When our protocol required us to keep A-LV constant at 120ms and pre-excite the RV by 40ms (i.e. A-RV time of 80 ms), we programmed AV delay to 80 ms and LV offset of +40ms.

7.3.3.2 Devices that define AV delay as time to first ventricular activation:

For devices manufactured by Medtronic™, St Jude Medical™, Biotronic™, and Sorin™, programmed AV delay is from the atrial lead to the first paced ventricle (Figure 7-2). For the VV delay, an additional offset is then programmed to one of the ventricles. Therefore, to keep A-RV constant at 120ms and pre-excite the LV by 40ms (i.e. A-LV of 80 ms), we programmed AV delay to 80ms, with an LV to RV time of 40ms. To keep A-LV time constant at 120ms and pre-excite the RV by 40ms (i.e. A-RV time of 80 ms), we programmed AV delay to 80ms, with an RV to LV time of 40ms.



(a) Devices that define AV delay as time to first ventricular activation



(b) Devices that define AV delay as time to activation of the right ventricle

Figure 7-2 A demonstration of how A-RV and A-LV delay change when a VV delay is introduced

The left panel demonstrates how a setting of "AV 120 ms, and LV first by 40 ms" can have dramatically different results on A-LV and A-RV time depending on the manufacturer. The right panel illustrates the same for AV 120 ms, and RV first by 40 ms. The panel in the centre for reference shows A-LV and A-RV when no offset is programmed.

7.3.4 Analysis and Statistics

Data were analysed using Matlab (MathWorks, Natick, MA, USA) and Microsoft Excel (Microsoft, Redmond, Washington, USA). To test whether adjusting VV delay produced a statistically significant difference in blood pressure compared with VV0 we used a two-tailed paired t-test. A p-value below 0.05 was considered statistically significant.

7.3.5 Power calculation

To detect an effect size of 0.3 standard errors with a 12 replicate protocol is equivalent to detecting an effect size of $0.3\times\sqrt{12}$ standard deviations. 80% power at

the 5% two-tailed significance level would need 10 patients. We recruited 11 to undergo optimisation at 120ms, and a further 11 to undergo optimisation at their individual AV optimum.

7.3.6 Reproducibility and randomisation

This method has good reproducibility of the AV optimisation protocol on the same day, and at three months (Zachary I Whinnett et al. 2006) and for AV and VV optimisation using a "time to first activated ventricle constant" protocol at baseline and two months (Z I Whinnett et al. 2006). The protocol of our present study enhances precision by performing at least 16 replicates for each AV/VV combination, which makes us confident that reproducibility will be at least as good. Each patient underwent the protocol in a single ~3 hour session, and did not undergo repeat testing. The error bars on the results of each AV delay in each individual patient might be used as an index of reproducibilty, and the full raw dataset is available to readers on request.

Because our protocol required manual implementation of at least 16×8×2=256 changes in programming, to minimise excess time required for documenting these changes and scope for error, there was no randomisation of order. There is therefore a risk of carryover effects although we found the variability between replicate transitions at each setting was large, suggesting little chance of major impact from carryover. Nevertheless, future researchers hoping to replicate this study might choose to implement randomisation of order, but would need either a simple and accurate means of documenting each transition or would need manufacturers to provide a method to programmatically run a pacemaker through a pre-planned random sequence of settings.

7.4 Results

Adjusting AV delay showed a curvilinear change in SBP (all data from all patients are shown in left panels of Figure 7-3 and Figure 7-4). The mean AV optimum (during atrial pacing) in the group of 11 patients who had the VV adjustment carried out at AV optimum, was 200ms (SD 29ms, range 160-250ms). The first and second groups of 11 patients had similar characteristics (see appendix). Participants had a mean age of 66 years (SD 8, range 54-82), QRS duration of 162ms (SD 24ms, range 132-220ms), LV end diastolic diameter 5.7cm (SD 1.2cm, range 4.2-9.2cm). Other patient characteristics are described in Table 7-1.

Table 7-1 Patient characteristics

LBBB: left bundle branch block, RBBB: right bundle branch block, CHB: complete heart block, NYHA: New York Heart Association, ACE-I: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker

	N	%
Male	19	*86%*
ECG Morphology		
LBBB	16	*73%*
RBBB	3	*14%*
CHB	3	*14%*
NYHA Class		
II	15	*68%*
III	7	*32%*
Device Type		
CRT-D	11	*50%*
CRT-P	11	*50%*
Heart Failure Aetiology		
Ischaemia	13	*59%*
Non-Ischaemic	9	*41%*
Betablocker	16	*73%*
ACE-I / ARB	19	*86%*
Aldosterone Antagonist	13	*59%*
Diuretic	14	*64%*

7.4.1 Hemodynamic changes are produced by changes in AV delay rather than by offset between ventricular stimuli, when VV delay is adjusted close to an AV delay of 120ms

At AV 120ms, adjusting the time to the first ventricular lead had a large haemodynamic effect, regardless of whether this was located in the left or right ventricle (Figure 7-5, fourth column; Table 7-2). In contrast adjusting the time to the second ventricular lead had no detectable haemodynamic effect, regardless of whether this was the left or right ventricle (Figure 7-5, third column).

Viewing the ventricles individually, adjusting A-LV keeping A-RV constant (Figure 7-5, second column), or adjusting A-RV keeping A-LV constant (Figure 7-5, third column), both had an effect which was composed of two asymmetrical halves: one half where one ventricle's AV delay is shortened and the other half where the other ventricle's AV delay is lengthened (AV delay to first paced ventricular lead remained constant at 120 ms). Amongst these, the only half which caused substantial change in pressure was the shortening of an AV delay, regardless of whether this was by shortening A-RV or A-LV. In contrast, the half which involved lengthening the delay in one ventricle produced no significant effect on blood pressure regardless of whether it was the LV or RV lead which was delayed.

The full pattern of all data in each individual patient is shown in Figure 7-3. This involves showing each data point twice so that the answer to each research question can be seen clearly.

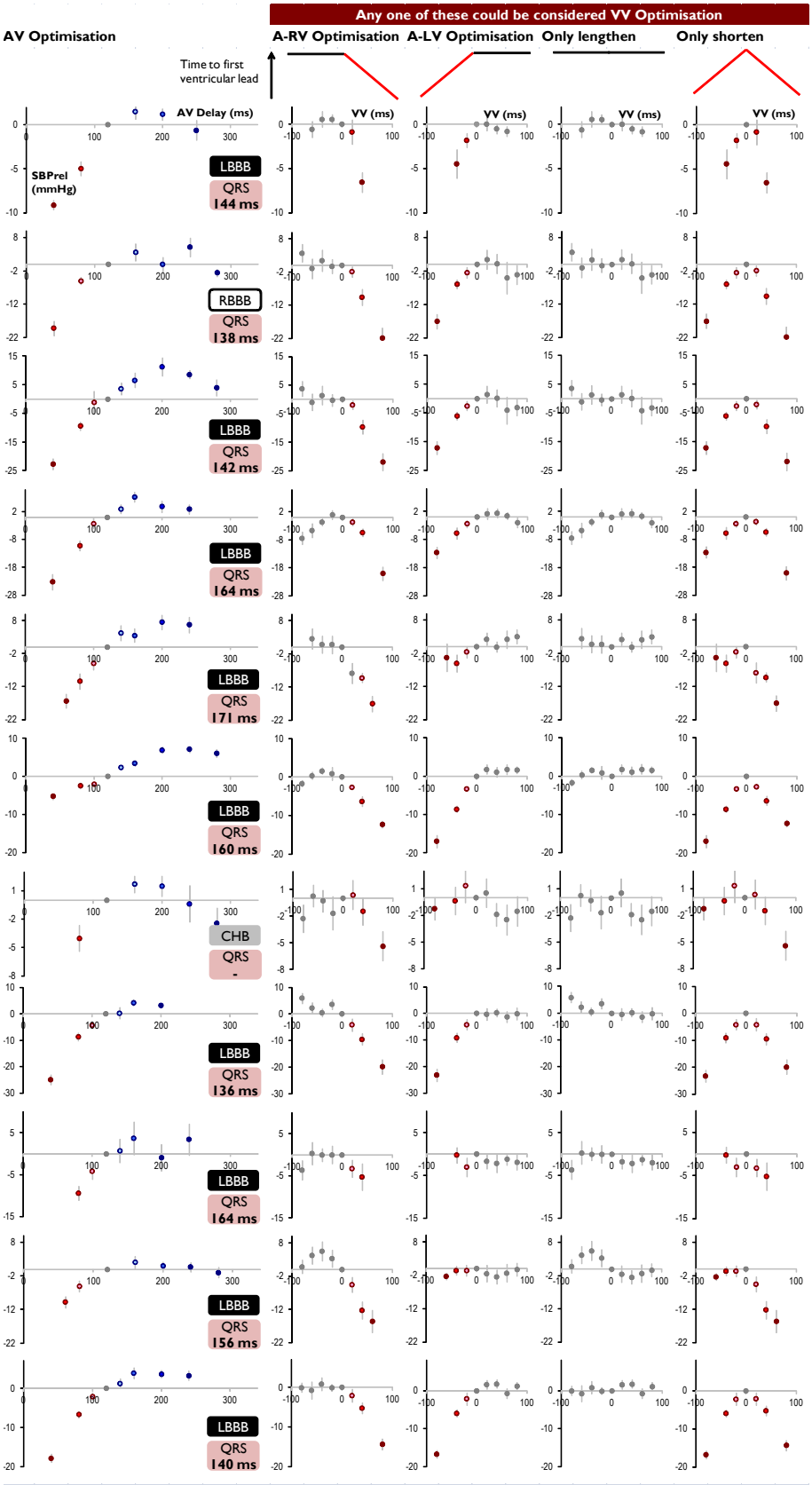


Figure 7-3 VV Optimisation in all 11 patients optimized from AV 120ms

The vertical axes represent change in systolic blood pressure relative to a reference setting. For the AV optima this is 120 ms, for the VV adjustments this is VV 0. The first column shows AV optimisation curves for individual patients. The next four columns depict VV adjustment

using the four different conventions: adjusting A-RV with A-LV constant, adjusting A-LV with A-RV constant, adjusting the choice and timing of the second lead while keeping the timing to the first ventricular lead constant, and vice versa.

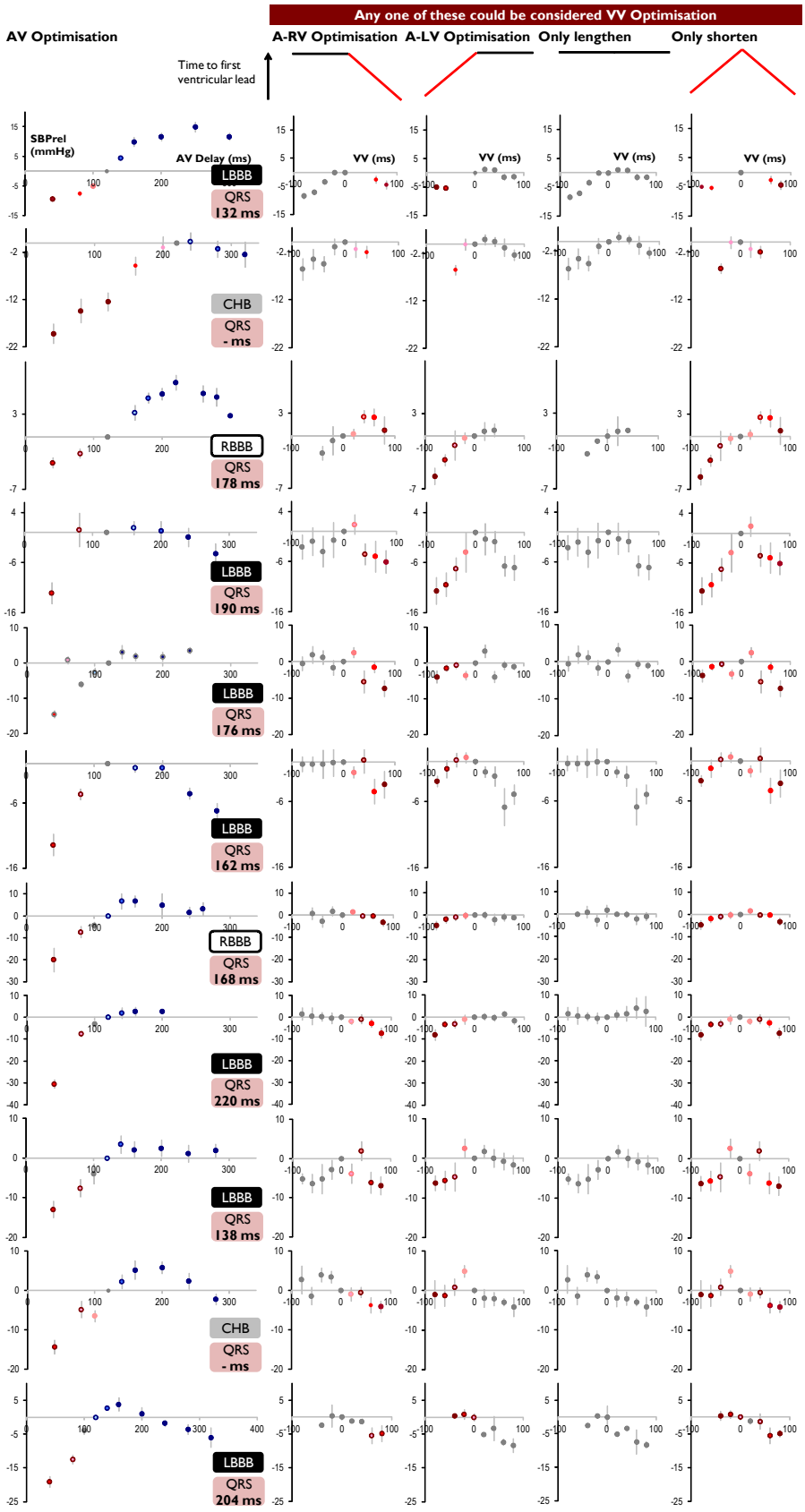


Figure 7-4 VV Optimisation in all 11 patients optimized from AV optimum

The panels are organised in the same way as Figure 3.

Table 7-2 Impact of choice of convention for maintaining AV delay, on haemodynamic responses to VV adjustment when optimizing from AV 120ms (upper panel) and AV optimum (lower panel)

The mean relative systolic blood pressure across the cohort of participants is tabulated and tested for a significant difference to zero. Only when there is a change in the time to the first paced ventricle is a significant difference seen. Once there is no longer a change in time to first paced ventricle, the difference attenuates or disappears. The first column lists the VV offset (negative means LV activated first; positive means RV activated first). The four columns list the response to the four different conventions with the time to first ventricular lead listed with each convention and average BP response. The p values are comparisons against VV0. (FVL time: time to First Ventricular Lead, SBPrel: Relative systolic blood pressure, SE: standard error, AVopt: Optimal AV delay).

VV optimisation with an AV delay of 120ms

VV Offset (ms)	A-RV Optimization				A-LV Optimization				Only Lengthen				Only Shorten			
	FVL time (ms)	Mean SBPrel	SE	*P*	FVL time (ms)	Mean SBPrel	SE	*P*	FVL time (ms)	Mean SBPrel	SE	P	FVL time (ms)	Mean SBPrel	SE	*P*
-80	120	-0.73	1.31	*0.59*	40	-13.45	2.84	*0.003*	120	-0.73	0.59	0.59	40	-13.45	2.84	*0.003*
-60	120	0.25	0.69	*0.72*	60	-2.81	0.50	*0.11*	120	0.25	0.72	0.72	60	-2.81	0.50	*0.11*
-40	120	0.79	0.55	*0.18*	80	-4.41	0.95	*0.0009*	120	0.79	0.18	0.18	80	-4.41	0.95	*0.0009*
-20	120	0.63	0.49	*0.22*	100	-1.96	0.45	*0.002*	120	0.63	0.22	0.22	100	-1.96	0.45	*0.002*
0	120	0.00	0.00		120	0.00	0.00		120	0.00			120	0.00	0.00	
20	100	-2.88	0.65	*0.0013*	120	0.37	0.42	*0.40*	120	0.37	0.40	0.40	100	-2.88	0.65	*0.0013*
40	80	-6.59	1.02	*0.0001*	120	-0.10	0.45	*0.83*	120	-0.10	0.83	0.83	80	-6.59	1.02	*0.0001*
60	60	-16.37	0.72	*0.03*	120	-0.84	0.54	*0.15*	120	-0.84	0.15	0.15	60	-16.37	0.72	*0.03*
80	40	-14.05	2.69	*0.002*	120	-0.24	0.60	*0.70*	120	-0.24	0.70	0.70	40	-14.05	2.69	*0.002*

VV optimisation with an optimized AV delay

VV Offset (ms)	A-RV Optimization				A-LV Optimization				Only Lengthen				Only Shorten			
	FVL time (ms)	Mean SBPrel	SE	*P*	FVL time (ms)	Mean SBPrel	SE	*P*	FVL time (ms)	Mean SBPrel	SE	P	FVL time (ms)	Mean SBPrel	SE	*P*
-80	AV_{Opt}	-2.35	1.37	*0.13*	AV_{Opt} -80	-5.41	1.02	*0.001*	AV_{Opt}	-2.35	1.37	0.13	AV_{Opt} -80	-5.41	1.02	*0.001*
-60	AV_{Opt}	-1.91	1.06	*0.11*	AV_{Opt} -60	-3.71	1.01	*0.01*	AV_{Opt}	-1.91	1.06	*0.11*	AV_{Opt} -60	-3.71	1.01	*0.01*
-40	AV_{Opt}	-1.76	0.84	*0.06*	AV_{Opt} -40	-2.19	0.88	*0.03*	AV_{Opt}	-1.76	0.84	*0.06*	AV_{Opt} -40	-2.19	0.88	*0.03*
-20	AV_{Opt}	-0.24	0.52	*0.65*	AV_{Opt} -20	-0.03	0.82	*0.98*	AV_{Opt}	-0.24	0.52	*0.65*	AV_{Opt} -20	-0.03	0.82	*0.98*
0	AV_{Opt}	0.00	0.00		AV_{Opt}	0.00	0.00		AV_{Opt}	0.00	0.00		AV_{Opt}	0.00	0.00	
20	AV_{Opt} -20	-0.52	0.61	*0.42*	AV_{Opt}	-0.20	0.67	*0.78*	AV_{Opt}	-0.20	0.67	*0.78*	AV_{Opt} -20	-0.52	0.61	*0.42*
40	AV_{Opt} -40	-1.02	0.80	*0.23*	AV_{Opt}	-1.24	0.50	*0.03*	AV_{Opt}	-1.24	0.50	*0.03*	AV_{Opt} -40	-1.02	0.80	*0.23*
60	AV_{Opt} -60	-2.96	0.83	*0.006*	AV_{Opt}	-2.72	0.99	*0.02*	AV_{Opt}	-2.72	0.99	*0.02*	AV_{Opt} -60	-2.96	0.83	*0.006*
80	AV_{Opt} -80	-4.69	0.78	*0.0002*	AV_{Opt}	-3.37	0.83	*0.003*	AV_{Opt}	-3.37	0.83	*0.003*	AV_{Opt} -80	-4.69	0.78	*0.0002*

7.4.2 Time from atrium to first ventricular lead has a greater haemodynamic impact than time to second ventricular lead, at AV optimum

In contrast, at AV optimum (Figure 7-4), the time to the first ventricular activation was no longer the sole determinant of pressure and the second ventricular lead timing was no longer unimportant. Both made a contribution (5.03mmHg at 80ms, $p<0.001$ and 2.92 mmHg at 80ms, $p=0.001$ respectively) but with the first lead more important than the second lead ($p = 0.02$). Viewing the ventricles individually, adjusting the A-LV keeping the A-RV constant (Figure 7-5, second column), or adjusting the A-RV keeping the A-LV constant (Figure 7-5, third column) generally reduced blood pressure. There was no evidence that when the AV delay was optimal, a statistically significant increase in blood pressure could be obtained from adjusting VV delay away from 0.

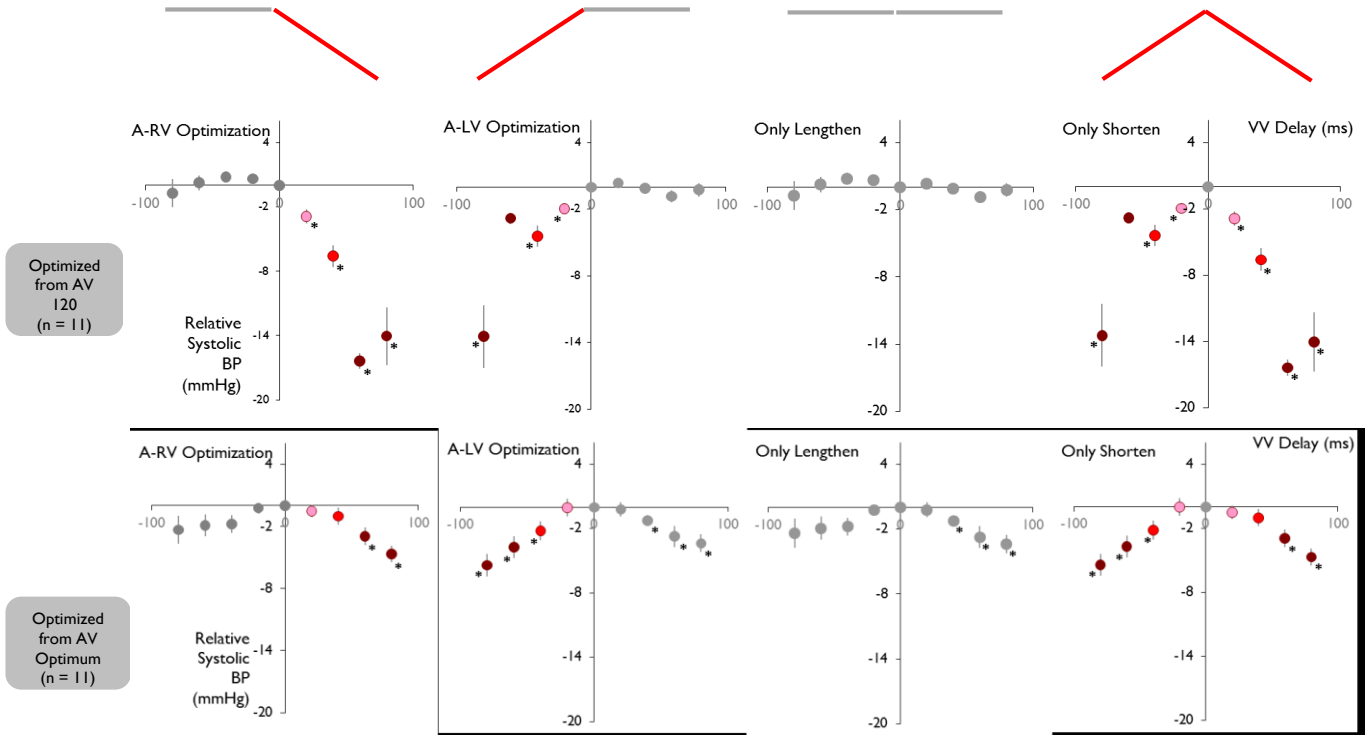


Figure 7-5 Mean impact on haemodynamic response optimizing from AV 120ms (upper panel) or AV Optimum (lower panel)

The vertical axes represent relative systolic blood pressure compared with a setting of VV 0. The horizontal axis represents VV delay, with a negative value indicating the LV is paced before the RV, and a positive value indicating the LV is paced after the RV. The mean relative systolic blood pressure are averaged for all the participants using the four different methods of VV optimisation. * indicates settings with a significant difference ($p<0.05$) in pressure compared to VV0. Grey indicates the time to the first ventricular lead is kept constant. The outlines at the top are sketches of how time from atrium to first ventricle changes with VV delay using the four different conventions.

7.5 Discussion

This study shows profoundly different responses to VV adjustment when different conventions are applied for keeping the AV delay constant, and may explain the discrepancy between the findings from different laboratories studying VV optimisation. Second, it indicates that the AV delay chosen can impact on the responses to VV adjustment. Third , with precise measurements for individual patients, it suggests that almost always a VV delay of 0 is suitable. Notably, in order to measure these changes with confidence it was necessary to make numerous replicate measurements to allow the subtle effects of pacemaker timing adjustment to be identified from biological beat-to-beat variability.

7.5.1 Contribution of VV adjustment to the physiological benefit of biventricular pacing

My data indicates that near an AV delay of 120ms, the time between atrial activation and the first ventricular activation is the overwhelming determinant of acute haemodynamic response. When time to first ventricular activation is kept fixed at 120ms, there is no detectable incremental benefit of varying the time (or choice of lead) for the second ventricular activation.

At an optimized AV delay, too, VV delay of zero continues to perform best. Shortening or lengthening of the A-LV appears detrimental. Shortening of the A-RV appears significantly detrimental, while lengthening of the A-RV shows only a non-significant trend to detriment. This non-significant trend could be due to intrinsic conduction through the right bundle branch at such long AV delays, and hence a shorter “effective A-RV” time at the longer programmed A-RV times. In other words, the effective VV delay (Bogaard et al. 2013), may not be changing as the programmed A-RV time is increased in this particular group, and so very little change

in blood pressure would be expected. A-LV optimisation may be of particular importance, as any deviation from this seems to lead to detriment.

These data also suggest that the impact of changing VV may be quantitatively different depending on whether it is assessed at short AV delays such as AV 120ms, or near the AV optimum. This is relevant because if investigators chose the "only lengthen" convention (default in many devices), then if they conducted studies at AV 120ms for example, they would likely find that any VV delay change (i.e. lengthening of A-LV or A-RV) would have no detectable effect. This would be because the 120ms time to first activation, is sufficiently short that no amount of delay of the second lead could significantly ameliorate the situation. Under these circumstances it would only be at longer AV delays, nearer the AV optimum, that it might be possible to detect the subtle deterioration arising from delaying one lead or the other.

7.5.2 Why might time to the first paced ventricle have the greatest haemodynamic impact?

Acute haemodynamic effects of AV delay adjustment were well documented before the advent of CRT (Brecker et al. 1992). Our data highlight that a delay to the first ventricular lead that is shorter than optimal (120ms during atrial pacing in our case) gave the same haemodynamic limitations regardless of whether the other lead was activated at the same time or later, and regardless of whether this was the LV or RV lead. We infer from this that programming a time for filling that is shorter than the ideal is so disadvantageous that no manipulation of the lag between the ventricular walls, or the order of the two walls, or of choice of which of the walls is responsible for the early initiation of contraction is able to significantly alleviate the haemodynamic harm. The magnitude of this adverse haemodynamic impact of changing from A-LV 120, A-RV 120 either to A-LV 40, A-RV 120 or to A-RV 40,

A-LV 120, was 14 mmHg ($p<0.001$), i.e. a highly undesirable drop in blood pressure that would be anticipated to equate to a reduction in cardiac output of more than 10%.

In contrast, when the AV delay is brought to its optimum (during which A-LV and A-RV are kept equal) then no subsequent change in interventricular delay, be it shortening or lengthening of either A-LV or A-RV, is consistently able to deliver higher blood pressures; in fact many such changes significantly reduce blood pressure. An 80ms pre-activation or post-activation of either lead caused blood pressure to fall by 3-4mmHg (statistically significant for all combinations except delayed activation of the RV lead).

7.5.3 Size of effect of interventricular delay adjustment

Except for interventricular delay adjustments that were achieved by shortening AV activation times to less than the already short time of 120ms, the adjustments had effects on blood pressure that were small in absolute terms, of the order of 1-4mmHg which is probably equivalent to a 1-4% change in cardiac output. Small changes are not necessarily clinically unimportant. The pressure increment achieved from CRT itself is of the order of 5-8mmHg according to measurements made acutely at the time of implant (Whinnett et al. 2013) and over the longer term according to the COMPANION and CARE-HF data (Cleland et al. 2005; Bristow et al. 2004), so a change in timings which reduces blood pressure by 1-4mmHg should not be assumed to be trivial. However, detecting such changes reliably is not easy because there are spontaneous beat–to-beat changes in blood pressure and stroke volume which are much larger than 1-4% and therefore there is a great risk that such biological variation is mistaken for the effect of VV delay adjustment. If this signal-to-noise problem is not carefully considered quantitatively at the time of protocol design (Whinnett et al. 2011; Francis 2013b; Francis 2011), then an optimisation process might actually turn

out to be little different to a process of selecting randomly between different pacemaker settings (Pabari et al. 2011).

7.5.4 Should VV delay always be kept at 0ms?

These findings have implications for pacing protocols and in particular whether VV optimisation should be performed at all. Participants in clinical trials of CRT which showed a prognostic benefit underwent AV optimisation, but not VV optimisation (Cleland et al. 2005; Bristow et al. 2004). A recent meta-analysis of VV optimisation versus empiric settings similarly showed no benefit from VV optimisation (Auger et al. 2013). While this could have been due to difficulties with study power or VV optimisation protocol, our high precision haemodynamic data presented here suggest that once AV delay is optimized, an interventricular delay of zero might be very suitable with little to gain (and possibly something to lose) by adjusting it away from zero.

7.5.5 Why different studies might report conflicting effects of VV delay adjustment

My data suggests that the phrase "keep AV delay fixed and adjust VV delay" is not a sufficiently clear description when we are describing a VV optimisation protocol. Three different interpretations of this could each be argued to be correct: keep time to first ventricular lead fixed and adjust time and choice of second ventricular lead (Z I Whinnett et al. 2006); keep A-RV fixed and adjust A-LV (Bogaard et al. 2010); keep A-LV fixed and adjust A-RV (León et al. 2005). These three produce completely different hemodynamic patterns. Purely for systematic completeness there is a fourth based on keeping the second ventricular lead fixed but this would never be clinically suggested.

Studies keeping the first ventricular lead fixed will find symmetrical effects of delaying the second lead regardless of whether it is LV or RV. If conducted at short

AV delays, the researcher may find that the effects are very small indeed. In contrast, studies keeping A-LV or A-RV fixed might find a substantial effect, especially for the offsets that make one of the leads activate much earlier than the AV optimum.

Studies reporting apparently contradictory effect sizes of VV optimisation may therefore, after all, not be contradictory.

7.5.6 Study Limitations

This experiment used a prolonged protocol of many replicates within each patient, and was specifically designed to detect differences in their haemodynamic implications of different definitions of AV and VV delay. This experimental protocol is designed to deliver high precision (Francis 2011; Francis 2013b) but is not intended as routine clinical practice.

For two reasons, we studied only immediate effects on pressure. First, with time, pressure tends to drift from its baseline value (in different directions on different occasions in a pattern called a random walk) which causes distributions of pressure changes *within* individual patients to become wider and thereby impair the power of a study to address a question reliably. Second, separate from the random walk, the pressure increment from a change in AV delay tends to reduce after a few seconds because of reflex vascular compensation (Manisty et al. 2012).

We studied only 22 patients, and only at a single centre. However, we did not select them for any baseline characteristic other than described in the methods. We therefore expect that if our study was re-conducted independently using similar methods, the same results would be obtained.

Unfortunately we do not have data on lead position, nor on whether the leads were considered to be optimally positioned which has been reported to be important.(Khan

et al. 2012) We are hoping that our sample of 22 patients, drawn without selection from CRT recipients in our institution, cover a typical spectrum of optimality of lead position. The pattern of haemodynamic results is similar across all patients which might suggest that the predominant driver is delay between atrium and first ventricular activation and not the precise position of the LV lead.

My study does not distinguish CRT recipients into responders versus non-responders, because my hospital no longer makes this distinction. Most of what is observed in clinical response is not the result of pacing (Sohaib, Chen, et al. 2013; Rosen et al. 2014) and most of the change in imaging measurements in individual CRT recipients also occurs in controls (Nijjer et al. 2012) who do not undergo CRT pacing and is therefore, for the purposes for evaluating the effect (Bouri et al. 2014) of CRT, noise. The haemodynamic responses measured in this study were measured with high precision but even still there is no possibility of them being strongly correlated with current measures of response except by chance (Nijjer et al. 2012).

At the longer AV delays, the range of VV delays which could be tested was occasionally limited by safety settings on the device which prevented the full planned range being tested. The individuals where this applied are indicated in Figure 7-3 and Figure 7-4.

All the measurements were performed at rest. I do not know whether the results would be similar during exercise. The beat-to-beat variability introduced by performing exercise during the protocol would necessitate acquiring far more measurements requiring each participant to spend many hours exercising at steady state.

My study used a relatively high heart rate. If a future study were to be designed with a lower heart rate, our previous work suggests it would likely show smaller effects

(Zachary I Whinnett et al. 2006). However, my study was designed to distinguish, with statistical validity within individual patients, small differences in haemodynamic response between protocols for adjusting VV delay. To achieve this level of precision required maximising signal-to-noise ratio, which we know requires elevated heart rate (Zachary I Whinnett et al. 2006). At lower heart rates if the effect size were half as large, each patient would have to undergo a protocol four times as longer to obtain a result with the same precision.

My patients were an unselected sample of patients with CRT at our centre. The majority had underlying LBBB, while a few had underlying RBBB or complete heart block. I did not set out to test for differences between, for example, LBBB and RBBB, which would require many more patients to undergo the experiment. Instead we show all the data for all the patients, indicating the native conduction pattern of each. Informally, patients of all patterns appear to have similar shapes to their results. Based on this any future study seeking to exclude a difference between LBBB and RBBB would have to have a very large sample size, of hundreds of patients, in order to be able to exclude a difference of a size that might have gone unobserved in our study.

My study does not have any data on mechanical dyssynchrony. This is because we do not test for this in our patients any more. My group have previously observed that in our hands mechanical dyssynchrony measurements do not have sufficient test-retest reproducibility under blinded conditions to be usefully (Nijjer et al. 2012; Pabari et al. 2012) tested as a predictor of anything else.

My study did not attempt the larger task of addressing whether optimal AV delay varies at different VV delays, because this would extend the duration of data acquisition from about three hours per patient to nine hours. Our study does suggest

that setting VV delays other than zero is not generally helpful at any AV delay. Therefore a practical approach might be to fix VV delay at zero and then optimise AV delay.

7.5.7 Clinical implications

Aside from the mechanistic implications, our study suggests that clinical CRT optimisation might use resources best by focusing on AV delay and leaving VV delay set at zero. It is also a reminder that reliable (i.e. reproducible) optimisation requires efforts to ensure that the subtle signal of between-setting differences is not obscured by spontaneous beat-to-beat biological variability.

7.5.8 Conclusion

The apparent size of the effect of VV delay adjustment is crucially dependent on the convention used to keep AV delay apparently constant. If constancy of AV delay means fixing the time to first ventricular lead, then VV delay adjustment (i.e. delaying the second lead) has little or no effect.

If, in contrast, AV delay is defined as the time to a particular ventricular lead (left or right), then the effect of VV delay adjustment can be large and adverse, particularly if making the other lead earlier. However, viewed from the other convention this large effect of pacing the "variable" lead earlier might be argued to be simply a manifestation of un-noticed shortening of AV delay.

In practice it may be pragmatic as well as physiological to leave VV delay at zero, after AV delay is optimized. In my cohort I found no sign that changing VV delay away from zero improves physiology, despite using large numbers of replicate measurements which might (with present routine techniques) be clinically impractical.

To avoid unnecessary appearance of conflict, future reports of VV optimisation might usefully specify which aspect of AV delay was kept constant, along with individual-patient assessments of precision.

7.6 Contributions

This chapter arise from a study conceptualised by myself with my supervisor. The data collection and analysis was conducted entirely by myself under the supervision of my supervisor. Seven consultants including my supervisor, as well as anonymous peer reviewers, guided me in the development of the discussion. The text of this chapter is in press: "Sohaib SMA, Kyriacou A, Jones S, Manisty CH, Mayet J, Kanagaratnam P, Peters NS, Hughes AD, Whinnett ZI, Francis DP. Evidence that conflict regarding size of haemodynamic response to VV delay optimisation of CRT may arise from differences in how AV delay is kept constant. Europace. 2015; In press."

8 AV optimised direct His bundle pacing improves acute hemodynamic function in patients with heart failure and PR prolongation without LBBB

8.1 Abstract

Background

Benefits of pacing for heart failure have previously been indicated by acute hemodynamic studies and verified in outcome studies. A new target for pacing in heart failure may be PR prolongation which is associated with 58% higher mortality regardless of QRS duration.

Objectives

We investigate whether heart failure patients with narrow QRS (or right bundle branch block, RBBB) but with long PR gain acute hemodynamic benefit from AV optimisation. We tested this with biventricular pacing and (to deliver pure AV shortening) direct His bundle pacing.

Methods and Results

We enrolled 16 consecutive patients with systolic heart failure, PR prolongation (mean 254±62ms) and narrow QRS (n=13, mean QRS 119±17ms) or RBBB (n=3, mean QRS 156±18ms).

We successfully delivered temporary direct His bundle pacing in 14 patients and temporary biventricular pacing in 14 participants. We performed AV optimisation using invasive systolic blood pressure (SBP) obtaining parabolic responses (mean R^2=0.90 for His, and 0.85 for biventricular pacing)

The mean increment in systolic BP compared to intrinsic ventricular conduction was 4.1±3.8mmHg (p=0.003) for His, and 4.3±4.2mmHg (p=0.003) for biventricular pacing. QRS duration lengthened with biventricular pacing (149±29ms, p=0.02) but not with His pacing (mean QRS 123±22ms, p=0.77).

Conclusion

AV optimised pacing improves acute hemodynamic function in patients with heart failure and long PR interval without LBBB. That it can be achieved by single site His pacing shows its mechanism is AV shortening. The improvement is ~ 60% of the effect size previously reported for biventricular pacing in LBBB. Randomized blinded trials are warranted to test for long term beneficial effects.

8.2 Introduction

Biventricular pacing is an important therapy for patients with heart failure and left bundle branch block. It improves hemodynamics (Auricchio et al. 1999; Kass et al. 1999; Blanc et al. 1997), symptoms (Sohaib, Chen, et al. 2013) and prognosis (Cleland et al. 2005; Goldenberg et al. 2014).

Only ~34% of patients with heart failure have LBBB (Clark et al. 2008). Currently patients with narrow QRS duration are not targeted for treatment with biventricular pacing because, when tested in a bias-resistant (Jabbour et al. 2015) manner, the results have not been favourable (Ruschitzka et al. 2013; Thibault et al. 2013). These studies did not, however, specifically target the group who are most likely to derive benefit, namely those with a long PR interval; rather they selected patients on the basis of whether there was echocardiographic evidence of mechanical dyssychrony.

PR prolongation is associated with poor outcomes (58% higher mortality) regardless of QRS duration (Crisel et al. 2011; Park et al. 2013). Improving LV preload by shortening AV delay appears to be an important mechanism through which biventricular pacing delivers its beneficial effect in patients with left bundle branch block and heart failure (Kyriacou, Pabari & Francis 2012). In the COMPANION Trial, patients with a long PR interval had a 17% greater reduction in risk than those with a normal PR interval (Olshansky et al. 2012). Similarly in the MADIT-CRT trial, participants with QRS prolongation which was not due to LBBB derived a prognostic benefit from biventricular pacing only when the PR interval was above 230 ms. (Kutyifa et al. 2014).

Applying biventricular pacing to patients with good intraventricular conduction appears to induce a degree of iatrogenic intraventricular dyssynchrony (Ploux et al. 2014). This has the potential to partly offset the benefits of PR interval shortening.

In patients with an intact intraventricular conduction system, direct His-bundle pacing preserves normal ventricular activation patterns (Deshmukh et al. 2000; Kronborg et al. 2014; Catanzariti et al. 2013; Barba-Pichardo et al. 2010). Permanent direct His pacing has been shown to be feasible when it has been applied in patients who have a bradycardia indication for pacing or to reverse proximal LBBB in patients where conventional LV lead implantation has not been possible (Lustgarten et al. 2010; Barba-Pichardo et al. 2013). However, it has not been tested as a method for delivering AV delay optimisation in patients with narrow QRS duration, a long PR interval and heart failure.

We have previously demonstrated that AV delay optimisation of biventricular devices, can be performed with high precision, using systolic blood pressure (SBP) measurements if a suitable protocol is used to minimize the effect of noise (Whinnett et al. 2013; Zachary I Whinnett et al. 2006; Whinnett et al. 2011; Kyriacou, Whinnett, et al. 2012). Non-invasive measurement of SBP correlates well with invasively measured SBP when used in this context (Finegold et al. 2014).

In this study I aimed to determine: Firstly whether AV delay optimisation delivered with direct His bundle pacing, in order to avoid inducing ventricular dyssynchrony, improves acute hemodynamic function in patients with left ventricular impairment, a long PR interval and narrow QRS duration. Secondly, whether AV optimisation delivered with biventricular pacing improves hemodynamic function in this population.

8.3 Methods

8.3.1 Study subjects

17 sequential patients in sinus rhythm, with a PR interval greater than 200 ms, an established diagnosis of systolic heart failure, and either a QRS duration of less than 140ms or typical RBBB, were recruited into the study. One recruited patient was excluded prior to collection of data because they developed atrial tachycardia.

Patient characteristics are displayed in Table 8-1 and Table 8-2. All patients gave written informed consent for the study, which was approved by the local Research Ethics Committee.

Table 8-1 Baseline characteristics

Characteristics of included participants. LV EDD: left ventricular end diastolic dimensions, NYHA: New York Heart Association, ACE: angiotensin converting enzyme, MRA: mineralocorticoid receptor antagonist. Mean values ± SD where applicable

Age	74 ± 10
Male	15
Ejection Fraction (%)	34 ± 10
LV EDD (cm)	5.4 ± 1.0
NYHA Class	
II	2
III	14
Ischemic heart disease	13
ACE inhibitor	12
Beta blockers	10
MRA	8
Diuretics	13
QRS morphology	
RBBB	3
Narrow QRS	13

Table 8-2 ECG Characteristics at baseline and during protocol

ECG charactistics and electrophysiologic data collected. Mean values ± SD

PR interval (ms)	254 ± 62
Intrinsic QRS duration (ms)	126 ± 22
Pacing rate (bpm)	83 ± 17
H-V intervals (ms)	58 ± 16
QRS with His pacing (ms)	123 ± 22
V-Stim to QRS duration with His pacing (ms)	53 ± 20
QRS with Biventricular pacing (ms)	149 ± 29
QRS with RV pacing (ms)	192 ± 25

8.3.2 Measurements

Patient preparation

Catheter insertion and manipulation was performed by my supervisor (Dr Zachary Whinnett) and I undertook data collection and analysis during the procedure. A pentapole electrode catheter (Josephson Curve, Bard Vikings) was positioned in the right atrial appendage or high right atrium and maintained in a constant position throughout the study. Adequate capture of the atrium was confirmed using standard techniques. Pacing was performed using custom made connectors attached to a Medtronic Insync III 8042 biventricular pacemaker (Kyriacou, Whinnett, et al. 2012).

Direct His bundle pacing

A quadripolar electrode catheter was used to locate and pace the His bundle. Continuous 12 lead ECG recordings were performed for the duration of the procedure (Bard Labsystem Pro, Bard Electrophysiology Division, Lowell, MA). Direct His bundle capture was confirmed using the criteria previously described by Deshmukh et al (Deshmukh et al. 2000). In brief these consist of confirming the following: a) 12 lead ECG morphology match with direct His bundle pacing compared with intrinsic conduction, b) similar time delay between the stimulation artefact and the onset of the QRS complex compared with the intrinsic His to QRS time (Figure 8-1), c) His bundle capture in an all or none-fashion, demonstrated by the absence of QRS widening at a lower pacing output.

If selective direct His bundle pacing could not be achieved then non-selective His bundle pacing was accepted. Non-selective His pacing was defined as the direct capture of the basal ventricular myocardium in addition to His bundle capture. We allowed a maximum of 10 minutes to try to obtain direct His pacing.

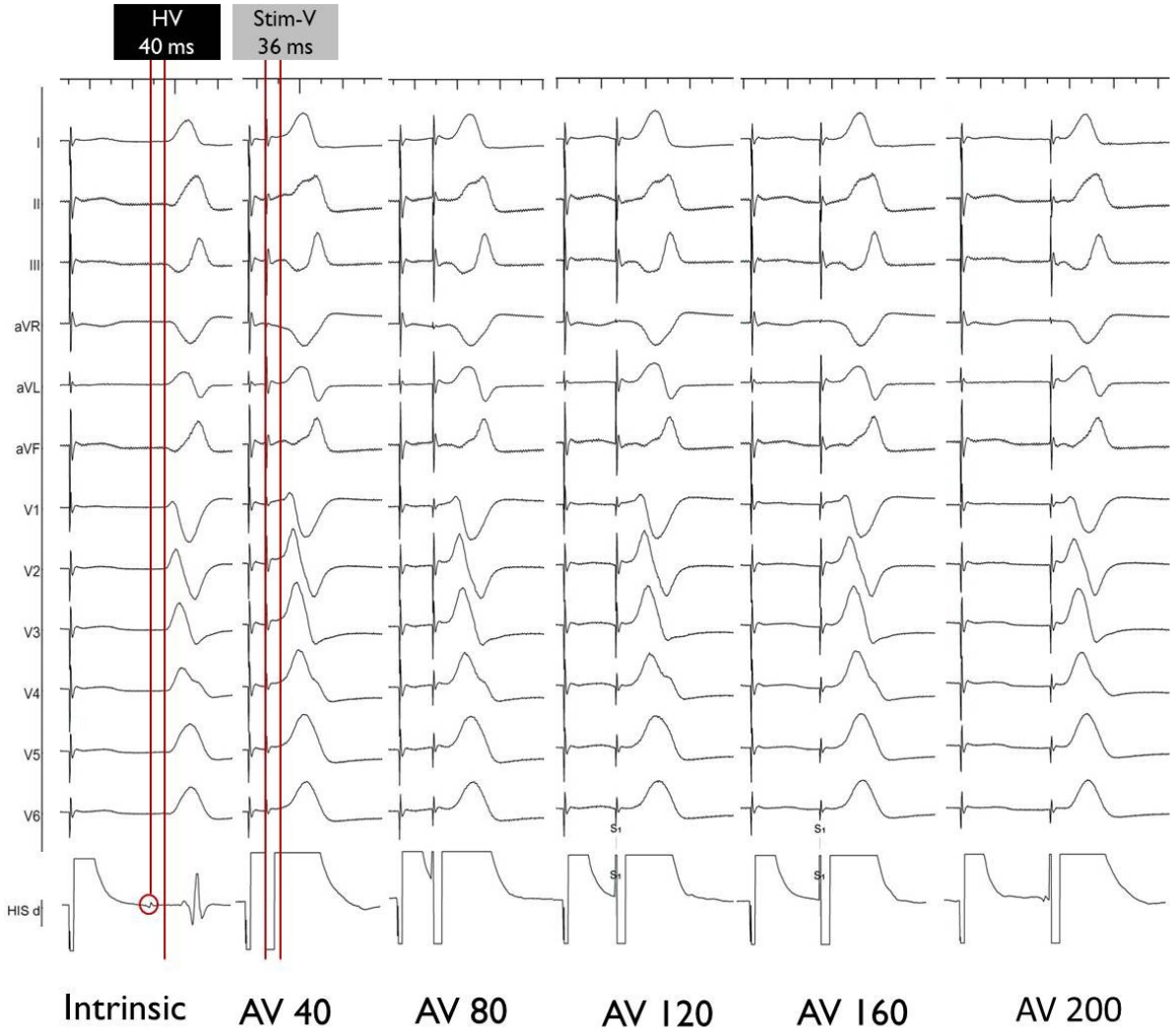


Figure 8-1 12 Lead ECG demonstrating His Capture

The ECG and His signal from a single patient is shown (These data are displayed for all participants in the online data supplement). The left panel shows the QRS morphology during intrinsic conduction and a series of different AV delays produced with His pacing are shown on the rightward five panels. The His to V delay is displayed (red lines in left panel) and stim to V delay is shown during His pacing with an AV delay of 40ms. At AV 200, an intrinsic His deflection is seen prior to the ventricular pacing artifact suggesting that ventricular activation has occurred as a result of intrinsic conduction rather than His pacing.

Cardiac resynchronisation therapy pacing

Temporary biventricular pacing was achieved by advancing the quadripolar catheter to the right ventricular apex. An AL1 sheath (Boston Scientific, Marlborough, MA, USA) was positioned in the coronary sinus via the femoral vein and an ATW wire (Cordis, East Bridgewater, NJ, USA) was placed in a posterolateral branch. The ATW wire was connected to the pacing system (Kyriacou, Whinnett, et al. 2012). Right ventricular, left ventricular and biventricular capture were confirmed using the 12 lead ECG.

AV delay optimisation

We recorded invasive arterial beat-by-beat systolic blood pressure from either the radial or femoral artery. The invasive hemodynamic data was used to perform AV delay optimisation.

In order to keep heart rate constant we collected hemodynamic data while pacing the atrium at 10 beats per minute above the sinus rate (mean heart rate during data acquisition 83±17bpm). However, if Wenkebach conduction or higher degree AV block occurred during atrial pacing then measurements were made during sinus rhythm (4 patients).

A series of AV delays were tested during both direct His pacing and biventricular pacing. The range of AV delays tested was 40ms to 280ms in 40ms increments (i.e. 40, 80, 120, 160, 200, 240 and 280ms). Fewer AV delays were tested if intrinsic conduction occurred at an AV delay less than 280ms. With biventricular pacing, if

there was evidence of fusion of pacing with intrinsic conduction, measurements were included. The order in which AV delays were tested was varied between patients.

We performed AV delay optimisation using invasive systolic blood pressure measurements. We used an algorithm designed to minimize the effect of noise, we have previously described this in detail (Zachary I Whinnett et al. 2006; Whinnett, Davies, et al. 2008; Whinnett et al. 2013; Whinnett et al. 2011).

For each tested AV delay we performed a minimum of eight alternations between the reference setting and tested AV delay and we calculated the mean relative change in SBP (ΔSBP).

In order to minimise bias we fitted a parabolic curve in order to identify the optimal AV delay (Francis 2011; Francis 2013b). Hemodynamic improvement for each pacing configuration was calculated as the difference between no pacing and the pressure at the peak of the fitted parabola.

In a subgroup of 12 patients, we also assessed the impact of dual chamber pacing delivered with right ventricular apical pacing.

Data Acquisition and Analysis

Hemodynamic and ECG data were acquired by using an analog-to-digital card (National Instruments, TX) and Labview (National Instruments, TX). They were analyzed with custom software written in Matlab (MathWorks, MA)(Kyriacou, Whinnett, et al. 2012).

8.3.3 Statistical analysis

Statistical analyses were performed on R 3.0.2. Data are presented as mean ±standard deviation (SD). Statistical comparisons of continuous data were made using repeated measures / one-way analysis of variance (ANOVA) for within- or between-individual

comparisons of more than 2 groups as appropriate. Post-hoc testing was performed if ANOVA was significant, using paired t-tests for within-individual two group comparisons and unpaired t-test for between group comparisons. All tests were two-tailed and $P<0.05$ was considered significant.

8.3.4 Power calculation

Using an acquisition protocol including 6 alternations, we have previously found the SDD in change in ΔSBP with repeated measurement at individual AV delays was 3.8 mmHg. In patients with LBBB when biventricular pacing is applied we have previously found a 7.7 mmHg increase in SBP. Therefore in order to detect a 3.5 mmHg increase in SBP (i.e. ~50% of that effect observed with biventricular pacing in LBBB) with AV delay optimisation delivered with His bundle pacing would require 10 patients (80% power 5% significance level). We recruited 16 patients in order to allow for failure of direct His Bundle capture in up to 1/3 of patients.

8.4 Results

We were able to successfully perform temporary direct His bundle pacing in 14 patients, with direct His bundle capture in 8 and non-selective His pacing in 6. In two patients neither selective nor non-selective direct His pacing could be achieved within the time limit of 10 minutes which our protocol allowed us to achieve His pacing. The data from two of the patients in which direct His pacing was achieved was not included in the analysis: In 1 patient the AV delay was not successfully adjusted because the atrial signal was sensed on the His lead and pacing was withheld (this was not recognised at the time of data acquisition). The second patient developed 2:1 AV block during the study after a period of atrial pacing. We did not include this data in the analysis since it would have given the impression of a larger effect size with His pacing.

Biventricular pacing was successfully achieved in 14 patients. In 2 patients it was not possible to achieve reliable LV pacing within the timeframe allowed by the protocol of the study (10 minutes to achieve LV pacing). In 1 patient it was not possible to complete data acquisition because they developed atrial tachycardia.

Figure 8-2 displays the flow of participants through the study.

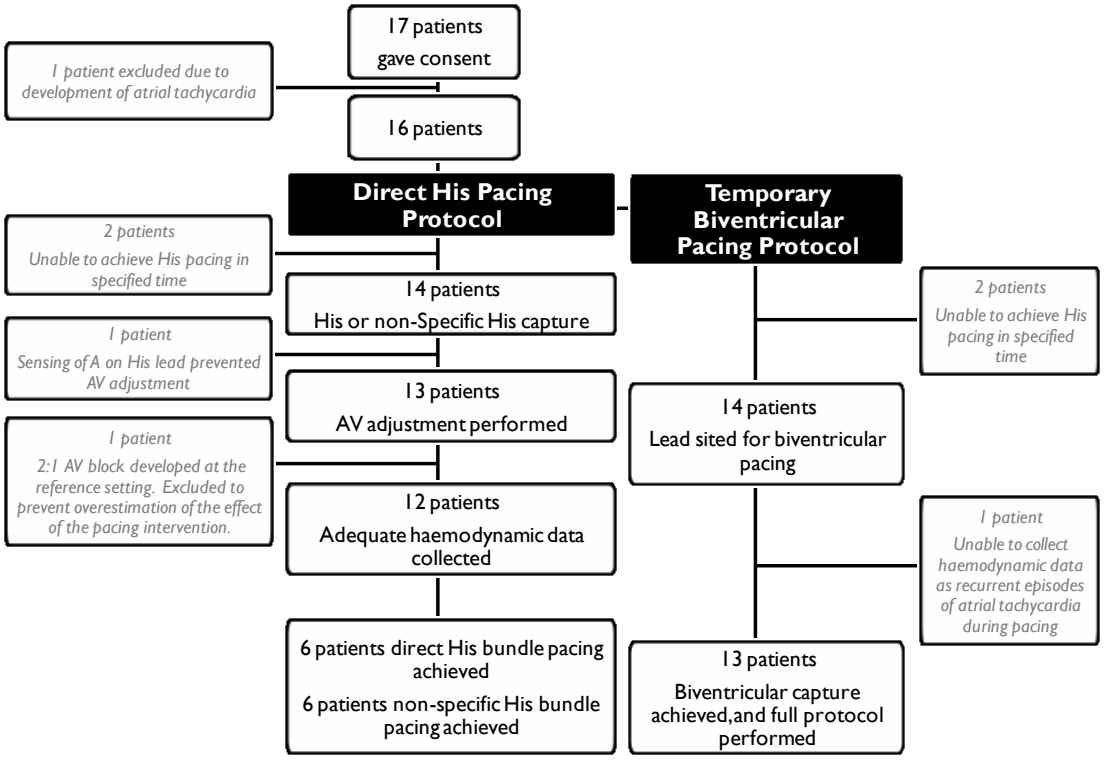


Figure 8-2 Participant flow

Flow chart indicating data collected in recruited subjects and reasons for exclusion.

8.4.1 Electrocardiographic parameters during pacing

There was no significant difference in QRS duration with direct His pacing compared to intrinsic conduction (123±22ms and 126± 22ms respectively, p=0.77 for difference). QRS duration was significantly longer with biventricular pacing (149±29ms, p=0.02), and RV apical pacing (192±25ms, p<0.0001), as shown in Figure 8-3.

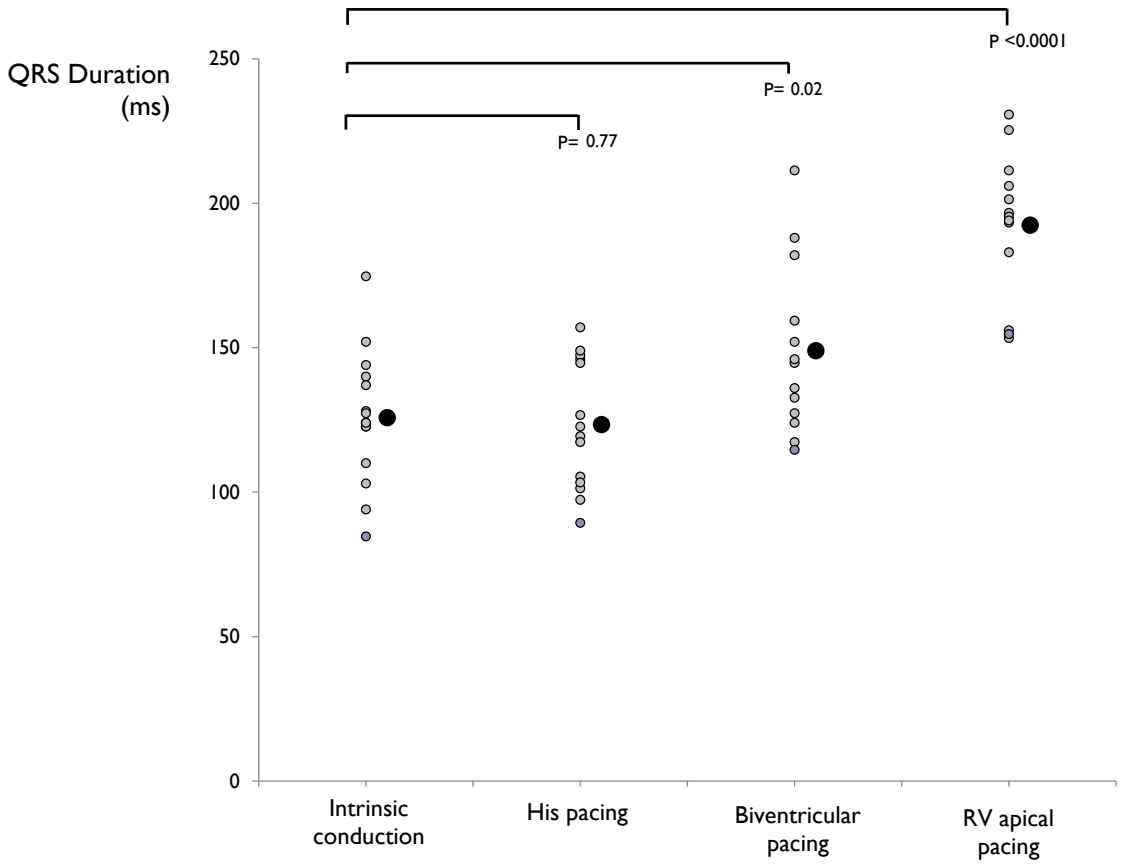


Figure 8-3 QRS durations with different pacing configurations

QRS durations are shown for the different pacing morphologies for each individual patient (grey dots) and the mean for the group (black dots). The p values for difference between the pacing configuration and intrinsic conduction are illustrated at the top.

8.4.2 Hemodynamic effect of AV optimized direct His bundle pacing

An acute hemodynamic improvement beyond baseline (intrinsic conduction) was seen in all patients where there was either confirmed His bundle or non-selective His bundle pacing. The underlying relationship between AV delay and hemodynamic improvement was parabolic, fitting to a second order polynomial (mean R^2=0.90). Individual hemodynamic response curves are shown for each individual patient (Figure 8-5). The mean improvement in blood pressure, between baseline and the peak of the fitted parabola, across all patients was 4.1 mmHg (p=0.003, Figure 8-4).

8.4.3 Hemodynamic effect of biventricular pacing

An acute hemodynamic improvement was seen in all patients. The mean improvement when calculating the response to the peak of a fitted parabolic curve in each individual patient was 4.3 mmHg (p=0.003) relative to intrinsic conduction. No significant difference between the peak pressure achieved with His pacing and biventricular pacing (p=0.90) was observed, but the study was not powered to detect this. The underlying relationship between AV delay and hemodynamic improvement showed good fit to a parabola (mean R^2=0.85)

8.4.4 Hemodynamic changes with AV optimised right ventricular apical pacing

AV optimised right ventricular apical pacing was performed as a sub-study in 11 of the participants. There was no significant improvement in systolic blood pressure across the cohort, mean increment 0.9 mmHg with parabolic peak, p=0.49.

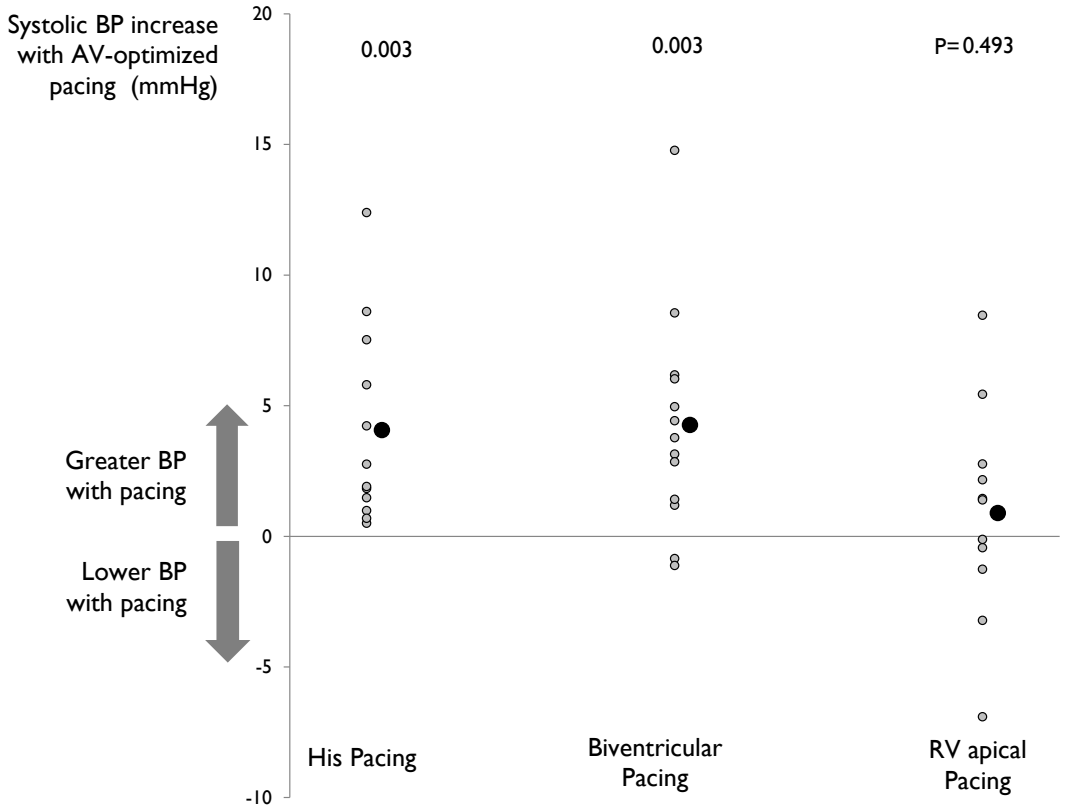


Figure 8-4 Increment in blood pressure with different pacing morphologies

Change in blood pressure with biventricular pacing, His Pacing, and RV apical pacing are demonstrated for individual patients (grey dots) and the mean for the group (black dots). A value of zero indicates no difference between the pacing configuration and intrinsic conduction. A value below zero favours intrinsic conduction, a value above zero favours pacing. P values for the difference between the pacing configuration and intrinsic conduction are marked.

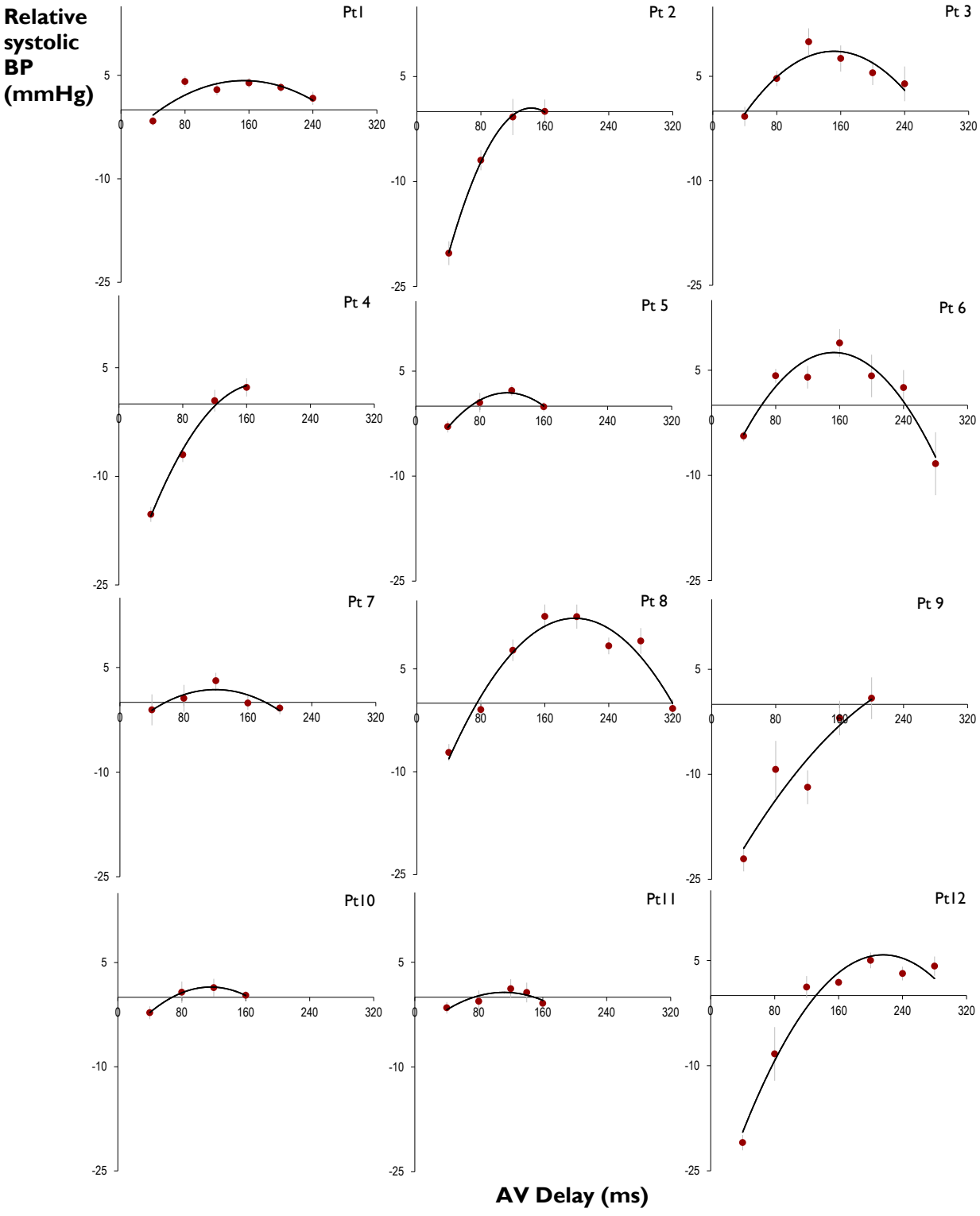


Figure 8-5 Acute hemodynamic response to His Pacing – Individual patient data

Each panel represents data from an individual patient. The vertical axis is change in relative systolic blood pressure (mmHg) compared to the baseline status of atrial pacing. The horizontal axis is the programmed AV delay (ms).

8.5 Discussion

In this study we demonstrate that AV optimised ventricular pacing, delivered with either direct His pacing or biventricular pacing, improves acute hemodynamic function in patients with heart failure and long PR without LBBB. That it can be achieved by single site His pacing shows that the mechanism of improvement is AV shortening. The improvement in acute hemodynamic function is ~ 60% of the effect size previously reported for biventricular pacing in LBBB. These findings suggest that randomized blinded trials are justified to establish whether these improvements translate into long term beneficial effects.

8.5.1 Relevance of hemodynamic improvements observed with direct His pacing

In order to put into context the hemodynamic improvements we observed with AV delay optimisation, in patients with a long PR interval without LBBB, we have compared this to the effect of delivering biventricular pacing to patients with LBBB (Figure 8-6).

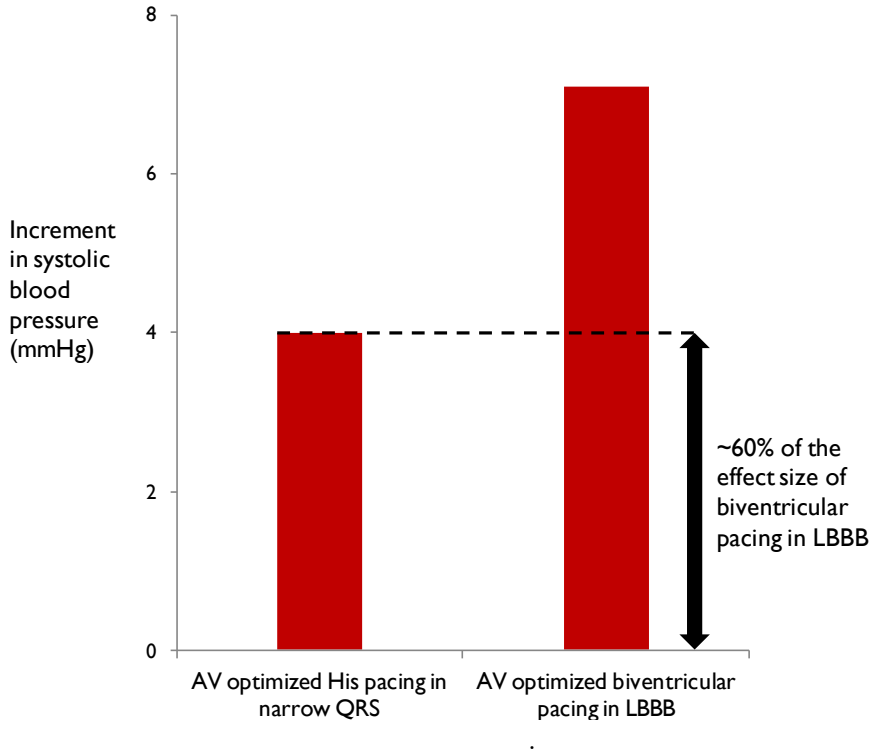


Figure 8-6 Comparison of the magnitude of improvement in hemodynamic function in patients with long PR interval without LBBB, with biventricular pacing applied to patients with LBBB

The acute hemodynamic increment of biventricular pacing is ~7 mmHg in LBBB (Auricchio et al. 1999; Kass et al. 1999; Blanc et al. 1997). In the absence of electrical ventricular dyssynchrony (narrow QRS) this study demonstrates a 4mmHg increase in acute hemodynamics with AV optmization in those with a long PR interval.

We observed a mean 4.1 mmHg increase in acute systolic blood pressure with AV delay optimisation when ventricular stimulation was delivered with direct His bundle pacing. This compares to a 5.6 mmHg increase observed in PATH-CHF (Auricchio et al. 1999), while Blanc et al. observed an 8.1mmHg increase (extracting data for patients with sinus rhythm and LBBB)(Blanc et al. 1997), we previously found a mean 7.7 mmHg increase when AV optimised biventricular pacing is initiated (Whinnett et al. 2013).

Therefore the increment observed with direct His bundle pacing in non-LBBB patients is ~60% of the effect size observed when biventricular pacing is applied to patients with LBBB (Figure 6).

The smaller effect size is to be anticipated since in this population direct His pacing is likely to produce a beneficial effect only through optimisation of LV preload. Biventricular pacing in patients with LBBB on the other hand has the potential to deliver more synchronous ventricular activation as well allowing AV delay to be optimized.

Biventricular pacing when delivered to patients with LBBB has previously been found to improve peak VO_2 by 24% and to improve quality of life scores by 59% (Auricchio, Stellbrink, et al. 2002). These large percentage improvements in markers of function and symptoms are accompanied by more modest percentage improvements in blood pressure (6.3%-7%) (Auricchio, Stellbrink, et al. 2002; Blanc et al. 1997).

8.5.2 Direct His bundle pacing versus biventricular pacing

This study was not designed to test whether direct His pacing is superior to biventricular pacing. We observed a hemodynamic improvement with both methods. Our results are not a direct comparison of direct His pacing versus biventricular pacing since the direct His group includes 2 patients in whom biventricular pacing could not be achieved. Likewise the biventricular pacing group includes 2 patients in whom direct His pacing could not be achieved. In the patients who had AV optimisation delivered by both His pacing and biventricular the mean increment in blood pressure was 4.3 mmHg with His pacing and 4.6 mmHg with biventricular pacing (p=0.74). In this population there are theoretical advantages for using direct

His pacing rather than biventricular pacing. Firstly, by utilising the His Purkinje system, direct His pacing is likely to avoid inducing dyssynchronous ventricular activation. In patients with normal QRS duration, biventricular pacing produces less efficient ventricular activation than occurs during intrinsic ventricular activation (Ploux et al. 2014).We observed no significant prolongation of QRS duration with direct His pacing compared to intrinsic conduction, whereas biventricular pacing produced significant prolongation of QRS duration by 23 ms.

Secondly, direct His pacing may potentially be less pro-arrhythmic than biventricular pacing, since the pacing stimulus is delivered endocardially and it is less likely to be positioned within a region of scar than with left ventricular pacing. Biventricular pacing is known to have the potential to precipitate ventricular arrhythmias (Shukla et al. 2005).

To determine whether one approach is superior to the other would require additional adequately powered studies. It is, however, encouraging that both approaches improve hemodynamics since this allows an alternative option for pacing should either method be technically challenging. In the current study we had a protocol which allowed 10 minutes to achieve direct His pacing and 10 minutes to achieve biventricular pacing. We were unsuccessful in achieving direct His pacing in two patients, however in both of these patients we successfully carried out biventricular pacing. In two other patients LV pacing was unsuccessful; in these patients direct His pacing was successful within the time allowed. It is likely that, with dedicated tools and allowing a longer time to achieve successful pacing, success rates would be higher. Nevertheless it is useful to have the option of an alternative strategy.

Our finding of an acute hemodynamic improvement with biventricular pacing, initially seems to contradict the findings from randomised controlled trials which have suggested an adverse effect associated with biventricular pacing in narrow QRS (Ruschitzka et al. 2013). However, we were not addressing all patients with narrow QRS, only those with prolonged PR.

Our findings of a beneficial effect in shortening AV delay in patients with a long PR interval in patients who do not have LBBB are supported by the findings from a sub-analysis of the MADIT-CRT trial. In the non-LBBB group of patients, mortality was increased with biventricular pacing in patients who had a short PR interval, in contrast mortality was decreased in those who had a long PR interval (Kutyifa et al. 2014).

8.5.3 Permanent direct His bundle pacing

Permanent direct His bundle pacing has not specifically been tested in the population of patients included in this study. It has, however, been found to be a safe and feasible method of pacing the heart when carried out in other groups of patients (Deshmukh et al. 2000). It has been mainly carried out in individuals with a bradycardia indication for pacing. In the non-heart failure setting, His bundle pacing may be superior to right ventricular pacing, when looking at a range of echocardiographic and functional markers (Occhetta et al. 2006; Catanzariti et al. 2013; Catanzariti et al. 2006; Kronborg et al. 2014; Kronborg et al. 2012). Some of the initial landmark studies of permanent His pacing in man did include those with heart failure, specifically those with atrial fibrillation who required AV node ablation (Deshmukh et al. 2000; Deshmukh & Romanyshyn 2004). When compared to right ventricular apical pacing,

markers of outcome including remodelling on echo and cardiopulmonary exercise test parameters have been favourable. In this cohort, these improvements were seen in the absence of the contribution of atrial contraction, so if these were replicated in sinus rhythm, the benefits may be greater still. It has also been applied to patients with heart failure and LBBB with conventional indications for biventricular pacing. A reversal of LBBB has been demonstrated if the LBBB is "proximal in origin" (Lustgarten et al. 2010; Barba-Pichardo et al. 2013). In one of these studies, this was associated with LV reverse remodelling and improvements in NYHA class, but there was no control arm (Barba-Pichardo et al. 2013) so interpretation should be cautious (Jabbour et al. 2015). Work to date indicates that direct His bundle pacing is feasible, but no studies have addressed the population of patients we have identified in this study.

8.5.4 Limitations

This study was not designed to measure the effect on longer term outcomes. It was adequately powered for its specific question namely whether AV delay optimisation in patients with a long PR interval and narrow QRS duration, improves acute hemodynamic function, and whether this could be achieved by AV delay shortening alone.

Our study covers a small group in a single centre, but measurements were made to a high degree of precision. There is no reason to expect that these findings should be dramatically different elsewhere, or with a greater number of patients should the protocol be repeated elsewhere.

The proximity of the ventricular lead to the atrium increases the likelihood of oversensing of the atrium by the His lead, so particular care is needed when programming the pacemaker to avoid this. This phenomenon prevented us from performing the complete protocol in one participant.

8.5.5 Clinical implications

The results of this study may be the first step towards extending pacing therapy for heart failure to a new population, namely patients with a long PR interval without left bundle branch block. Between 17%-33% of heart failure patients in stable sinus rhythm have evidence of PR prolongation (Park et al. 2013; Chowdhury et al. 2014).

In patients with LBBB, biventricular pacing has been demonstrated to reduce both mortality (Cleland et al. 2005) and symptoms (Sohaib, Chen, et al. 2013). Improvements in cardiac function are likely to be the mechanism for these beneficial effects. The early studies of biventricular pacing in LBBB demonstrated an acute hemodynamic benefit of biventricular pacing (Butter, a. Auricchio, et al. 2001; Breithardt et al. 2002; Auricchio et al. 1999). Seeing hemodynamic improvements when another defect, in another part of the conduction system upstream of the bundle branches, is targeted with pacing therapy is encouraging. The next step, like with biventricular pacing, is to see whether the acute improvements in function also translate into longer term clinical benefit.

8.5.6 Conclusions

AV delay optimisation delivered with direct His bundle pacing results in acute improvements in hemodynamic function, in patients with a long PR interval and left ventricular impairment without LBBB. The magnitude of improvement is ~ 60% of that observed when biventricular pacing is applied to patients with left bundle branch block. Randomized control studies are now justified to determine whether these benefits are translated into improvements in clinical outcomes.

9 High precision AV optimised acute haemodynamics to assess lead position in biventricular pacing: the conventional position is not always the best

9.1 Abstract

9.1.1 Background

Left ventricular lead implantation in biventricular pacing is conventionally targeted to the left lateral wall via a postero-lateral or lateral branch of the coronary sinus. Measurement imprecision often hinders reliable assessment of alternative lead positions, within individual patients, and it easy to be misled by the effects of noise which may incorrectly suggest one lead position is better than another. It is also not know whether the AV optimum varies between lead positions.

9.1.2 Methods & Results

20 patients were recruited at the time of biventricular pacemaker implant to asses AV optimised acute haemodynamic response in different LV lead positions using a high precision protocol using multiple replicates of systolic BP measurements. An anterior basal position was targeted as the non-conventional location, and the final targeted position of the LV lead was a conventional mid-lateral position. Two different lead positions were successfully obtained in 15 patients. In 9 patients there was no significant difference between either lead position, in 3 patients, the non-conventional position was in fact significantly better. There was no significant difference in the AV optimum between the two different positions ($p=0.88$).

9.1.3 Conclusion

For different lead positions within the same patient, the haemodynamic response to AV delay adjustment has the same shape and the same AV optimum. The level of response, however, differs between lead positions. A multiple replicate measurement protocol has sufficient precision to be certain that the apparent differences between lead position are not chance artefacts.

9.2 Introduction

The question of where the left ventricular lead is placed is not only of interest because it affects clinical practice during implantation, but because it gets to the heart of what CRT is. Clinical practice is to site LV lead in the most lateral position possible, in an opposite and complementary place to the RV apical lead (Khan et al. 2009). Although there has been work examining the haemodynamic consequences of different lead positions, no study has optimised AV and VV delay at suboptimal lead position and therefore (since different positions may have different optima) we do not know if the position has been compared fairly. Moreover often studies do not report the reproducibility of the selection of the ideal site (Derval et al. 2010), and therefore it is not possible to likelihood that apparent differences between sites are merely chance findings (Pabari et al. 2011).

In this study, I use rapid, reproducible AV optimisation techniques to address the question of lead position without disadvantaging any position through suboptimal AV. This will provide a definitive and reproducible answer to this question of importance of lead position within individual subjects. Moreover, if much of the benefit of CRT can be delivered by AV optimisation from a non-conventional position, then it shows that resynchronisation is not as important as commonly suspected and AV optimisation may be more so.

9.3 Methods

9.3.1 Study subjects

Patients in sinus rhythm with broad QRS (>130 ms) who were due to undergo a planned biventricular pacemaker implant were recruited for this study. All patients gave written informed consent for the study, which was approved by the local Research Ethics Committee.

9.3.2 Patient preparation

After conventional placement of RA (appendage) and RV (apex) leads, the LV lead was placed temporarily in a non-conventional position. The anterior basal wall will be targeted as the non-conventional position using previously published fluoroscopic definitions, with the basal segment identified in the right anterior oblique view, and the anterior position in the left anterior oblique view (Albertsen et al. 2005). The optimum AV was determined haemodynamically at 100 bpm relative to atrially-paced LBBB(Zachary I Whinnett et al. 2006). If AV block occurred with rapid atrial pacing, the protocol was performed 10 beats above sinus rhythm to ensure 1:1 conduction. The LV lead was finally placed in a conventional posterolateral position. Optimisation was repeated in the final position.

9.3.3 AV delay optimisation

I recorded invasive arterial beat-by-beat systolic blood pressure from either the radial or femoral artery. The invasive hemodynamic data was used to perform AV delay optimisation.

A series of AV delays were tested during biventricular pacing. The range of AV delays tested was 40ms to 280ms in 40ms increments (i.e. 40, 80, 120, 160, 200, 240 and 280ms). Fewer AV delays were tested if intrinsic conduction occurred at an AV delay less than 280ms. With biventricular pacing, if there was evidence of fusion of

pacing with intrinsic conduction, measurements were included. The order in which AV delays were tested was varied between patients.

I performed AV delay optimisation using invasive systolic blood pressure measurements. I used an algorithm designed to minimize the effect of noise, as described in the experimental methods (Zachary I Whinnett et al. 2006; Whinnett, Davies, et al. 2008; Whinnett et al. 2013; Whinnett et al. 2011).

For each tested AV delay a minimum of eight alternations between the reference setting and tested AV delay were performed and this was used to calculate the mean relative change in SBP (ΔSBP).

In order to minimise bias I fitted a parabolic curve in order to identify the optimal AV delay (Francis 2011; Francis 2013b). Haemodynamic improvement for each pacing configuration was calculated as the difference between no pacing and the pressure at the peak of the fitted parabola.

9.3.4 Data Acquisition and Analysis

Haemodynamic and ECG data were acquired by using an analog-to-digital card (National Instruments, TX) and Labview (National Instruments, TX). They were analyzed with custom software written in Matlab (MathWorks, MA)(Kyriacou, Whinnett, et al. 2012).

9.3.5 Statistical analysis

Statistical analyses were performed on R 3.0.2. Data are presented as mean ±standard deviation (SD). Repeated measures ANOVA was used to assess if there was a statistically significant difference in haemodynamic profile between different lead positions. Two tailed paired t-tests were performed to assess for statistically significant differences between the two groups. A p-value of <0.05 was considered significant (Francis 2011).

9.4 Results

Twenty patients were consented to take part in this study. Two lead positions were successfully obtained in 15 patients. The characteristics of these patients are highlighted in Table 9-1

9.4.1 Differences in peak haemodynamic effect between lead positions

In the majority of cases (nine participants) there was no significant difference in haemodynamic profile between lead positions (Figure 9-1). In three cases, the position which would usually be considered non-conventional delivered a significantly better haemodynamic profile. In three cases only did the conventional lateral position show a significantly better profile than the less optimal position.

9.4.2 Differences in AV optimum between different lead positions

There was no difference in the mean AV optima between the lateral position (195±31 ms) and the anterior position (196±37 ms, p=0.89). This is visible in the individual participant data presented in Figure 9-1 where the haemodynamic profiles for the individual lead positions in the individual patients appear to run approximately in parallel.

9.4.3 QRS duration between the different positions

The paced QRS durations in the lateral positions (154±32 ms) were on average shorter than the QRS durations in the anterior positions (163±31 ms, p=0.004)

Table 9-1 Patient Characteristics

Characteristics of included participants. RBBB: right bundle branch block; LBBB: left bundle branch block; MRA: mineralocorticoid receptor antagonists, ACE inhibitor: angiotensin converting enzyme inhibitor; LV EDD: left ventricular end diastolic diameter.

Age	67 ± 12
Male	12
Ejection Fraction (%)	23 ± 8
LV EDD (cm)	6.0 ± 1.0
NYHA Class	
II	8
III	7
Ischemic heart disease	7
ACE inhibitor	15
Beta blockers	11
MRA	8
Diuretics	13
CRT-D	11
CRT-P	4
QRS morphology	
LBBB	13
RBBB	2
QRS duration (ms)	176 ± 29
PR interval (ms)	195 ± 42

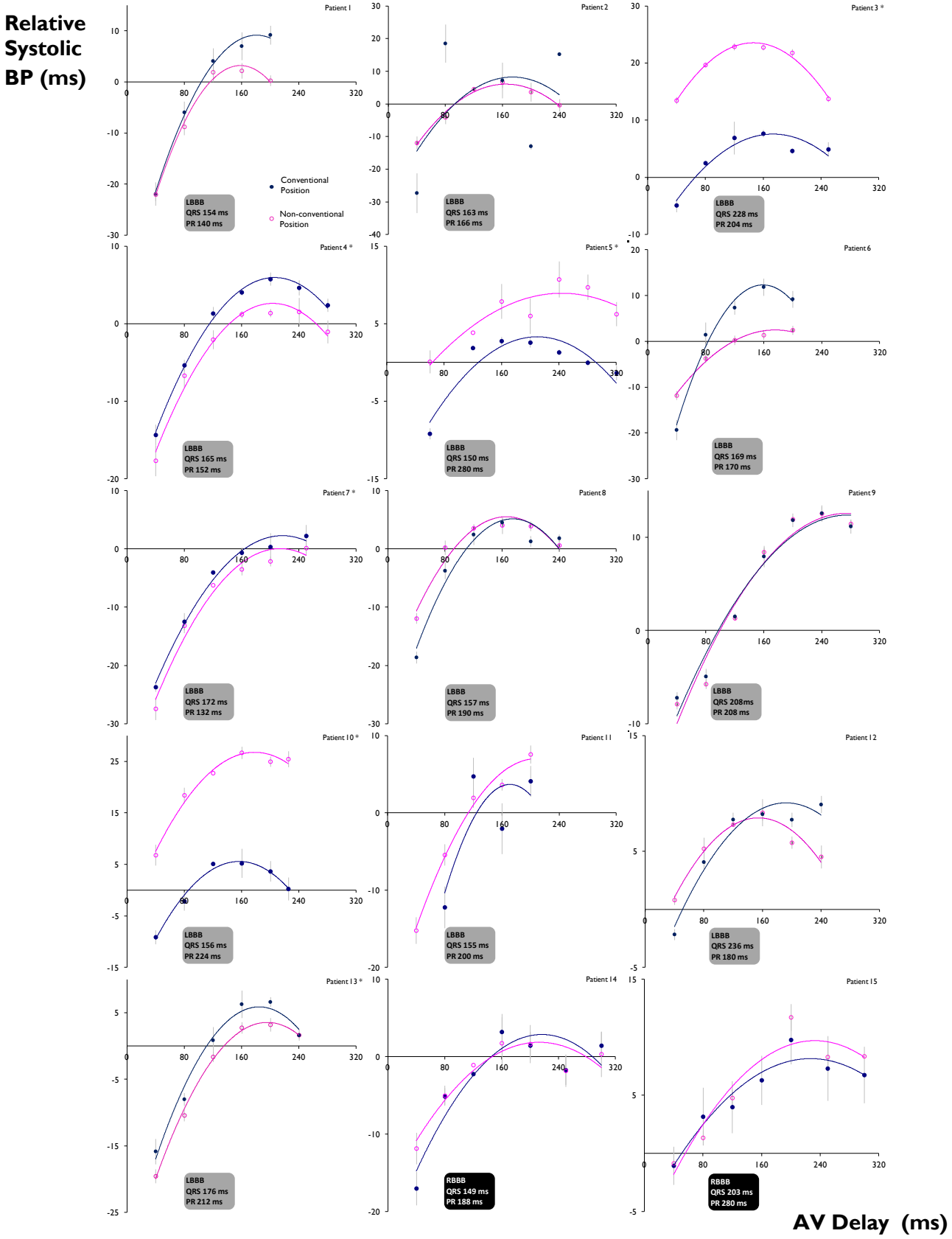


Figure 9-1 Haemodynamic profile for lead position in all 15 participants

QRS morphology, PR, and QRS duration are also presented. A * marks a significant difference between lead positions.

9.5 Discussion

This study is unique in demonstrating high resolution data on individual lead positions in individual patients across the full spectrum of AV delays in both lead positions. I have demonstrated, that in the majority of cases, when either one of two coronary sinus lead positions is targeted, in many cases there is little difference in the haemodynamic profile. In addition, I have demonstrated that there is on average, no significant difference in the AV optimum between the two different lead positions. This important finding may influence the development of future protocols which assess lead positions, where it may be better to focus on a single AV delay, and perform multiple replicate measurements to improve precision.

9.5.1 Deciding where to place the LV lead

Previous studies have used acute haemodynamics to judge the difference between potential lead sites, either via the coronary sinus (Bogaard et al. 2010) or endocardially (Derval et al. 2010; Spragg et al. 2010). Whether the site chosen is reproducibly the best site chosen is often not made clear, and the results can often be misleading (Stegemann & Francis 2012). The protocol used in this study, by testing the full range of AV delays, and comparing measurements at both sites to a fixed reference, and taking multiple measurements at each AV delays minimises the chances that the findings demonstrated here are due to the effects of noise. In a lead position study, a simple approach may be to compare a haemodynamic measure to a set of baseline measurements taken at either the beginning or end of the study. The weakness with this approach is that any presumed increment in pressure could be falsely low or high if there is any drift in baseline. The strength with the approach used in this study is that at each lead position, multiple haemodynamic measurements are compared at that position to baseline (AAI), so even if there is a drift in baseline,

the relative increments compared to that baseline are always used to judge haemodynamic changes in that given lead position.

In addition, our approach of fitting a parabola to identify the peak systolic blood pressure reduces the possibility of a spurious high measurement at one AV delay inadvertently allowing one site to be identified as the optimum. Where one site has been found to be superior to another, it is usually where the haemodynamic improvement is higher at all tested AV delays (Figure 9-1). While this means that it is only in the minority of our participants that one site has been identified as superior to another, it means that the case is far more compelling that this site is superior than if a single AV delay was tested.

9.5.2 The AV optimum between differing sites

This study demonstrates that there is no significant difference between AV optimum between two different lead positions. This is a reassuring finding, as in any study where lead positions are considered, there may be a doubt that if only a single AV delay is used to test lead positions, if the AV optima of the two sites are different, using a single value to compare the sites may yield misleading results. If a single AV delay is to be used in future protocols, it is essential that a suitable number of alternations are performed to allow signal (i.e. a true difference in haemodynamics between lead positions) to be differentiated from noise (biological and measurement variability).

9.5.3 Limitations

This study was a relatively small study, performed in a single centre, and limited by the number of patients who have an underlying ventricular rhythm and who are able to undergo the full protocol. Furthermore, it is not possible to test two lead positions in all patients who are recruited to the study. There may not be an adequate

alternative vein, and even if there are two different veins to test, if there is no capture of the LV at one site, which may, for example, be due to the presence of scar, will prevent the adequate comparison of the two sites. Whether there is a different pattern in patients with right or left bundle branch block, or between patients with ischaemic or non-ischaemic heart disease could not be ascertained from a study of this size, although presentation of all the results for all the patients allows readers to discern for themselves that in general, the pattern for the AV optima to stay the same between sites holds across the whole cohort.

This study only assessed acute haemodynamic response, and did not investigate whether the sites which offered the best haemodynamic response translate into a greater long term outcome from biventricular pacing. However, we know from the early studies of biventricular pacing that acute haemodynamic benefits were seen with biventricular pacing and these did translate into longer term benefits (Auricchio, Stellbrink, et al. 2002).

9.5.4 Clinical implications

The best haemodynamic profile in many cases can be obtained from sites that would not have previously been considered optimal. This suggests that many recipients of biventricular pacing may not be receiving the best possible benefit pacing can offer. Acute haemodynamic test may offer an opportunity to improve the way that lead sites are tested to select the best vein to use for implant. In this study I did not find a systematic difference between lead sites which suggests that a single AV delay could be tested at alternative sites, which would allow such a haemodynamic assessment to be performed relatively rapidly.

9.5.5 Conclusion

High precision haemodynamic measurements across all AV delays between two different potential lead positions sites for biventricular pacing demonstrate that a conventional lateral site is not always the best, and occasionally a site which would usually be considered non-conventional may offer a better haemodynamic profile, or in many cases one that is at least not inferior.

Section 4: Clues to guide the future direction of research in biventricular pacing from randomised clinical trials

10 Opportunity to increase lifespan in narrow QRS Cardiac Resynchronisation Therapy recipients by deactivating ventricular pacing: Evidence from randomized controlled trials

10.1 Abstract

Background & Objectives

Recent randomised controlled trial results suggest that in heart failure with narrow QRS, biventricular pacing (cardiac resynchronisation therapy, CRT) may increase mortality. The authors proposed implant complications as the cause, rather than a progressive adverse physiological effect. We examine the time course of clinical events in CRT trials to explore this assumption.

Method

We identified all trials comparing CRT against no CRT, which reported Kaplan-Meier curves in groups defined by QRS: narrow, non-LBBB broad, and LBBB broad. For each trial we calculated the change in lifespan every three months up to 3.5 years (the longest time for which data are available) and fitted a power law, i.e. $\propto \text{time}^{n}$.

Results

Four trials (MADIT-CRT, RAFT, REVERSE, and EchoCRT), totalling 4,717 patients, reported curves for mortality-or-heart failure related hospitalization, or for mortality.

In LBBB broad QRS patients (within MADIT-CRT), lifespan *gain* increased in proportion to $\text{time}^{1.94}$.

In contrast, in non-LBBB broad QRS patients (within MADIT CRT), and narrow QRS patients (EchoCRT), lifespan was *lost* in proportion to $\text{time}^{1.92}$ and $\text{time}^{1.96}$ respectively. Hospitalisation-free-survival showed similar patterns.

Conclusion

The non-linear growth of lifespan gained when CRT is implanted in patients with LBBB broad QRS is unfortunately mirrored by a similarly progressive loss in lifespan in narrow QRS heart failure. This suggests the culprit is a progressive physiological

effect of pacing rather than implant complications. If these data are not sufficient, an RCT of deactivating CRT in patients with narrow QRS may now be needed, with a primary endpoint of increasing survival.

10.2 Introduction

Cardiac resynchronisation therapy (CRT) has strong evidence of benefit in symptomatic heart failure patients with wide QRS and reduced left ventricular (LV) ejection fraction (EF) (Cazeau et al. 2001; Cleland et al. 2009; Linde et al. 2008; Daubert et al. 2009; Goldenberg et al. 2014; Tang et al. 2010). More recently it has been shown that the benefits may be limited to patients with left-bundle branch block (LBBB)(Zareba et al. 2011; Gold et al. 2012) or very wide QRS (Cleland et al. 2013). The benefits of CRT tend to be progressive with lifespan gain occurring in a non-linear manner suggesting an ongoing beneficial therapeutic effect of biventricular pacing over a number of years (J. A. Finegold et al. 2013). Over many years, however, patients with a variety of electrocardiographic (ECG) characteristics were implanted with CRT. Data from the European CRT Survey suggest that as many as 32% of CRT recipients did not have underlying left bundle branch block (LBBB) (Bogale et al. 2012), for example implanted instead for mechanical dyssynchrony (Bogale et al. 2012; Nijjer et al. 2012). In patients with narrow QRS, even when selected for having mechanical dyssynchrony on echocardiography, CRT increased mortality by 81% ($p=0.02$) in an international randomised controlled trial (Ruschitzka et al. 2013). If this is true, a relatively large CRT population may be at potential risk of adverse effects of CRT instead of benefiting from the assumed benefits of CRT.

How these findings should affect clinical practice depends upon the cause of increased mortality, specifically whether it is the result of implant complications or whether it is an undesirable effect of ventricular of pacing. Device implant complications will tend to cluster around the time of implant. For example, for dual

chamber pacing, one study shows 75% of all complications occurring over a three year period occur in the first three months post implant (Ellenbogen et al. 2003) and for CRT, one centre has reported 59% of complications in a mean follow up of 2.7 years occur in the first 90 days post-implant (Ahsan et al. 2013). These event rates in the first 3 months are, respectively, 33 and 14 times the rates in the remaining periods. If early implant complications are responsible, then there remains no issue for the remainder of patients who did not suffer implant complications to continue with CRT pacing. In contrast, if the excess mortality is driven by a detrimental effect from the action of pacing from CRT, then we may have an opportunity to improve outcomes in surviving recipients by deactivating CRT.

These two possibilities should generate different time courses of effect on mortality. Implant complications predominantly occur early, whereas progressive consequences of the detrimental activation sequence of CRT compared to intrinsic conduction may occur gradually throughout follow up. Mathematically, the pattern can be quantified by fitting the change in lifespan gain to a power law of time. In this study we did this with the data published by the randomised controlled trials assessing CRT in heart failure.

10.3 Methods

10.3.1 Eligibility and search strategy

We searched MEDLINE and Google Scholar from inception to April 2014 using search criteria: cardiac resynchronisation therapy, survival, mortality, left bundle branch block, right bundle branch block, and QRS morphology. Reference lists of the retrieved articles were hand-searched for additional publications.

We identified all randomized controlled trials comparing CRT against no CRT (either CRT-pacemaker or CRT-defibrillator) and reported Kaplan Meier survival curves for mortality stratified by QRS morphology (LBBB, non-LBBB broad QRS, and narrow QRS). We similarly identified studies, which provided Kaplan-Meier curves for a combined endpoint such as death or heart failure hospitalization.

Where studies stratified results by ECGs, we check whether methods were used to ensure there was a blinded analysis of ECG morphology.

10.3.2 Calculation of lifespan gain or lost

The segmental area between the two curves was calculated for three-monthly intervals. This represented lifespan gain or loss per patient randomized, during that period. The cumulative area between the curves up to each timepoint (lifespan gain up to that point per patient) was also calculated. The process has been previously described (Salukhe et al. 2004; J. A. Finegold et al. 2013) and is illustrated in Figure 10-1. As an example, to calculate the life years gained between three months and six months, the following calculation is used, with each survival rate expressed as a proportion between 0 and 1:

$$\text{Lifespan gained} = \frac{\left(\begin{matrix}\text{survival in CRT}\\ \text{at 3 months}\end{matrix} - \begin{matrix}\text{survival in controls}\\ \text{at 3 months}\end{matrix}\right) + \left(\begin{matrix}\text{survival in CRT}\\ \text{at 6 months}\end{matrix} - \begin{matrix}\text{survival in controls}\\ \text{at 6 months}\end{matrix}\right)}{2} \times 3 \text{ months}$$

Equation 3 Calculating lifespan gained from Kaplan Meier Curves

The cumulative gain in lifespan at any time point was defined as the sum of the gains in each 3-month period from zero to that time point. This cumulative lifespan gain at each three month interval was then re-expressed as a proportion of the total lifespan lost or gained at the end of the period analysed.

Where studies included patients with LBBB, non-LBBB QRS widening, and a control arm, Kaplan Meier curves for the different ECG morphologies were analysed separately.

Each trial had different follow up durations. The latest time point at which overall mortality data were available consistently in *all* the trials was 3.5 years. The latest time point at which there were data describing death or heart failure hospitalisation available consistently in *all* the trials was 2 years.

10.3.3 Data analysis

The effect on lifespan loss or gain per year was calculated for each ECG morphology group. and fitted to a power law. All statistical analyses were performed using the R software for statistical computing version 3.0.2

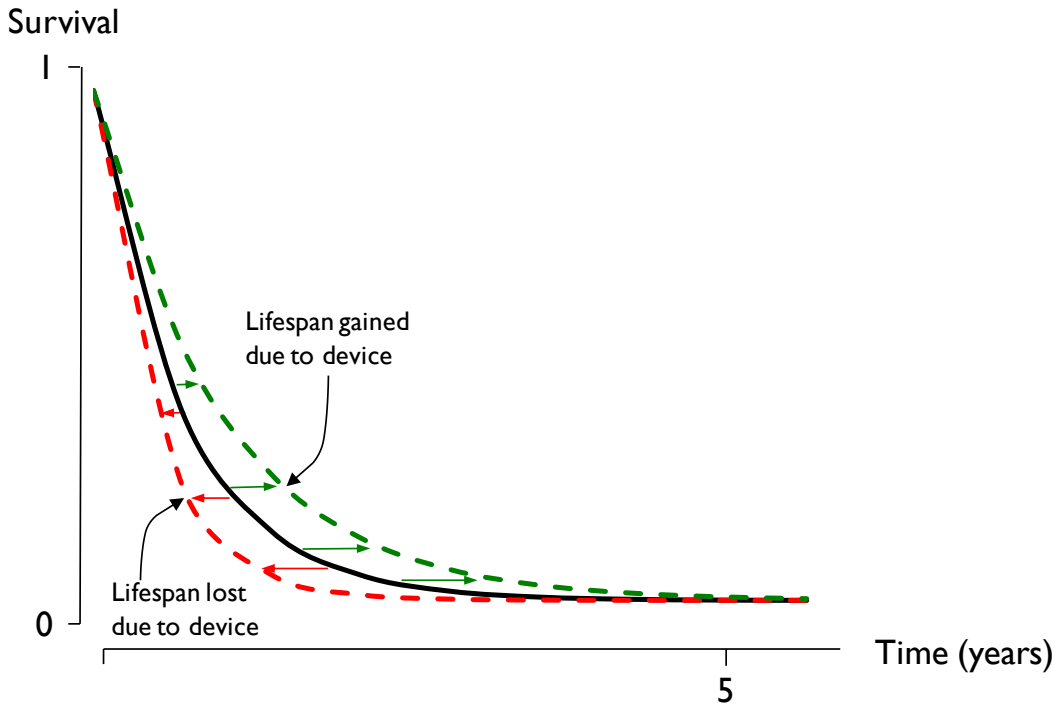


Figure 10-1 Calculation of lifespan loss or gain

Graphical representation of how lifespan gain or lost due to an intervention is calculated at any given time point. The black curve represents survival in a control group. The green curve represents an intervention which prolongs life, the area between the two represents lifespan gained. The red curve represents an intervention where lifespan is lost due to an intervention and the horizontal distance between the control and intervention represents lifespan lost.

10.4 Results

10.4.1 Eligible trials

Data were available from five groups in four trials totalling 4,717 patients. Three trials each showed data for LBBB and non-LBBB broad QRS (Goldenberg et al. 2014; D. H. Birnie et al. 2013; Gold et al. 2012) patients and one trial for narrow QRS patients (Ruschitzka et al. 2013) (Table 10-1). In all cases the data were randomised comparisons between CRT and no CRT. All trials stratifying subjects by ECG morphology had sufficient blinding of ECG morphology to treatment and outcome: ECGs for MADIT CRT were analysed in a core laboratory (Zareba et al. 2011); ECGs for REVERSE were analysed by investigators blinded to treatment allocation and outcome, with a further 50 randomly chosen ECGs assessed for intra and interobserver variability (Gold et al. 2012); and QRS verification in RAFT was performed by three different investigators blinded to treatment allocation and outcomes (D. H. Birnie et al. 2013).

Table 10-1 Characteristics of included studies

Characteristics of the studies included in the analysis are described below. For the control arms, where available, the modes of bradycardia pacing used are described (e.g. VVI) and the lower rate limit (e.g. 40 bpm). MVP: minimized ventricular pacing; RAFT: Resynchronization-Defibrillation for Ambulatory Heart Failure; REVERSE: Resynchronization reverses remodelling in systolic left ventricular dysfunction; MADIT-CRT: Multicenter Automatic Defibrillator Trial with CRT. *Complete details of bradycardia pacing settings not available, trial methods describe algorithms used to minimise ventricular pacing.

ECG Morphology	Study	Inclusion criteria	Total participants	Treatment	(n)	Control	(n)
LBBB wide QRS	RAFT	EF≤30% QRS≥120 NYHA II-III	1175	CRT-D	581	ICD *(VVI 40 / VVIR 50 / DDI 40 (MVP) / DDIR 50 (MVP)*	594
	MADIT-CRT	EF≤30% QRS≥130 NYHA I-II	1281	CRT-D	761	ICD *(VVI / DDI 40)*	520
	REVERSE	QRS≥120 EF≤40% NYHA I-II	369	CRT-D/P On	256	CRT-D/P with CRT Off *(VVI 40)*	113
Non-LBBB wide QRS	RAFT	EF≤30% QRS≥120 NYHA II-III	308	CRT-D	165	ICD *(VVI 40 / VVIR 50 / DDI 40 (MVP) / DDIR 50 (MVP)*	143
	MADIT-CRT	EF≤30% QRS≥130 NYHA I-II	537	CRT-D	328	ICD *(VVI / DDI 40)*	209
	REVERSE	QRS≥120 EF≤40% NYHA I-II	238	CRT-D/P On	160	CRT-D/P with CRT Off *(VVI 40)*	78
Narrow QRS	EchoCRT	EF≤35% QRS ≤130 NYHA III-IV	809	CRT-D	404	CRT-D with CRT Off *(MVP)**	405

10.4.2 Life years gained from CRT in LBBB

In patients with LBBB the increase in lifespan achieved with CRT grew with time, and much more than linearly. This is evident on assessment of the Kaplan Meier data of the individual trials (Figure 10-2). The best-fit power-law relationship was lifespan gain proportional to follow up time 1.94 (R^2=0.998, p<0.0001, Figure 10-3). This finding is consistent with a favourable physiological effect of CRT, with progressively more lifespan gain increment as the window of observation lengthens.

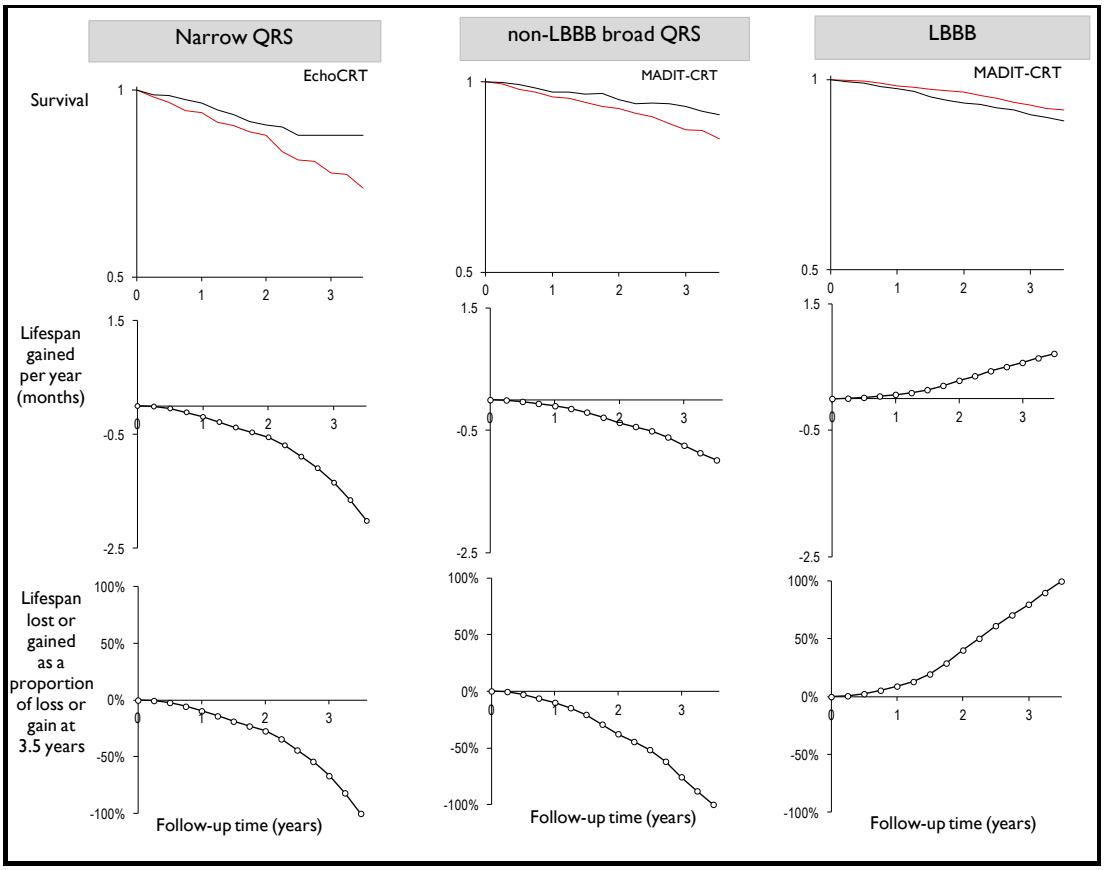


Figure 10-2 Lifespan gained or lost, stratified by ECG morphology and trial

The upper panels show the Kaplan Meier curves (CRT pacing arm in red and control arm in black). The cumulative area between the trial arms, at each time point, which represents the lifespan gain to that time point, is shown in the middle panels. Each study showed a different magnitude of impact in terms of absolute lifespan gain or loss. In the lower panels, these time courses are rescaled to reach 100% at the end of 3.5 years, so that the shape of development of lifespan gain or loss can be appreciated and compared between the groups.

10.4.3 Life year impact of CRT in non-LBBB broad QRS

In the non-LBBB broad QRS group, lifespan gain was numerically shorter in the patients randomised to CRT than control. This is evident in the curves of the individual trials (Figure 10-2). The best-fit power-law relationship was lifespan gain proportional to follow up time$^{1.92}$ (R^2=0.996, p<0.0001, Figure 10-3). This is consistent with there being an adverse effect of pacing from CRT, reducing lifespan further as the window of observation lengthens.

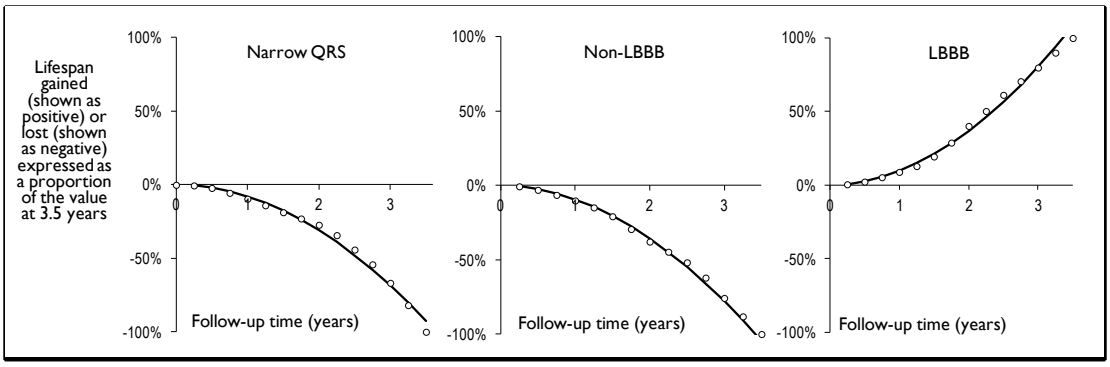


Figure 10-3 Survival gained or lost stratified by ECG morphology

Proportion of lifespan gained or lost as a proportion of lifespan gained or lost at 3.5 years stratified by QRS morphology with curves fitted according to a power law. Left panel: narrow QRS, Middle panel: Non-LBBB, Right panel: LBBB

10.4.4 Life year impact from CRT in narrow QRS

In patients undergoing CRT with narrow QRS, lifespan gain was numerically shorter in the patients randomised to CRT than control. This is visible in the curves of the individual trials (Figure 10-2). The best-fit power-law relationship was lifespan gain proportional to follow up time$^{1.96}$ (R^2 0.994, $p<0.0001$, Figure 10-3). This is consistent with there being an adverse effect of pacing from CRT, which produces progressively more lifespan decrement as the window of observation lengthens.

10.4.5 Impact of CRT on survival time free of first hospitalization

In the LBBB broad QRS group, time free from hospitalization and mortality was numerically longer in the patients randomised to CRT than those randomised to control. (Figure 10-4, right panels). The narrow QRS group showed the opposite direction of effect (Figure 10-4 left panels). The non-LBBB broad QRS group were mixed (Figure 10-4 middle panels).

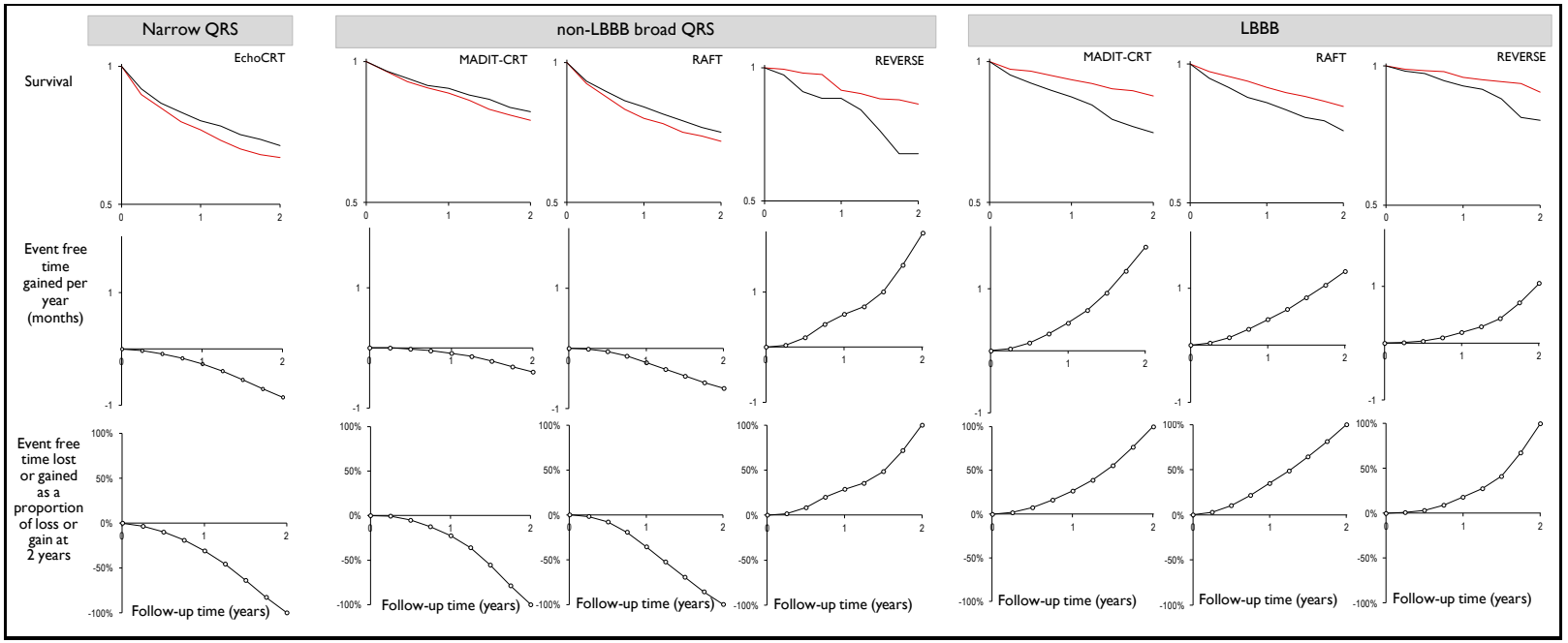


Figure 10-4 Survival time free of mortality or hospitalization, stratified by ECG morphology and trial

The upper panels show the Kaplan Meier curves (CRT pacing arm in red and control arm in black). The cumulative area between the trial arms, at each time point, which represents the gain in time free from hospitalization or mortality to that time point, is shown in the middle panels. Each study showed a different magnitude of impact in terms of absolute time gained or lost free of mortality or hospitalization. In the lower panels, these time courses are rescaled to 100% at the end of 2 years, so that the shape of development of lifespan gain or loss can be appreciated and compared between the groups. The panel with the smallest number of patients, the non-LBBB cohort of REVERSE, showed a non-significant trend to benefit from pacing, but also manifested the greatest irregularity in the shape of the survival curves. This may be a manifestation of the greater susceptibility to chance effects in small groups.

10.5 Discussion

Lifespan gain from CRT develops progressively with time after implantation. The same shape of time course is seen in all three groups of patients, although the direction of the effect is different. This is consistent with the effect being mediated by the physiological consequences of pacing.

The non-linear growth of lifespan gain from CRT was originally documented in trials which recruited patients with predominantly LBBB (J. A. Finegold et al. 2013). The present study analyzes separately patients with narrow QRS and non-LBBB broad QRS. In these patients, CRT impacts lifespan in a similarly shaped time course but, crucially, the effect is inverted, meaning there is a loss of lifespan which expands with approximately the square of time. This shape implies that this is due to the pacing effect of CRT rather than due to initial risk associated with device implantation.

10.5.1 Mechanisms for adverse impact on mortality

EchoCRT was the landmark study demonstrating a clear increase in mortality in patients undergoing CRT with narrow QRS, despite being designed to identify and recruit those patients with the best prospect of showing a benefit, namely those with mechanical dyssynchrony.

The discussion of the EchoCRT publication suggested that implantation or subsequent lead manipulation might have caused the increased mortality (Ruschitzka et al. 2013). However, this is not a plausible cause. First, the controls had implantation too.

Second, mortality from implantation would be expected to manifest early and not many years later as evidenced in the data reported. Moreover, lead manipulation is a relatively unlikely cause of excess mortality, with infection being the most likely adverse outcome (Baddour et al. 2010). Our interpretation of the EchoCRT mortality data differs, since we observe that the reported mortality was driven by over 20 excess cardiovascular deaths ($p<0.01$) of which the great majority were classified as "heart failure" or "arrhythmic events" rather than infection. Instead, the pattern suggests that CRT in these patients unintentionally contributes to heart failure progression.

The main study publication does not appear to specify that the increase in mortality was a progressive process more suggestive of a pathophysiological consequence of pacing rather than a procedural consequence of the implant. Using a systematic approach we identified the articles citing this publication and examine them to see if they drew this inference for themselves. I used Google Scholar to identify citing documents. The 37 citing documents that were accessible from Imperial College, London were read independently by myself and my junior doctor colleague Dr Ruhella Hossain, with disagreements resolved by my supervisor (Darrel Francis). 25 documents (68%) mentioned that harm could be caused by CRT, whilst the remainder either stated that there was no benefit or did not comment. Of the 37 documents, only 2 (5%) demonstrated awareness that the harm was due to the ongoing effects of pacing rather than implantation (full details in appendix).

10.5.2 Difference between device and medical therapy

If a drug is found to increase mortality, administration can be stopped. Moreover, information on side effects in established drug therapy is readily available for

patients. Understanding benefits and adverse effects of implanted devices is more complex. For CRT in heart failure, for example, this information is not fully established. If an adverse effect is suspected, interrupting therapy from a device that has already been implanted may appear unfamiliar and uncomfortable to both patients and physicians, unless the evidence to do so is very compelling. However, as information accumulates on who will benefit or be harmed by CRT, it is becoming increasingly clear that randomization to stopping CRT in an already-implanted device may indeed be ethical, and perhaps may even be an ethical imperative. Thus, if the ongoing action of an implanted device is found to be a progressive increase in mortality, there should be no reluctance to turning off the device in the survivors.

10.5.3 Call for a trial: deactivating CRT in non-LBBB patients

It has been reported that one third of already implanted CRT recipients in Europe have neither underlying LBBB or broad QRS (Bogale et al. 2012). This amounts to approximately 20,000 individuals in Europe alone (Arribas et al. 2014). In North America and elsewhere, there may be a similarly non-trivial number. This poses two opportunities. First, we may still be able to provide extra lifespan to a larger number of patients enrolled in these trials. Second, there is a large pool of patients suitable for enrolment in a randomised controlled trial to answer definitively the hypothesis generated in this study. Such an RCT would randomise these patients into leaving on versus turning off the CRT mode. This trial could be done at low cost since there is no need to implant a device, rather only reprogramming of the currently implanted device. The study would only require informed consent and online randomisation with follow up limited to all-cause mortality in the interests of simplicity and to avoid the substantial costs of segregating causes of death or determining hospitalisation. If the hazard ratio of 1.8 seen in EchoCRT is representative, then the hazard ratio for

switching off CRT would be approximately 0.6 and therefore the number of patients and duration of follow up needed would be modest. Moreover the potential enrolees are already under regular routine device follow up and therefore the device community could conveniently approach all ~40,000 patients promptly with minimal additional visits and cost.

A perceived difficulty may be explaining to the patient why, having implanted a device, there was a proposal to deactivate the CRT element. One option might be to explain that the device can be programmed in a variety of different ways, and it is not known which is best. On the one hand, the AV delay could be set to always capture the ventricle. On the other hand, it could be set to only capture the ventricle when natural ventricular activation fails. Thus the trial would have one arm using the currently programmed AV delay, and the other arm set to an AV delay longer than the intrinsic AV delay, or set to a low backup rate solely to protect against bradycardia. In the case of narrow QRS, the informed consent process would also require that patients are informed that new clinical trial evidence, which might have not been available at the time of their implant, suggests that such a device would not usually be implanted with their current ECG morphology, and that therefore switching off the pacing may be beneficial at present. However, should the QRS later broaden or the AV delay prolong unacceptably, the device would already be in place and the CRT function could then be usefully switched on. In the meantime the patient would be protected against asystole and (if it is a defibrillator) tachyarrhythmias.

Such a trial might enrol patients who were not reliant on pacing, whose LV lead was functioning, whose native QRS was below a threshold duration and was not in an

LBBB pattern, and are free of serious non-cardiac pathology that would limit lifespan. It might exclude patients with long PR intervals because in this subgroup of non-LBBB there seems to be a beneficial effect of CRT (Kutyifa et al. 2014). To minimise cost the baseline data collected could be a simple set of widely available clinical variables such as the elements of the modified Seattle heart failure score validated in SCD-HeFT (Levy et al. 2009; Levy et al. 2006).

It may be tempting to plan to restrict such a trial to those who had not experienced a favourable symptomatic response. However, this may be unwise. Randomised trial data show that when compared with a placebo control arm, the incremental rate of patients who experience a symptomatic response with CRT pacing is only approximately 15% (Sohaib, Chen, et al. 2013). This means that the remainder of patients experiencing a symptomatic response with CRT, who are twice as numerous in trials and may be more numerous outside carefully monitored trial environments, have not necessarily received any symptomatic benefit from the pacing itself since they would have felt as well without it. Excluding symptomatic responders would have the undesirable effect of causing patients who express an optimistic view of their condition and their care to miss the opportunity to participate in a trial which might have given them an opportunity for additional lifespan. Blinded randomized controlled data on these patients would be the most valuable and practice changing information from such a trial since it may show that patients that have CRT switched off gain a better symptomatic state than those who continue CRT. If the consent process is designed carefully with as much opportunity for positive placebo, there might conceivably be net symptomatic improvements for both arms. Not every specialist might consider this trial necessary. Some may consider the information in

Figures 2 and 3 to be a sufficient indication of harm to merit routine deactivation of biventricular pacing in this cohort.

There is some evidence to suggest that there is a benefit for CRT in those with a non-LBBB ECG, but a very broad QRS (>140-150 ms) (Cleland et al. 2013). This trial would also present an opportunity to address this question.

10.5.4 Study Limitations

This study uses the published mortality time course data from randomised controlled trials of CRT versus no CRT, in studies which present Kaplan Meier curves for both arms of strata defined by QRS characteristics. There are other trials which did not present data stratified by ECG morphology (Cleland et al. 2005; Bristow et al. 2004; Linde et al. 2008) and therefore were not included. Such information is likely to add further information, particularly in those with non-LBBB QRS widening.

Moreover the evidence of increased mortality in subgroups of patients receiving CRT is only in the short term. It is not known whether such effects might halt or reverse over longer periods of time. However, when the effects of CRT are beneficial they tend to grow with time (J. A. Finegold et al. 2013; Linde et al. 2013). It might not be prudent to hope that physiological harm would behave differently.

Except for the EchoCRT study, the studies eligible for our analysis covered the milder parts of the spectrum of heart failure. An even more pronounced effect on

mortality in non-LBBB might be seen when the trials restricting inclusion to individuals in NYHA III-IV are included.

Our study relied on the evaluation of the ECG as performed in the original clinical trial. If that classification was incorrect, then our analysis would suffer accordingly.

10.5.5 Conclusion

The impact of CRT on survival time is non-linearly dependent on the window on which it is dependent growing approximately with the square of time. In patients with underlying LBBB this impact is a benefit, but in those without underlying LBBB this non-linearly expanding impact on survival duration is unfortunately adverse. The time course fits a progressive adverse physiological effect of pacing rather than implant complications. This suggests an opportunity for benefit by deactivating pacing in such patients. We should consider a randomized controlled trial of deactivating CRT in recipients with narrow QRS or who do not have underlying LBBB, with a primary endpoint of survival.

10.6 Contributions

This chapter was conceptualised by myself. Two international collaborators and four Consultants including my supervisors helped guide the structure of the discussion. Data extraction was performed predominantly by myself with the assistance of two colleagues. Data analysis was performed entirely by me. The text of this chapter is published as "Sohaib SMA, Finegold JA, Nijjer SS, Hossain R, Linde C, Levy WC, Sutton R, Kanagaratnam P, Francis DP, Whinnett ZI. Opportunity to increase lifespan in narrow QRS Cardiac Resynchronization Therapy recipients by deactivating

ventricular pacing: Evidence from randomized controlled trials. *JACC: Heart Failure*. 2015 Mar 3. pii: S2213-1779(15)00022-0. 2015"

11 Synthesis

In this thesis, I have explored the physiological mechanisms which underpin biventricular pacing, in particular developing a closer understanding of the contributions from improved ventricular filling by adjustment of the AV delay.

11.1 Challenges of quantifying response and optimisation.

To understand how different mechanisms may contribute to the benefit of biventricular pacing, it was first necessary to have a clearer understanding from the existing studies how much individuals benefit from biventricular pacing. Non-response rates are often quoted as motivation for trying to improve the way biventricular pacing is delivered. From analysing the existing literature I found that in the published scientific literature, a mean quoted response rate of 66% is given. However, when I performed a meta-analysis of the existing randomised controlled trials, it becomes apparent that the symptomatic response rate based on NYHA class is 51%, and once the symptomatic improvement in the control arm is deducted, this values is in fact closer to 16%.

I also evaluated acute markers of response which are used for optimisation of biventricular pacing. Markers of acute response are often the only practical way to judge therapeutic decisions where one of a multitude of options needs to be chosen. With a group of international experts I developed a stepwise approach for the characteristics required for the ideal optimisation protocol. The first step is for the optimum which is selected should be single, i.e. the scheme should not suggest different regions on the spectrum of the AV delay which might represent the optimum. The second step is that the optimum should be reproducible. The third step is for the value to be physiologically plausible, for example not suggesting settings that will obviously cause harm. Once these basic requirements are met, any

optimisation scheme can then be tested against an "elite group" of optimisation schemes which meet these requirements. The schemes can be tested to see if they "cluster" or pick AV optima which are all in the same region. If a range of different clusters are seen within group of optimisation schemes, it will be necessary to pick one cluster. At this stage, a clinical trial could be justified to select the appropriate cluster. One this final stage is reached, and a cluster of high quality optimisation schemes is selected, the choice of scheme could simply be made based on costs and convenience.

From my analysis it was clear that many of these steps have not been performed for many existing optimisation schemes and may be a contributor to their lack of benefit in randomised controlled trials to date.

11.2 High resolution methods to probe the current methods

I performed two experiments to closely probe two common methods which are use for AV optimisation: left ventricular outflow tract Doppler, and electrogram based optimisation scheme. I used a novel method to acquire and trace around large numbers of LVOT Doppler velocities to assess the feasibility of acquiring long traces of Doppler to improve the precision of this tool for optimisation, and whether breath holding is required. One weakness of LVOT Doppler for optimisation is that beat-to-beat variability is high, and often only three beats are used per AV delay when in fact for an optimisation, previous analyses have suggested that many more beats, often in the hundreds are required (Francis 2013b; Pabari et al. 2011). I found that neither the magnitude nor variability of measurements were affected by breath holding. This would imply that a better way to improve the precision of LVOT Doppler for optimisation is to acquire a large number of beats during quiet breathing.

An algorithm using multiple alternations of systolic blood pressure between reference and tested pacing setting has been developed by my supervisors for reproducible AV optimisation (Z I Whinnett et al. 2006; Zachary I. Whinnett et al. 2006), I used this technology to evaluate the different electrogram based AV optimisation schemes and found that agreement between the different methods is poor, and none agree with the haemodynamic optimum. It may be that the weakness in these optimisation schemes has arisen as they have often been tested or validated against uncertain gold standards. (Chapter 4)

11.3 Resolving controversies using high resolution physiology

I used high precision haemodynamic measurements to explore different controversies in the field of biventricular pacing. The first was to try to understand why reported responses to VV optimisation were so varied, and looked at how different conventions for keeping the AV delay constant during a VV optimisation have an effect. I used four different methods for holding the AV delay constant (A-LV constant, A-RV constant, time to first ventricular lead constant, and time to second ventricular lead constant), and found that the acute haemodynamic effect at AV 120 ms was determined by the time to the first paced ventricle. Once one ventricle had been activated, it made very little difference how long after the second ventricle was activated. From a practical point of view these findings suggest it is much simpler to leave the VV setting at zero, and instead focus programming efforts on the AV delay.

For biventricular pacing to be effective, there will always be an element of AV shortening to ensure capture of the ventricles, but to explore the isolated effect of AV shortening without the resynchronising effect of pacing a wide QRS with a biventricular pacemaker, I examined a group of patients with PR prologation and a narrow QRS. During an invasive study, temporary pacing of the His bundle allowed

us to maintain the same, narrow QRS morphology and examine the effect of purely optimising the AV delay. I found a mean increment of 4 mmHg in systolic pressure, approximately 60% of that seen in heart failure with LBBB. This also demonstrates the pure effect of AV shortening without an associated adverse haemodynamic effect of right ventricular pacing. Permanent direct His bundle pacing has previously been demonstrated (Deshmukh & Romanyshyn 2004) and these results suggest it there may be a benefit in implementing this in patients with narrow QRS and PR prolongation. Its longer term benefits would need to be demonstrated in a randomised controlled trial, in a similar way that encouraging results from haemodynamic studies preceded the outcome studies in biventricular pacing for patients with heart failure and broad QRS (Butter, A. Auricchio, et al. 2001).

I used similar techniques to explore whether the AV optimum varies between different LV lead positions, a conventional position on the lateral left ventricular wall, and a non-conventional position, targeted as the basal anterior wall. Using high precision haemodynamic measures, and evaluating response across the full range of AV delays, I found that often, there is no significant difference in haemodynamic response between lead positions, but in some instances there was. This was usually seen across the full spectrum of AV delays tested, and occasionally in a position that would usually be considered sub-optimal. Across the group, there was no significant difference between the AV optimum in the conventional position and non-conventional positions. This suggests that if measurements are made with sufficient precision, one AV delay could be used to determine the best lead position.

11.4 Limitations

While the acute haemodynamic studies performed during this thesis allow us to examine some of the difficult questions with a higher resolution than many other

available technologies, some limitations remain. All the haemodynamic studies were performed with patients in a semi-recumbent or supine positions, rather than in during standing or during exercise which may me a closer representation of their haemodynamic status in their ambulant state. The group have previously performed haemodynamic studies during exercise and what is apparent is that signal to noise ratio is adversely affected (Whinnett, Briscoe, et al. 2008), and thus performing these experiments to sufficient resolution would have made already long protocols prohibitively long for our participants. For the invasive studies this would have not been logistically possible.

My thesis studied acute haemodynamics of different pacing configurations and did not attempt to assess longer term clinical effects. The reason for this is that many contributors affect the evolution of a patients outcome in the long term, which dwarf the effects of a small difference in pacemaker configuration. Even the entire effect of CRT pacing is difficult to detect clinically in an individual patient. By this I mean the 50% in of patients who report clinical improvements on CRT pacing in blinded randomised controlled trials must be considered in context of the 35% of their counterparts who report symptomatic improvement after having a pacemaker implanted and left switched off. Of the 50/100 patients who appeared to have been made better by pacing, 35 out of 50 would have still felt better if the pacemaker had been implanted but left switched off. A similar pattern is seen among those who fail to improve or become worse. Therefore it would be unsound to ascribe the individual changes in symptoms, or individual outcomes, seen in clincial practice to the presence of pacing and foolish to ascribe such effects to the likely much smaller effects of changes in pacing configurations. The only way to reliably assess the affects on symptoms and clincal event endpoints in the longer term is to study a large number of patients with both randomisation and blinding. This is not practicable in the duration

of a PhD thesis and I explicitly set out not head along a doomed path. In my thesis I have addressed mechanistic questions and have used acute haemodynamic measurements to assess changes in acute cardiac function occurring as result of specific interventions detailed in the relevant chapters. In order to address these mechanistic questions a reliable and reproducible measure of cardiac function is required.

My choice to focus on systolic blood pressure is centred on the ability to measure it non-invasively so that sufficient numbers of measurements can be made so that any differences in pacing configurations observed within an individual are not simply the result of chance. Where invasive measurements were possible, I used them. It is conceivable that LV dP/dt, is different in a way that makes it more clinically important than measures that summate individual LV dP/dt increments over the entirety of systole such as pressure. However I cannot think of a reason why it would be preferable to have a single LV dP/dt increment that was larger if this was achieved at the cost of having the sum of all these increments smaller. I do not see how any organ outside the heart benefits more from the peak instantaneous rise in pressure in the ventricle being higher than from the pressure perfusing it being higher. Turning back to the heart, I do not see why a change that causes one segment of time to show a steeper rise in pressure should be better than another change that causes the sum of all the rises of pressure to be larger.

Our group has recently reported the incremental changes in pressure in relation to those in LV dP/dt max in a multicentre iSPOT trial (Shun-shin et al. 2016). The graph is reproduced below (Figure 11-1):

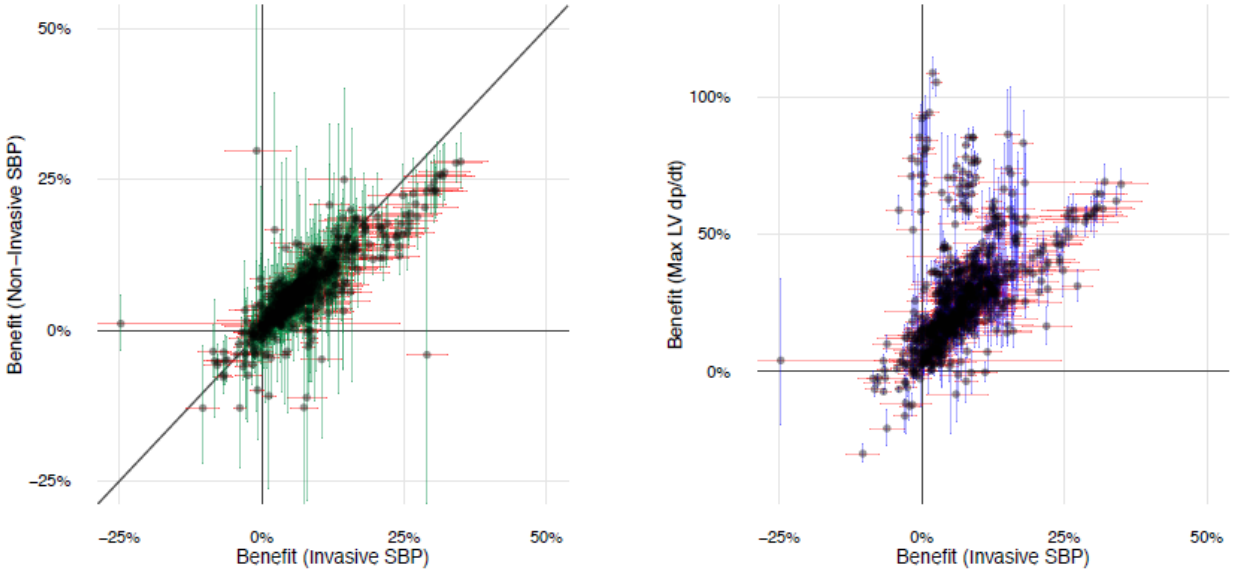


Figure 11-1 Correlation of systolic blood pressure with dP/dt

Data from the iSpot Study comparing benefit of pacing measured using blood pressure and from measure maximum LV dP/dt (Shun-shin et al. 2016).

These show that in general changes in non invasive blood pressure are correlated with those of invasive blood pressure ρ=0.82). Changes in LV dP/dt_{max} are less well correlated with changes in blood pressure (ρ= 0.60), because it is a different physical quanitity with different units.

To assess whether these acute changes lead to a sustained benefit in the longer term, adequately powered studies would be required. This work has been used to help design larger clinical randomised studies which are described below. We do know from the work on biventricular pacing in sinus rhythm and LBBB, that studies demonstrating acute haemodynamic improvements from initiating biventicular pacing (Auricchio et al. 1999; Blanc et al. 1997; Kass et al. 1999) preceded the large randomised controlled trials demonstrating a survival benefit (Cleland et al. 2005).

11.5 Randomised controlled trials evaluating the use of acute haemodynamic data in pacing for heart failure

The reproducibility and high resolution of the protocol used to measure acute haemodynamic changes in pacing is well documented throughout this thesis. This protocol was originally designed for AV optimisation for biventricular pacing but the principles of the alternation protocol have been extended and applied to answer a number of other questions in the field for biventricular pacing. During the course of this thesis, the alternation protocol for AV optimisation was undergoing evaluation as part of the British Randomised AV Optimisation (BRAVO) Trial, a non-inferiority study comparing haemodynamic optimisation against iterative echocardiography based optimisation with peak VO_2 as the primary outcome measure (Whinnett et al. 2014). Recruitment for this trial is now complete and is due to report shortly. This non-inferiority study may allow us to more closely understand the relationship between longer term physiological changes from acute haemodynamic optimisation.

The work on His optimised pacing in Chapter 8 formed the basis for a British Heart Foundation funded grant for a randomised controlled trial of AV optimised permanent direct His pacing for patients with heart failure, non-LBBB morphologies, and PR prolongation (His Optimised Pacing Evaluated for Heart Failure Trial "HOPE-HF"). In this randomised double blind crossover trial, 160 participants will be recruited for permanent direct His bundle pacing and randomised to six months of AV optimised His pacing and six months of no pacing. The primary endpoint will be exercise capacity measured using peak oxygen uptake (VO_2). If the haemodynamic improvements presented in this thesis translate into longer term physiological benefit in this trial, this could allow another group of patients with heart failure to benefit from pacing.

11.6 Clues to guide the future direction of research in biventricular pacing from randomised clinical trials

The findings of the analyses from this thesis can be used to plan future studies of biventricular pacing. The approach of examining evidence from randomised controlled trial combined with the use of high resolution physiological methods can guide how we extend or retract the use of biventricular pacing. The population of patients with narrow QRS or non-LBBB are one such group.

The harms of biventricular pacing in patients with narrow QRS have recently been demonstrated in a large randomised controlled trial, EchoCRT.(Ruschitzka et al. 2013) An increased rate of mortality was noted in patients randomised to receive biventricular pacing. Analysing the data more closely I found that rather than due to implant complications, this was more likely due to an ongoing harmful physiological effect from pacing. Additionally the benefits of biventricular pacing in patients with non-LBBB QRS widening have been difficult to demonstrated and I found a similar trend in this group also. Almost 32% of patients with biventricular pacing have either narrow QRS or non-LBBB widening (Bogale et al. 2012). This is likely to be the equivalent of 20,000 patients in Europe alone. This substantial population may yet benefit from increased survival, and improved symptoms from having the biventricular pacing feature of their devices switched off. To date, there has been no clinical trial which has tested withdrawal of therapy in patients with an implanted cardiac electrical device.

While the results of the EchoCRT may be compelling enough for some clinicians to deactivate biventricular pacing in patients with narrow QRS, there are many who may be reluctant to do so for a number of reasons. First, such patients may have noticed a

significant improvement in their symptoms following implantation of their device. It may be that these patients are demonstrating the strong positive placebo effect seen with device implantation which was also seen in the randomised controlled trials of biventricular pacing in broad QRS as seen in my analysis of symptom improvement of randomised controlled trials of biventricular pacing. Secondly, there has been a suggestion in the Discussion of the EchoCRT trial that the harm seen in this treatment arm was attributable to implant complications. This argument can also be questioned as both control and treatment arms received the device, and an analysis of the long term outcome of patients for EchoCRT demonstrates that the harm seen in the treatment arm is ongoing and increasing almost in proportion to time^2 since the device was implanted his suggests that the harm is due to an ongoing physiological harmful effect associated with pacing.

Third, there is a possibility that patients who have a narrow QRS, but PR prolongation may benefit from the AV shortening benefits of biventricular pacing. The benefits of AV optimisation were suggested before the advent of biventricular pacing.(Brecker et al. 1992)

In patients with non-LBBB widening the benefits of biventricular pacing are much less clear. In the MADIT-CRT trial there certainly appeared to be a trend towards harm associated with CRT implantation (Zareba et al. 2011). Further subgroup analysis from this trial suggests that individuals with a long PR interval (>230ms) and non-LBBB benefit from CRT with the reverse in those with PR <230 ms (Kutyifa et al. 2014). Conversely, another large meta-analysis of individual patients from different CRT trials has suggested a benefit from CRT with very wide QRS regardless of morphology (Cleland et al. 2013). We are currently relying on subgroup data to answer a question for which these trials were not powered to answer.

Non-invasive acute haemodynamic protocols offer a tool to assess whether a patient might benefit from having their biventricular pacemaker deactivated. We have previously demonstrated that non-invasive systolic blood pressure can be used to reproducibly select the AV optimum (Zachary I Whinnett et al. 2006). Using this same protocol we can assess whether patients demonstrate a positive blood pressure response to biventricular pacing across a range of AV delays. We demonstrate this in Figure 11-2 with a patient with right bundle branch block. For every AV delay tested, the blood pressure is lower than a reference value of atrial pacing with intrinsic ventricular activation. Such a candidate may well benefit from having their CRT de-activated.

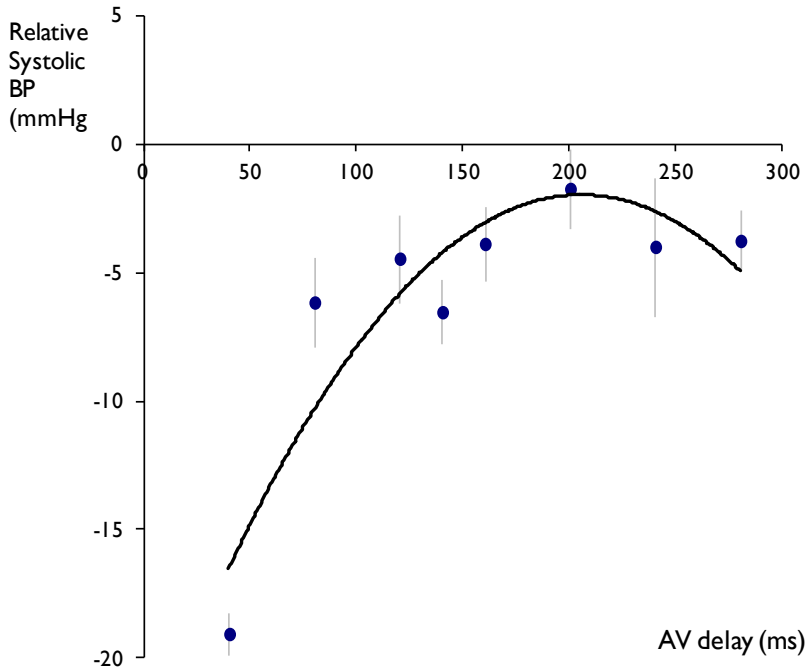


Figure 11-2 Haemodynamic profile of a patient with RBBB

Blood pressure across a range of AV delays is compared to the patient's intrinsic ventricular conduction with atrial pacing. Values of relative systolic blood pressure suggest there is a harm associated with biventricular pacing.

Taken together, we can propose hypotheses for further studies:

1. Deactivating biventricular pacing in patients with narrow QRS will lead to an improvement in symptoms and decrease in mortality and heart failure hospitalisation.

2. In patients where the decision for CRT is equivocal, such as individuals with narrow QRS and PR prolongation, or patients with non-LBBB QRS widening, haemodynamically guided device deactivation will lead to an improvement in symptoms and decrease in mortality.

11.7 Conclusion

In this thesis, my experiments and analyses have shown helped to understand how the benefits and harms from biventricular pacing can be measured, understood, and where appropriate, guide future approaches to using this therapy. The potential to improve symptoms may be greater than usually thought, and more systematic approaches to developing AV optimisation algorithms may offer such a benefit, with less of a focus on VV optimisation where many of the previous reported effects may have been due to the unintentional effects of AV manipulation. AV optimised direct His pacing may offer a novel option for patients with heart failure, PR prolongation, and narrow QRS, whereas the physiological harm from biventricular pacing in narrow QRS and normal AV conduction could be averted by considering switching off of biventricular pacing in this group.

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13 Appendix

13.1 Supplemental Data from Chapter 6

Table A: Coefficient of variation (CV) per 7.5-second intervals (%)

	Free breathing (per quartile, Q)	P value (Q1 vs Q2)	Breath-hold 1 (per half, H)	P value (H1 vs H2)	Breath-hold 2 (per half, H)	P value (H1 vs H2)
VTI	7.37 ± 5.37 7.24 ± 4.06 7.96 ± 6.53 8.98 ± 5.74	0.88	8.93 ± 6.60 8.91 ± 7.75	0.99	7.98 ± 4.96 7.03 ± 4.85	0.30
Peak velocity	6.11 ± 4.22 5.23 ± 2.33 6.33 ± 4.53 6.76 ± 4.14	0.19	6.66 ± 5.42 5.73 ± 5.01	0.21	6.30 ± 4.19 5.14 ± 3.78	0.16

Table B: Regression coefficients, and T-tests

	Free breathing (15s)	*P value*	*Free breathing (30s)*	*P value*	*Breath-hold 1*	*P value*	*Breath-hold 2*	*P value*
VTI	-0.04 ± 0.05	0.19	-0.04±0.03	0.01	-0.11 ± 0.12	0.08	-0.08 ± 0.08	0.03
Peak velocity	-0.21 ± 0.24	0.08	-0.17 ±0.15	0.03	-0.28 ± 0.49	0.27	-0.46 ± 0.37	0.02

Table C: F test values comparing variability between free breathing (15s) and two repeat breath-holds for individual patients

	VTI		Peak velocity	
Pt	Breath-hold 1	Breath-hold 2	Breath-hold 1	Breath-hold 2
1	0.59	0.01	0.91	0.22
2	0.04	0.28	0.08	<0.01
3	0.59	0.01	0.10	0.90
4	<0.01	0.60	<0.01	0.47
5	<0.01	<0.01	<0.01	<0.01
6	0.91	0.48	0.53	<0.01
7	<0.01	0.44	<0.01	0.61
8	Removed as too breathless to breath-hold			
9	<0.01	<0.01	0.37	0.03
10	0.05	0.03	0.27	<0.01
11	<0.01	0.97	<0.01	0.38
12	0.04	0.41	0.08	0.33
13	0.64	0.49	0.19	0.07
14	<0.01	0.01	0.06	0.42
15	0.73	0.03	0.30	0.25
16	0.88	<0.01	0.35	0.01
17	<0.01	<0.01	<0.01	<0.01
18	0.17	0.13	0.11	<0.01
19	0.08	0.11	0.26	0.21
20	0.86	0.52	0.13	0.51
21	0.35	0.08	0.05	0.74
22	0.19	0.81	0.29	0.29
23	0.10	0.03	<0.01	0.57
24	0.46	0.07	<0.01	0.19
25	0.76	0.26	<0.01	0.89
26	0.08	0.01	0.64	0.60
27	0.05	0.03	0.08	<0.01
28	<0.01	0.17	0.02	0.32
29	0.28	0.28	0.10	0.14
30	0.33	0.85	0.38	0.68
31	0.08	0.11	0.48	0.01
32	0.32	0.74	0.04	0.02
33	0.78	0.46	0.01	0.25
34	0.04	0.84	0.48	<0.01
35	0.01	<0.01	0.16	0.08
36	0.58	0.28	0.48	0.83

13.2 Supplemental data from Chapter 7

Patient characteristics categorised by protocol performed:

	Mean		SD	Reference 120	Reference Opt	P
Age, years	66		*8*	68	65	0.45
Male	19	*86%*		8	11	0.06
ECG Morphology						
LBBB	16	*73%*		9	7	0.34
RBBB	3	*14%*				
CHB	3	*14%*				
QRS, ms	162.3		*24.1*	151.5	174.2	0.04
LVEDD, cm	5.7		*1.2*	5.6	5.8	0.72
NYHA Class						
II	15	*68%*		7	8	
III	7	*32%*		4	3	0.65
Device Type						
CRT-D	11	*50%*		5	6	0.67
CRT-P	11	*50%*		6	5	
Heart Failure Aetiology						
Ischaemia	13	*59%*		6	7	0.66
Non-Ischaemic	9	*41%*		5	4	
Betablocker	16	*73%*		6	10	0.06
ACE-I / ARB	19	*86%*		10	9	0.53
Aldosterone Antagonist	13	*59%*		6	7	0.66
Diuretic	14	*64%*		8	6	0.38

13.3 Supplemental data from Chapter 10

The following studies all reference the EchoCRT study results. This table presents whether these publications have mentioned if CRT is associated with harm in narrow QRS, and if this harm is due to the ongoing effects of pacing.

Citing publication	Mentions harm	Mentions Pacing as the cause of harm	Weblink
C1	Yes	No	http://informahealthcare.com/doi/abs/10.1517/13543784.2014.881799
C2	Yes	No	http://circ.ahajournals.org/content/128/22/2407.short
C3	Yes	No	http://www.nejm.org/doi/full/10.1056/NEJMe1310406
C4	Yes	No	http://link.springer.com/article/10.1007/s12265-014-9546-8#page-1
C5	No	No	http://jaha.ahajournals.org/content/2/6/e000410.short
C6	Yes	No	http://www.sciencedirect.com/science/article/pii/S0894731714002582
C7	No	No	http://eurheartj.oxfordjournals.org/content/early/2014/01/02/eurheartj.eht555.s
C8	Yes	No	http://www.wjgnet.com/2308-3840/pdf/v2/i1/1.doc
C9	No	No	http://heart.bmj.com/content/early/2014/05/09/heartjnl-2013-304690.short
C10	Yes	No	http://www.sciencedirect.com/science/article/pii/S0002870314005006
C11	Yes	No	http://orca-mwe.cf.ac.uk/60107/1/2014russellsjmd.pdf
C12	Yes	No	http://onlinelibrary.wiley.com/doi/10.1002/ejhf.43/full
C13	No	No	http://link.springer.com/article/10.1007/s11897-013-0181-5#page-1
C14	Yes	No	http://www.sciencedirect.com/science/article/pii/S0022073614003173
C15	No	No	http://www.sciencedirect.com/science/article/pii/S0002914913024600
C16	Yes	No	http://www.futuremedicine.com/doi/pdf/10.2217/fca.13.91
C17	Yes	No	http://circ.ahajournals.org/content/130/1/87.short
C18	Yes	No	http://informahealthcare.com/doi/abs/10.1586/14779072.2014.909284
C19	Yes	No	http://www.sciencedirect.com/science/article/pii/S0001299814000245
C20	Yes	No	http://journals.lww.com/jcardiovascularmedicine/Citation/2014/04000/Cardiac_r
C21	No	No	http://tsoc.iware.com.tw/upload/journal/1/20131115/4.pdf
C22	Yes	Yes	http://link.springer.com/article/10.1007/s12350-013-9822-z#page-1
C23	Yes	No	http://www.sciencedirect.com/science/article/pii/S0001299814000257
C24	Yes	No	http://www.nature.com/nrcardio/journal/v11/n8/full/nrcardio.2014.67.html
C25	Yes	No	http://link.springer.com/article/10.1007/s12325-014-0141-9#page-1
C26	Yes	No	http://www.nature.com/nrcardio/journal/v11/n2/full/nrcardio.2013.212.html
C27	Yes	No	http://www.nejm.org/doi/full/10.1056/NEJMe1402676
C28	No	No	http://www.sciencedirect.com/science/article/pii/S0002870314004384
C29	Yes	No	http://esciencecentral.org/journals/assessing-the-prevalence-of-mechanical-dyssy
C30	Yes	No	http://eurheartj.oxfordjournals.org/content/35/8/485.short
C31	No	No	http://www.nejm.org/doi/full/10.1056/NEJMc1407182
C32	No	No	http://www.sciencedirect.com/science/article/pii/S1875213614000515
C33	No	No	http://www.sciencedirect.com/science/article/pii/S0167527314001843
C34	No	No	http://informahealthcare.com/doi/abs/10.1586/14779072.2014.921117
C35	No	No	http://link.springer.com/article/10.1007/s12350-014-9905-5#page-1
C36	Yes	Yes	http://circep.ahajournals.org/content/7/3/532.short
C37	Yes	No	http://www.hospitalchronicles.gr/index.php/hchr/article/view/613
	25	2	
% Yes	68%	5%	