Improving haemodynamic optimization of cardiac resynchronization therapy for heart failure*

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Abstract

Objective: Optimization of cardiac resynchronization therapy using non-invasive haemodynamic parameters produces reliable optima when performed at high atrial paced heart rates. Here we investigate whether this is a result of increased heart rate or atrial pacing itself.

Approach: Forty-three patients with cardiac resynchronization therapy underwent haemodynamic optimization of atrioventricular (AV) delay using non-invasive beat-to-beat systolic blood pressure in three states: rest (atrial-sensing, 66 ± 11 bpm), slow atrial pacing (73 ± 12 bpm), and fast atrial pacing (94 ± 10 bpm). A 20-patient subset underwent a fourth optimization, during exercise (80 ± 11 bpm).

Main results: Intraclass correlation coefficient (ICC, quantifying information content mean ± SE) was 0.20 ± 0.02 for resting sensed optimization, 0.45 ± 0.03 for slow atrial pacing (p < 0.0001 versus rest-sensed), and 0.52 ± 0.03 for fast atrial pacing (p = 0.12 versus rest-paced). 78% of the increase in ICC, from sinus rhythm to fast atrial pacing, is achieved by simply atrially pacing just above sinus rate. Atrial pacing increased signal (blood pressure difference between best and worst AV delay) from 6.5 ± 0.6 mmHg at rest to 13.3 ± 1.1 mmHg during slow atrial pacing (p < 0.0001) and 17.2 ± 1.3 mmHg during fast atrial pacing (p = 0.003 versus slow atrial pacing). Atrial pacing reduced noise (average SD of systolic blood pressure measurements) from 4.9 ± 0.4 mmHg at rest to 4.1 ± 0.3 mmHg during slow atrial pacing (p = 0.28). At faster atrial pacing the noise was 4.6 ± 0.3 mmHg (p = 0.69 versus slow-paced, p = 0.90 versus rest-sensed). In the exercise subgroup ICC was 0.14 ± 0.02 (p = 0.97 versus rest-sensed). Significance: Atrial pacing, rather than the increase in heart rate, contributes to ~80% of the observed information content improvement from sinus rhythm to fast atrial pacing. This is predominantly through increase in measured signal.

Introduction

Current guidelines recommend atrioventricular (AV) optimization of cardiac resynchronization therapy (CRT) devices be conducted at resting heart rates, and do not specify whether it is worthwhile to also perform optimization during atrial pacing (Daubert et al 2012, Brignole et al 2013). Optimization using blood pressure (BP) with continuous finger photoplethysmography (Finometer), is a rapid and less labour intensive method than echocardiography based protocols and we have demonstrated it is non-inferior to this method in a

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randomised controlled trial (Whinnett et al 2018). Studies using this technique have shown optimization is more reliable when it is performed with faster atrial pacing (Whinnett et al 2006a). Faster, atrially paced heart rates produce a greater signal (Whinnett et al 2006a) and signal-to-noise ratio (Whinnett et al 2008a) during photoplethysmographic optimization, and an analysis of previously published studies (Pabari et al 2011) demonstrated a positive correlation between ICC and increased heart rate during the optimization process regardless of protocol used.

This study investigates whether any improvement observed in the reliability of optimization with faster, atrially paced heart rates, is due solely to the increase in heart rate, or whether the change in atrial activation from native to paced is responsible. We investigated this by assessing signal to noise characteristics of optimizations performed at resting sinus rate, during a slowly paced atrial rate, and at higher heart rates by faster atrial pacing and, in a subset of patients, during exercise.

Methods

Participants

Forty-three consecutive outpatients with biventricular pacemakers or biventricular defibrillators implanted for clinical indications were enrolled in this study (table 1). The only exclusion criteria were presence of atrial fibrillation, or an inability for the patient to comfortably lie flat for an extended period. Patients gave written informed consent for this study, which complied with the Declaration of Helsinki and was approved by the local ethics committee.

| Characteristic                          | Mean ± SD or number (%) |
|----------------------------------------|-------------------------|
| Age                                    | 67 ± 10                 |
| Male                                   | 26 (60)                 |
| NYHA class:                            |                         |
| I                                      | 1 (2)                   |
| II                                     | 19 (44)                 |
| III                                    | 20 (47)                 |
| IV                                     | 3 (7)                   |
| Aetiology of heart failure:            |                         |
| Ischemic cardiomyopathy                | 17 (40)                 |
| Non-ischaemic cardiomyopathy           | 26 (60)                 |
| Left ventricular ejection fraction     | 28 ± 8                  |
| Drugs:                                 |                         |
| β-blocker                              | 39 (91)                 |
| ACE inhibitor/angiotensin receptor blocker | 40 (93)              |
| Diuretic (loop diuretic/spironolactone) | 32 (74)                |
| Digoxin                                | 4 (9)                   |

Data collection

Non-invasive, beat-to-beat BP was measured using a Finometer (Finapres Medical Systems, Amsterdam, Netherlands). This system utilises an inflating finger cuff and volume-clamp photoplethysmography to produce a continuous arterial pressure waveform. Pressure exerted by the cuff is automatically adjusted, such that a constant blood volume within the finger (as measured by photoplethysmography) is maintained. Thus, pressure exerted by the cuff is a surrogate of intra-arterial pressure (Whinnett et al 2006a, 2006b, 2008a, 2008b, 2011, Kyriacou et al 2012).

An ECG signal was recorded using a Hewlett-Packard 78351A monitor. Analogue signals were taken via a National Instruments DAQ-Card AI-16E-4 (National Instruments, Austin, TX, USA) and Labview (National Instruments, Austin, TX, USA).

Off line analysis was performed using custom software based on the Matlab platform (MathWorks, Natick, MA, USA) (Davies et al 1999).

AV optimization protocol

The optimization protocol involves defining at which AV delay systolic BP (SBP) is greatest. SBP is plotted against the AV delay, and a parabolic curve is fitted. The AV delay identified as the peak of the parabola is selected as the AV optimum. To minimise the effects of any spontaneous fluctuations in BP, absolute SBP values were not measured; instead, change in SBP between a fixed reference AV delay (such as AV 120 ms) and a number of pre-
specified AV delays were tested (Whinnett et al 2006a, 2006b, 2008a, Kyriacou et al 2012). Tested AV delays were 40, 80, 140, 200, 240, 280 and 300 ms, but only included those delays which produced ventricular capture, i.e. excluded the long AV delays which allowed solely intrinsic ventricular activation.

At each tested AV delay, the change in SBP from the reference AV delay was determined by taking the mean SBP of ten beats immediately post-transition, and subtracting the mean SBP of ten beats immediately pre-transition. By taking an average of ten beats, effect of respiratory noise and other periodic fluctuations in BP were reduced (Whinnett et al 2006a, 2006b, 2008a, Kyriacou et al 2012).

Transitions between each tested AV delay and the reference were repeated, with an equal number of forward (reference to tested delay) and backwards (tested delay to reference) transitions, and absolute values of mean change in SBP were calculated. In this way, any upwards or downwards trend in BP during the measurement were negated. At all tested AV delays (at all rates) we performed the same number of transitions (eight transitions) to enable valid comparisons of ICC (Whinnett et al 2006a, 2006b, 2008a, Kyriacou et al 2012).

To calculate optimal AV delay from the data recorded, values for AV delay were plotted against mean SBP change of the eight transitions. A quadratic curve was fitted, the peak of which was taken as representing optimal AV delay.

Atrial pacing versus heart rate

To assess the impact of heart rate versus atrial pacing on the accuracy of AV optimum value obtained, the 43 patients had the optimization procedure repeated at three pacing modes. From these, signal, noise and ICC were calculated:

1. Atrial sensed, resting heart rate (rest-sensed).
2. Atrial paced, at the lowest programmable rate above resting sinus rate that generated consistent atrial capture (slow-paced).
3. Atrial paced ~25 bpm above slow-paced (fast-paced).

In addition, 20 patients had the optimization procedure performed during exercise to give a non-paced elevated heart rate (exercise-sensed). To enable easy measurements using the Finometer, participants were exercised on a supine bicycle (Medical Positioning Inc, Kansas City, MO, USA). From this group, signal, noise and ICC were also calculated.

Signal and noise

For all of the tested AV delays at each heart rate, the mean change in SBP for the eight transitions and the standard error of the mean (SEM) were calculated. In this study, signal was defined as the difference in SBP between the worst and optimal AV delays, and noise by the average of all the standard deviations (SD) of the mean change of systolic blood pressure, at all tested AV delays in each pacing mode.

Intraclass correlation coefficient

ICC provides a measure of information content similar to the signal-to-noise ratio. It has the major advantage of varying between 0 and 1, as opposed to extending to infinity (Pabari et al 2011). This makes it a more tangible concept, with zero indicating that a measurement is just noise, and at the other end of the spectrum, one indicating pure signal and no noise.

ICC is equal to the ratio of signal variance to the total variance of signal and noise (Pabari et al 2011) (Box 1). For practical purposes, in this study we have defined signal variance as the between-individual variance between the means at each individual AV setting. The total variance is the variance of all the data points from all individuals which contribute to these means and is the sum of the between and within individual variance. If all the measurements at any particular AV delay setting within an individual are identical, then these two variances are the same, i.e. ICC = 1. At the other extreme, if all the measurements at each setting are show considerable variance within an individual and this accounts for almost all of the total variance, then the ICC will be almost zero.

Box 1. Calculation of ICC

$$ICC = \frac{R}{R - 1} \frac{V_m}{V_{raw}} - \frac{1}{R - 1}$$

$R =$ number of replicate sets of optimisations in patient
$V_{raw} =$ variance of all raw measurements
$V_m =$ variance of mean measurement at each AV delay
Assessment of curvature
Optimization curves were constructed using least squares fitting to a parabola. The degree of curvature of the optimization response was quantified by the curvature coefficient of the fitted curve, i.e. the ‘a’ from the quadratic formula $ax^2 + bx + c$.

Statistics
Data are presented as mean ± SEM. To quantify the differences between the different pacing configurations a two way ANOVA was performed with patient and pacing configuration as factors. Where significant we used post hoc testing with Tukey’s HSD. A $p$-value < 0.05 was considered statistically significant. Statistical analysis was performed using R (R Foundation for Statistical Computing, Vienna, Austria).

Results
Separating the impact of atrial pacing from the impact of increased heart rate
The change from resting (atrial sensed) to fast atrial pacing provides two contributions: the regularization of heart rate by institution of atrial pacing, and the substantial increase in heart rate.

The atrial pacing contribution, defined as the rise in ICC from resting to slow paced, was large: from $0.20 \pm 0.02$ to $0.45 \pm 0.03$ ($p < 0.0001$). It should be remembered that this contains a small component of heart rate increase, from $66 \pm 11$ bpm (rest-sensed) to $73 \pm 12$ bpm (slow-paced).

The contribution from the substantial increase in heart rate, defined as the rise in ICC from slow atrial pacing ($73 \pm 12$ bpm) to fast atrial pacing ($94 \pm 10$ bpm), was smaller: from $0.45 \pm 0.03$ to $0.52 \pm 0.03$ ($p = 0.12$).

On this basis, the contributions to the increase in optimization efficiency provided by fast atrial pacing (instead of rest) could be summarised as 78% from institution of atrial pacing plus 22% from the substantial increase in heart rate.

Attempting to raise the ICC by increasing heart rate substantially without atrial pacing (i.e. by exercise) was not successful: ICC showed no sign of rising, going from $0.20 \pm 0.02$ to $0.14 \pm 0.02$ ($p = 0.9$, figure 1). The average exercise-sensed heart rate achieved was $80 \pm 11$ bpm.

Does improvement in signal-to-noise ratio arise from increase in signal or decrease in noise?
For optimization, the relevant signal is the size of the difference in SBP between different AV delays. A simple quantification of this is the difference between the highest and lowest.

The atrial pacing component increased measured signal from $6.5 \pm 0.6$ mmHg during rest-sensed to $13.3 \pm 1.1$ mmHg during slow-paced ($p < 0.0001$). At the higher rates the atrial pacing component increased signal from $4.7 \pm 0.6$ mmHg during exercise-sensed to $17.2 \pm 1.3$ mmHg during fast-paced ($p < 0.0001$), as shown in the upper panel of figure 2.

The heart rate increase component improved measured signal from $13.3 \pm 1.1$ mmHg during slow-paced to $17.2 \pm 1.3$ mmHg during fast-paced ($p = 0.003$). Without atrial pacing, there was no evidence of an increase in signal when heart rate was increased: $6.5 \pm 0.6$ mmHg at rest, and $4.7 \pm 0.6$ mmHg on exercise ($p = 0.8$) as shown in lower panel of figure 2.

On this basis, the contributions to the increase in signal provided by fast atrial pacing (instead of rest) could be summarised as 78% from institution of atrial pacing plus 22% from the substantial increase in heart rate.

Meanwhile the relevant noise is the uncertainty in the measurement of the SBP at each AV delay, which can be quantified as the average of the SDs across all AV delays. There was no statistically significant decrease in noise with the initiation of atrial pacing ($p = 0.28$) nor between rest and fast pacing (figure 2 lower panel).

Parabola curvature
Identifying an optimal AV delay with precision (i.e. with a small uncertainty) requires a strong curvature of the haemodynamic response when plotted against AV delay (Francis 2011, Francis 2013).

There was no evidence that atrial pacing affected curvature; curvature was $3.8 \pm 0.6 \times 10^{-4}$ mm/Hg/s² at rest and $4.9 \pm 0.5 \times 10^{-4}$ mm/Hg/s² with slow pacing ($p = 0.38$) as shown in figure 3.

The effect of an increase in heart rate, defined as the increase in curvature from slow atrial pacing to fast atrial pacing, was substantial: from $4.9 \pm 0.5 \times 10^{-4}$ mm/Hg/s² to $7.2 \pm 0.5 \times 10^{-4}$ mm/Hg/s² ($p = 0.006$). Increasing heart rate substantially without atrial pacing (i.e. by exercise) did not increase curvature ($p = 0.40$ versus rest and $p = 0.99$ versus slow atrial pacing, figure 3).

Discussion
This study casts light on why it is easier to establish a precise (i.e. reproducible) AV optimum at fast paced heart rates than in the resting state. It appears that both components, imposition of atrial pacing and the substantial
increase in heart rate, play a role in improving of the optimization process. However, the effect of atrial pacing is greater.

**Elements that could improve signal-to-noise ratio**

The improvement in signal-to-noise ratio is predominantly due to an increase in signal. However, in retrospect we realise that even the increase in signal has two distinct mechanisms. First, and more obvious, this can arise by the shape of the haemodynamic response changing from a shallow parabola to a steep parabola as we have previously reported (Whinnett et al 2006a) to occur with increase in paced heart rate. Expressed briefly, as heart rate is raised it is diastole rather than systole whose duration is shortened. Time for filling is more exquisitely sensitive to reduction of cycle length. This effect is illustrated in figure 4.

There is a second, more subtle mechanism. Our protocol used the same range of programmed A V delays for sensed and paced. Thinking more deeply about the physiological consequence of using the same range for sensed and paced reveals that these would be addressing different ranges of the spectrum of mechanical atrioventricular delay.

The same programmed electrical A V delay creates a shorter left mechanical A V delay during atrial paced than atrial sensed biventricular pacing (figure 5). This ‘sensed-paced difference’ at rest is in the region of 64 ms (Whinnett et al 2008a) and can be attributed to three factors: atrial sensing delay, atrial pacing latency, and differences in intra/interatrial conduction between atrial sensing and pacing (Whinnett et al 2008a).

When the same range of programmed values is examined under atrial pacing as was examined under atrial sensing (figure 6) the spectrum of mechanical delays being examined includes some shorter values that lead to poorer haemodynamics. Thus, when signal is defined as the maximum minus minimum SBP, the signal is larger. The curvature of the response curve, which for a parabola is consistent in all parts of the spectrum, is not detectably affected by this mechanism (figures 3 and 6).

Our study suggests that increasing heart rate through exercise during atrial sensed optimizations does not improve the measured signal nor improve the ICC to a useful extent. Elevating heart rate by exercise achieved a lower increment in heart rate than by fast pacing. Moreover, the range of mechanical A V delays accessed by a given range of programmed A V delays is rightward (i.e. towards higher mechanical A V delays) for atrially sensed rather than atrially paced optimizations. These two effects together may explain why elevating heart rate by exercise did not increase signal to the extent seen with fast atrial pacing.

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**Figure 1.** Effect of the atrial pacing mode and heart rate on the ICC. Atrial pacing significantly improves information content, and is primarily responsible for the large increase in ICC seen between resting sensed and fast paced optimizations. The ICC did not improve during exercise.
To optimize reliably, signal must be maximised and noise minimised. Increasing the number of replicate acquisitions decreases the impact of noise (Pabari et al. 2011). However, without automation this can be time consuming, and expensive. Additionally, until noise becomes smaller than the signal, information content may not begin to improve (Pabari et al. 2011).

Our study suggests that increasing heart rate through exercise during atrial sensed optimizations does not improve the measured signal nor improve the ICC to a useful extent. Instead, atrial pacing is the most effective means of maximising information content.

We have previously reported (Whinnett et al. 2006a) that performing optimizations at faster atrially paced heart rates increases signal. This study indicates that atrial pacing itself is the predominant factor, contributing 78% of the improvement observed. This results from a greater range of tested mechanical AV delays in paced compared with sensed optimizations. Graphically on figure 6 this is represented by reaching further left on the

**Clinical implications**

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haemodynamic response curve. Adapting protocols to maximise signal to noise using an approach such as in this study has the potential to improve the clinical efficacy of optimization.

Study limitations
This study was only designed to investigate the effect of atrial pacing and heart rate on information content of haemodynamic optimization. It was not a study of the clinical benefits of optimization.

Blood pressure was measured non-invasively in the finger rather than invasively in the aorta although previous studies have shown good agreement between changes in non-invasive and invasive BPs in optimization protocols (Kyriacou et al 2012).

We did not study multiple heart rates but instead only a slow heart rate and a fast heart rate for each of atrial sensed and atrial paced. We do not know if the trends observed would continue to even higher or lower heart rates.
We did not study VV delay in this particular study. For VV delay we would not expect there to be a change in the range of VV delays tested by moving from sensed to paced. In this setting only the effect of modifying heart rate could be studied.

Most of our patients were on beta blockers. This potentially prolongs a patient’s PR interval. However, we would not expect this to affect our findings, as the difference in testable ranges in AV delay would remain consistent.
Conclusions

The act of atrial pacing itself, as opposed to an increase in heart rate, is the principle contributor to the large increase in ICC observed with haemodynamic optimisation at higher atrially paced rates. Optimising during atrial pacing enables the testing of shorter mechanical AV delays, which cannot be tested during atrially sensed heart rates; this gives a wider range of blood pressure changes that explains the improved information content.

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Conflicts of interest

Darrel Francis is a consultant to Medtronic and Sorin. Zachary Whinnett acts as a consultant to St Jude Medical and Medtronic.

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References

Brignole M et al 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on Cardiac Pacing and Resynchronization Therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA) Europace 15 1070–118

Daubert J-C et al 2012 EHRA/HRS expert consensus statement on cardiac resynchronization therapy in heart failure: implant and follow-up recommendations and management Heart Rhythm 9 1524–76

Davies I C, Francis D, Jurák P, Kára T, Piepoli M and Coats A J 1999 Reproducibility of methods for assessing baroreflex sensitivity in normal controls and in patients with chronic heart failure Clin. Sci. 97 515–22

Francis D P 2011 Precision of a parabolic optimum calculated from noisy biological data, and implications for quantitative optimization of biventricular pacemakers (cardiac resynchronization therapy) Appl. Math. 02 1497–506

Francis D P 2013 How to reliably deliver narrow individual-patient error bars for optimization of pacemaker AV or VV delay using a ’pick-the-highest’ strategy with haemodynamic measurements Int. J. Cardiol. 163 221–5

Kyriacou A et al 2012 Fully automatable, reproducible, noninvasive simple plethysmographic optimization: proof of concept and potential for implantability Pacing Clin. Electrophysiol. 35 948–60

Pahari P A et al 2011 When is an optimization not an optimization? Evaluation of clinical implications of information content (signal-to-noise ratio) in optimization of cardiac resynchronization therapy, and how to measure and maximize it Heart Fail. Rev. 16 277–90

Whinnett Z I et al 2006a Determination of optimal atrioventricular delay for cardiac resynchronization therapy using acute non-invasive blood pressure Europace 8 358–66

Whinnett Z I et al 2006b Haemodynamic effects of changes in atrioventricular and interventricular delay in cardiac resynchronization therapy show a consistent pattern: analysis of shape, magnitude and relative importance of atrioventricular and interventricular delay Heart 92 1628–34

Whinnett Z I et al 2008a The atrioventricular delay of cardiac resynchronization can be optimized hemodynamically during exercise and predicted from resting measurements Heart Rhythm 5 576–86

Whinnett Z I et al 2008b Efficiency, reproducibility and agreement of five different hemodynamic measures for optimization of cardiac resynchronization therapy Int. J. Cardiol. 129 216–26

Whinnett Z I et al 2011 Maximizing efficiency of alternation algorithms for hemodynamic optimization of the AV delay of cardiac resynchronization therapy Pacing Clin. Electrophysiol. 34 217–25

Whinnett Z I et al 2018 Multicenter randomized controlled crossover trial comparing hemodynamic optimization against echocardiographic optimization of AV and VV delay of cardiac resynchronization therapy: the BRAVO trial JACC Cardiovasc. Imaging