

Improving haemodynamic optimization of cardiac resynchronization therapy for heart failure

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Manuscript word count: 2,633

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

43 patients with cardiac resynchronization therapy underwent haemodynamic optimization of 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 \pm 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 slow-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).

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5 **Significance**
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7 Atrial pacing, rather than the increase in heart rate, contributes to ~80% of the observed information content
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9 improvement from sinus rhythm to fast atrial pacing. This is predominantly through increase in measured signal.
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13 **Key Words**
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15 Heart failure; cardiac resynchronization therapy; haemodynamic optimization; atrioventricular delay
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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^{1,2}. 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 randomised controlled trial³. Studies using this technique have shown optimization is more reliable when it is performed with faster atrial pacing⁴. Faster, atrially paced heart rates produce a greater signal⁴ and signal-to-noise ratio⁵ during photoplethysmographic optimization, and an analysis of previously published studies⁶ demonstrated a positive correlation between intraclass correlation coefficient (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

43 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.

Table 1. Patient characteristics

Characteristic	Mean \pm SD or Number (%)
Age	67 \pm 10
Male	26 (60)
NYHA Class:	
<i>I</i>	1 (2)
<i>II</i>	19 (44)
<i>III</i>	20 (47)
<i>IV</i>	3 (7)
Aetiology of Heart Failure:	
<i>Ischemic cardiomyopathy</i>	17 (40)
<i>Non-ischaemic Cardiomyopathy</i>	26 (60)
Left Ventricular Ejection Fraction	28 \pm 8
Drugs:	
<i>β-blocker</i>	39 (91)
<i>ACE inhibitor/Angiotensin receptor blocker</i>	40 (93)
<i>Diuretic (Loop diuretic/spironolactone)</i>	32 (74)
<i>Digoxin</i>	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^{4,5,7,8,9,10}.

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)¹¹.

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 120ms) and a number of pre-specified AV delays were tested^{4,5,7,8}. Tested AV delays were 40, 80, 140, 160, 200, 240, 280 and 300ms, 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 10 beats immediately post-transition, and subtracting the mean SBP of 10 beats immediately pre-transition. By taking an average of 10 beats, effect of respiratory noise and other periodic fluctuations in BP were reduced^{4,5,7,8}.

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

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3 change in SBP were calculated. In this way, any upwards or downwards trend in BP during the measurement
4 were negated. At all tested AV delays (at all rates) we performed the same number of transitions (8 transitions)
5 to enable valid comparisons of Intraclass Correlation Coefficient (ICC)^{4,5,7,8}.
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10 To calculate optimal AV delay from the data recorded, values for AV delay were plotted against mean SBP
11 change of the 8 transitions. A quadratic curve was fitted, the peak of which was taken as representing optimal
12 AV delay.
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18 **Atrial Pacing versus heart rate**

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20 To assess the impact of heart rate versus atrial pacing on the accuracy of AV optimum value obtained, the 43
21 patients had the optimization procedure repeated at three pacing modes. From these, signal, noise and intraclass
22 correlation coefficient (ICC) were calculated:
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- 26 1. Atrial sensed, resting heart rate (rest-sensed)
 - 27 2. Atrial paced, at the lowest programmable rate above resting sinus rate that generated consistent atrial
28 capture (slow-paced)
 - 29 3. Atrial paced ~25bpm above slow-paced (fast-paced)
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36 In addition, 20 patients had the optimization procedure performed during exercise to give a non-paced elevated
37 heart rate (exercise-sensed). To enable easy measurements using the Finometer, participants were exercised on a
38 supine bicycle (Medical Positioning Inc, Kansas City, MO, USA). From this group, signal, noise and intraclass
39 correlation coefficient (ICC) were also calculated.
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45 **Signal and noise**

46 For all of the tested AV delays at each heart rate, the mean change in SBP for the 8 transitions and the standard
47 error of the mean (SEM) were calculated. In this study, signal was defined as the difference in SBP between the
48 worst and optimal AV delays, and noise by the average of all the standard deviations (SD) of the mean change of
49 systolic blood pressure, at all tested AV delays in each pacing mode.
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Intraclass correlation coefficient

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 infinity⁶. This makes it a more tangible concept, with zero indicating that a measurement is just noise, and at the other end of the spectrum, 1 indicating pure signal and no noise.

ICC is equal to the ratio of signal variance to the total variance of signal and noise⁶ (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.

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

Box 1. Calculation of ICC

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

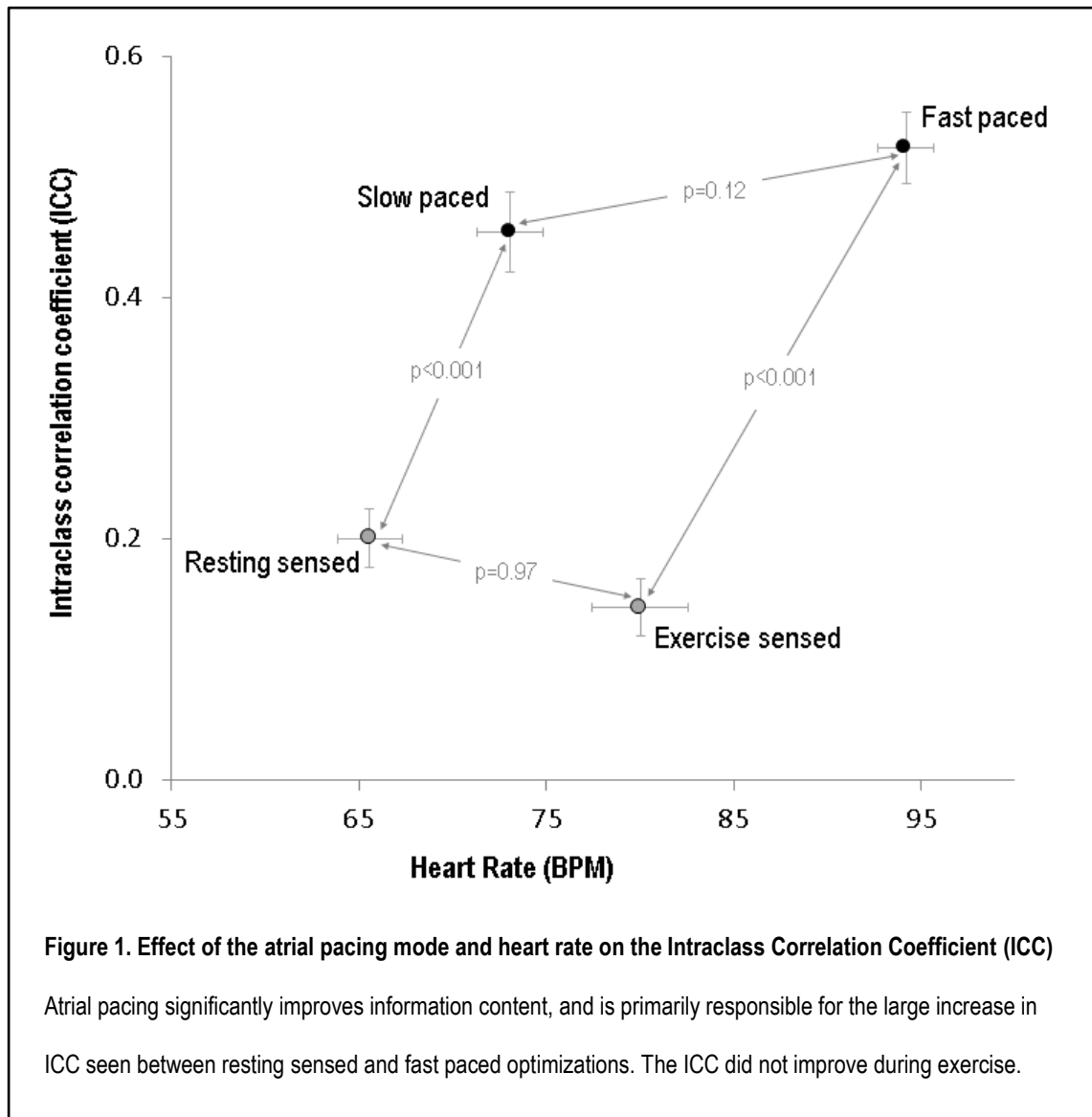
The change from resting (atrial sensed) to fast atrial pacing provides two contributions: the regularization of heart rate by institution of atrial pacing, and the substantial increase in heart rate.

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

The contribution from the substantial increase in heart rate, defined as the rise in ICC from slow atrial pacing (73 ± 12 bpm) to fast atrial pacing (94 ± 10 bpm), was smaller: from 0.45 ± 0.03 to 0.52 ± 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 ± 0.02 to 0.14 ± 0.02 ($p = 0.9$, Figure 1). The average exercise-sensed heart rate achieved was 80 ± 11 bpm.



Does improvement in signal-to-noise ratio arise from increase in signal or decrease in noise?

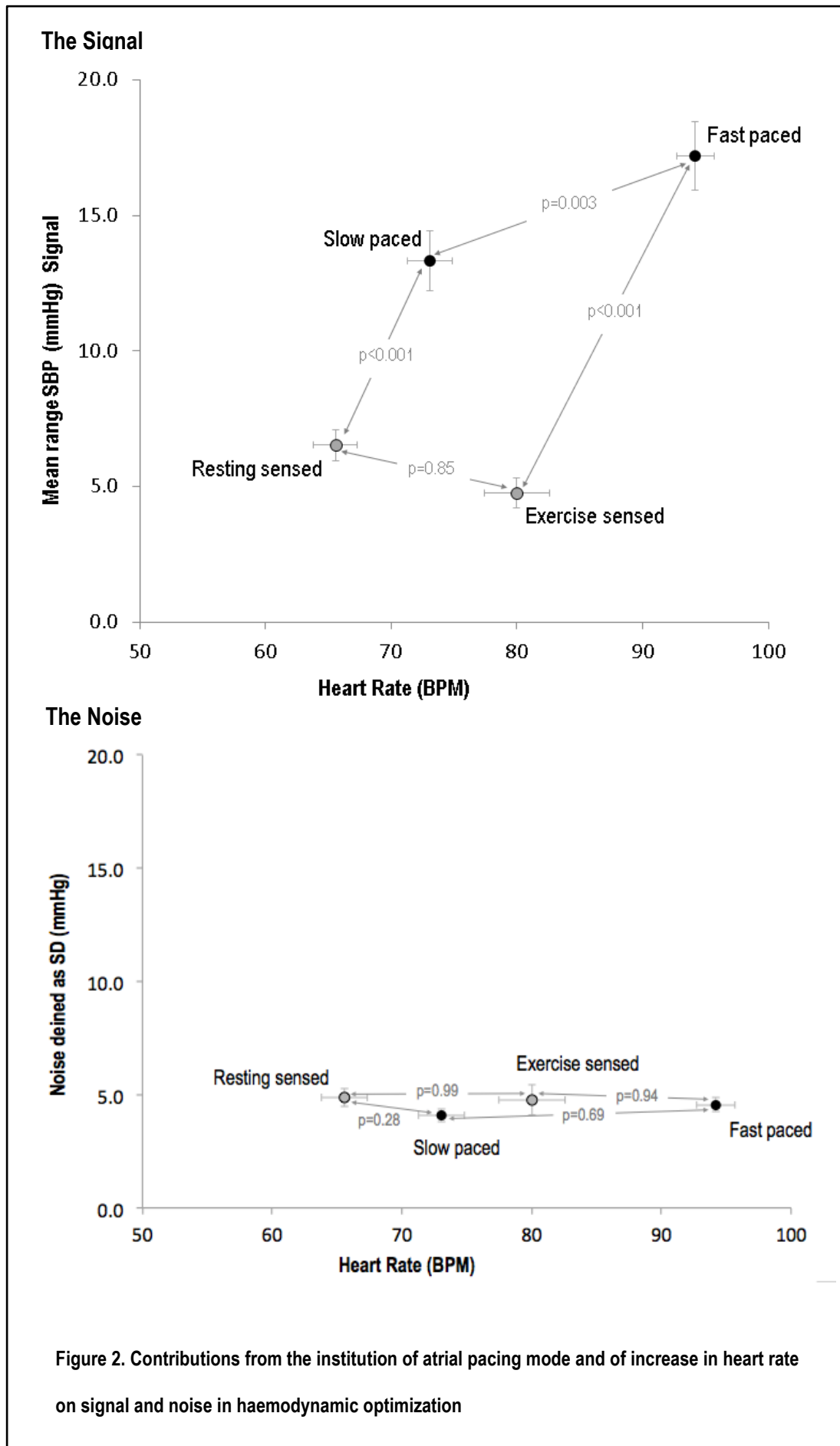
For optimization, the relevant signal is the size of the difference in SBP between different AV delays. A simple quantification of this is the difference between the highest and lowest.

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

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3 The heart rate increase component improved measured signal from 13.3 ± 1.1 mmHg during slow-paced to
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5 17.2 ± 1.3 mmHg during fast-paced ($p=0.003$). Without atrial pacing, there was no evidence of an increase in
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7 signal when heart rate was increased: 6.5 ± 0.6 mmHg at rest, and 4.7 ± 0.6 mmHg on exercise ($p=0.8$) as shown in
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9 lower panel of Figure 2.

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

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18 Meanwhile the relevant noise is the uncertainty in the measurement of the SBP at each AV delay, which can be
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20 quantified as the average of the SDs across all AV delays. There was no statistically significant decrease in
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22 noise with the initiation of atrial pacing ($p=0.28$) nor between rest and fast pacing (Figure 2 lower panel).
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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^{12,13}.

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 ($p=0.40$ vs rest and $p=0.99$ vs slow atrial pacing, Figure 3).

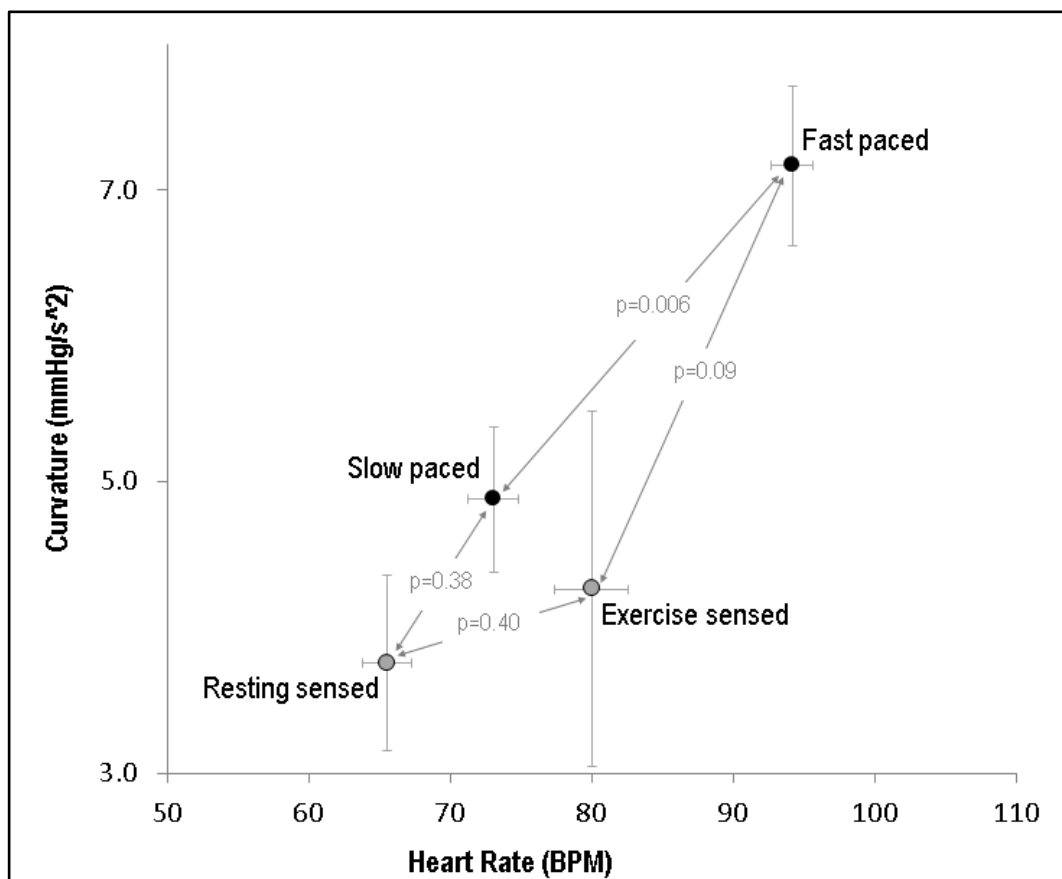


Figure 3: Contributions of atrial pacing mode and of increase in heart rate to the increase in curvature of the haemodynamic optimization parabola

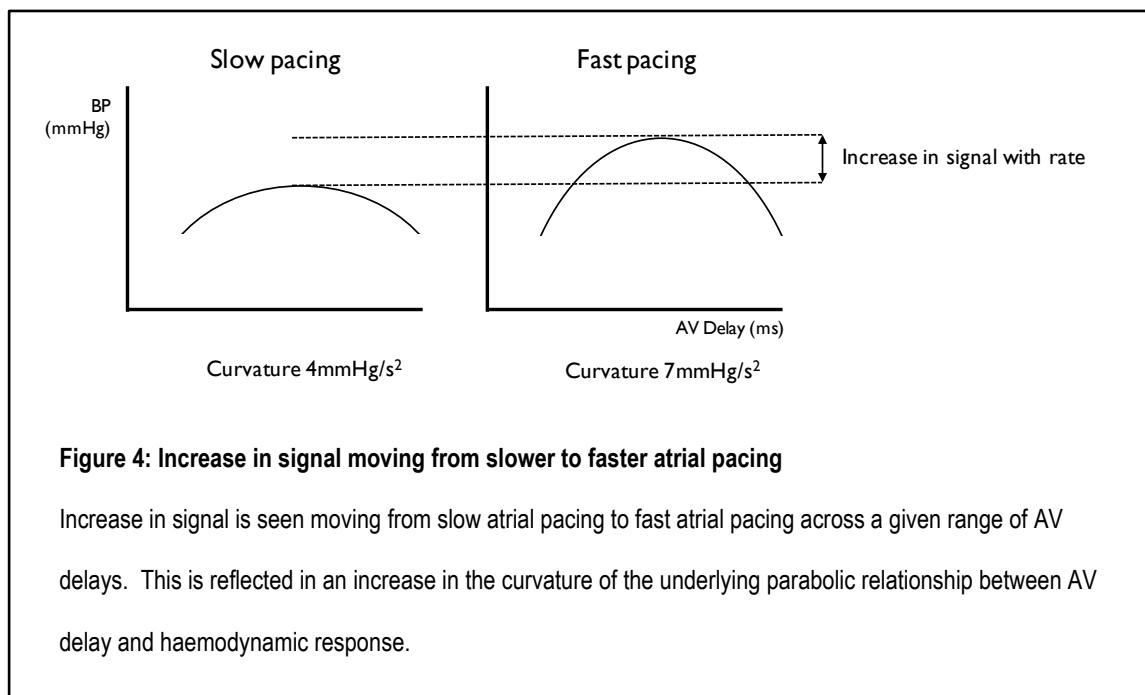
The main contributor to the increase in curvature from resting to fast paced is the substantial increase in heart rate.

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

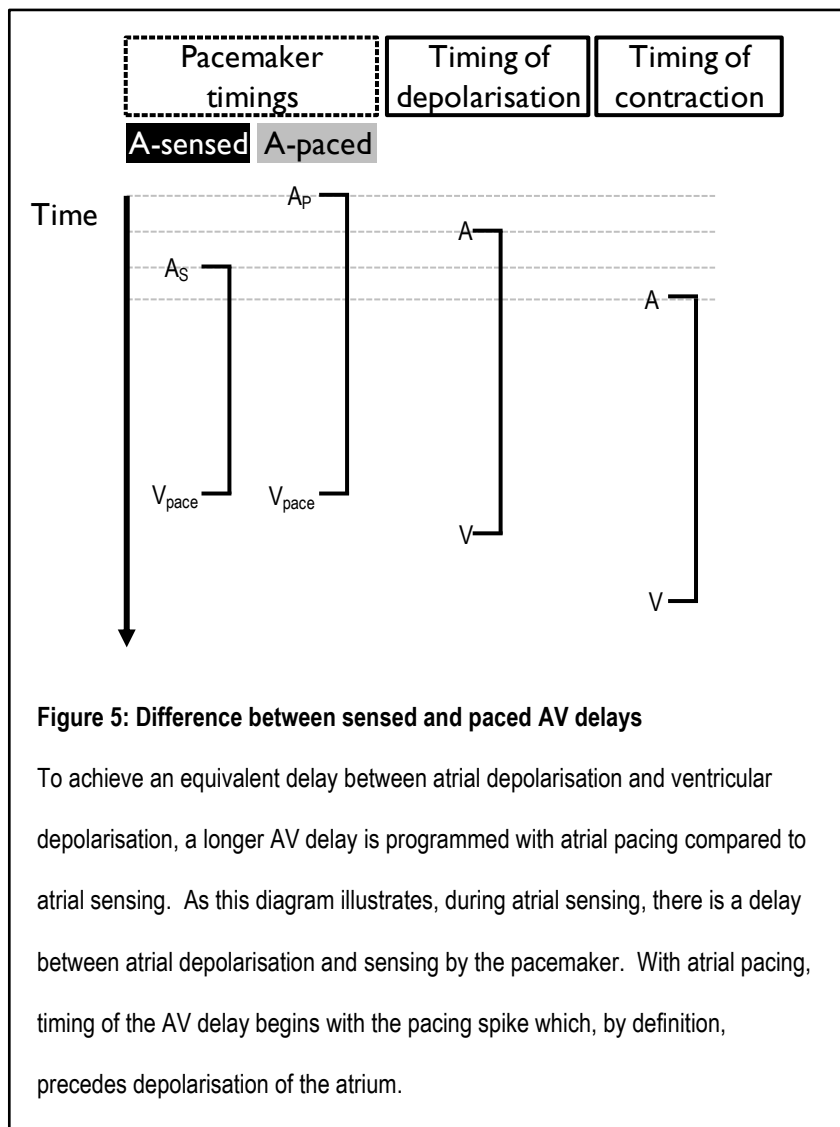
The improvement in signal-to-noise ratio is predominantly due to an increase in signal. However, in retrospect we realise that even the increase in signal has two distinct mechanisms. First, and more obvious, this can arise by the shape of the haemodynamic response changing from a shallow parabola to a steep parabola as we have previously reported⁴ 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 AV delays for sensed and paced. Thinking more deeply about the physiological consequence of using the same range for

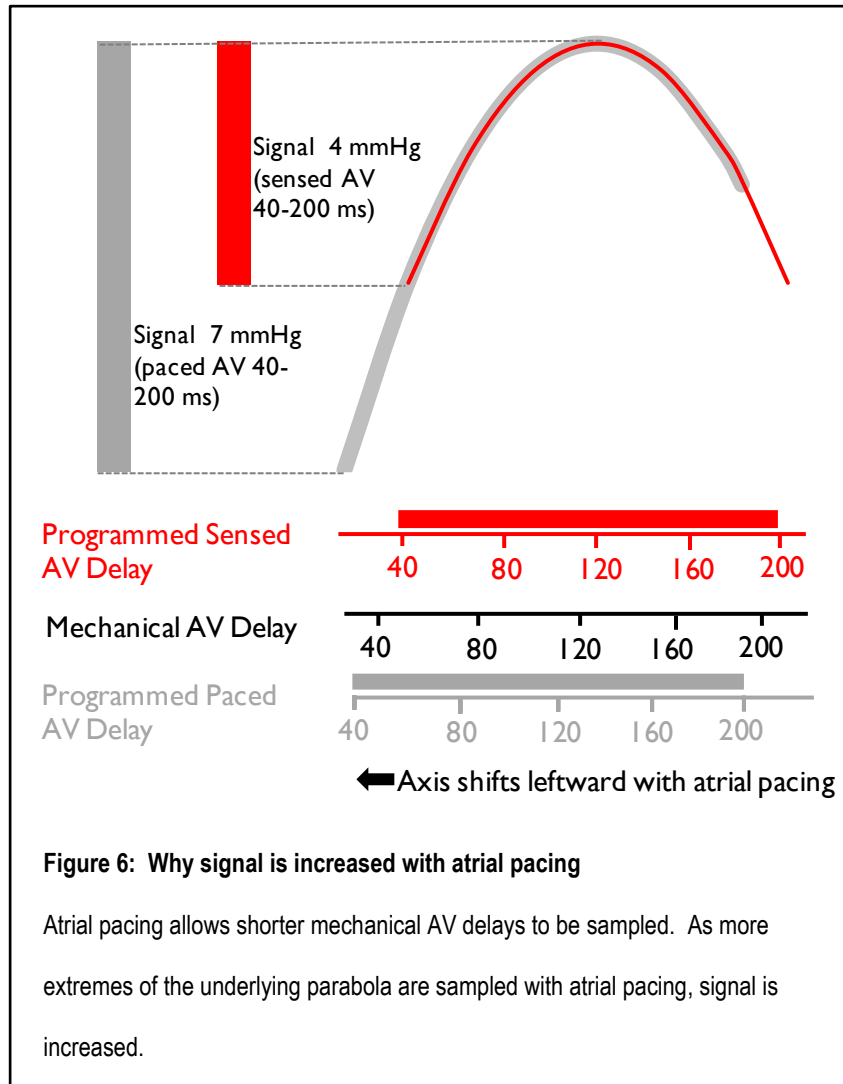
sensed and paced reveals that these would be addressing different ranges of the spectrum of mechanical atrioventricular delay.

The same *programmed* electrical AV delay, creates a shorter left *mechanical* AV delay during atrial paced than atrial sensed biventricular pacing (Figure 5). This “sensed-paced difference” at rest is in the region of 64ms⁵ and can be attributed to three factors: atrial sensing delay, atrial pacing latency, and differences in intra/interatrial conduction between atrial sensing and pacing⁵.



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 AV delays accessed by a given range of programmed AV delays is rightward (i.e. towards higher mechanical AV 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.

Clinical implications

To optimize reliably, signal must be maximised and noise minimised. Increasing the number of replicate acquisitions decreases the impact of noise⁶. However, without automation this can be time consuming, and expensive. Additionally, until noise becomes smaller than the signal, information content may not begin to improve⁶.

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 reported⁴ 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 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 protocols⁸.

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.

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3 We did not study VV delay in this particular study. For VV delay we would not expect there to be a change in
4 the range of VV delays tested by moving from sensed to paced. In this setting only the effect of modifying heart
5 rate could be studied.
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10 Most of our patients were on beta blockers. This potentially prolongs a patient's PR interval. However, we
11 would not expect this to affect our findings, as the difference in testable ranges in AV delay would remain
12 consistent.
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18 **Conclusions**

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

This work was supported by the British Heart Foundation to SMAS, PP, AK, ZIW, and DPF [grant numbers FS/11/92/29122, PG-08-114-25766, SP/10/002/28189, FS/08/027/24763, FS/13/44/30291, FS/10/038].

Acknowledgements

The authors are grateful for infrastructural support from the National Institute for Health Research (NIHR) Biomedical Research Centre based at Imperial College Healthcare NHS Trust and Imperial College London.

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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