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A systematic approach to designing reliable VV optimization methodology: Assessment of internal validity of echocardiographic, electrocardiographic and haemodynamic optimization of cardiac resynchronization therapy

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ABSTRACT

Background: In atrial fibrillation (AF), VV optimization of biventricular pacemakers can be examined in isolation. We used this approach to evaluate internal validity of three VV optimization methods by three criteria.
Methods and results: Twenty patients (16 men, age 75 ± 7) in AF were optimized, at two paced heart rates, by LVOT VTI (flow), non-invasive arterial pressure, and ECG (minimizing QRS duration). Each optimization method was evaluated for: *singularity* (unique peak of function), *reproducibility* of optimum, and biological *plausibility* of the distribution of optima.
The reproducibility (standard deviation of the difference, SDD) of the optimal VV delay was 10 ms for pressure, versus 8 ms ($p = NS$) for QRS and 34 ms ($p < 0.01$) for flow.
Singularity of optimum was 85% for pressure, 63% for ECG and 45% for flow ($Chi^2 = 10.9$, $p < 0.005$).
The distribution of pressure optima was biologically plausible, with 80% LV pre-excited ($p = 0.007$). The distributions of ECG (55% LV pre-excitation) and flow (45% LV pre-excitation) optima were no different to random ($p = NS$).
The pressure-derived optimal VV delay is unaffected by the paced rate: SDD between slow and fast heart rate is 9 ms, no different from the reproducibility SDD at both heart rates.
Conclusions: Using non-invasive arterial pressure, VV delay optimization by parabolic fitting is achievable with good precision, satisfying all 3 criteria of internal validity. VV optimum is unaffected by heart rate. Neither QRS minimization nor LVOT VTI satisfy all validity criteria, and therefore seem weaker candidate modalities for VV optimization. AF, unlinking interventricular from atrioventricular delay, uniquely exposes resynchronization concepts to experimental scrutiny.

1. Introduction

Of all the aspects of optimization, VV optimization of biventricular pacing is the most challenging. The term "Cardiac Resynchronization Therapy" itself implies that dyssynchrony between regional ventricular contraction is the disease being treated: if this is true then it must matter what interventricular delay is programmed. Although the PROSPECT trial [1] showed no worthwhile prediction of echocardiographic response from echocardiographic markers of dyssynchrony, clinical progress over months in patients with heart failure is dependent on a very wide spectrum of intercurrent environmental, neurohormonal, compliance, dietary, infectious, arrhythmic, ischaemic, and psychological phenomena, and the measurement techniques for dyssynchrony have very large beat-to-beat variability [2,3] so their failure to correlate with anything is unsurprising [4] and therefore uninfluential on the specific question of whether ventricular timings make any detectable difference in an environment where all else is unchanged.

Even this tightly-described question is difficult to answer. First, the effect of changing the VV delay is less than that of changing the AV delay [5], making it even more difficult to separate the genuine effect (signal) of changing a setting, from random variability (noise) [6]. Because the effect of VV optimization may be 5–10 times smaller than that of CRT implantation, an endpoint study would have to be 25–100 times larger than, for example, CARE-HF, to give reliable results. Second, changing the VV delay in patients with sinus rhythm

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inevitably affects the AV delay on one side of the heart or the other, so it is impossible to know for certain if any effects seen come from the AV or VV changes, or both [7].

For these reasons, whilst the benefits of AV optimization are well established [8–10], the benefits of VV optimization are less well understood. Although a few small studies have suggested that optimization of the VV delay may provide benefits beyond AV optimization alone [8,11,12], clinical trials have so far failed to show significant clinical improvements at 6 months [13–15].

In atrial fibrillation however, there is no AV delay to confound VV optimization (Fig. 1). Therefore any impact of a VV delay change is a direct consequence of that change in the VV delay alone. In this study, we recruited patients in AF as a model for 'pure' VV optimization.

As it is not yet realistic to look for differences in clinical outcomes between different markers of optimization, a practical way to compare these is to evaluate the relative performance of each method, head to head, in an identical patient group. Any marker of optimality used to select a pacemaker setting must fulfil three essential features that can be efficiently assessed:

1) *Singularity*; there should be only one region of optimality, with progressively poorer function as settings are changed away from this region. If the optimal region is at one extreme of settings, then there could be one rather than two regions of optimality, but it is not possible for there to be two regions of optimality separated by a region of non-optimality.
2) *Reproducibility*; if the optimization process is repeated immediately with a new operator blinded to the previously found optimal setting, the newly-found optimum should be very similar.
3) *Plausibility*; the distribution of optimum settings should not contradict established physiological principles. For example, frequently finding apparent VV optima with large RV pre-excitation would contradict the principle in resynchronization that the LV wall should usually be paced simultaneously with, or earlier than, the RV.

In this study, we tested three different optimization markers that might be used [16–18] to identify a VV delay optimum in the AF cohort, in which there was no possibility of VV delay alteration causing confounding changes in the AV delay. The markers tested were ECG (QRS duration minimization), LVOT VTI maximization (flow) and non-invasive arterial BP (pressure).

2. Methods

2.1. Patients

Twenty patients (16 men, mean age 75 ± 7 years) in atrial fibrillation, with a CRT device were enrolled in the study. Average NYHA class was 2.4 ± 0.5. The underlying cause of heart failure was ischemic heart disease in 10, dilated cardiomyopathy in 8 and valvular disease in 2 patients.

The study was approved by the Imperial College Healthcare NHS Trust ethics committee, and all patients provided written informed consent.

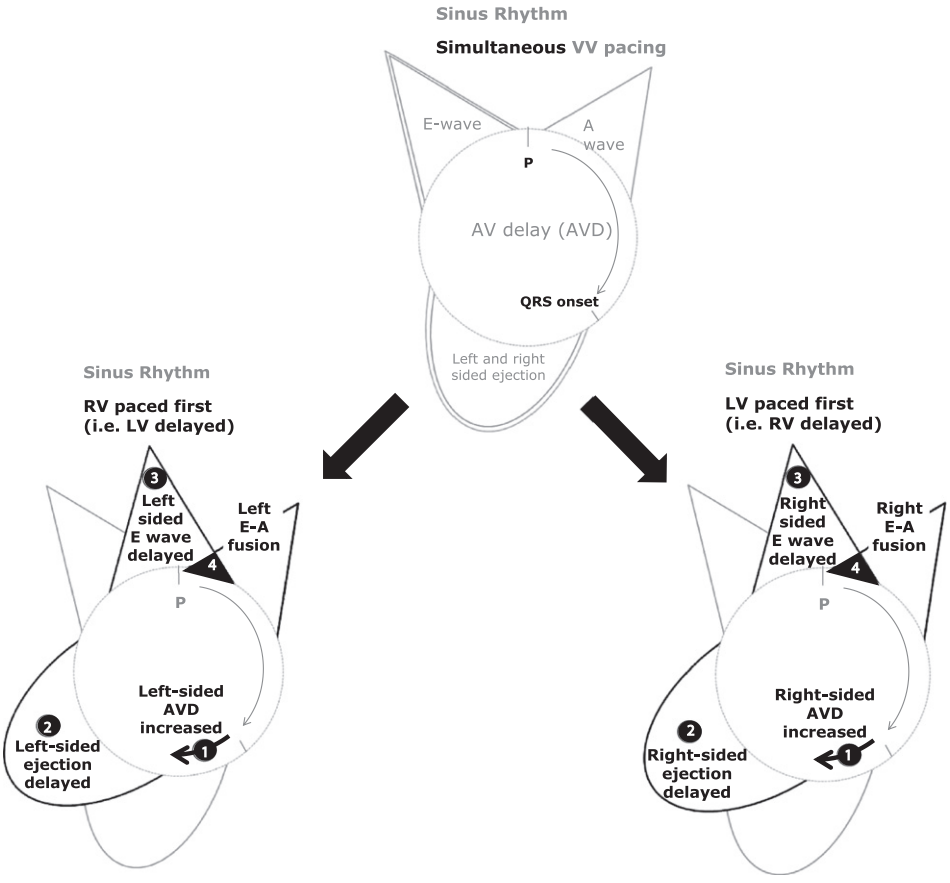

Fig. 1. Each circle shows 1 cardiac cycle in sinus rhythm, with electrical activity shown on the inside and mechanical activity on the outside. The E-wave is passive ventricular filling and the A-wave is active ventricular filling. For example, in a Medtronic pacemaker, selecting RV pre-excitation instead of simultaneous, while keeping programmed AV delay constant, increases the actual effective AV delay to left-sided pacing, because the programmed AV delay is to the "first lead to be activated" in this manufacturer's convention. The E-wave, which can only occur after the ventricle finishes ejecting, therefore occurs later (in relation to the A-wave) on the left side than it did before the VV delay change. Conversely, selecting LV pre-excitation has the mirror image effect on the right side of the heart. Other manufactures have different conventions for labelling the delays, but the constraint remains: the VV delay cannot be changed without changing the mechanical AV delay on one side of the heart or the other. All apparent VV optimizations in sinus rhythm therefore include an occult element of AV optimization.

2.2. Study design

Measurements, using transthoracic echocardiography, finger photoplethysmography (Finometer) and electrocardiography, were made at six VV delays (−40 ms, −20 ms, 0 ms, 20 ms, 40 ms and 60 ms, where a negative VV delay indicates right ventricular pre-excitation). All patients were optimized at 2 heart rates; at a slow paced rate just above the rate of intrinsic conduction (always ensuring 100% biventricular pacing); and at a faster paced rate (mean of 27 ± 7 bpm above slow). Optimization was repeated within one hour using all three optimization modalities, at both heart rates.

Because beat-to-beat biological noise exceeds between-setting variability, often by a large margin, it is not possible to reliably define the optimum as the setting which generates the highest observed pressure or flow (or smallest QRS duration) [3,18,19]. Instead, for each variable a curve-fitting approach was used which minimises the impact of noise and makes maximal use of scarce signal [6].

2.3. Finger photoplethysmography

Beat-to-beat blood pressure was recorded using a Finometer (Finapres Medical Systems, Amsterdam, Netherlands). Optimization of the VV delay was performed using a protocol described in previous work [5,6,20–23] and algorithmically similar that used by others [24] Transitions to the tested VV delay from a fixed reference VV delay (of 0 ms) were performed. A minimum of eight transition replicates were recorded for each tested VV delay. Within each replicate, the 10 beats after the transition were compared with the 10 beats before the transition, to calculate the relative systolic blood pressure. Analysis was performed using software based on the Matlab platform (MathWorks, Natick, MA, USA) but could equally have been carried out with a standard spreadsheet. The relationship was fitted to a parabola by standard least-squares regression, and the optimum VV delay defined by interpolation as the position of the peak of the parabola [6].

2.4. Echocardiography

Images were obtained using a ProSound SSD-5500SV system (Aloka, Tokyo, Japan), with the operator blinded to the VV delays which were randomly programmed by a second operator. Six consecutive beats, of left ventricular outflow tract (LVOT) and mitral valve (MV) flow were acquired with the patient positioned in the dorsal decubitus or left lateral decubitus position, at passive end expiration. The average of the 6 beats was taken as the value for that setting. Medcon software (McKesson, San Francisco, USA) was used for offline analysis. The myocardial performance index (MPI) [25] was calculated by measuring the time from cessation to the start of mitral flow (A) and left ventricular ejection time (ET). Therefore, IVCT + IVRT = A − ET and as a result MPI = (A − ET)/ET.

The VTI optimum was defined by parabolic fitting of the average values for each setting, as the interpolated position of the greatest VTI.

2.5. Electrocardiography

12 lead ECG traces were obtained using a MAC 1200 ST system (GE Healthcare, Chalfont St Giles, UK) at each VV delay and at both heart rates for all patients. In this system, the QRS width is calculated using synchronously sampled and time aligned data across 12 leads, measuring the time from first deflection of the median QRS complex in any lead to the latest deflection in any lead. The average QRS duration from 2 recordings was used for each setting. Recordings which contained ventricular ectopics were excluded and the 12 lead ECG repeated. The optimum was defined by the same principle as above, as the interpolated position of the narrowest QRS.

2.6. Statistical analysis

Reproducibility and agreement of the parabola-determined [5] optima by different optimization methods were assessed by using Bland–Altman plots and the standard deviation of the difference (SDD) between the optimal VV delays. Paired comparisons of normally-distributed continuous variables were made using Student's paired *t* test. Paired comparisons of non-normally-distributed continuous variables were made using Wilcoxon's matched-pairs signed rank test. A p value of <0.05 was taken as statistically significant. Statview 5.0 (SAS Institute Inc., Cary, NC) was used for statistical analysis.

All studied patients are presented. All data are presented. We believe these findings are representative of patients with CRT and AF and know of no undisclosed biases in recruitment, analysis or presentation. DPF is guarantor of scientific integrity [34].

3. Results

20 patients were included in this study. Their characteristics are shown in Table 1.

Table 1
Baseline patient characteristics.

Demographics	Mean and SD or n (%)
Age	75 SD 7
Age range	58–91
Male	16 (80%)
Aetiology	
Ischaemic	10 (50%)
Dilated	8 (40%)
Valvular	2 (10%)
NYHA class	
II	13 (65%)
III	7 (35%)
LVEF (%)	31 SD 13
Medications	
ACEi/ARB	19 (95%)
β-blocker	17 (85%)
Diuretic	17 (85%)
Spironolactone	8 (40%)
Digoxin	12 (60%)

3.1. Criterion 1: Singularity—one optimum region

All 20 patients' optimization curves for LVOT VTI maximization, pressure maximization and QRS minimization are shown in Figs. 2, 3 and 4, respectively.

Only instances in excess of 50% were evidence of the physiological validity of a measure, as shown in Table 2. The percentage of singularity was 85% for pressure, 63% for QRS and 45% for flow. The extent of singularity was significantly different between modalities ($Chi^2 = 10.9$, $p<0.005$). The percentage of singularity for all parameters tested is shown in Fig. 5.

3.2. Criterion 2: Reproducibility—the same optimum when retested

Reproducibility of optimization was quantified by the standard deviation of the difference (SDD). This is shown for all measures at the slow and fast heart rates in Tables 3 and 4, respectively.

Optimization by LVOT VTI showed a wide scatter between successive optima (SDD 35.4 ms). Other echo markers also performed poorly if considered as potential methods of optimization. The most reproducible methods of optimization were SBP maximization (SDD 9.4 ms) and QRS minimization (SDD 6 ms). Bland–Altman plots for the three key modalities being studied (flow, pressure and QRS) are shown in Fig. 6.

3.3. Criterion 3: Plausibility of the distribution of optima

The distribution of optimal VV delays at the fast heart rate, of all 3 optimization methods is shown in Fig. 7. By pressure, the optimum was often near a 0 ms VV delay: 75% were within 20 ms of zero. A significant majority (80%, $p = 0.007$) of pressure optima had a degree of LV pre-excitation.

In contrast, the flow and QRS optima tended to be further away from zero: only 60% and 50%, respectively were within 20 ms of zero. Moreover, the proportion of optima by these modalities that had a degree of LV pre-excitation was not significantly different from chance (45% for flow and 55% for QRS, p = NS in each case).

3.4. Agreement of the optimal VV delay between LVOT VTI, QRS width and beat-to-beat systolic blood pressure

Incidentally available was agreement between modalities, also displayed in Tables 3 and 4. Agreement between methods was poor, typically with a SDD of the order of 40 ms, meaning that if a method gave an optimum of X, the other method would be expected 95% of the time to give an optimum between X-80 ms and X + 80 ms, a very wide range.

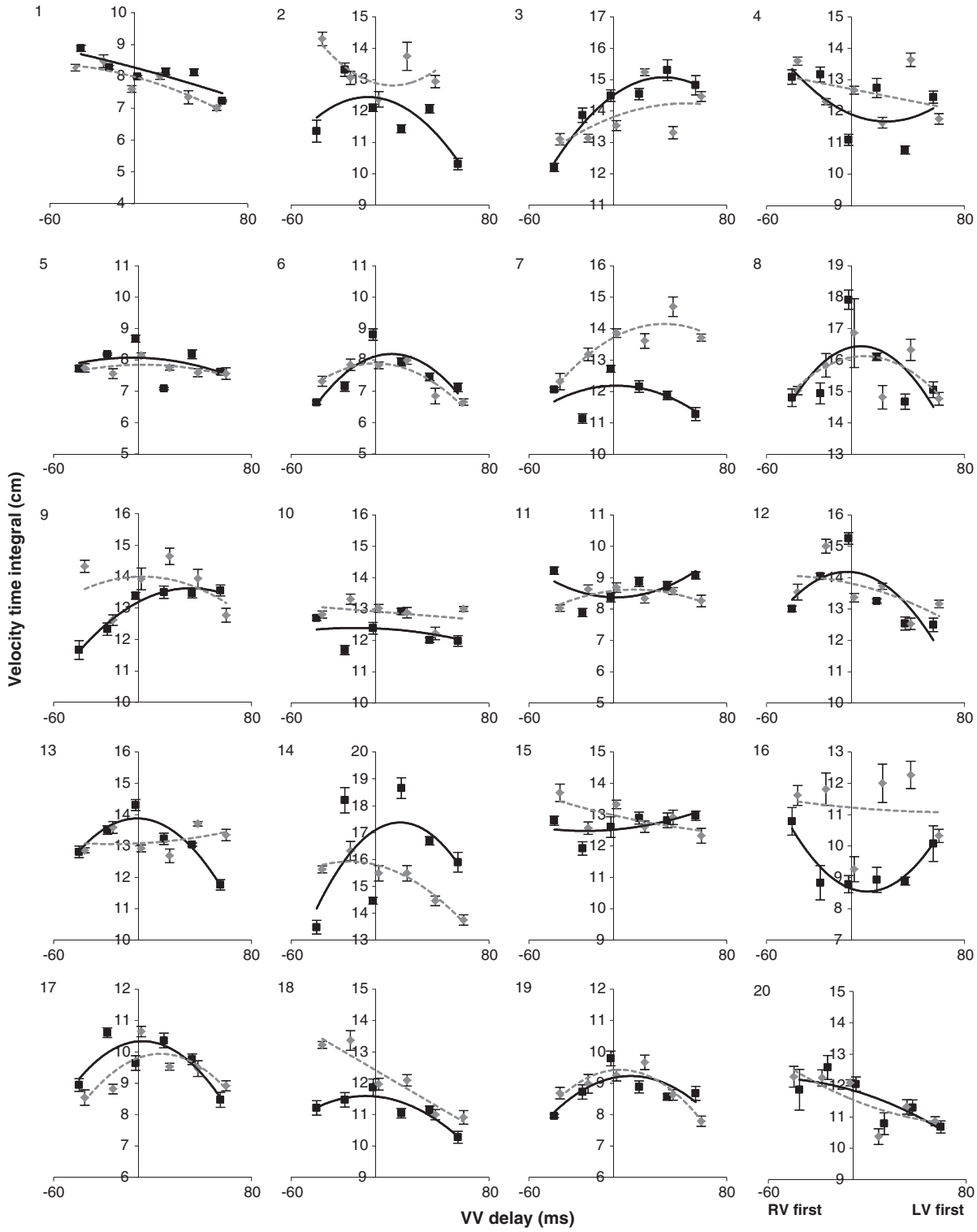

Fig. 2. First (black) and second (grey) sessions of optimization on the same day, using LVOT VTI at each VV delay (RV 40 to LV 60), for all 20 patients. A parabola was fitted in all optimization sessions and the peak of the parabola was considered to represent the optimal VV delay (optimum = largest VTI).

We should be mindful that no irreproducible method can ever agree with any other method [4]. Thus, it could be argued that the only scientifically valuable numbers on the table are the principal diagonal (reproducibility of each modality) and the twin values of "43.9" in the bottom right corner, which shows the between-modality test for the only two modalities (QRS minimization and SBP maximization) that show good reproducibility.

4. Discussion

This study evaluated the performance of three potential approaches for VV optimization, using the three key criteria for internal validity of an optimization. Of the approaches tested, optimization by pressure appears to offer all 3 criteria: *singularity*, *reproducibility* and biological *plausibility*. QRS minimization offers singularity and

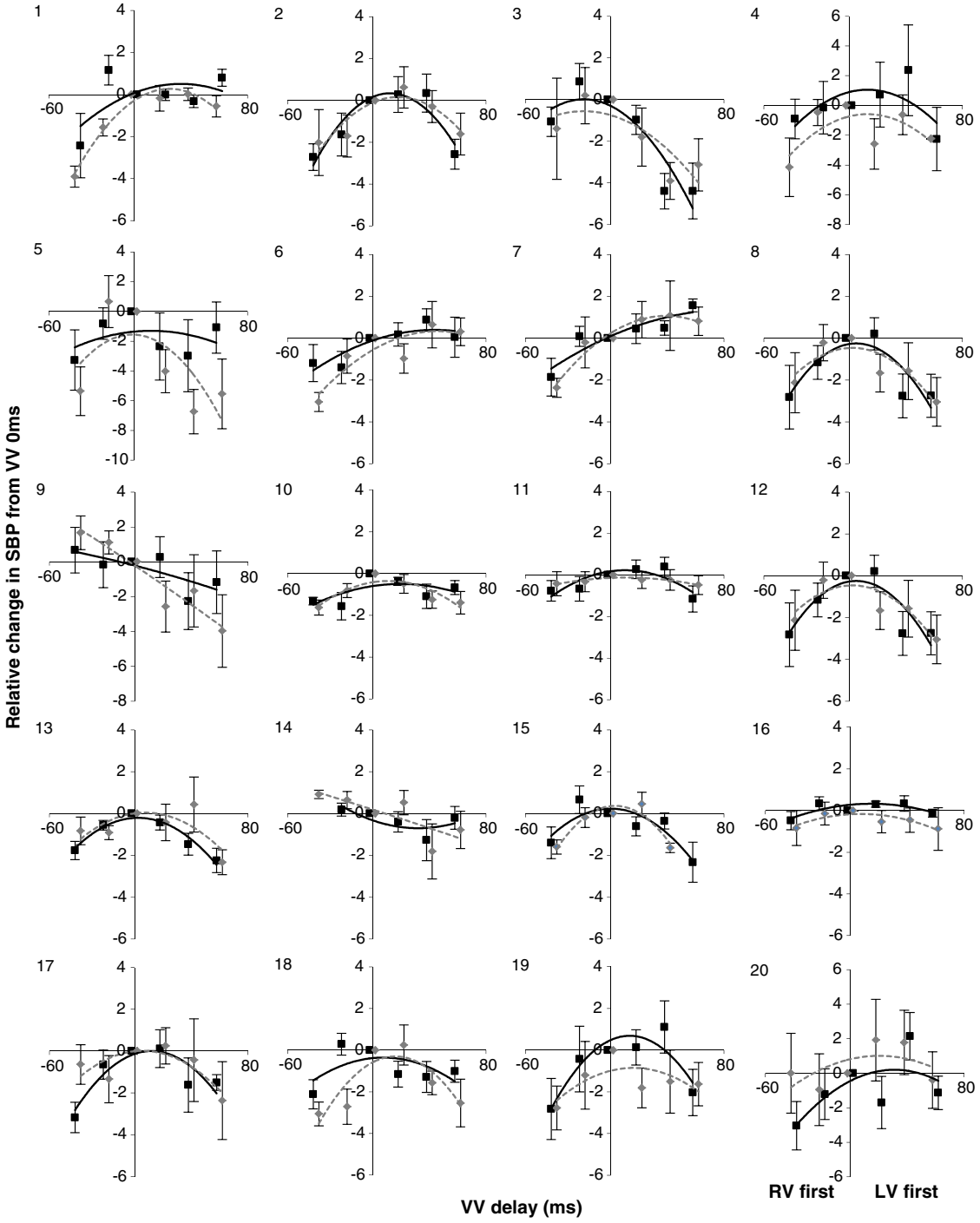

Fig. 3. First (black) and second (grey) sessions of optimization on the same day, using non-invasive SBP at each VV delay (RV 40 to LV 60) for all 20 patients. A parabola was fitted in all optimization sessions and the peak of the parabola was considered to represent the optimal VV delay (optimum = highest relative SBP).

reproducibility, but the distribution of optimum settings obtained appears biologically implausible. Optimization by flow performed disappointingly on all 3 criteria of internal validity.

4.1. Three criteria for internal validity

Reproducibility is a key criterion for any method of optimization. If an individual patient is given multiple discrepant proposed 'optima' in rapid succession by a single method, most of these apparent optima must be incorrect. While reproducibility alone is not sufficient criterion to judge an optimization approach to be internally valid, it is a necessary one.

Singularity indicates that there is only a single region which appears to be optimal, rather than two optimal regions separated by non-optimality. This is relevant because the principle of CRT is to improve cardiac function by bringing the walls of the heart into more closely coordinated times of contraction (although not necessarily to VV 0 ms). Moving away from this optimal timing of contraction in either direction should worsen cardiac function. In some cases (when the true optimal region is at the extremes of the range of tested settings) there might reasonably be only one non-optimal region, but singularity can still be tested by the shape of the curve. Because the shape of the curve should be almost flat at the optimal region, becoming steep as one moves away, fitting a parabola will

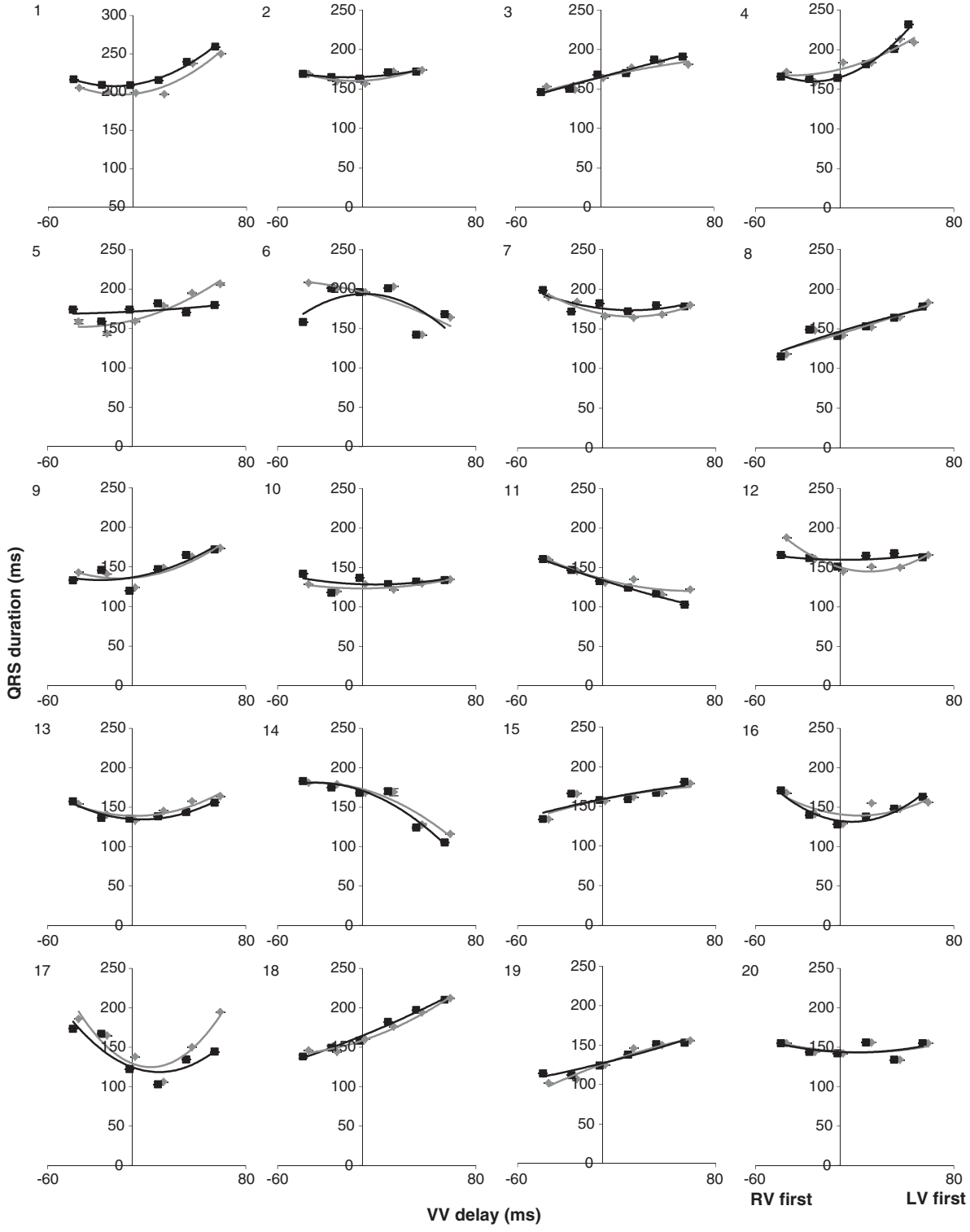

Fig. 4. First (black) and second (grey) sessions of optimization on the same day, using 12-lead ECG QRS width, at each VV delay (RV 40 to LV 60) for all 20 patients. A parabola was fitted in all optimization sessions and the trough of the parabola was considered to represent the optimal VV delay (optimum = narrowest QRS).

still verify singularity (i.e. the orientation of curvature would indicate that there would have been 2 non-optimal regions, if more settings beyond the optimal had been tested).

Biological *plausibility* of the distribution of the obtained optima is the final criterion. It is less fundamental than the others because it relies on separately-acquired beliefs of what distribution of optima is expected. CRT is generally accepted to exert benefits by decreasing rather than increasing dyssynchrony of the myocardial walls. It is therefore rational to expect the distribution of the optima to show that for many patients, their optimum setting is near to the VV delay of 0 ms, with only few patients being at an optimum with marked pre-activation of one lead. It is left, rather than right, bundle branch block in which the salutary effects of biventricular pacing are most prominent, and invasive studies [10,26–28] have shown that left ventricular pacing can achieve most of the effect of biventricular pacing but right ventricular pacing cannot. These prior observations

Table 2
Comparison of optima singularity between modalities. Optimization by pressure provided a high degree of optima singularity (expressed in % above chance alone). QRS optimization had a reasonable degree of singularity, but flow optimization was the least convincing. The difference in degrees of singularity between modalities was significant ($p<0.005$).

Optimization method	Number of optimizations, out of 40, having a single optimal region		Number out of 80	Degree of singularity, beyond expectation of chance
	Slow rate	Fast rate	Overall	
Pressure	36	38	74	85%
Flow	30	28	58	45%
QRS	35	30	65	63%
Difference between modalities:			Chi_2:	10.9
			p value:	<0.005

are reasons to expect the VV delay optimum to more often involve pre-activation of the left ventricle than the right.

4.2. Internal validity as an endpoint in a "basic science" of optimization

This study specifically focussed on the three key characteristics of internal validity of an optimization approach. We did this because these are essential criteria that may be definitively established in controlled circumstances, and which enables early identification of potentially unsuitable optimization approaches so that any large clinical event trials can focus resources appropriately.

In this study, only optimization by pressure fulfilled all 3 criteria.

4.3. Does VV delay matter at all?

The term "resynchronization"—which can only mean interventricular because atrioventricular timing is never synchronous in health—implies that VV timing matters, but appears contradicted by data [29]. For example, the prospectively-enrolled PROSPECT study appeared to contradict the belief that mechanical dyssynchrony is relevant; and several well-conducted studies of VV optimization appear to contradict the belief that interventricular delay matters *at all*.

However, the fact that various imaging markers in PROSPECT were mutually contradictory guarantees that most of them must fail to predict benefit. That they all failed highlights the fact that the study's process of choosing markers was arbitrary, based on availability rather than any detectable scientific process (which would screen out those with poor test–retest reproducibility). PROSPECT therefore casts no light on whether interventricular delay matters.

The 3 VV optimization studies are also less decisive than might be assumed. First, the Decrease-HF [14] study demonstrated that programming VV delay according to a formula obtained purely during intrinsic conduction gave no benefit, but it was not a process of measuring values at different settings to select an optimum. Second, the Rhythm II ICD [13] study used echocardiographic maximization of LVOT VTI, and found no benefit, did not report whether the method of optimization had good test–retest reproducibility: without knowing this we cannot tell whether it was VV delay that was unimportant or the optimization process that was unreliable [3]. Third, the Insync III [15] study was not a randomized trial but a comparison with historical controls. Moreover, although it conducted more than one optimization per patient, the test–retest reproducibility data remains at present undisclosed. Without this information on whether patients retested had the same optima as before, or only just fitting the same overall distribution, conclusions cannot yet be drawn.

4.4. Need for, and plausibility of, reports of clinical endpoint effects of optimization

Some interventions, such as device implantation, impose a large cost and substantial risk for the patient, and therefore judgements on whether to carry them out universally are dependent on the results of randomised trials of clinical outcomes. The financial investment required for these trials typically runs into many millions of dollars, so they are mainly carried out when an industrial organisation, hoping to profit from the conclusions, is willing to invest.

But clinicians make many choices. Not all are "whether" to do something extra which might have a cost or impose risk. Others are "which" of many options: selection of pacemaker settings is an example of such a choice. For such decisions, awaiting an adequately-powered industry-supported clinical endpoint trial may be a forlorn vigil.

In this study we did not attempt to acquire clinical endpoint data from these differences in VV delay. We made this choice because the effect was not as large as the effect of simply switching on a CRT device, and so the number of patients required for the clinical endpoints to be realistically informative—which rises with 1/(effect size) 2—would be very large.

Instead we concentrated on haemodynamic responses whose reproducibility is easily verifiable by any reader and which avoid the illusions of response arising from using optimization data itself to measure response [3], and accidentally generated correlations arising from confounding exclusions or optimistic reanalysis [30]. We are confident our findings will stand the test of time.

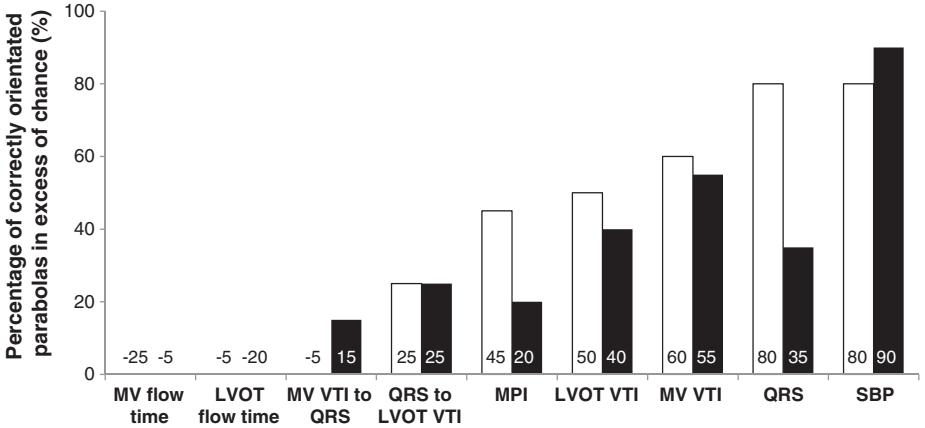

Fig. 5. By random chance alone, 50% of the parabolic curves fitted would be expected to be in the physiologically meaningful orientation. Therefore the raw percentage (x) of correctly orientated curves needs be transformed to $2(x-50)$ to obtain the proportion in excess of chance. On this scale, Ø represents the average expectation by chance alone, and 100 represents perfect orientation. SBP had a significantly higher percentage of correctly orientated optimization curves than LVOT VTI and QRS, at both the slow and fast heart rates.

Table 3
Agreement of optima between modalities at the *slow* heart rate. Values on the principal diagonal of the table indicate reproducibility (in bold) of the optimum using the same modality twice; other values indicate the agreement between modalities. All agreements are quantified as the standard deviation of difference (SDD, ms) between the two optima obtained, in the 20 subjects.

	LVOT VTI	QRS to LVOT VTI	LVOT ejection time	MV VTI	MV VTI to QRS	MV ejection time	MPI	QRS	SBP
Echocardiography									
LVOT VTI	**34.0**	41.1	64.7	34.3	43.6	56.9	31.4	44.8	37.0
QRS to LVOT VTI	41.1	**39.2**	62.6	43.1	51.6	49.5	35.8	23.8	36.1
LVOT ejection time	64.7	62.6	**58.1**	57.9	67.9	51.5	67.5	60.6	61.7
MV VTI	34.3	43.1	57.9	**46.8**	46.4	59.2	38.7	42.0	44.6
MV VTI to QRS	43.6	51.6	67.9	46.4	**39.8**	52.9	51.4	49.0	47.2
MV ejection time	56.9	49.5	51.5	59.2	52.9	**42.2**	62.8	57.7	53.0
MPI	31.4	35.8	67.5	38.7	51.4	62.8	**55.8**	39.0	33.2
Electrocardiography									
QRS width	44.8	23.8	60.6	42.0	49.0	57.7	39.0	**8.0**	33.3
Finometer									
SBP	37.0	36.1	61.7	44.6	47.2	53.0	33.2	33.3	**10.2**

LVOT indicates left ventricular outflow tract; MV, mitral valve; VTI, velocity time integral; MPI, myocardial performance index; SBP, acute change in systolic blood pressure.

4.5. LVOT VTI as a modality for VV optimization

There is a strong *a priori* rationale for the use of LVOT VTI (flow) as a marker of cardiac function, for optimization. Given that the diameter of the LVOT remains constant, changes in stroke volume are solely dependent on velocity and duration of blood flow. Therefore, the LVOT VTI is a perfect index of stroke volume which in turn is, in principle, a very plausible marker of cardiac function since other characteristics are kept constant.

In this study, conducted in a research setting with less time constraint than occurs in routine clinical practice, we measured a number of LVOT VTIs (6 beats) that would be considered large by routine clinical standards. The reason was to improve the signal-to-noise ratio and therefore improve the reproducibility of the optimal VV delay [3]. Resource constraints often limit routine clinical practice to only 3, 2 or even 1 beat.

Despite taking this step, LVOT VTI optimization performed poorly on all counts of internal validity. This may be an explanation for the inconsistent findings reported by other studies testing clinical outcomes following VV optimization [13–15].

Singularity, (test–retest) reproducibility and plausibility of the optimum have rarely been commented upon in studies of LVOT VTI optimization.

4.6. QRS minimization as a modality for VV optimization

QRS width is a highly reproducible measurement that is quickly and cheaply acquired, potentially automatically, and it avoids the problems of needing good echocardiographic windows and a trained operator with enough time to perform and analyse a lengthy series of measurements. There are studies showing some association between a reduction in the QRS width and clinical benefits [31,32].

However, our findings showed that although reproducible and generally singular, QRS minimization frequently proposed optimal VV delays that had marked right ventricular pre-activation (Fig. 7). This is not biologically plausible if the current understanding of cardiac resynchronization process is correct.

Moreover, in our study, QRS and pressure optima agreed poorly. Because we have quantitative data on reproducibility of these techniques in the same patients at the same session, we know that the discrepancy between methods is not due to imprecision of our ability to establish each optimum, but rather that the two optima are providing fundamentally contradictory information.

It is inescapable from our data that QRS minimisation definitely results in a lower blood pressure. Forced to choose between a pressure maximum and a QRS minimum, our interpretation is that the pressure maximum is both intrinsically a better physiological target as well as showing a biologically more plausible distribution of VV optima. The numerous elements contributing to mechanical dyssynchrony, and cardiac function overall, go far beyond QRS width, as has been documented in several studies [33,34]. Therefore, even though wide QRS may predict benefit for CRT [1,35–37], first principles do not require that QRS minimization must be the ideal approach to VV optimization.

4.7. VV optimum unchanged by heart rate, if measured reproducibly

Using pressure optimization, the internally valid method, we concluded that heart rate had no discernible effect on optimal VV delay. This not to say that the observed optimum was the same at slow as

Table 4
Agreement of optima between modalities at the *fast* heart rate. Values on the principal diagonal of the table indicate reproducibility (in bold) of the optimum using the same modality twice; other values indicate the agreement between modalities. All agreements are quantified as the as standard deviation of difference (SDD, ms) between the two optima obtained, in the 20 subjects.

	LVOT VTI	QRS to LVOT VTI	LVOT ejection time	MV VTI	MV VTI to QRS	MV ejection time	MPI	QRS	SBP
Echocardiography									
LVOT VTI	**35.4**	46.9	43.1	49.7	51.9	52.1	47.8	41.4	45.3
QRS to LVOT VTI	46.9	**27.7**	46.6	47.3	69.5	59.4	47.8	43.6	53.2
LVOT ejection time	43.1	46.6	**39.2**	58.7	68.7	54.1	56.2	48.4	54.6
MV VTI	49.7	47.3	58.7	**38.7**	56.6	64.6	46.1	33.1	38.0
MV VTI to QRS	51.9	69.5	68.7	56.6	**31.7**	58.2	57.6	51.1	40.6
MV ejection time	52.1	59.4	54.1	64.6	58.2	**54.5**	69.2	59.9	52.7
MPI	47.8	47.8	56.2	46.1	57.6	69.2	**45.2**	48.6	42.9
Electrocardiography									
QRS width	41.4	43.6	48.4	33.1	51.1	59.9	48.6	**6.0**	43.9
Finometer									
SBP	45.3	53.2	54.6	38.0	40.6	52.7	42.9	43.9	**9.4**

LVOT indicates left ventricular outflow tract; MV, mitral valve; VTI, velocity time integral; MPI, myocardial performance index; SBP, acute change in systolic blood pressure.

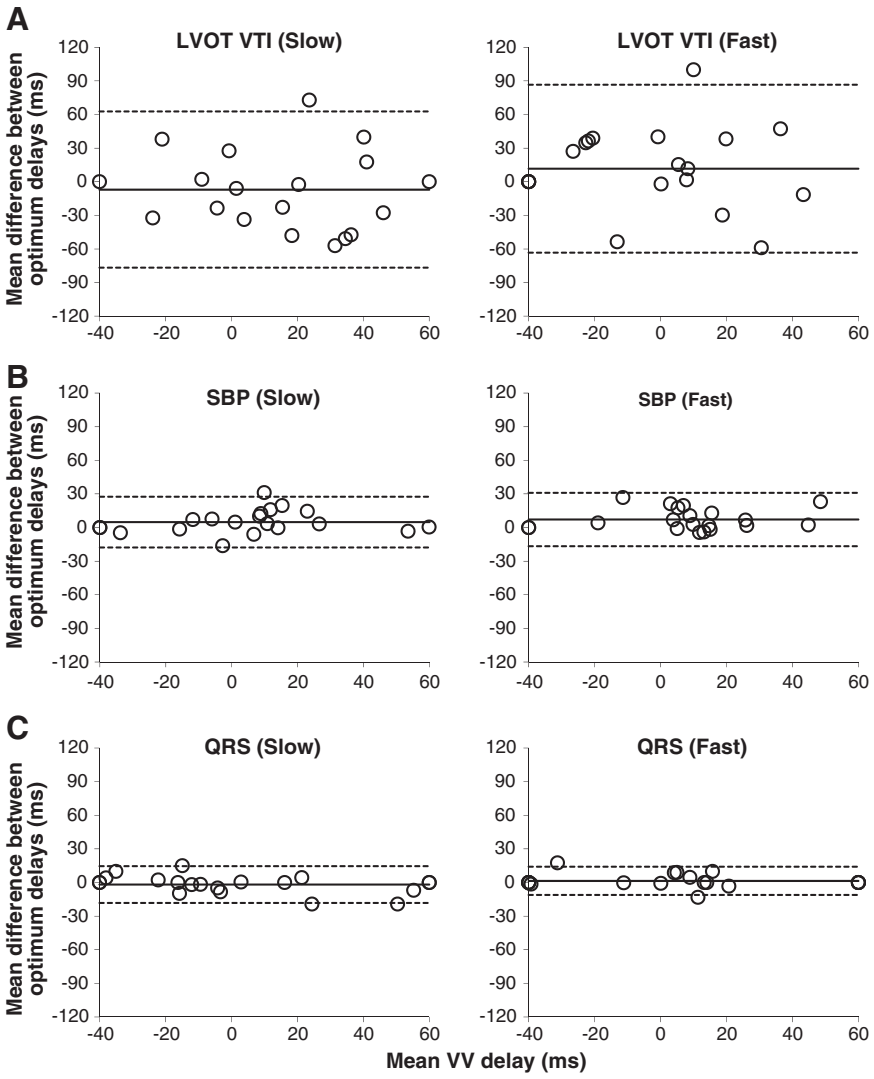

Fig. 6. The reproducibility (standard deviation of the difference—SDD in ms) of LVOT VTI (A) is equally poor at the slow (34 ms) and fast (35 ms) heart rates. SBP reproducibility (B) was better than LVOT VTI at slow (10 ms, $p<0.01$) and fast heart rates (9 ms, $p<0.01$). The reproducibility of the QRS width (C) was also better at slow (8 ms, $p<0.01$) and fast (6 ms, $p<0.01$) rates.

fast heart rate. On the contrary, in each patient, the observed optimum was different between slow and fast. However, this change was as frequently an increase as a decrease, and its scatter was the same as the test–retest scatter of individual patients' optimal settings at slow or fast heart rates. This means that no mechanism other than natural biological variability (unrelated to heart rate change) is necessary to explain the changes observed between heart rates. While we cannot exclude a small heart rate effect, any such effect must be small.

Judgement of reports of change in optimum of a pacemaker with the passage of time or after an intervention should always be reserved until it has a context of blinded short-term test–retest reproducibility data for that optimization process.

4.8. Clinical implications

Optimization techniques vary in their ability to detect the optimum reliably as we have seen in this study and have reviewed with a generalizable framework previously [3].

If there is insufficient time to perform a reliable optimization [3], unreliable optimization should not be performed except perhaps where mandated as part of a randomized controlled trial, or as part of an evaluation such as this study. It consumes resources and attention; moreover it may cause clinical harm by shifting patients away from default settings (near which the true optimum may lie in most patients) to VV delays far away which could worsen cardiac function. This concern is sound grounds for a clinician to leave default VV settings unchanged until optimization methods with good reliability become available locally.

Disobeying guidelines systematically takes courage if they are well-founded [37]. However, this study provides quantitative reasoning and measurements—both of which can be tested afresh by any party—to hold guideline recommendations to account. For example, if a clinical service uses LVOT VTI to optimize the VV delay, at the slow heart rate the scatter between repeated optimization using flow is 34 ms. This means after one optimization, the next identical procedure will, 95% of the time, report an optimization within $\pm 1.96 \times 34$, i.e. ± 67 ms; in other words a range *as wide as all the settings tested*. Clinical wisdom may prevail, preventing extreme values being selected, but if so, what is the net effect other than random selection amongst clinically-reasonable VV delays?

4.9. Study limitations

This study was not designed to test the clinical benefit of VV optimization, nor to attempt to separate responders from non-responders. It

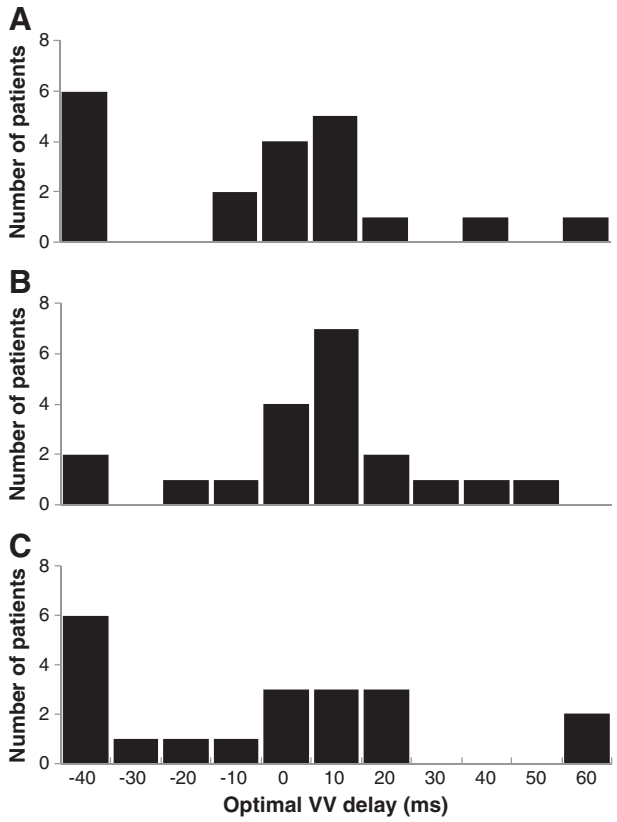

Fig. 7. LVOT VTI (A) and QRS (C) optima distributions contain a high proportion of optima with significant (−40 ms) RV pre-excitation. In contrast, the SBP (B) optima distribution is more central, around VV 0 ms, and most optima are LV pre-excited.

aimed to evaluate the qualities of non-invasive candidate modalities for VV optimization relevant to internal validity.

Although measurements were performed in a teaching hospital by experienced clinical research staff, there may be centres with greater skills in, for example, echocardiography which might be able to achieve better performance from flow optimization (LVOT VTI) than what we achieved. Superficially, that would appear to be the case from the fact that guidelines recommend flow optimization of the VV delay [37]. Nevertheless, we note that the guidelines do not cite independent data on the 3 key principles of internal validity (singularity, reproducibility and plausibility) of flow optimization, or any comparison of these principles between flow and any other alternatives, and therefore it is possible that flow optimization was recommended only because there appeared to be no alternative.

Ventricular ectopy was completely excluded from echocardiography images and from QRS measurements, but not eliminated from the semi-automated analysis of pressure optimization. This may have adversely affected the precision of the pressure data. However, results in terms of singularity, reproducibility and plausibility, were still no worse for pressure than for flow and QRS. The practical advantage of pressure over flow is that it could be monitored by automated systems without manual beat-by-beat calculation, and therefore it is fitting that pressure measurement was calculated in this study in the same way that might happen in a real-world clinical system operating without beat-by-beat supervision.

Optimal VV delays were calculated using data taken with the patient lying down, and this may not necessarily reflect the optimal VV delay during other physiological states such as exercise. However, for the purpose of genuine head-to-head comparison of several optimization methods we had to select a posture suitable to all modalities including echo, and which did not introduce unnecessary noise.

We performed pressure optimization by measuring the changes that occurred in pressure only for a short interval after a change in the VV delay was programmed and did not measure pressure during steady state pacing. We have recently shown [23] that any change in pressure that occurs due to a change in AV delay decays to a lower level only a few seconds later. This phenomenon means that signal-to-noise ratio for pressure optimization is highest soon after a transition, and therefore systematically measured changes just shortly after the VV delay change.

Moreover, we assessed the test–retest reproducibility of the optimum over a short of period of time (within an hour) to guarantee that any differences could not be attributed to large physiological or volume changes between optimization sessions.

Finally, this is a study of AF only. Sinus rhythm may be different, not least because changes in the VV delay always change the AV delay on either the left or right side of the heart.

5. Conclusions

Singularity, reproducibility and *plausibility* are sine qua nons for an optimization modality to undergo the next steps of mutual comparison between high-quality modalities, trialling for impact on clinical endpoints, or adoption in clinical practice. Methods that do not have these characteristics may be, unintentionally, a random selection amongst settings. At best this could be useless. At worst, since the patients would be moving away from the vicinity of the optimum in which they begin by factory default (0 ms), optimization might be on average harmful.

Although LVOT VTI is the “final common pathway” of all processes within the heart and—being an index of cardiac output—is in principle a perfect marker for pacemaker optimization, it has a poor singularity and reproducibility even in an ideal research setting where time and resources are artificially abundant. Its singularity and reproducibility could be improved, but only by massively increasing the number of replicates to a level intolerable even in a research setting and certainly in a routine clinical setting.

In our study, only pressure optimization provided singularity, reproducibility and plausibility. This study cannot truly compare pressure optimization against flow or QRS optimization, because neither flow nor QRS optimization were suitable candidates since they both failed to fulfil criteria that are rudimentary.

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