

Evidence that conflict regarding size of haemodynamic response to interventricular delay optimization of cardiac resynchronization therapy may arise from differences in how atrioventricular delay is kept constant

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Aims

Whether adjusting interventricular (VV) delay changes haemodynamic efficacy of cardiac resynchronization therapy (CRT) is controversial, with conflicting results. This study addresses whether the convention for keeping atrioventricular (AV) delay constant during VV optimization might explain these conflicts.

Method and results

Twenty-two patients in sinus rhythm with existing CRT underwent VV optimization using non-invasive systolic blood pressure. Interventricular optimization was performed with four methods for keeping the AV delay constant: (i) atrium and left ventricle delay kept constant, (ii) atrium and right ventricle delay kept constant, (iii) time to the first-activated ventricle kept constant, and (iv) time to the second-activated ventricle kept constant. In 11 patients this was performed with AV delay of 120 ms, and in 11 at AV optimum. At AV 120 ms, time to the first ventricular lead (left or right) was the overwhelming determinant of haemodynamics (13.75 mmHg at ± 80 ms, $P < 0.001$) with no significant effect of time to second lead (0.47 mmHg, $P = 0.50$), $P < 0.001$ for difference. At AV optimum, time to first ventricular lead again had a larger effect (5.03 mmHg, $P < 0.001$) than time to second (2.92 mmHg, $P = 0.001$), $P = 0.02$ 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.

Keywords

Heart failure • Cardiac resynchronization therapy • Physiology • Mechanisms

Introduction

The advent of cardiac resynchronization therapy (CRT) marked a step change improvement in the care of eligible heart failure patients, providing a powerful reduction in morbidity and mortality.¹ Cardiac resynchronization therapy 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 atrioventricular (AV) delay adjustment^{2–4} while others have reported a substantially smaller effect.⁵

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What's new?

- Vastly different haemodynamic effects are seen with interventricular (VV) optimization depending on the method used to keep the atrioventricular (AV) delay constant (e.g. keeping the time from atrium to the LV constant during the VV optimization).
- It illustrates in detail why dramatically different results will be reported by investigators using different approaches.
- Future studies addressing VV optimization should specify exactly how AV delay is kept constant.
- These data suggest that the greatest haemodynamic increment comes from setting the time to the first ventricular lead. Setting the time to the second ventricular lead to be different to this (i.e. later) in almost all cases does not improve haemodynamics and in many cases worsens it.

In this study, we explored whether this disagreement between groups could be explained by differences in convention on how exactly AV delay is kept constant while VV delay is adjusted.

Traditionally, optimization of pacemaker timing is divided into AV optimization and VV optimization. The reality is that the two are intertwined, and how the two are related is rarely discussed in detail in studies of VV optimization. When an offset is introduced between the right ventricle (RV) and left ventricle (LV) in a VV optimization, 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 optimization 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 optimization. Consequently, studies have differed in their approaches for fixing the AV delay while varying VV delay.^{2,6,7} 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.^{2,7} The reverse is also described with A-RV kept constant.⁸

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,^{9,10} which ventricle is first and which is second depends on the sign of the interventricular delay, e.g. an AV delay of 120 ms and an interventricular delay of 40 ms (LV first) would mean the A-LV is 120 ms and the A-RV 160 ms, while in contrast an interventricular delay of 40 ms (RV first) would mean the A-LV is 160 ms and the A-RV is 120 ms.

Many authors, including our group in the past,^{2,5} did not consider the distinction important and therefore did not report their choice of convention.⁵

It is not known whether the choice of convention for keeping AV delay constant determines the magnitude of the haemodynamic response to adjusting VV delay.^{4,11}

This study explores the effect of different choices of what is kept constant during a VV optimization. We do this by presenting data showing VV optimizations 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 optimization);
- Keeping the time to the second ventricle constant while adjusting time to the first ventricle.

Methods

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, and raw data are available from any author.

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.

Interventricular optimization 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 120 ms (using four different conventions for keeping AV delay constant). For the second 11, we first performed AV delay optimization and then conducted the study keeping AV delay fixed at the patients' individual AV delay optimum.

The VV optimization protocol⁵ consisted of alternations in VV delay between 0 ms and the tested delay (20 ms increments between -80 and 80 ms) on a repeated basis for each tested delay (Figure 2). Non-invasive blood pressure monitoring (Finapres Medical Systems) 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 transition. We 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 maximize the signal-to-noise ratio.¹² 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.¹³ 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 our previous study of efficiency and reproducibility.¹⁴ All data are shown and all raw data are available from the authors unconditionally.

Interventricular optimization was performed using four different conventions for how AV delay is kept constant (Figure 1):

- (1) Interventricular optimization 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 (120 ms for the first 11 patients, or the AV optimum for the second 11).

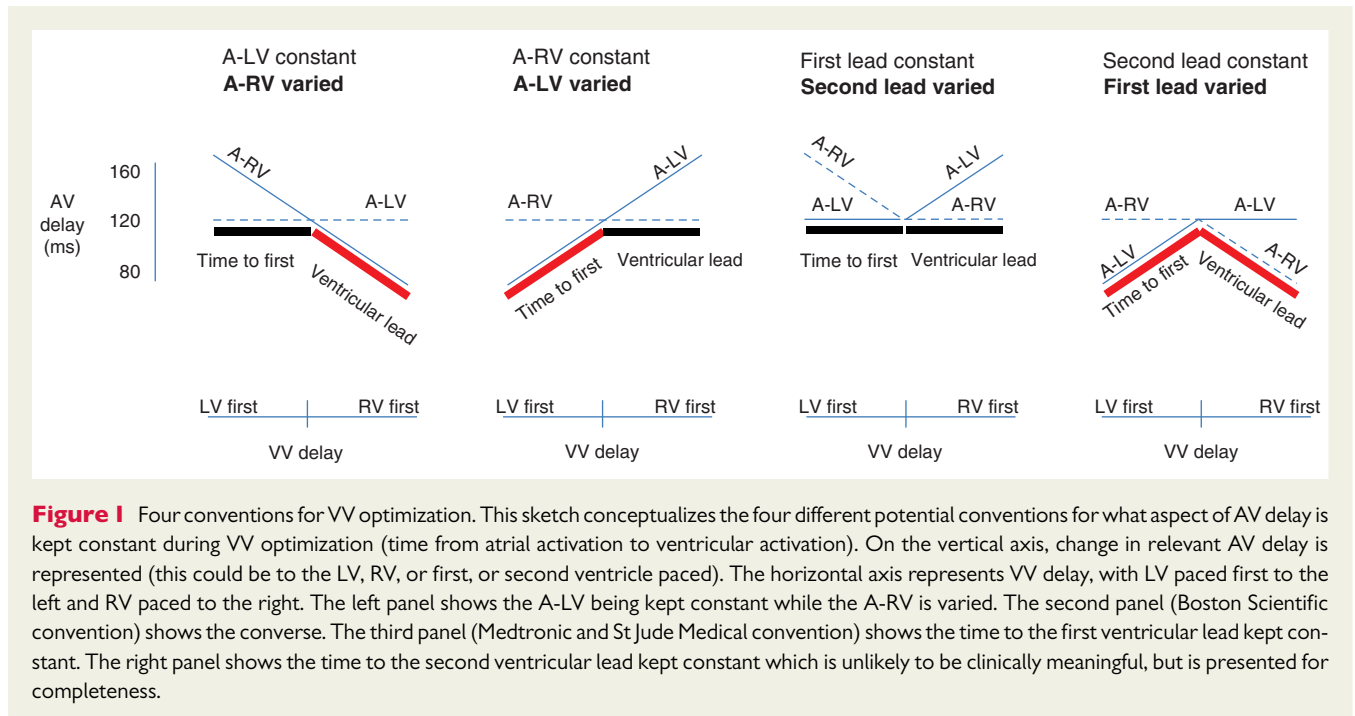


Figure 1 Four conventions for VV optimization. This sketch conceptualizes the four different potential conventions for what aspect of AV delay is kept constant during VV optimization (time from atrial activation to ventricular activation). On the vertical axis, change in relevant AV delay is represented (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.

- (2) Interventricular optimization 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 (120 ms or AV optimum).
- (3) Interventricular optimization by only lengthening: Keeping the delay from the atrium to the first ventricular lead constant (at 120 ms or AV optimum) while delaying either the LV or the RV lead.
- (4) Interventricular optimization by only shortening: Keeping the delay from the atrium to the second ventricular lead constant (at 120 ms or AV optimum) while activating either the LV or RV lead earlier. This has never been proposed as a convention for optimization, but we included it for analytical 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 optimization so that the fixed AV delay used for them would be their own individual AV optimum. The AV optimization process was by our standard protocol.¹²

Owing 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. These are described in the Supplementary material online, *Methods*.

Analysis and statistics

Data were analysed using Matlab (MathWorks) and Microsoft Excel (Microsoft). 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 of <0.05 was considered statistically significant. Power calculations are described in the data supplement.

Results

Adjusting AV delay showed a curvilinear change in SBP (all data from all patients are shown in left panels of *Figures 3* and *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 200 ms (SD 29 ms, range 160–250 ms). The first and second groups of 11 patients had similar characteristics (Supplementary material online, *Table S1*). Participants had a mean age of 66 years (SD 8, range 54–82), QRS duration of 162 ms (SD 24 ms, range 132–220 ms), LV end diastolic diameter 5.7 cm (SD 1.2 cm, range 4.2–9.2 cm). Other patient characteristics are described in *Table 1*.

Haemodynamic changes are produced by changes in atrioventricular delay rather than by offset between ventricular stimuli, when interventricular delay is adjusted close to an atrioventricular delay of 120 ms

At AV 120 ms, 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 5*, fourth column; *Table 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 5*, third column).

Viewing the ventricles individually, adjusting A-LV keeping A-RV constant (*Figure 5*, second column), or adjusting A-RV keeping A-LV constant (*Figure 5*, first 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). Among these, the only half that 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

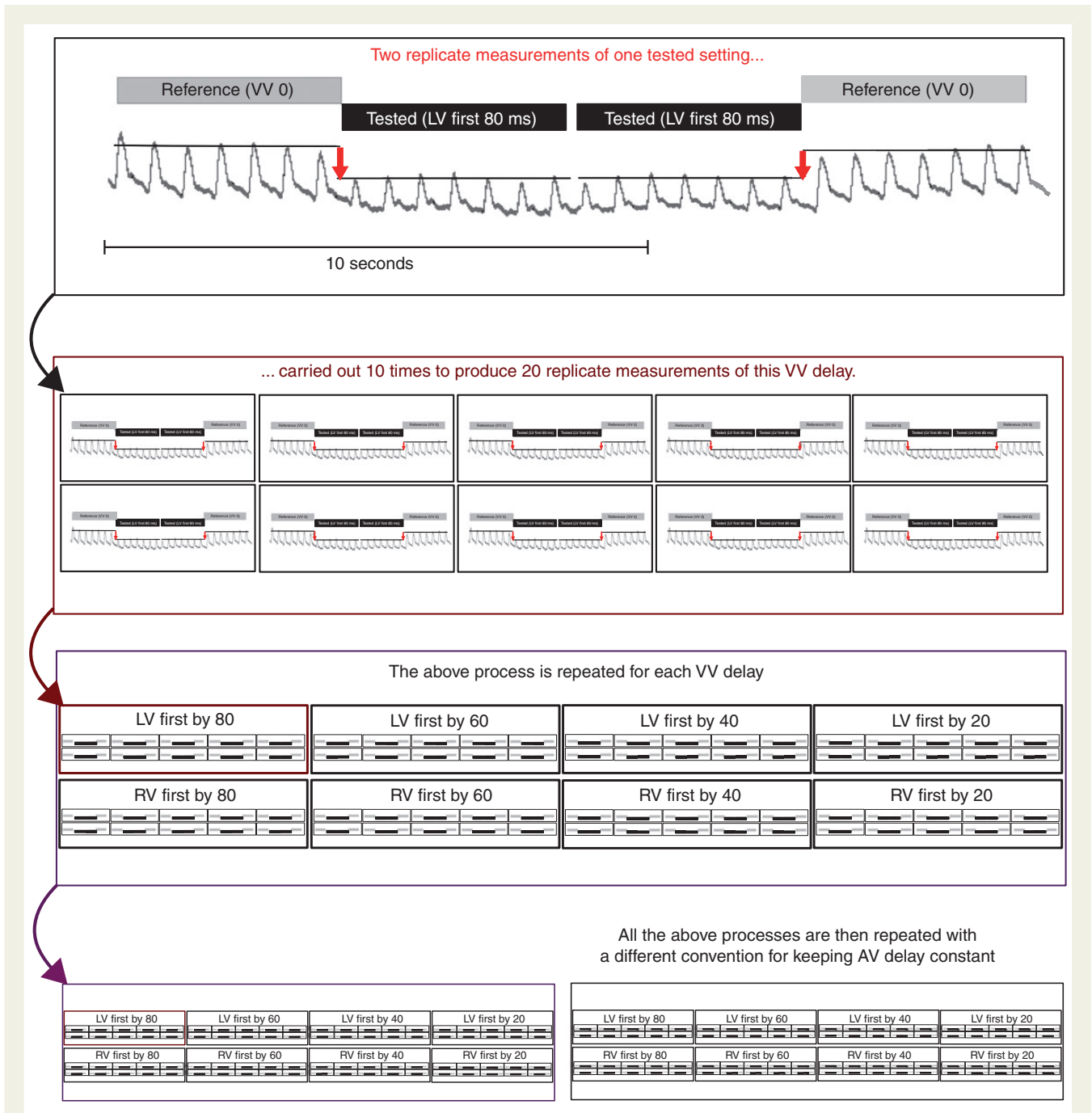


Figure 2 Structure of protocol. The measurement protocol involved a large number of repeat measurements to minimize the impact of biological noise. The fundamental measurement is of the change in systolic pressure when the setting is changed from reference VV delay (0 ms) to a tested VV delay. This change can also be measured on the reverse transition, recognizing that its sign should be reversed. The top panel shows two such measurements of a single tested setting, 80 ms. The second panel shows how 10 repeats of this produce 20 replicates for one tested VV delay. The third panel shows that the entire process is then conducted for each other tested VV delay. The bottom panel shows that all the processes above are then repeated for a different convention for keeping AV delay constant. In practice, it is only necessary to study two conventions (A-RV fixed, A-LV fixed) since combinations of these produce all the settings that will be obtained by the other two conventions.

lengthening the delay in one ventricle produced no significant effect on blood pressure regardless of whether it was the LV or RV lead that was delayed.

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

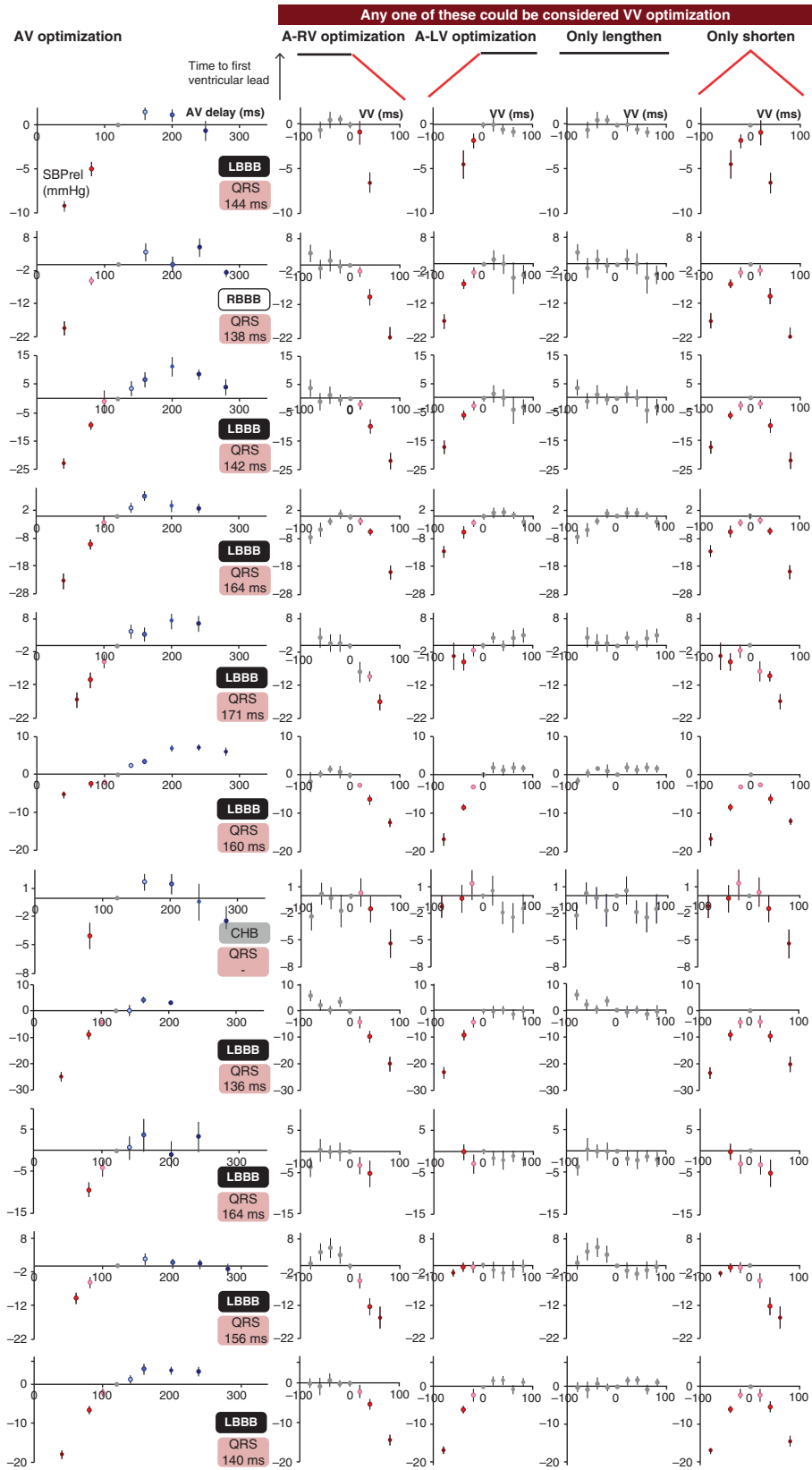


Figure 3 Interventricular optimization in all 11 patients optimized from AV 120 ms. The vertical axes represent change in systolic blood pressure relative to a reference setting. For the AV optimization this is 120 ms, for the VV adjustments this is VV0. The first column shows AV optimization curves for individual patients. The next four columns show their individual VV adjustments 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.

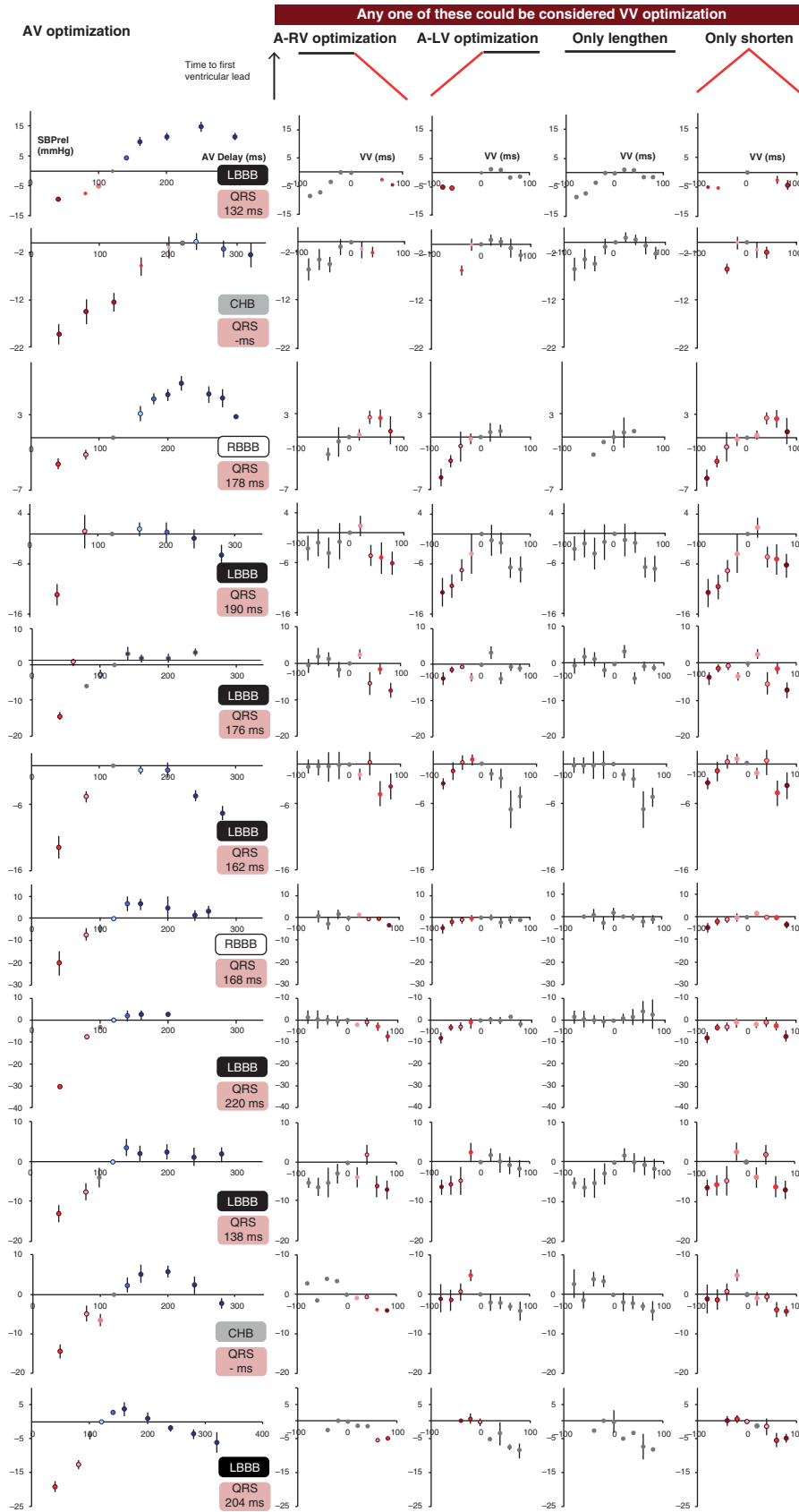


Figure 4 Interventricular optimization in all 11 patients optimized from AV optimum. The panels are organized in the same way as Figure 3.

Table 1 Patient characteristics

	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
Beta blocker	16	73
ACE-I/ARB	19	86
Aldosterone antagonist	13	59
Diuretic	14	64

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.

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

In contrast, at AV optimum (Figure 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 (5.03 mmHg at 80 ms, $P < 0.001$ and 2.92 mmHg at 80 ms, $P = 0.001$, 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 5, second column), or adjusting the A-RV keeping the A-LV constant (Figure 5, first 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.

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 optimization. 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.

Contribution of interventricular adjustment to the physiological benefit of biventricular pacing

Our data indicate that near an AV delay of 120 ms, 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 120 ms, 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 delay¹¹ 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. Atrium and left ventricle delay optimization 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 120 ms, 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 120 ms, 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 120 ms time to first activation is sufficiently short that no amount of delay of the second lead could significantly ameliorate the situation. In 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.

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.¹⁵ Our data highlight that a delay to the first ventricular lead that is shorter than optimal (120 ms 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 $> 10\%$.

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 VV delay, be it shortening or lengthening of either A-LV or A-RV,

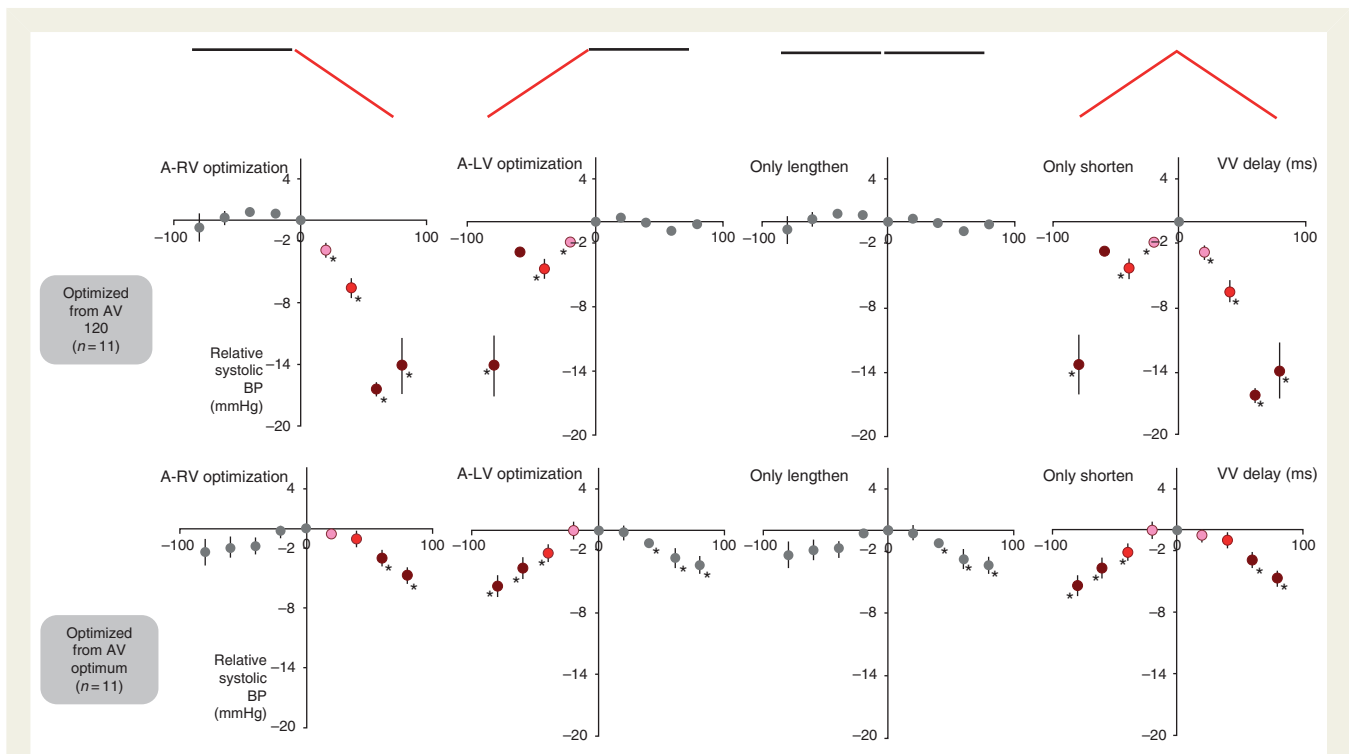


Figure 5 Mean impact across all patients on haemodynamic response optimizing from AV 120 ms (upper panel) or AV optimum (lower panel). The vertical axes represent relative systolic blood pressure compared with a setting of VV0. The horizontal axis represents VV delay, with a negative value indicating 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 is averaged for all the participants using the four different methods of VV optimization. *Settings with a significant difference ($P < 0.05$) in pressure compared with 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.

is consistently able to deliver higher blood pressures; in fact, many such changes significantly reduce blood pressure. An 80 ms pre-activation or post-activation of either lead caused blood pressure to fall by 3–4 mmHg (statistically significant for all combinations except delayed activation of the RV lead).

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 120 ms, the adjustments had effects on blood pressure that were small in absolute terms, of the order of 1–4 mmHg 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 5–8 mmHg according to measurements made acutely at the time of implant¹⁶ and over the longer term according to the COMPANION and CARE-HF data,^{17,18} so a change in timings that reduces blood pressure by 1–4 mmHg 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 that 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,^{19–21} then an optimization process might actually turn out to be little different to a process of selecting randomly between different pacemaker settings.¹³

Should interventricular delay always be kept at 0 ms?

These findings have implications for pacing protocols and in particular whether VV optimization should be performed at all. Participants in clinical trials of CRT who showed a prognostic benefit underwent AV optimization, but not VV optimization.^{17,18} A recent meta-analysis of VV optimization vs. empiric settings similarly showed no benefit from VV optimization.⁶ While this could have been due to difficulties with study power or VV optimization 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.

Why different studies might report conflicting effects of interventricular delay adjustment

Our data suggest that the phrase ‘keep AV delay fixed and adjust VV delay’ is not a sufficiently clear description when we are describing a VV optimization protocol. Three different interpretations of this could each be argued to be correct: keep time to first ventricular

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

VV offset (ms)	A-RV optimization				A-LV optimization				Only lengthen				Only shorten			
	FVL time (ms)	Mean SBPrel (mmHg)	SE	P value	FVL time (ms)	Mean SBPrel (mmHg)	SE	P value	FVL time (ms)	Mean SBPrel (mmHg)	SE	P value	FVL time (ms)	Mean SBPrel (mmHg)	SE	P value
VV optimization with an AV delay of 120 ms																
-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 optimization with an optimized AV delay																
-80	AVOpt	-2.35	1.37	0.13	AVOpt-80	-5.41	1.02	0.001	AVOpt	-2.35	1.37	0.13	AVOpt-80	-5.41	1.02	0.001
-60	AVOpt	-1.91	1.06	0.11	AVOpt-60	-3.71	1.01	0.01	AVOpt	-1.91	1.06	0.11	AVOpt-60	-3.71	1.01	0.01
-40	AVOpt	-1.76	0.84	0.06	AVOpt-40	-2.19	0.88	0.03	AVOpt	-1.76	0.84	0.06	AVOpt-40	-2.19	0.88	0.03
-20	AVOpt	-0.24	0.52	0.65	AVOpt-20	-0.03	0.82	0.98	AVOpt	-0.24	0.52	0.65	AVOpt-20	-0.03	0.82	0.98
0	AVOpt	0.00	0.00		AVOpt	0.00	0.00		AVOpt	0.00	0.00		AVOpt	0.00	0.00	
20	AVOpt -20	-0.52	0.61	0.42	AVOpt	-0.20	0.67	0.78	AVOpt	-0.20	0.67	0.78	AVOpt-20	-0.52	0.61	0.42
40	AVOpt -40	-1.02	0.80	0.23	AVOpt	-1.24	0.50	0.03	AVOpt	-1.24	0.50	0.03	AVOpt-40	-1.02	0.80	0.23
60	AVOpt -60	-2.96	0.83	0.006	AVOpt	-2.72	0.99	0.02	AVOpt	-2.72	0.99	0.02	AVOpt-60	-2.96	0.83	0.006
80	AVOpt -80	-4.69	0.78	0.0002	AVOpt	-3.37	0.83	0.003	AVOpt	-3.37	0.83	0.003	AVOpt-80	-4.69	0.78	0.0002

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.

lead fixed and adjust time and choice of second ventricular lead⁵; keep A-RV fixed and adjust A-LV²; keep A-LV fixed and adjust A-RV.⁷ These three produce completely different haemodynamic 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 optimization may therefore, after all, not be contradictory.

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^{20,21} 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) that 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.²²

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 section. 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.²³ 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 that might suggest that the predominant driver is delay between atrium and first ventricular activation and not the precise position of the LV lead.

Our study does not distinguish CRT recipients into responders vs. non-responders, because our hospital no longer makes this distinction. Most of what is observed in clinical response is not the result of pacing^{24,25} and most of the change in imaging measurements in individual CRT recipients also occurs in controls²⁶ who do not undergo CRT pacing and is therefore, for the purposes for evaluating the effect²⁷ 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.²⁶

At the longer AV delays, the range of VV delays that could be tested was occasionally limited by safety settings on the device that

prevented the full planned range being tested. The individuals in whom this situation arose is visible in the full data disclosure in *Figures 3 and 4*.

All the measurements were performed at rest. We 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.

Our 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.¹² However, our present 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 maximizing signal-to-noise ratio, which we know requires elevated heart rate.¹² At lower heart rates if the effect size were half as large, each patient would have to undergo a protocol four times as long to obtain a result with the same precision.

Our patients were an unselected sample of patients with CRT at our centre. The majority had underlying left bundle branch block (LBBB), while a few had underlying right bundle branch block (RBBB) or complete heart block. We 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.

Our study does not have any data on mechanical dyssynchrony. This is because we do not test for this in our patients any more. We have previously observed that in our hands mechanical dyssynchrony measurements do not have sufficient test–retest reproducibility under blinded conditions to be usefully^{26,28} tested as a predictor of anything else.

Our 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 3 h per patient to 9 h. 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 optimize AV delay.

Clinical implications

Aside from the mechanistic implications, our study suggests that clinical CRT optimization 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) optimization requires efforts to ensure that the subtle signal of between-setting differences is not obscured by spontaneous beat-to-beat biological variability.

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 our cohort, we 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 optimization might usefully specify which aspect of AV delay was kept constant, along with individual-patient assessments of precision.

Supplementary material

Supplementary material is available at *Europace* online.

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