**Variation in Optimal Haemodynamic Atrio-ventricular Delay of Biventricular Pacing with Different Endocardial Left Ventricular Lead Locations using Precision Haemodynamics**

Short title: Variation in AV delay during targeted endocardial LV lead placement in CRT.

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**Abstract**

**Background:** It is not known whether the optimal Atrioventricular delay (AVopt) varies between left ventricular (LV) pacing site during endocardial biventricular pacing (BiVP) and may therefore needs consideration.

**Methods:** We assessed the haemodynamic AVopt in patients with chronic heart failure undergoing endocardial LV lead implantation. AVopt was assessed during atrio-biventricular pacing (BVP) with a “roving LV lead”. Up to four locations were studied: mid lateral wall, mid septum (or a close alternative), site of greatest haemodynamic improvement and LV lead implant site. The AVopt was compared to a fixed AV delay of 180ms.

**Results:** Seventeen patients were included (12 male, aged 66.5 +/- 12.8 years, ejection fraction 26 +/- 7%, 16 left bundle branch block or high percentage of right ventricular pacing (RVP), QRS duration 167 +/-27 ms). In most locations (62/63), AVopt increased systolic blood pressure during BiVP compared with RVP (relative improvement 6 mmHg, IQR 4-9mmHg). Compared to a fixed AV delay the haemodynamic improvement at AVopt was higher (1mmHg, IQR 0.2-2.6mmHg, p<0.001). Within most patients (16/17), we observed a difference in AVopt between pacing sites (median paced AVopt 209 ms, IQR 117-250). Within this range, the haemodynamic impact of these differences was small (median loss 0.6 mmHg, IQR 0.1-2.6mmHg).

**Conclusion:** Within a patient, different endocardial LV lead locations have slightly different haemodynamic AVopt which are superior to a fixed AV delay. The haemodynamic consequence of applying an optimum from a different lead location is small.

**Graphical Abstract**

**Diagram

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**Central illustration**: **Assessment of the Haemodynamic Optimum Atrioventricular Delay during Biventricular Pacing with and Endocardial Left Ventricular Lead.** The image on the left shows four atrioventricular haemodynamic optimisation curves during biventicular pacing with an endocardial left ventricular lead. The left ventricle was divided into nine segments and each curve presented is with the endocardial left ventricular lead at each site. The graph on the right compares the heamodynamic benefit of using a fixed atrioventricular delay of 180ms with the left ventricular lead at each site compared to the calculated optimum atrioventricular delay during biventricular pacing. Key: AV- Atrioventricular, LV - Left ventricular. Depicted on the haemodynamic curves the red line identifies the greatest mean optimal blood pressure improvement recorded during testing. The optimal atrioventricular delay was taken at the peak of the curve (grey line).

**Introduction**

The large survival benefit delivered in eligible patients by atrio-biventricular pacing can only come from its two proximate electrical effects: improvement of atrioventricular timing and improvement of ventricular timing (1, 2). There is evidence that placing the left ventricular lead in a better position delivers better clinical outcomes (3, 4). What is not known is how the choice of lead position affects what atrioventricular delay delivers the best haemodynamic effect from pacing (the AVopt).

When the left ventricular lead is placed transvenously there is a very restricted choice of positions for the lead tip. The alternative approach of endocardial left ventricular pacing permits the left ventricular lead to be placed in any location (5). There are limited data assessing the difference in AVopt, during endocardial atrio-biventricular pacing with the LV lead atdifferent locations. The haemodynamic consequences of this variation in the AVopt , if present withina patient, is also not known.

In this study we use high precision haemodynamics to look for changes in AVopt when the left ventricular lead is moved to different endocardial positions during atrio-biventricular pacing. We then compared the AVopt to a fixed AV delay of 180ms.

**Methods**

**Study participants**

Seventeen patients, with conventional indications for cardiac resynchronisation therapy (CRT) but who had failed conventional left ventricular (LV) lead placement via a coronary sinus branch or had limited response to therapy, were enrolled at a single centre. All were implanted with an endocardial LV lead guided to a location that delivered the greatest improvement in systolic blood pressure during biventricular pacing (BiVP). Patients provided written consent. All procedures and protocols complied with Declaration of Helsinki and received prior approval both from the local institutional research office and from the national research ethics service (LO/14/0400) and publicly registered (clinical trials.gov - NCT02174289).

**Patient Preparation and Anatomic Mapping protocol**

All procedures were performed under general anaesthetic. Activated clotting time was maintained above 250 seconds throughout the study with intravenous unfractionated heparin

Right atrial (RA) and right ventricular (RV) pacing was performed with standard, fixed curve, quadripolar diagnostic catheters (VikingTM soft tip, Boston Scientific, MA) sited at the location of the patient’s existing RA and RV leads. Atrio Biventricular pacing was performed with a 7.5fr bi-directional, open irrigated, magnetically tracked ablation catheter (IntellaNav OI, Boston Scientific, MN) used as a roving LV lead. This was placed in the LV via an 8.5fr steerable sheath (Agillis NXT, St Jude Medical). The RA, RV and LV catheters were connected to an external cardiac resynchronisation pacekamer (Medtronic Syncra. Medtronic, MN), through the mapping system via custom made leads (Biomedical Engineering, Royal Brompton and Harefield, UK). This allowed for quick and simple alternation between dual chamber (RA and RV) and BiVP using a conventional programmer (Carelink programmer, Medtronic, MN).

A three-dimensional anatomic map of the LV was created with a high-resolution basket mapping catheter (OrionTM, Boston Scientific, MA) using the RhythmiaTM mapping system (Boston Scientific, MA) via the trans septal route. The shell was marked with 3D geo location tags at nine predefined locations (Basal septum/anterior/lateral/inferior, mid septum/anterior/lateral/inferior and apex). The roving LV lead was then manipulated to each location for testing, *Figure 1*.

**Haemodynamic** **Assessment**

Systolic blood pressure was transduced through the tip of the steerable sheath. Raw blood pressure wave forms and 12 lead ECG signals were outputted from a conventional mapping system (LabSystem Pro EP recording system, Boston Scientific, MA) into a custom designed recording system (Biomedical Engineering, Royal Brompton and Harefield, UK). All recordings were performed during steady state anaesthesia. Any dampening of blood pressure recordings from the sheath tip prompted a repeat assessment. The effect of each pacing setting on systolic blood pressure was assessed using the alternation technique described and validated by Whinnett et al (6). In brief, this averages the change in systolic blood pressure during multiple alternations between a reference pacing setting (SBPref) and a test pacing setting (SBPtest). This accounts for the beat-to-beat variability in pressure from respiration and peripheral vascular resistance. SBPref throughout the study set as dual chamber pacing, ten beats above intrinsic sinus rate, with a fixed atrioventricular (AV) delay of 120ms SBPtest was set to atrio BiVP across each tested AV delay for the haemodynamic AV optimisation curve at each location. During BiVP the LV-RV pacing offset was kept at 0ms for all assessments and kept at the same rate as SBPref. A minimum of 8 alternations were performed for each AV delay tested.

**Atrioventricular Optimisation Curve**

The SBPtest AV delay test settings started at 40ms, and were increased in 40ms increments to either the intrinsic AV delay or 350ms (in the case of complete heart block). Curve-fitting was then used to identify the AV delay which delivered the greatest improvement in systolic blood pressure during BiVP, the AVopt , *Figure 2* (7). A full BiVP haemodynamic AV optimisation curve was performed with the roving LV lead placed in four predefined locations. These were preferentially: mid lateral wall, mid septum (or a close alterative site if no capture), site of greatest improvement in systolic blood pressure and final LV lead implant site.

### **Data processing**

**Optimal AV delay and Standard Error at the optimum**

AVopt was calculated from the fitted curve’s equation. Standard error at AVopt was calculated using the formula described by Francis et al. (8).

**Assessing the haemodynamic change with a fixed AV delay and the haemodynamic loss of using the AVopt from one LV Lead location at a different lead location.**

We assessed the haemodynamic change with a fixed pre-defined AV delay (atrially paced AV delay 180ms) at each location. This was chosen as a commonly pre programmed AV delay across device manufacturers. The haemodynamic change was calculated using the locations fitted curve’s equation. The haemodynamic change with the fixed AV delay was compared that of the AVopt.

Assessment of the potential haemodynamic loss of using the AVopt from one location at an alternative LV lead location was performed. This was achieved by taking the AVopt from one location, i.e. location AVopt 2. This was then used in the equation of the haemodynamic curve from an alternative location, i.e. location 1. This calculated the improvement in blood pressure (i.e. Blood pressure improvement in Location 1 using AVopt 2). The parabolic nature of the AV optimisation curve will ensure that the improvement in blood pressure in Location 1 anywhere other than the AVopt for that location will always be lower. The haemodynamic improvement from AVopt 2 is subtracted from of AVopt 1 and this is the potential haemodynamic loss in systolic blood pressure. This process is repeated multiple times for all AVopt at all lead locations to identify the median potential blood pressure loss, **online figure 1.**

### **Statistics**

Data is presented as mean (+/- standard deviation, +/- standard Error), Median (and IQR) and as proportion for continuous, categorical and count variable as appropriate. Normality was assessed using the Shapiro-Wilk method. Non-parametric comparisons were made using Wilcoxon Signed Ranks test. Correlation was assessed using linear regression and means compared using ANOVA. All analysis was performed using SPSS version (IBM SPSS, Version 24, USA). A p-value of <0.05 was considered to indicate a statistically significant difference.

## **Results**

Seventeen patients with conventional underwent endocardial LV pacing site mapping. Demographics are presented in ***Table 1***.

### **Haemodynamic Effect of AV delay during Biventricular Pacing**

Each of the included 17 patients underwent pacing at each of four locations, except for one patient where mid septal capture could not be achieved. Four further datasets were removed (one in patient 7 and 9 and two in patient 15) as the AV curve R2 was less than 0.8, which left 63 datasets. In 98% (62/63), CRT pacing improved systolic blood pressure against RV pacing (median improvement 6 mmHg, IQR 4-9mmHg) *Online Table 1.* Within each patient, in most cases, the haemodynamic curves had similar shapes at all locations *Figure 4****.*** Signal to noise ratio was good, averaging 24.4 (SD 18.2). The haemodynamic curves fitted well to a parabola, with mean R2 = 0.95 (SD 0.1).

**The Overall Difference in improvement in Systolic Blood Pressure at the Optimal AV delay vs at a Fixed paced AV delay of 180ms.**

Across all locations in all patients the median improvement in blood pressure at the AVopt was 6mmHg (IQR 4-9mmHg). This was significantly higher than that with a fixed paced AV delay of 180ms (5mmHg, 3-7mmHg, p<0.001), *Figure 5***.** The range in differences in blood pressure at each site between the AVopt and a fixed AV delay was 0-11mmHg.

### **Difference in Optimal AV delay at each location during Biventricular Pacing**

Across all locations in all patients the median AVopt was 209 ms (IQR 117-250). The median calculated AVopt range within each patient was 39ms (IQR 20-62), *Online Table 1***.** Within each patient, in all but 1 case, there were significant differences in the AVopt at different locations (p<0.001). 37% of the time location 2, 3 or 4 had an AVopt that was more than 20ms different from the AVopt of location 1.

The median difference in AVopt between the lateral wall and mid septal locations was 16ms (IQR 7-29). This difference in AVopt was statistically significant 85% of the time.The AVopt with the LV lead at the lateral wall was greater than the septum in 50% of cases**.** The difference in AVopt between the septum and the lateral wall was >20ms 31% of the patients, *Online Table 2*.

### **Difference in Blood pressure with all AV delay at each location during Biventricular Pacing**

The haemodynamic consequence of using the optimal AV delay derived at one location, at a different pacing site was calculated. By definition this this would be a lower blood pressure than would be obtained at the alternative location’s own AVopt. The extent to which it was lower was calculated.

The median loss in blood pressure from using the AVopt from a different location was a median loss of 0.6 mmHg (IQR 0.1-2.6) across all patients and lead locations. This is small compared to the impact of BiVP (median improvement in systolic blood pressure of 6 mmHg, IQR 4-9mmHg). Therfore, once AVopt was identified, endocardial LV lead location had a greater impact, *Online Figure 1*.

## **Discussion**

This study shows that AV delay optimum differs between patients and that programming patients with to a nominal AV delay may lead to sub-maximal acute haemodynamic improvement. Second, it shows that within an individual patient, LV pacing site does impact the AV delay determined as optimal and this is superior to a fixed AV delay of 180ms. Thirdly, programming the optimal AV delay identified at a different LV location, in the same patient, has only a very small impact on acute haemodynamic function.

This suggests there may be a benefit in conducting an AV delay assessment, but this does not need to be performed at each individual pacing site when evaluating different pacing sites.

**Identifying the Optimal AV delay has Important Haemodynamic benefits**

The acute haemodynamic effects of AV optimisation are well documented. Improving active and passive filling times contribute to stroke volume and overall cardiac output (9). The ideal AV delay between patients is also known to vary (10), with the optimum delay being conventionally identified using doppler echocardiography aiming to maximise the separation between E and A wave on trans mitral doppler (11). The CARE HF and MIRACLE trials used this method to optimise all patients randomised to CRT and this may have impacted on outcomes (12, 13).

Several studies have addressed targeting the ideal location for the left ventricular lead in order to improve patient response to therapy (3, 14, 15). Although these have shown significant acute haemodynamic benefit in placing the lead in different locations, little attention has been paid to the relative contribution of AV delay when pacing at different sites. Importantly, if this contribution is large and the optimal AV delay different as LV location differs, the potential benefit of pacing at a particular location may be underestimated. Our study confirms the greatest difference in haemodynamic change when pacing the at different endocardial sites in the left ventricle is driven by lead location rather than AVopt. However, we also show the additional haemodynamic benefit of AV optimisation within each patient which is superior to a standard fixed AV delay. Overall, this difference may be small however, we noted an important range of differences between 0-11mmHg at each location that may not be identified unless assessed.

A number of strategies have been tested to identify the ideal AV delay including echocardiography, haemodynamic, implantable sensors and the use of device algorithms (16). Outcomes from prospective trials formally assessing the benefits of these different techniques have been mixed. The largest trials have tended to either be based around either device algorithms deriving the ideal AV delay from the assessment of intracardiac electrograms or novel sensors. They have shown either no difference between AV optimisation and a fixed delay of 120ms (17), or some benefits with at least equivalency to echo optimisation (18, 19).

Current expert consensus suggests that optimisation strategies should fulfil three criteria; 1) The values attained when testing are singular 2) they are reproducible and 3) biologically plausible (16). There is a suggestion based on these three criteria that the optimisation strategies employed in the large prospective trials may not have been ideal. Echocardiographic methods have their drawbacks and may be prone biological noise if not conducted by an expert lab (16) and may be at risk of variable interpretation (20). Considering these challenges, there is a potential that the clinical benefit of optimising AV delay has not been fully realised. Haemodynamic curve fitting is a promising, reproducible technique that accurately assess the optimal AV delay and may prove helpful at improving response in patients with CRT (10).

**The optimal AV delay differs between people and this has an important haemodynamic effect**

Two previous acute haemodynamic studies have observed significant effects of changing AV delay. One tested delays of 30, 60, 100 and 140 ms (21) and the other tested two AV delays, a short (defined as the minimum AV delay to allow complete ventricular capture) and long (50ms longer) (22). The benefits may have been even greater if other AV delays could have been tested. Indeed, our study found that the optimal AV delay was over 200ms.

One further study of 20 patients has performed full haemodynamic AVopt curves, using the same protocol which we employed, from 2 epicardial locations along the coronary sinus. It demonstrated that, within patients, the curve shape and AVopt are usually similar. The locations compared tended to be between the basal anterior and mid lateral (in either the antero-lateral, lateral or postero-lateral positions). This study also shows that between locations the shape of the curves tend to be similar, albeit with a slightly greater variation in the AVopt. (23).

We had expected that, within the individual patients, the more lateral the LV lead position, the longer would be the A to LV time required to obtain optimal filling. This expectation was not borne out by the data. In 50% of cases the septal AVopt was greater than the lateral AVopt. The reason for this is unclear but may be due to the underlying pattern of myocardial scar affecting ventricular depolarisation or contraction patterns.

**Differences in AV delay optimum between positions are small, and therefore their haemodynamic impact is very small indeed**

The of the shape of the haemodynamic response is broadly a parabola. In a parabola, for every halving of a horizontal distance, the vertical distance is not halved but quartered. Setting an AV delay slightly away from the true optimum (a small horizontal displacement) produces an extremely small downward impact in haemodynamics (vertical displacement). So while large errors in AV delay programming (eg of the order of 50 ms), can have a large impact on haemodynamics, a small error (eg of the order of 10ms) has a haemodynamic impact that is not 1/5 but 1/25 as large.

Moreover, different patients have different degrees of curvature of their parabolas. In some patients the parabolas are relatively shallow so that even large changes in AV delay do not have a sizable impact on haemodynamics. Our study did not deliberately select patients with steep or shallow curves and instead shows a representative sample illustrating the spectrum of possibilities.

The combination of the consistency within a patient on which AV delay is optimal, and the parabolic nature of the haemodynamic response curve, results in their being no substantial haemodynamic loss from programming an AV delay derived from a different lead location.

Even though small, this haemodynamic decrement will always meet criteria for statistical significance since the statistical test is determining whether the haemodynamic changes are consistent with being drawn from a pool with mean zero. Since all the values must be negative by definition, they are not derived from a pool of mean zero, and unless a study is too small it will certainly find the haemodynamic effect to be statistically significant.

**Clinical implications**

There is a range of AV delays near the AV optimum where the haemodynamics are very similar to each other. Shortening or lengthening AV delay beyond this range has a disproportionally large effect on cardiac function and can render CRT to be no better than RV pacing or even worse. The deleterious effects of chronic RV pacing on outcomes in patients with heart failure are well described (24). Programming markedly inappropriate AV delay in CRT is haemodynamically as harmful as applying RV pacing and could have similar harmful clinical outcomes.

There is a practical benefit to knowing that haemodynamics are effected by AV delay disproportionately as one moves AV delay further from the optimum, and knowing that there is little haemodynamic loss from programming an AV that is the optimum AV from a different lead position. It means that if using haemodynamics to guide lead placement there is no need to conduct a high-resolution haemodynamic curve for every tested lead location. It is sufficient to use one lead location to calculate the AV delay optimum and then use that optimum as a single AV delay setting to compare different reachable lead positions.

**Limitations**

Our study was conducted in patients under general anaesthetic. This was to allow other aspects of the study procedure to be performed safely. It is not known whether ambulatory patients will show the same pattern.

Time constraints limited our experimental plan to four haemodynamic curves per patient and were therefore unable to test all locations. Because our study enrolled patients who had failed lead implantation through the coronary sinus, the protocol could only compare different endocardial LV lead positions.

We do not know if identifying and programming patients acute AVopt improves either symptoms or outcome. However, assessing AVopt using acute haemodynamic curve fitting in combination with optimising the VV delay by the same method, is non-inferior to echocardiographic optimisation on the improvement of symptoms, oxygen consumption, ejection fraction and NT pro BNP at 6 months (10).

Our patient cohort consisted of a heterogenous group of pathologies with different patterns of diseased myocardium. Nevertheless, for almost all patients, almost all the responses showed a stereotyped parabolic pattern. This suggests that despite their underlying heterogeneity there is a common principle at work.

## 

**Conclusions**

The optimum haemodynamic AV delay differs between patients. It differs, to a more limited extent, between lead positions in a single patient but is superior to a pre programmed AV delay of 180ms. As a consequence of the relatively small variation in AVopt between lead position and the parabolic shape of the haemodynamic response curve, an AVopt calculated from one lead position can be applied to a different lead position with no meaningful reduction in haemodynamics. There may be a clinical benefit in using an optimised AV delay over a pre-programmed AV delay when assessing the optimal LV lead location. However, the process of identifying the optimal location for a lead can be disassociated from the process of finding the optimal AV delay, so that each process can be process can be conducted once with time spent on precision rather than having to test every combination of the two.

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**Tables**

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| --- | --- |
| Demographics | |
| Age yrs, mean (SD) | 66.5 (12.8) |
| Male, n (%) | 12 (71) |
| LVEF %, mean (SD) | 26 (7) |
| Aetiology, n (%)  Ischaemic  DCM  Sarcoid  Valvular | 10 (59)  4 (24)  2 (12)  1 (6) |
| QRS duration ms, mean (SD) | 167 (27) |
| QRS morphology, n (%)  LBBB  CHB RBBB/ICVD | 11 (65)  4 (24)  1 (6) |
| NYHA III-IV, n (%) | 6 (35) |

**Table 1 Baseline Patient Demographics:** Overall 17 patients included, Data presented as either mean (± standard deviation) or total number (percentage of total). LVEF – Left ventricular ejection fraction (%), DCM: Dilated cardiomyopathy, LBBB: Left bundle branch block, CHB: Complete heart block, RBBB: Right bundle branch block, IVCD: Interventricular conduction delay, AF: Atrial fibrillation, NYHA: New York Heart Failure symptom classification.

**Figures**

Graphical user interface

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**Figure 1 Three-Dimensional Anatomic Maps:** 3D anatomic shells of the left ventricle (LV) and right ventricle (RV) shown in both a modified right anterior oblique view (A) and modified left anterior oblique view (B) which also shows the Mitral and Aortic valve cut-outs. The Nine locations are marked on each shell and correlate to predefined locations shown on the polar plot (C). The mitral and aortic valve cutouts and RV shell are used to orientate the location of each location. The magnetically tracked roving LV lead is manipulated as close as possible to each location for pacing.

Diagram

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**Figure 2 Atrioventricular Optimisation Curve and Identifiying Opitmal Haemodynamic Left Ventricular Lead Location.** *Atrioventricular Optimisation Curve:*A - the mean of all peak systolic blood pressures (SBP) between each pacing transition are taken from the test (SBPtest) bi ventricular pacing setting and subtracted from the reference (SBPref) setting to give the relative change in systolic blood pressure between each setting (SBPrel).B - At least 8 replicates of SBPrel are performed. The mean change (and standard error) in systolic blood pressure pressure from the reference baseline is plotted (C). C - This process is repeated for each test atrioventricular delays at 40ms increments until intrinsic rhythm (or 350ms if in complete heart block). Curve fitting is used to then identify the optimal haemodynamic atrioventricular delay. *Left ventricular lead location haemodynamic assessment.*D - ECG and systolic blood pressure transduced from the left ventricle. Alternation technique performed between a reference of right ventricular pacing, DDD mode, AV delay of 120ms and a test setting of biventricular pacing at the the optimal AV delay. E - Column graph showing the mean (and standard error) improvement in systolic blood pressure during bi ventircular pacing when compared to right ventricular pacing with the roving left ventricular lead at each of the nine pre defined left ventricle sites. The red oval denotes the left ventricular lead site which delivers the greatest improvement in systolic blood pressure during biventicular pacing.

***Diagram

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**Figure 3 Assessing the potential loss in systolic blood pressure using the AVopt from one location in a different location**.This patient had optimisations done in 4 lead locations. Using each lead location in turn as a reference, the loss of blood pressure that would be obtained had we used the optimum from one of the other lead locations rather than this lead location was calculated. For example, taking Location 1 as the reference, had the AV optimum from Location 2 (ie 169 ms) been used, the blood pressure generated would have been an estimated 0.1 mmHg lower. Had we used the AV optimum from Location 3 (157 ms) it would have been 0.3 mmHg lower and so on. This calculation was then rerun with Location 2 used as the reference, testing the consequences of using the AV optima from Locations 1, 3 and 4. In total there are 4 possible references and 3 other lead location in each case, ie a total of 12 blood pressure decrements. The mean of these 12 is an estimate of the haemodynamic consequences of using the AV optimum from a different lead locations.

**Diagram

Description automatically generated**

**Diagram

Description automatically generated**

**Figure 4 a / b** **Atrio-biventricular haemodynamic optimisation curves with the left ventricular lead placed endocardially in up to 4 different locations**. (two panels with AV optimisation curves of all 17 patients)/ Acute blood pressure improvement (mmHg) assessed during atrio biventricular pacing across a range of AV delays. Pacing reference in all cases right ventricular dual chamber pacing with an AV delay of 120ms. Red line identifies the greatest mean optimal blood pressure improvement recorded during testing. The optimal AV delay was taken at the peak of the calculated curve and denoted with the grey line. Across each patient, although the AV delay varies between location this variation has little haemodynamic impact.

**Chart, box and whisker chart

Description automatically generated**

**Figure 5: Box and whisker plot showing the overall difference across all paitents and all locations in systolic blood pressure improvement at the optimal AV delay.** The improvement at the optimal AV delay is in green and that at a fixed paced AV delay of 180ms is in blue.