Variation in optimal hemodynamic atrio-ventricular delay of biventricular pacing with different endocardial left ventricular lead locations using precision hemodynamics

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Abstract

Introduction: It is not known whether the optimal atrioventricular (AV\textsubscript{opt}) delay varies between left ventricular (LV) pacing site during endocardial biventricular pacing (BiVP) and may therefore needs consideration.

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

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), AV\textsubscript{opt} increased systolic blood pressure during BiVP compared with RVP (relative improvement 6 mmHg, interquartile range [IQR] 4–9 mmHg). Compared to a fixed AV delay, the hemodynamic improvement at AV\textsubscript{opt} was higher (1 mmHg, IQR 0.2–2.6 mmHg, \( p \) < .001).

Within most patients (16/17), we observed a difference in AV\textsubscript{opt} between pacing sites (median paced AV\textsubscript{opt} 209 ms, IQR 117–250). Within this range, the hemodynamic impact of these differences was small (median loss 0.6 mmHg, IQR 0.1–2.6 mmHg).

Conclusion: Within a patient, different endocardial LV lead locations have slightly different hemodynamic AV\textsubscript{opt} which are superior to a fixed AV delay. The hemodynamic consequence of applying an optimum from a different lead location is small.

Keywords: atrioventricular delay, cardiac resynchronization therapy, endocardial left ventricular lead, heart failure, hemodynamic optimization
INTRODUCTION

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

When the LV lead is placed transvenously, there is a very restricted choice of positions for the lead tip. The alternative approach of endocardial LV pacing permits the LV lead to be placed in any location.\textsuperscript{5} There are limited data assessing the difference in AV\textsubscript{opt}, during endocardial atrio-BiVP with the LV lead at different locations. The hemodynamic consequences of this variation in the AV\textsubscript{opt}, if present within a patient, is also not known.

In this study, we use high-precision hemodynamics to look for changes in AV\textsubscript{opt} when the LV lead is moved to different endocardial positions during atrio-BiVP. We then compared the AV\textsubscript{opt} to a fixed AV delay of 180 ms.

METHODS

Study participants

Seventeen patients, with conventional indications for cardiac resynchronization therapy (CRT) but who had failed conventional LV lead placement via a coronary sinus branch or had limited response to therapy, were enrolled at a single center. All were implanted with an endocardial LV lead guided to a location that delivered the greatest improvement in systolic blood pressure (SBP) during BiVP. Patients provided written consent. All procedures and protocols complied with the 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 anesthetic. Activated clotting time was maintained above 250 s throughout the study with intravenous unfractionated heparin.

Right atrial (RA) and right ventricular (RV) pacing was performed with standard, fixed curve, quadripolar diagnostic catheters (Viking\textsuperscript{™} soft tip, Boston Scientific) placed at the location of the patient’s existing RA and RV leads. Atrio-BiVP was performed with a 7.5 Fr bidirectional, open irrigated, magnetically tracked ablation catheter (IntellaNav 8I, Boston Scientific) used as a roving LV lead. This was placed in the LV via an 8.5 Fr steerable sheath (Agilis NXT, St Jude Medical). The RA, RV, and LV catheters were connected to an external cardiac resynchronization pacemaker (Medtronic Syncra. Medtronic), through the mapping system via custom-made leads (Biomedical Engineering, Royal Brompton and Harefield). This allowed for quick and simple alternation between dual chamber (RA and RV) and BiVP using a conventional programmer (CareLink programmer, Medtronic).

A three-dimensional anatomic map of the LV was created with a high-resolution basket mapping catheter (Orion\textsuperscript{™}, Boston Scientific) using the Rhythmia\textsuperscript{™} mapping system (Boston Scientific) via the transseptal route. The shell was marked with three-dimensional (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.

LV electrical delay was measured with QLV and assessed at each of the tested locations during the patient’s baseline rhythm. This was performed in a standard fashion by measuring from the onset of the QRS in V1 on the surface electrocardiogram to the first large positive or negative peak of the local electrogram measured from the roving LV lead.

Hemodynamic assessment

SBP was transduced through the tip of the steerable sheath. Raw blood pressure waveforms and 12 lead ECG signals were outputted from a conventional mapping system (LabSystem Pro EP recording system, Boston Scientific) into a custom-designed recording system (Biomedical Engineering, Royal Brompton and Harefield). All recordings were performed during steady-state anesthesia. Any dampening of blood pressure recordings from the sheath tip prompted a repeat assessment. The effect of each pacing setting on SBP was assessed using the alternation technique described and validated by Whinnett et al.\textsuperscript{6} In brief, this averages the change in SBP during multiple alternations between a reference pacing setting (SBP\textsubscript{ref}) and a test pacing setting (SBP\textsubscript{test}). This accounts for the beat-to-beat variability in pressure from respiration and peripheral vascular resistance. By protocol, the SBP\textsubscript{ref} paced setting throughout the study was set as DDD, 10 beats above intrinsic sinus rate, with a fixed AV delay of 120 ms and RV pacing. This was chosen to provide a reliable reference which could be used for all patients and prevent fusion. SBP\textsubscript{test} was set to atrio-BiVP across each tested AV delay for the hemodynamic AV optimization curve at each location. During BiVP the LV-RV pacing offset was kept at 0 ms for all assessments and kept at the same rate as SBP\textsubscript{ref}. A minimum of eight alternations were performed for each AV delay tested.

AV optimization curve

The SBP\textsubscript{test} AV delay test settings started at 40 ms, and were increased in 40 ms increments to either the intrinsic AV delay or 350 ms (in the case of complete heart block). Curve-fitting was then used to identify the AV delay which delivered the greatest improvement in SBP during BiVP, the AV\textsubscript{opt}. Figure 2.\textsuperscript{7} A full BiVP hemodynamic AV optimization curve was performed with the roving LV lead placed in four predefined locations.
These were preferentially mid-lateral wall, mid-septum (or a close alternative site if no capture), site of greatest improvement in SBP, and final LV lead implant site.

2.5 | Data processing

2.5.1 | 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

2.5.2 | Assessing the hemodynamic change with a fixed AV delay and the hemodynamic loss of using the AVopt from one LV lead location at a different lead location

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

Assessment of the potential hemodynamic 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, that is, location AVopt 2. This was then used in the equation of the hemodynamic curve from an alternative location, that is, 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 optimization 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 hemodynamic improvement from AVopt 2 is subtracted from of AVopt 1 and this is the potential hemodynamic loss in SBP. This process is repeated multiple times for all AVopt at all lead locations to identify the median potential blood pressure loss (Figure 3).

2.6 | Statistics

Data are presented as mean (±standard deviation, ±standard error), median (and interquartile range [IQR]), and as the proportion for continuous, categorical, and count variables as appropriate. Normality was assessed using the Shapiro–Wilk method. Nonparametric comparisons were made using Wilcoxon’s signed ranks test. Correlation was assessed using linear regression and means compared using using t test or ANOVA as required. All analysis was performed using SPSS version (IBM SPSS, Version 24). A p value of <.05 was considered to indicate a statistically significant difference.

3 | RESULTS

Seventeen patients with conventional indications for BiVP underwent endocardial LV pacing site mapping. Demographics are presented in Table 1. The overall mean QLV from all tested locations was 90 ms (standard deviation [SD] 33 ms). There was no difference between the mid-lateral wall and the mid-septum (QLV mid-lateral vs. mid-septum; 96 ms [SD 31 ms] vs. 71 ms [SD 31 ms], p = .12).
FIGURE 2  AV optimization curve and identifying optimal hemodynamic left ventricular lead location. **AV optimization curve:** (A) the mean of all peak SBP between each pacing transition are taken from the test (SBP_{test}) biventricular pacing setting and subtracted from the reference (SBP_{ref}) setting to give the relative change in SBP between each setting (SBP_{rel}). (B) At least eight replicates of SBP_{rel} are performed. The mean change (and standard error) in SBP from the reference baseline is plotted (C). (C) This process is repeated for each test AV delays at 40 ms increments until intrinsic rhythm (or 350 ms if in complete heart block). Curve fitting is used to then identify the optimal hemodynamic AV delay. **Left ventricular lead location hemodynamic assessment.** (D) ECG and SBP transduced from the left ventricle. Alternation technique performed between a reference of right ventricular pacing, DDD mode, AV delay of 120 ms and a test setting of biventricular pacing at the optimal AV delay. (E) Column graph showing the mean (and standard error) improvement in SBP during biventricular pacing when compared to right ventricular pacing with the roving left ventricular lead at each of the nine predefined left ventricle sites. The red oval denotes the left ventricular lead site which delivers the greatest improvement in SBP during biventricular pacing. AV, atrioventricular; ECG, electrocardiography; SBP, systolic blood pressure.
3.1 | Hemodynamic effect of AV delay during BiVP

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 Patients 7 and 9 and two in Patient 15) as the AV curve \( R^2 = 0.8 \), which left 63 datasets. In 98% (62/63), CRT pacing improved SBP against RV pacing (overall median improvement 6 mmHg, IQR 4–9 mmHg, left bundle branch block [LBBB] only median improvement 6.5 mmHg, IQR 4–7 mmHg). Supporting Information: Table 1. Each patient, in most cases, the hemodynamic curves had similar shapes at all locations Figure 4. Signal to noise ratio was good, averaging 24.4 (SD 18.2). The hemodynamic curves fitted well to a parabola, with mean \( R^2 = 0.95 \) (SD 0.1).

3.2 | The overall difference in improvement in SBP at the optimal AV delay versus at a fixed paced AV delay of 180 ms

Across all locations in all patients, the median improvement in blood pressure at the \( AV_{opt} \) was 6 mmHg (IQR 4–9 mmHg), this was similar in those patients with LBBB (median improvement 5 mmHg, IQR 4–8 mmHg). When comparing all locations, this was significantly higher than that with a fixed-paced AV delay of 180 ms (5 mmHg, 3–7 mmHg, \( p < .001 \)), Figure 5. The range in differences in blood pressure at each site between the \( AV_{opt} \) and a fixed AV delay was 0–11 mmHg, and was no different when examining those with LBBB only (range 0–11 mmHg).

3.3 | Difference in optimal AV delay at each location during BiVP

Across all locations in all patients, the median \( AV_{opt} \) was 209 ms (IQR 117–250) and in those with LBBB was 218 ms (IQR 174–251). The median calculated \( AV_{opt} \) range within each patient was 39 ms (IQR 20–62), and for those for LBBB were 42 ms (IQR 27–67). Supporting Information: Table 1. Within each patient, in all but one case, there were significant differences in the \( AV_{opt} \) at different locations \((p < .001)\). A total of 37% of the time Locations 2, 3, or 4 had an \( AV_{opt} \) that was more than 20 ms different from the \( AV_{opt} \) of Location 1.

The median difference in \( AV_{opt} \) between the lateral wall and mid-septal locations was 16 ms (IQR 7–29). This difference in \( AV_{opt} \) was statistically significant 85% of the time. The \( AV_{opt} \) with the LV lead at the lateral wall was greater than the septum in 50% of cases. The difference in \( AV_{opt} \) between the septum and the lateral wall was >20 ms 31% of the patients, Supporting Information: Table 2.
This study shows that AV delay optimum differs between patients and that programming patients with a nominal AV delay may lead to submaximal acute hemodynamic 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 180 ms. Third, programming the optimal AV delay identified at a different LV location, in the same patient, has only a very small impact on acute hemodynamic 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.

### 4.1 Identifying the optimal AV delay has important hemodynamic benefits

The acute hemodynamic effects of AV optimization are well documented. Improving active and passive filling times contribute to stroke volume and overall cardiac output. The ideal AV delay between patients is also known to vary, with the optimum delay being conventionally identified using Doppler echocardiography aiming to maximize the separation between E and A wave on trans mitral Doppler. The CARE HF and MIRACLE trials used this method to optimize all patients randomized to CRT and this may have impacted on outcomes.

Several studies have addressed targeting the ideal location for the LV lead to improve patient response to therapy. Although these have shown significant acute hemodynamic 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 hemodynamic change when pacing the different endocardial sites in the left ventricle is driven by lead location rather than AVopt. However, we also show the additional hemodynamic benefit of AV optimization 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 and 11 mmHg 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, hemodynamics, implantable sensors, and the use of device algorithms. 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 optimization and a fixed delay of 120 ms, or some benefits with at least equivalency to echo optimization.

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

4.2 \hspace{1em} The optimal AV delay differs between people and this has an important hemodynamic effect

Two previous acute hemodynamic studies have observed significant effects of changing AV delay. One tested delays of 30, 60, 100, and 140 ms\textsuperscript{21} and the other tested two AV delays, a short (defined as the minimum AV delay to allow complete ventricular capture) and long (50 ms longer).\textsuperscript{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 200 ms.
One further study of 20 patients has performed full hemodynamic AV_{opt} curves, using the same protocol which we employed, from two epicardial locations along the coronary sinus. It demonstrated that, within patients, the curve shape and AV_{opt} are usually similar. The locations compared tended to be between the basal anterior and mid-lateral (in either the antero-lateral, lateral or posterolateral positions). This study also shows that between locations the shape of the curves tends to be similar, albeit with a slightly greater variation in the AV_{opt}.^{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 AV_{opt} was greater than the lateral AV_{opt}. The reason for this is unclear but may be due to the underlying pattern of myocardial scar affecting ventricular depolarization or contraction patterns.

4.3 | Differences in AV delay optimum between positions are small, and therefore their hemodynamic impact is very small indeed

The shape of the hemodynamic 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 hemodynamics (vertical displacement). So while large errors in AV delay programming (e.g., of the order of 50 ms) can have a large impact on hemodynamics, a small error (e.g., of the order of 10 ms) has a hemodynamic 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 hemodynamics. 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 hemodynamic response curve, results in there being no substantial hemodynamic loss from programming an AV delay derived from a different lead location.

Even though small, this hemodynamic decrement will always meet the criteria for statistical significance since the statistical test is determining whether the hemodynamic 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 hemodynamic effect to be statistically significant.

4.4 | Clinical implications

There are a range of AV delays near the AV optimum where the hemodynamics 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 hemodynamically as harmful as applying RV pacing and could have similar harmful clinical outcomes.

There is a practical benefit to knowing that hemodynamics are affected by AV delay disproportionately as one moves AV delay further from the optimum, and knowing that there is little hemodynamic loss from programming an AV that is the optimum...
AV from a different lead position. It means that if using hemodynamics to guide lead placement, there is no need to conduct a high-resolution hemodynamic 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.

LV endocardial pacing provides many more options in terms of LV pacing site compared with epicardial pacing via the coronary sinus. Therefore, it is useful to have a way of comparing different pacing sites when selecting the final implant location. Acute hemodynamic assessment is one way of comparing the impact of pacing at different sites. The aim of our study was to assess whether a range of different AV delay needs to be tested at each pacing site which would prolong the assessment process. Fortunately, it appears that performing one AV assessment at one location is sufficient to identify a patient’s individual AV optima which will greatly simplify the protocol. This is likely to be true regardless of which ever hemodynamic measure is used.

Our findings suggest that the AV$_{\text{opt}}$ is patient-specific and, therefore, we would advocate that this is assessed in future studies that investigating different pacing techniques. We would encourage using an approach which assesses the overall impact on cardiac function such as SBP or stroke volume rather than specific measures looking at one aspect such as filling or activation time. The protocol performed should also take adequate steps to reduce biological noise.

4.5 Limitations

Our study was conducted in patients under general anesthetic. 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 hemodynamic 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 used SBP to ensure high precision. It is possible that if we used a different hemodynamic measure that we may have identified a slightly different optimum.$^{25}$ However, the purpose of this experiment was a within-patient comparison of the impact of LV endocardial pacing site on optimal AV delay during atrio-BiVP. Therefore, it is highly likely that if a different hemodynamic measure was used, the results would be similar.

We do not know if identifying and programming patients acute AV$_{\text{opt}}$ improves either symptoms or outcomes. However, assessing AV$_{\text{opt}}$ using acute hemodynamic curve fitting in combination with optimizing the VV delay by the same method, is non-inferior to echocardiographic optimization on the improvement of symptoms, oxygen consumption, ejection fraction, and NT pro-BNP at 6 months.$^{10}$

Our patient cohort consisted of a heterogeneous 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.

5 | CONCLUSIONS

The optimum hemodynamic AV delay differs between patients. It differs, to a more limited extent, between lead positions in a single patient but is superior to a preprogrammed AV delay of 180 ms. As a consequence of the relatively small variation in AV$_{\text{opt}}$ between lead position and the parabolic shape of the hemodynamic response curve, an AV$_{\text{opt}}$ calculated from one lead position can be applied to a different lead position with no meaningful reduction in hemodynamics. There may be a clinical benefit in using an optimized AV delay over a preprogrammed 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 conducted once with time spent on precision rather than having to test every combination of the two.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data is available on appropriate request to the corresponding author.

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SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

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