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Atrioventricular optimization in cardiac resynchronization therapy with quadripolar leads: should we optimize every pacing configuration including multi-point pacing?

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Aims

This study aims to define an atrioventricular (AV) delay optimization method for cardiac resynchronization therapy (CRT) with a quadripolar left ventricular (LV) lead based on intrinsic conduction intervals.

Methods and results

Heart failure patients with a left bundle branch block underwent CRT implantation with a quadripolar LV lead. Invasive LV pressure–volume loops were recorded during four biventricular and three multi-point pacing (MPP) settings, using four patient-specific paced AV delays. Haemodynamic response was defined as change in stroke work ($\Delta\%SW$) compared to intrinsic rhythm and was related to the following conduction intervals: right atrial pacing to right ventricular sensing interval (RAP-RVs), Q to LV sensing interval normalized to QRS duration (QLV/QRSD), PR-interval, and P-wave duration. In 44 patients, the largest $\Delta\%SW$ ($104 \pm 76\%$) occurred at a paced AV delay of 128 ± 32 ms, at $47 \pm 9\%$ of RAP-RVs. Optimal AV delay of biventricular pacing (126 ± 26 ms) did not differ from MPP (126 ± 21 ms, $P = 0.29$). Intra-class correlation coefficient between optimal AV delays of different pacing configurations was 0.64 (0.45–0.78, $P < 0.001$). Although not statistically significant, $\Delta\%SW$ at 50% of RAP-RVs ($98 \pm 74\%$) was closer to the maximal achievable $\Delta\%SW$ increase than a fixed interval of 120 ms ($96 \pm 73\%$, $P = 0.60$). RAP-RVs, QLV/QRSD, PR interval, and P-wave duration were associated with the optimal AV delay in univariate analysis, but only RAP-RVs remained significantly associated in multivariate analysis ($R = 0.69$).

Conclusion

The AV delay that provides highest haemodynamic response is similar for various LV pacing configurations and for MPP. An AV delay $\sim 50\%$ of RAP-RVs creates an acute haemodynamic response close to the maximal patient-specific response.

Keywords

Cardiac resynchronization therapy • Atrioventricular delay • Pressure–volume loops • Optimization • Multi-point pacing • Quadripolar lead

Introduction

Cardiac resynchronization therapy (CRT) is an effective treatment for patients with advanced systolic heart failure and left ventricular

(LV) electrical conduction delay.¹ Cardiac resynchronization therapy aims to improve LV function with biventricular pacing, leading to electromechanical resynchronization.² Cardiac resynchronization therapy may thereby induce reverse remodelling and may lead to

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What's new?

- Atrioventricular (AV) delay optimization is determined based on invasive pressure–volume loops in patients with cardiac resynchronization therapy (CRT).
- The AV delay optimization increases haemodynamic response compared to fixed delays in most patients eligible for CRT with a quadripolar left ventricular (LV) lead.
- The AV delay with highest LV dP/dt_{max} is significantly longer compared to that providing highest increase in stroke work.
- An AV delay 50% of the right atrial pacing to right ventricular sensing interval provides an acute haemodynamic response that is close to the maximal patient-specific response.
- The paced AV delay with optimal haemodynamic response is similar for multiple LV pacing configurations and multi-point pacing.

improvements in functional status, exercise tolerance, and subsequently in morbidity and mortality.¹ These effects are however not seen in all CRT patients, as a considerable amount of patients do not respond significantly.³ Non-response to CRT is partly attributed to suboptimal device programming,⁴ which can be optimized using the atrioventricular (AV) delay. The AV delay influences several intracardiac mechanisms that directly impact LV filling, among which atrioventricular interaction is best known.⁵ The AV delay also affects intra- and interventricular interaction^{5,6} and optimization may lead to fusion of intrinsic conduction with either LV and/or right ventricular (RV) pacing.⁷ Optimization of the AV delay can increase acute haemodynamic performance.⁸ Numerous AV delay optimization methods have been proposed, with variable results.⁹ While algorithms using invasive optimization methods may be more reliable, non-invasive methods are more feasible for implementation in clinical practice.^{8,9} A relatively easy, fast, and non-invasive method is the use of intracardiac electrograms (IEGM) to define the AV delay based on measured conduction intervals.¹⁰ Although IEGM-based algorithms to optimize the AV delay are already included in current devices, most algorithms lack proper physiological support and are at best non-inferior to echocardiographic optimization methods.⁹ Moreover, it is unknown whether different LV pacing configurations of a quadripolar LV lead require different AV delays to achieve the maximum potential of CRT.

This study aims to define an AV delay optimization method for CRT with a quadripolar LV lead based on intrinsic conduction intervals. Patient-specific optimal AV delays are determined using pressure–volume (PV) loop analysis, obtained invasively and directly after CRT implantation. The optimal AV delay obtained during multiple pacing configurations of a quadripolar LV lead is compared.

Methods

This study is part of the OPTICARE-QLV trial, a multicentre observational study performed in three university medical centres in the Netherlands (University Medical Center Utrecht; VU University Medical Center, Amsterdam; and Maastricht University Medical Center, Maastricht), designed to investigate the benefits of quadripolar LV leads in

CRT by invasive PV loop analysis.¹¹ In total, 51 consecutive patients with moderate to severe heart failure New York Heart Association (NYHA Class II or III), LV ejection fraction $\leq 35\%$, sinus rhythm, optimal medical therapy, and a left bundle branch block (LBBB) according to the Strauss criteria were included.¹² Exclusion criteria were severe aortic valve stenosis, aortic valve replacement, or the presence of LV thrombus. All patients gave written informed consent. The study was performed according to the Declaration of Helsinki and in agreement with the local medical ethics committees.

Study protocol

An ECG was recorded prior to implantation for all patients, of which PR interval, P wave duration, QRS duration, and QRS morphology were noted. Patients also underwent echocardiography and cardiac magnetic resonance (CMR) imaging prior to device implantation. Cardiac magnetic resonance or echocardiography-derived LV volumes were used to calibrate the conductance catheter-derived baseline volumes. Cardiac resynchronization therapy implantation was performed under local anaesthesia. Right ventricular and right atrial (RA) leads were placed transvenously at conventional positions. The quadripolar LV lead was aimed at a tributary of the coronary sinus overlying the LV free wall at an anterolateral, lateral, or posterolateral site. After electrophysiological measurements, the three leads were connected to a CRT device.

Electrophysiological measurements

Electrophysiological measurements were performed using an on-site dedicated system. The electrophysiological system was connected to the surface ECG, and the implanted pacemakers lead to obtain simultaneous recordings. Delays of specific pacing modalities were recorded and delays between pacing spikes and local depolarization were measured. For each patient, the RA sensing to RVs interval (RAs-RVs) and RA pacing to RV sensing interval (RAp-RVs) was measured. For each quadripolar lead electrode, the Q on surface ECG to local LV depolarization (QLV), QLV normalized for intrinsic QRS duration (QLV/QRSD), and RV pacing to LV sensing interval (RVp-LVs), was measured.

Haemodynamic measurements

Directly after device implantation, a dedicated PV loop conductance catheter (CD Leycom, Zoetermeer, the Netherlands) was inserted via the femoral artery and placed in the LV cavity. Pressure–volume-loops were recorded for CRT with four paced AV delays during four biventricular pacing settings (BIV, i.e. RV and with one of the four electrodes of the quadripolar LV lead) and three multi-point pacing settings (MPP). The paced AV delay was set to approximate 80%, 60%, 40%, and 20% of the RAp-RVs interval. The measurements were non-randomized, and pacing configurations were programmed in a fixed order, to minimize programming errors. Only the order of the biventricular pacing configurations varied between patients, while the order of atrioventricular delays per pacing configuration was fixed. Biventricular pacing configurations always preceded MPP configurations. The protocol was limited to atrial pacing, to stabilize cardiac rhythm. The interventricular (VV) delay was kept constant at 40 ms LV first. Pressure–volume-loops of pacing configurations were recorded for 60 beats and 5–10 b.p.m. above intrinsic rhythm, after excluding all inappropriate beats (i.e. extra systoles and two subsequent beats). Pressure–volume-loops during intrinsic conduction (i.e. RA pacing) were recorded as baseline measurements before and after each biventricular pacing run for a period of 30 beats. Change in stroke work (SW) of pacing configurations was calculated as a percentage change ($\Delta\%SW$) compared to the mean of the two adjoining baseline measurements. This method allows for reliable assessment of the effects of CRT, by correction of potential baseline drift.¹³ For each BIV and MPP setting, a

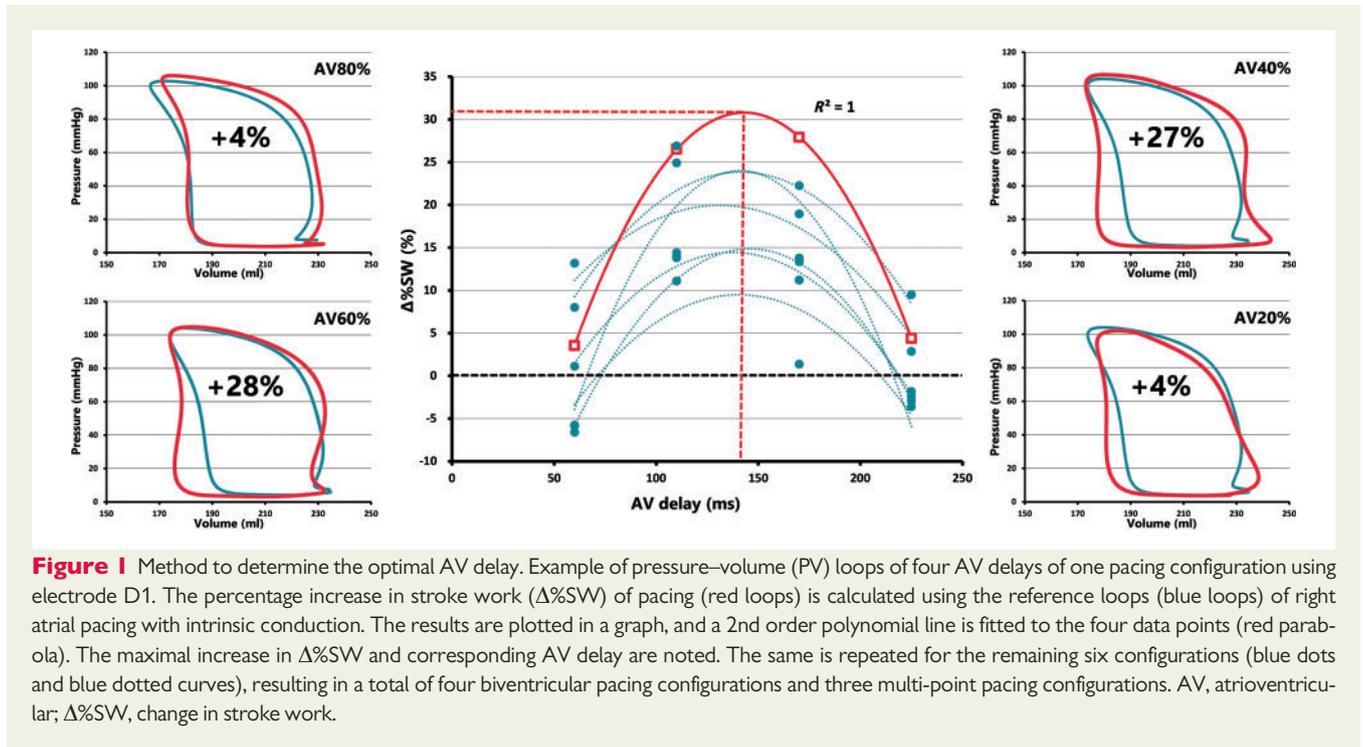


Figure 1 Method to determine the optimal AV delay. Example of pressure–volume (PV) loops of four AV delays of one pacing configuration using electrode D1. The percentage increase in stroke work ($\Delta\%SW$) of pacing (red loops) is calculated using the reference loops (blue loops) of right atrial pacing with intrinsic conduction. The results are plotted in a graph, and a 2nd order polynomial line is fitted to the four data points (red parabola). The maximal increase in $\Delta\%SW$ and corresponding AV delay are noted. The same is repeated for the remaining six configurations (blue dots and blue dotted curves), resulting in a total of four biventricular pacing configurations and three multi-point pacing configurations. AV, atrioventricular; $\Delta\%SW$, change in stroke work.

parabolic curve was fitted to the four data points (Figure 1). All fitted curves with a physiological plausible shape (i.e. downward opening with a determinable maximum) and a coefficient of determination ($R^2 \geq 0.7$) were used for further analysis. Of these curves, the maximal increase in $\Delta\%SW$ and corresponding AV delay were determined. For each patient, the maximal $\Delta\%SW$ and corresponding AV delay (AV_{OPT}) was compared to $\Delta\%SW$ based on a fixed AV delay of 120 ms, 130 ms, 160 ms, and 180 ms, determined in the fitted curve. Lastly, the change in $\Delta\%SW$ based on 50% of the RAP–RVs delay ($AV_{50\%}$) was calculated using the co-ordinates of the fitted optimization curve (Figure 2).

Statistical analysis

Statistical analysis was performed using SPSS (SPSS statistics 23.0, IBM, New York, NY, USA). Mean and standard deviation or median and interquartile range are given depending on normality of data. The difference in baseline characteristics between patients in- and excluded in the study was analysed using a Student's *t*-test or Mann–Whitney *U* test, dependent on normality of data, or a χ^2 test in case of categorical variables. Subgroups were compared using similar tests. Optimal AV delays per pacing setting, for SW and dP/dt_{max} , for BIV and MPP, and increase in $\Delta\%SW$ of each AV-optimization strategy were compared using paired *t*-tests. The optimal AV delay per setting was compared with a Pearson correlation coefficient and intra-class correlation coefficient. The univariate relation of predictors for the optimal AV delay were analysed with linear regression analysis. Univariate predictors with a *P*-value < 0.10 were tested in a multivariate linear regression analysis. A *P*-value below 0.05 was considered significant for all tests.

Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Results

Fifty-one patients were included in the main study, of which 44 were used for the present analysis. Reasons for exclusion were: unreliable baseline loops ($n = 3$), AV optimization curves without a physiological plausible curvature or curves with a low ($R^2 < 0.7$) coefficient of determination ($n = 4$). Patients excluded from the analysis had worse diastolic function, with statistically significant higher E/E' , while left atria tended to be larger (Table 1). In patients included in the final analysis, the paced AV delay with maximal increase in $\Delta\%SW$ was 128 ± 32 ms, while the intra-individual variation was 30 ± 14 ms. Paired *t*-tests showed that there were no statistically significant differences in the optimal AV delay between electrodes (D1: 134 ± 32 ms, M2: 125 ± 29 ms, M3: 123 ± 23 ms, P4: 123 ± 24 ms, all *P* = non-significant). There was also no difference in the optimal AV delay between biventricular pacing (126 ± 26 ms) and MPP (126 ± 21 ms, $P = 0.29$). Correlation of the optimal AV delay between the pacing configurations was high (Table 2). Intra-class correlation coefficient for average measures of the optimal AV delay was 0.64 (0.45–0.78, $P < 0.001$). Examples of AV delay optimization for three patients are depicted in Figure 2. The optimal AV delay lead to an increase in $\Delta\%SW$ of $104 \pm 76\%$. The AV delay with maximal increase in $\Delta\%dP/dt_{max}$ was longer compared to the optimal AV delay for $\Delta\%SW$ (160 ± 33 vs. 128 ± 32 ms $P < 0.001$). Atrioventricular optimization led to a mean increase in $\Delta\%dP/dt_{max}$ of $16 \pm 11\%$ as compared to intrinsic conduction.

Conduction intervals and optimal atrioventricular timing

A longer optimal paced AV delay was observed in patients with prolonged PR-interval (> 200 ms) compared to patients with a normal

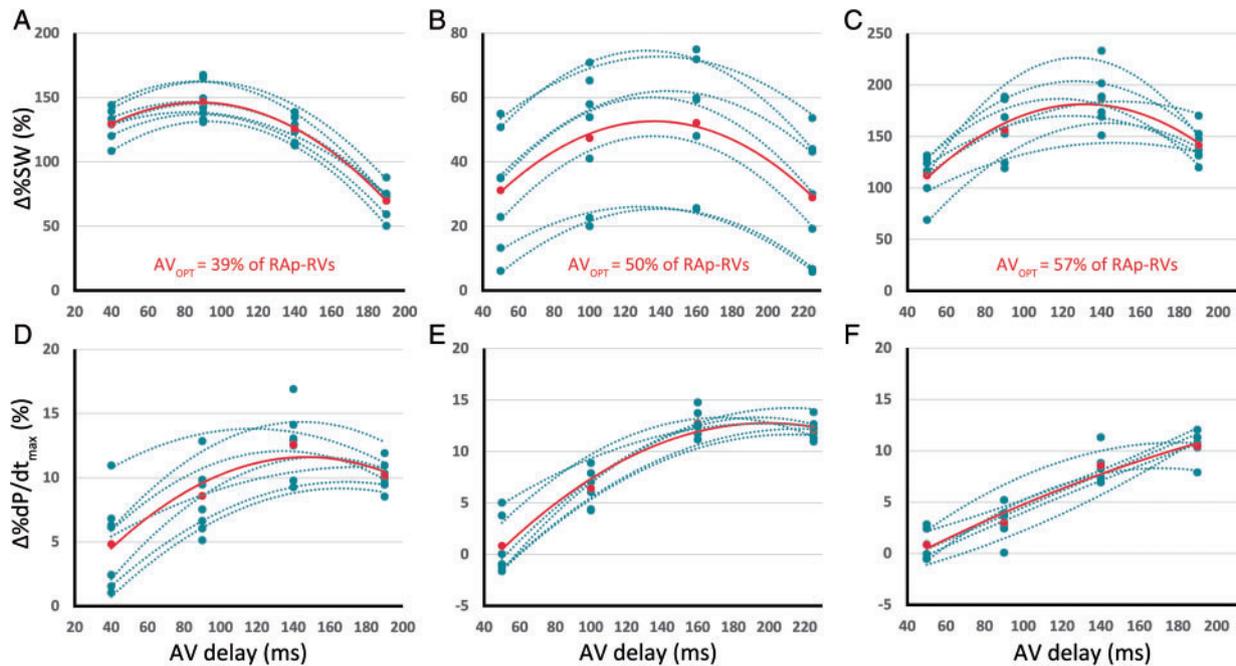


Figure 2 Example of AV delay optimization. Change in stroke work ($\Delta\%SW$) in the upper panels (A–C) and $\Delta\%dP/dt_{max}$ in the lower panels for three cases (D–F). For each case, up to seven pacing configurations (single- and multi-point) were tested using four AV delays, which are represented by blue dots. The average of all measurements is indicated with black dots. A 2nd order polynomial curve was fitted for each set: pacing configurations (blue dotted curves), average (black dotted curve), and maximum (red solid curve). AV, atrioventricular; $\Delta\%SW$, change in stroke work.

PR-interval (154 ± 32 ms vs. 118 ± 27 ms, $P = 0.001$, Figure 3). Male patients tended to have longer AV delays compared to females (135 ± 32 vs. 117 ± 31 ms, $P = 0.08$). Patients with a NYHA functional Class II also tended to have longer optimal AV delays compared to those NYHA III patients (135 ± 31 ms vs. 115 ± 33 ms, $P = 0.05$). The correlation of ECG derived parameters (i.e. P-wave duration and PR-interval) with the optimal AV delay were all statistically significant (Figure 4). The same accounted for the intracardiac electrogram derived parameters (i.e. RAp-RVs and RAs-RVs). Univariate linear regression showed that several parameters of conduction delay (RAp-RVs, RAs-RVs, P-wave duration, PR interval, and QL/QRsd) were significantly related to the optimal AV delay (Table 3). The strongest relation was seen between RAp-RVs and AV_{OPT} . The optimal AV delay was $47 \pm 9\%$ of the RAp-RVs delay and 4 ± 29 ms longer than P-wave duration. The optimal AV delay can be more precisely calculated using the equation: $AV_{OPT} = 1.15 \times RAp-RVs - 186$ ms. The multivariate linear regression analysis showed that only RAp-RVs remained associated with the optimal AV delay ($R = 0.69$, $P < 0.001$).

Haemodynamic response

Compared to the other strategies, the change in $\Delta\%SW$ with $AV_{50\%}$ ($98 \pm 74\%$) was closest to the maximal benefit achievable. The patient-specific effect $AV_{50\%}$ showed heterogeneous results, with a considerable amount of patients with an over- or underestimation of the optimal AV delay (Figure 5). Nevertheless, only a four patients with normal PR conduction (PR interval: 156 ms) required much shorter AV delays and showed a difference in $\Delta\%SW$ of $>10\%$

between $AV_{50\%}$ and AV_{OPT} . However, the benefit of $AV_{50\%}$ was small and not significantly different compared to fixed delays of 120 ms ($96 \pm 73\%$, $P = 0.29$) or 130 ms ($95 \pm 72\%$, $P = 0.08$). Nevertheless, pacing at longer AV delays (i.e. 160 ms, 180 ms, and at 70% of RAp-RVs) showed significantly lower $\Delta\%SW$ values ($85 \pm 66\%$, $73 \pm 61\%$, $73 \pm 63\%$, respectively, $P < 0.005$ compared to $AV_{50\%}$, AV_{120ms} , and AV_{130ms}).

Discussion

Conduction intervals derived from the intracardiac electrogram can be used to estimate the AV delay with optimal haemodynamic response in patients with CRT. The mean optimal AV delay was dependent on intrinsic conduction delays and corresponded with $\sim 50\%$ of the RAp-RVs delay. Therefore, an AV delay based on 50% of the RAp-RVs interval can be used to optimize the AV delay, to achieve an almost optimal, patient specific, effect in haemodynamic response. The AV delay with optimal haemodynamic benefit is similar for all pacing configurations of a quadripolar LV lead, advocating optimization of a single setting before comparison of all possible pacing sites and MPP.

Atrioventricular delay optimization: patient specific or fixed?

To our knowledge, this is the first study on AV delay optimization in CRT with quadripolar LV leads using PV-loop analysis. Our study showed that the optimal paced AV delay is ~ 130 ms determined by

Table 1 Baseline characteristics of study population and excluded subjects

	Study population (n = 44)	Excluded subjects (n = 7)	P-value
Age (years)	66 ± 10	69 ± 5	0.320
Sex (% male)	28 (63%)	4 (57%)	0.741
NYHA class, n (%)			
II	29 (66%)	5 (71%)	0.774
III	15 (34%)	2 (29%)	
Type of CMP, n (%)			
DCM	28 (63%)	4 (57%)	0.741
ICM	16 (36%)	3 (43%)	
P-wave duration (ms)	123.5 ± 12.7	122.0 ± 18.8	0.776
PR interval (ms)	184.0 ± 31.5	179.1 ± 25.4	0.694
QRS duration (ms)	175.1 ± 13.8	178.5 ± 9.9	0.535
QLV/QRSd (%)	83.5 ± 9.5	87.9 ± 4.3	0.246
LV EDV (mL)	198 (169–241)	240 (184–304)	0.268
LV ESV (mL)	148 (106–172)	180 (136–252)	0.234
LV EF (%)	28.9 ± 8.4	23.4 ± 6.5	0.105
E/A ratio	0.65 (0.49–0.99)	1.30 (0.72–1.50)	0.118
E/E'	12.2 (10.1–16.0)	18.4 (13.7–27.1)	0.042
LA size (mL/m ²)	35.7 (28.2–41.2)	40.8 (35.1–60.2)	0.052
¹⁰ log BNP (pmol/L)	1.87 ± 0.56	2.15 ± 0.47	0.219
Creatinine (μmol/L)	90.4 ± 23.5	100.6 ± 41.2	0.549
RAp-RVs (ms)	274.3 ± 49.1	273.6 ± 23.4	0.970
RAs-RVs (ms)	201.9 ± 31.4	202.1 ± 47.4	0.985
QLV _{max} (ms)	146.2 ± 19.7	156.9 ± 11.8	0.172
QLV/QRSd (%)	83.5 ± 9.5	87.9 ± 4.3	0.246
RVp-LV _{smax} (ms)	157.6 ± 24.9	173.9 ± 23.0	0.112
Optimal AV delay for SW (ms)	128.0 ± 32.2	126.8 ± 59.6 ^a	0.940
Optimal AV delay for dP/dt _{max} (ms)	159.5 ± 33.0	158.7 ± 23.1	0.950

LV volumes and ejection fraction are based on echocardiography.

AV, atrioventricular; BNP, brain natriuretic peptide; CMP, cardiomyopathy; DCM, dilated cardiomyopathy; ECG, electrocardiogram; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; ICM, ischaemic cardiomyopathy; LA, left atrial; LV, left ventricular; NYHA, New York Heart Association; QLV_{max}, maximal delay between Q on surface ECG and LV depolarization; QLV/QRSd, ratio between QLV and intrinsic QRS duration; RAp-RVs, right atrial pacing to right ventricular sensing interval; RAs-RVs, right atrial sensing to right ventricular sensing interval; RVp-LV_{smax}, maximal conduction interval between right ventricular pacing to left ventricular sensing; SW, stroke work.

^aSome patients were excluded because of unreliable baseline loops and still showed AV optimization curves with a physiological shape and R² > 0.7.

Bold P-values are below 0.05 and therefore statistically significant.

Table 2 Correlation of optimal atrioventricular delays between pacing configurations

	BIV1	BIV2	BIV3	BIV4	MPP1	MPP2	MPP3
BIV1		0.690*	0.872*	0.763*	0.833*	0.895*	0.668*
BIV2	0.690*		0.878*	0.806*	0.885*	0.836*	0.732*
BIV3	0.872*	0.878*		0.785*	0.951*	0.925*	0.796*
BIV4	0.763*	0.806*	0.785*		0.916*	0.871*	0.791*
MPP1	0.833*	0.885*	0.951*	0.916*		0.940*	0.850*
MPP2	0.895*	0.836*	0.925*	0.871*	0.940*		0.498 [†]
MPP3	0.668*	0.732*	0.796*	0.791*	0.850*	0.498 [†]	

Matrix of Pearson correlation coefficients of the optimal atrioventricular delays for each pacing configuration. BIV1 to -4 are biventricular pacing configurations with one of the quadripolar electrodes. MPP1 to -3 are multi-point pacing configurations.

*P < 0.001;

[†]P < 0.05.

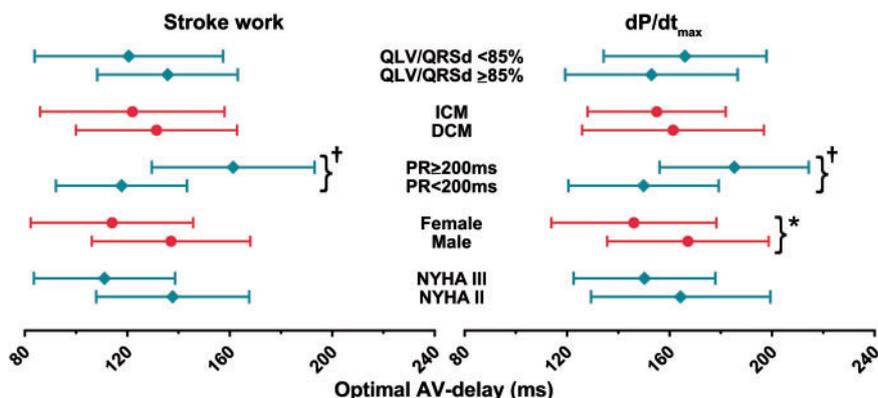


Figure 3 Optimal atrioventricular delay of specific subgroups. Atrioventricular (AV) delay with optimal haemodynamic response measured as change in stroke work and dP/dt_{max} . Categories include the QLV/QRSD, type of cardiomyopathy: DCM and ICM. PR interval above or below the cut-off value for 1st degree AV block (i.e. 200 ms), gender, and type of NYHA functional class. Statistical significant difference with * $P < 0.05$; † $P < 0.002$. AV, atrioventricular; DCM, dilated cardiomyopathy; ICM, ischaemic cardiomyopathy; QLV/QRSD, ratio between Q to left ventricular sensing delay and QRS duration ratio; NYHA, New York Heart Association.

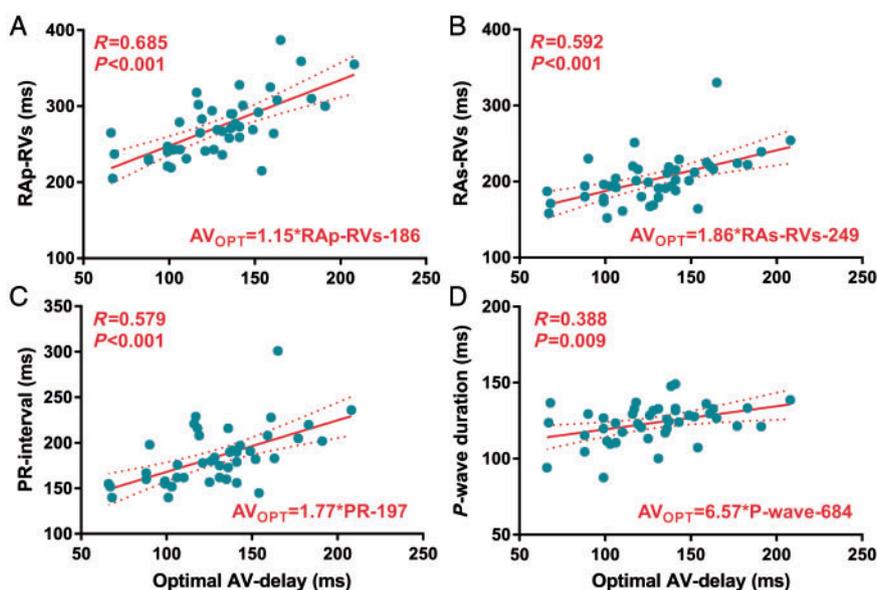


Figure 4 Correlation plots of parameters with the optimal AV delay based on stroke work. Correlation of (A) RAp-RVs delay, (B) right atrial sensing to right ventricular sensing delay (RAs-RVs), (C) PR interval, and (D) P-wave duration with the optimal AV delay based on maximal percentage change in stroke work. The correlation coefficient (R) and P -value (P) are given for each plot, as well as the equation of the fitline between the predictor and the optimal AV delay. The outlier in B and D is caused by a patient with severe AV conduction delay. AV, atrioventricular; AV_{OPT} , optimal atrioventricular delay; RAp-RVs, right atrial pacing to right ventricular sensing.

$\Delta\%SW$ and ~ 160 ms by LV dP/dt_{max} , which is shorter than earlier results of our group (i.e. optimal paced AV delay with LV dP/dt_{max} of 180 ms).⁸ The difference between RAs-RVs and RAp-RVs was ~ 70 ms in this study and implementation of the $AV_{50\%}$ algorithm would result in an optimal sensed AV delay 35 ms shorter than the paced AV delay (i.e. ~ 100 ms). The sensed AV delay would be shorter compared to values found in previous studies (i.e. SMART-

AV: 120 ms) and work of our own group (i.e. 130 ms).^{8,9} However, those results were based on LV dP/dt_{max} , which only reflects the rate of LV pressure changes in the isovolumetric contraction phase. Left ventricular dP/dt_{max} is highest at fusion of intrinsic conduction and ventricular pacing, which occurs at relative long AV delays,⁸ despite reduced diastolic filling properties. Results on PV-loops incorporate information on pressure and volume changes throughout the entire

Table 3 Univariate and multivariate relation of predictors for the optimal AV delay

Variable	Univariate			Multivariate		
	B (SD)	R	P-value	B (SD)	R	P-value
RAp-RVs (ms)	0.55 (0.09)	0.69	<0.001	0.54 (0.09)	0.69	<0.001
RAs-RVs (ms)	0.60 (0.13)	0.59	<0.001			0.977
P-wave duration (ms)	0.99 (0.36)	0.39	0.009			0.167
PR interval (ms)	0.59 (0.13)	0.58	<0.001			0.190
QRS duration (ms)	-0.09 (0.36)	0.04	0.800			.
QLV (ms)	-0.43 (0.24)	0.26	0.087			.
QLV/QRSD (%)	-1.01 (0.50)	0.30	0.049			0.343
RVp-LVs (ms)	-0.05 (0.20)	0.04	0.797			.

AV, atrioventricular; B, Beta coefficient; QLV, Q on surface ECG and LV depolarization; QLV/QRSD, ratio between Q to left ventricular sensing delay and QRS duration ratio; R, correlation coefficient; RAp-RVs, right atrial pacing to right ventricular sensing; RAs-RVs, right atrial sensing to right ventricular sensing; RVp-LVs, right ventricular pacing to left ventricular sensing interval; SD, standard deviation.

Bold P-values are below 0.05 and therefore statistically significant.

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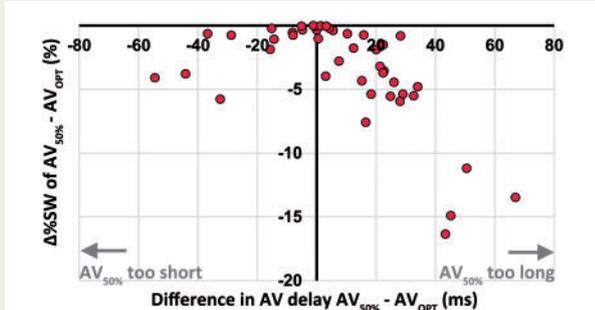


Figure 5 Difference in stroke work and atrioventricular delay of AV_{50%} vs. AV_{OPT}. The patient-specific effect of an AV delay based 50% of the right atrial pacing to right ventricular sensing interval (AV_{50%}) compared to the AV_{OPT}. Difference between AV_{50%} and AV_{OPT} on Δ%SW and the AV delay is given. AV, atrioventricular; AV_{OPT}, optimal atrioventricular delay; Δ%SW, change in stroke work.

cardiac cycle, and thus include the systolic and diastolic performance. Shortening of the AV delay during CRT will lead to an increase in preload, as shown by Jones *et al.*,¹⁴ which is directly visualized in a PV-loop. The effect of increased preload is reflected by the shorter optimal AV delays found with Δ%SW compared to LV dp/dt_{max} . Some patients in our study benefited in terms of Δ%SW with rather short AV delays. These short AV delays will decrease the effect of intrinsic conduction on ventricular activation, which indicates that interventricular interaction due to LV and RV pacing is more important in some patients. These heterogeneous effects, even in a cohort of patients with LBBB, show that there is no ‘one size fits all’ method for AV optimization. The observation that the optimal AV delay is close to 50% of RAp-RVs indicates that filling parameters may be important. Since absolute values of the optimal AV delay are longer for patients with prolonged PR intervals, optimized atrioventricular filling seems more important than fusion of intrinsic conduction and LV and RV pacing in most patients. The RAp-RVs is moreover influenced by the position of the RV lead. Although all leads were positioned

towards the RV apex, small differences in RV lead position might have influenced the correlation between RAp-RVs and the optimal AV delay. The mean AV delay for RV pacing in our study (50% of RAp-RVs + 40 ms = 177 ms) was also shorter than the intrinsic PR interval (184 ms). The association between PR interval and optimal AV delay may be ascribed to conduction delay in the atria, requiring a longer interval between complete atrial activation and ventricular activation. This is supported by the association between P wave duration and the optimal AV delay. As seen in prior studies,⁸ a trend towards a longer PR interval is seen in men compared to women. Men have larger hearts compared to women, indicating that cardiac size influences optimal AV timing. The effect of CRT in patients with prolonged PR interval is of interest, as a benefit was found in a sub-analysis of the COMPANION trial and in a sub-analysis of non-LBBB patients in the MADIT-CRT.^{15,16} In these sub-analyses, patients with a prolonged PR interval benefited more from CRT in terms of reduced heart failure hospitalizations and mortality.¹⁷

Comparison to current device algorithms

All CRT devices have built in algorithms for AV delay optimization based on intracardiac electrograms. Patients may benefit more from CRT with the AV_{50%} method, as current algorithms do not shorten the AV delay far enough. Current methods, such as QuickOpt (St. Jude Medical, St. Paul, Minnesota, USA), rely on a fixed sum of several milliseconds on measured P-wave duration (i.e. 80 ms if P-wave duration <100 and 110 ms if P-wave duration >100 ms). In our study population, QuickOpt would result in relatively long paced AV delays (i.e. 205 ± 10 ms). Moreover, the increase with 30ms based on a P-wave duration above 100 ms is not physiological.¹³ The Adaptiv-CRT algorithm of Medtronic (Minneapolis, MN, USA) implements LV only pacing and uses an AV delay at 70% of the RAp-RVs delay or RAp-RVs -40 ms (i.e. whichever is shorter, and the paced AV delay never exceeds 180 ms), for fusion with intrinsic conduction. Adaptiv-CRT has been proven to be effective on clinical outcome and echocardiographic response.^{10,18} The Adaptiv-CRT algorithm is different for patients with a RAp-RVs interval above or below 270 ms (or 250 ms in other Medtronic devices). However, the optimal AV delay in the

24 patients with RAp-RVs ≤ 270 ms in our study was significantly shorter compared to Adaptiv-CRT (i.e. 111 ms vs. Adaptiv-CRT: 168 ms). The AV optimization method described by Gold *et al.*¹⁹ closely resembles the AV_{50%} strategy, as it also uses a fraction of measured pacing intervals between atria and ventricles. Nevertheless, the resulting paced AV delays of Gold *et al.*¹⁹ were longer (i.e. 208 ± 62 ms) than ours. The difference between prior mentioned optimization algorithms and our results suggest that LV dP/dt_{max} measurements were used for these algorithms.

As most of these algorithms, AV delay optimization with the RAp-RVs interval facilitates continuous AV optimization after implantation. Atrioventricular conduction may be influenced by LV reverse remodelling and changes in pharmacological therapy after CRT. Changes in the atrioventricular conduction may influence RAp-RVs and subsequent programmed AV delay for optimal haemodynamic response. Periodic optimization of the AV delay by periodic measurements of the RAp-RVs may therefore be of additional benefit.

Limitations

There are some limitations to take into account. The AV delay was optimized directly after device implantation and translation of these results to AV delay optimization after evidence of reverse remodelling is unknown. The benefit of patient-specific AV delay optimization on long-term benefit of CRT is controversial. There is no clear benefit of any chosen strategy compared to fixed AV delays.²⁰ Nevertheless, increase in $\Delta\%SW$ is known to predict long-term CRT response,²¹ and every percentage of increase in $\Delta\%SW$ may potentially improve the patient's prognosis. Measurements were performed at rest, which may influence optimal AV timing. Exercise, and thereby increased sympathetic drive, leads to an increase in haemodynamic function, an increased heart rate and relative shorter diastolic phase compared to the systolic phase. A rate-adaptive approach may therefore be of benefit to haemodynamic response, as intrinsic AV conduction shortens during exercise. Implementation of the proposed method (AV_{50%}) in a rate-adaptive algorithm is of interest for future studies. Atrioventricular delay optimization was performed with a fixed VV delay of 40 ms LV first because previous studies showed that LV pre-activation produces the highest haemodynamic response.⁸ To avoid programming errors, the pacing protocols were applied in a fixed order and were therefore non-randomized. As the implemented optimization protocol was time consuming and to stabilize heart rhythm, only optimization of the paced AV delay was performed. However, CRT patients are generally in sinus rhythm, and ventricular pacing after atrial sensing is more common in clinical practice. Although there was no significant benefit of an IEGM-based method compared to fixed AV delays, this study might have been underpowered to find a significant difference between strategies. Lastly, comparison to AV delay optimization strategies based on shortening of the QRS complex or QRS area on vector cardiography are of interest.²² However, these optimization strategies went beyond the scope of this article.

Conclusion

A paced AV delay optimization strategy based on 50% of the intrinsic AV conduction interval is closest to the maximal achievable and

patient-specific acute haemodynamic effect. As the AV delay for optimal haemodynamic response is similar between pacing configurations of a quadripolar LV lead in a single patient, optimization is only necessary for one pacing configuration.

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