

Contribution to the V-V interval optimization in patients with cardiac resynchronization therapy

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Short Title: V-V interval optimization in BiV pacing

Summary

Aim: Proposing a procedure for predicting an optimal left and right ventricular pacing interval delay (V-V interval). *Methods:* In 16 patients (heart failure, left bundle branch block, biventricular pacing) two methods (A and B) identifying optimal V-V interval were tested. A: predicted optimal V-V interval A (POVV-A) = electromechanical delay of the segment paced by left ventricle lead minus electromechanical delay of the segment paced by right ventricle lead. B: predicted optimal V-V interval B (POVV-B) = difference in the onset of aortic and pulmonary flows. Both methods were validated using echocardiography and right-sided heart catheterization. *Results:* Cardiac output during POVV-A (4.6 l.min^{-1}) was significantly better than that during POVV-A minus 20 ms (4.3 l.min^{-1} , $p < 0.01$) and POVV-A plus 20 ms (4.3 l.min^{-1} , $p < 0.01$), and than that during POVV-B (4.4 l.min^{-1} , $p < 0.05$). LV dP/dt during POVV-A (818 mm Hg.s^{-1}) exceeded that during POVV-A plus 20 ms (717 mm Hg.s^{-1} , $p < 0.05$) and POVV-A minus 20 ms (681 mm Hg.s^{-1} , $p < 0.05$), and that during POVV-B (727 mm Hg.s^{-1} , $p < 0.01$). *Conclusion:* The time difference in onsets of myocardial deformation of left ventricle segment paced by the left ventricle and right ventricle lead allows identifying the optimal V-V interval and improves left ventricle performance.

Key words:

BiV pacing • Inter-ventricular asynchrony • Intra-ventricular asynchrony • V-V interval • Cardiac resynchronization therapy

Introduction

Implantation of a biventricular (BiV) PM has been repeatedly demonstrated to represent an efficient way of treating patients (pts) with congestive heart failure (HF) and conduction disturbances (Linde *et al.* 2002, Cleland *et al.* 2005). The functional benefit in such pts is achieved by improving the atrio-ventricular, inter-ventricular, and intra-ventricular synchrony. Several authors have demonstrated the superiority of sequential right ventricle (RV) and left ventricle (LV) pacing with the individually optimized time difference in the delivery of stimuli into both ventricles (V-V interval) as compared with simultaneous ventricular pacing (Bordachar *et al.* 2004, Bader *et al.* 2004, Naqvi *et al.* 2006, Burri *et al.* 2006). In previous studies, however, the selection of the “optimal V-V interval“ was always identified by testing numerous accidentally selected time intervals with no guarantee that the V-V interval chosen really represents that providing the maximal functional benefit. Thus, the aim of this study was to propose and validate a new non-invasive method of identifying the optimal V-V interval in pts with symptomatic HF treated with BiV pacing.

Methods

Patient population

The study included 16 consecutive pts (9 men and 7 women, mean age 64, range 40 to 78 years) with successful BiV pacing for drug-resistant HF of NYHA class III despite long-term adequate medication (furosemide, spironolactone, beta blocker, ACE inhibitor) who had at least mild functional mitral regurgitation. All were in sinus rhythm with left bundle branch block (LBBB) of QRS duration ≥ 130 ms. The etiology for HF was ischemic (≥ 70 % angiographically verified luminal diameter narrowing in at least one major coronary artery or documented myocardial infarction - 4 pts) or non-ischemic (12 pts). The mean LV ejection

fraction was 25 (17–32) % as assessed by 2D echocardiography. The implanted cardiac resynchronization therapy devices included Stratos LV (9), InSync III 8042 (3), Contak Renewal TR 2 H145, Contak Renewal 4 H195, Epic+ HF V-339, and Atlas+ HF V-341 (each 1x). The atrio-ventricular (AV) delay was set according to our method published previously (Meluzín *et al.* 2004). Informed consent was obtained from each patient (pt) and the study approved by the local ethics committee.

Prediction of optimal V-V interval

Theoretical background and description of the two methods investigated.

Method A: In pts with BiV pacing there are three potential sources of LV activation: the intrinsic conduction system formed by the His-Purkinje system, RV lead, and LV lead (Figure 1). The contribution of the His-Purkinje system depends on the AV delay setting. With a long AV delay, the upper part of the septum is activated by the His-Purkinje system, as in the absence of any pacing. With a short AV delay, the septal depolarization comes exclusively or predominantly from the pacing sites. In case all these sources are involved in LV activation, the LV deformation starts at the points where RV and LV leads are attached to the myocardium, and in the upper septal or anteroseptal area activated by the intrinsic system. From the theoretical point of view, the maximum intra-ventricular synchronization is achieved by zeroing the differences in the onset of myocardial deformation of all segments initially activated by the intrinsic system and both leads. Such an approach is supposed to optimize primarily the intra-ventricular synchrony with a potential beneficial impact also on the inter-ventricular synchrony. The optimal V-V interval (designated as A) was predicted based on the determination of the onsets of deformation of individual LV segments using strain-rate Doppler tissue echocardiography. The regional electromechanical delays of 18 segments (basal, mid, and apical segments of the septum, anteroseptal, anterior, lateral,

posterior and inferior walls) were measured as the time from the onset of the QRS complex on the electrocardiogram (ECG) to the onset of segmental myocardial deformation. Segments with the attachment of RV and LV lead were identified by 2D echocardiography, chest X-ray and computed tomography (CT), and these two segments were designated as “paced segments“. If the onset of basal septal or anteroseptal segments preceded the onset of deformation of at least one of the “paced segments“, the AV delay was shortened to a point at which the shortest electromechanical delay of segments activated through the intrinsic system was identical to the shorter electromechanical delay of one of the two “paced segments“. Otherwise, no changes in AV delay setting were performed. The “optimal V-V interval A” was calculated as the difference between the regional electromechanical delays of the two “paced segments“. For its testing, the “paced segment” with the longer regional electromechanical delay was pre-activated by the calculated “optimal V-V interval A“.

Method B. Another approach to optimizing the sequential BiV pacing may be derived from achieving the maximal inter-ventricular synchrony, which is mostly defined by the time interval between the onset of aortic and pulmonary blood flows (Bordachar *et al.* 2004, Achilli *et al.* 2003, Bader *et al.* 2004, Ghio *et al.* 2004, Chan *et al.* 2003). The optimal V-V interval (designated as B) was determined based on the differences in LV and RV pre-ejection times identified by pulsed-wave Doppler echocardiography. For the testing of optimal V-V interval B, the ventricle with the longer pre-ejection period was pre-activated by the calculated “optimal V-V interval B”.

To validate these theoretical considerations and to compare the methods A and B in the determination of the V-V interval, which really provides the maximum cardiac performance, six V-V interval configurations were tested: optimal V-V interval A, optimal V-V interval A plus 20 ms, optimal V-V interval A minus 20 ms, optimal V-V interval B, optimal V-V interval B plus 20 ms, optimal V-V interval B minus 20 ms. If the PM did not

allow setting exactly the predicted “optimal V-V interval A or B”, the predicted optimal delay was rounded off to the nearest programmable V-V interval value. This rounding off was not allowed to exceed 5 ms, otherwise the testing of such an optimal V-V interval was not performed.

Sequence of procedures

Three months after the implantation of BiV PM, pts were admitted to our clinic to assess their functional and hemodynamic status and to optimize their inter- and intra-ventricular contractile synchrony. On the first hospital day, the “paced myocardial segments” were defined, the electromechanical delays of all 18 myocardial segments were determined, and the “optimal V-V intervals A and B” were identified. To assure a constant heart rate during the whole study, the PM was programmed for AV sequential pacing with a pacing rate of at least 10 beats per minute above the intrinsic sinus rate. The myocardial segment paced by the RV lead was identified by 2D echocardiography; the myocardial segment paced by the LV lead was determined using CT and chest X-ray. Both predicted optimal V-V intervals were identified during the simultaneous RV and LV activation (V-V interval = 0). AV delay was adjusted if necessary (Meluzin *et al.* 2004). On the following day the LV systolic function was evaluated for all six V-V interval configurations using simultaneous echocardiography and the right-sided heart catheterization. The sequence of testing the individual six V-V intervals was determined randomly and the evaluating physician had no knowledge of the predicted “optimal V-V intervals A and B”.

Chest X-ray and CT

The position of the tip of the LV lead was identified by chest X-ray and CT. The plain chest radiogram at postero-anterior and left lateral projections was helpful in the identification whether the tip of the LV lead was in contact with basal, mid or apical part of the individual

walls. Relationship to individual walls was evaluated by CT, through planar reconstruction in frontal and oblique projections.

Echocardiography

Echocardiography was done using Vivid 7 (GE/Vingmed, Milwaukee, Wisconsin, U.S.A.) with an M3S probe. Two-dimensional echocardiography (apical 4-chamber view and in one of the parasternal short axis views) was used to determine the RV lead tip position and to identify the myocardial segment paced by this lead. For inter-ventricular asynchrony determination, the systolic flows from the left ventricle to the aorta and from the right ventricle to the pulmonary artery were imaged by pulsed-wave Doppler echocardiography. For the analysis of electromechanical delays of LV myocardial segments, colour Doppler tissue images of the six individual LV walls were obtained in the apical long axis and apical 4- and 2-chamber views. The narrow angle sector (30-45 degrees) depicting individual walls was used to reach high frame rates of mostly 196 (172-234) frames per second to achieve precise measurements. In all projections cine-loops of 3-4 cardiac cycles were collected for off-line analysis using commercially available software incorporated in Vivid 7 (Echopac 7 version 1.3, GE/Vingmed). Electromechanical delays of all 18 myocardial segments were evaluated by curved M-mode strain-rate imaging of individually stored walls. The principle and the methodology of strain-rate evaluation have already been described in detail (Edwardsen *et al.* 2001, Stoylen *et al.* 2000, Voigt *et al.* 2000).

On the second hospital day, echocardiography was done simultaneously with the right-sided heart catheterization, and the dp/dt values reflecting LV contractility were determined during the individual V-V intervals tested. The continuous-wave Doppler echocardiography was utilized to record mitral regurgitation using the apical 4-chamber view. From the descending limb of the mitral regurgitant flow, the rate of pressure rise in the left ventricle

(dP/dt) was derived by a technique described earlier (Bargiggia *et al.* 1989). The effect of V-V optimization on strain-rate imaging was not reevaluated.

Right-sided heart catheterization

The investigations were performed via the right subclavian vein or the right jugular vein. A 7F thermodilution catheter was inserted through the right heart cavities into the pulmonary capillary wedge position so that the pulmonary capillary wedge pressure (PCWP) was obtained after balloon inflation. Cardiac output was measured by the thermodilution technique.

Statistical analysis

All statistical tests were performed on the intention-to-treat principle and no case was excluded prior to the analyses. A value $p < 0.05$ was taken as universal limit for statistical significance. Standard descriptive statistics were used to summarize the sample distribution of individual variables (mean supplied with 95 % confidence limits). All analyses comparing methods A and B and the results of different settings within each method respected the paired design of the experiment. Extracted differences of pair values were assessed for normality (Shapiro-Wilk's test) and then evaluated by the standard t-test for dependent variables. Correlation between primary variables was verified by Pearson's product-moment coefficient.

Results

Inter-ventricular asynchrony quantified by pulsed-wave Doppler echocardiography

Good quality recordings of the pulmonary flow were obtained in 15 pts. The onset of blood flow to the pulmonary artery preceded the onset of flow to the aorta in all the pts. The mean difference was 29 (6 to 80) ms.

Identification of “paced segments” and determination of intra-ventricular asynchrony by curved M-mode strain-rate imaging

The “paced segments” activated by the RV lead were apical septal segments (9 pts), midseptal segments (4 pts), apical anteroseptal segments (2 pts), and a midanteroseptal segment (1 pt). The “paced segments” activated by the LV lead were midlateral segments (7 pts), basal lateral segments (3 pts), basal anterior segments (2 pts), and an apical anterior, a midanterior, and a midposterior segment (each in 1 pt). In one pt, the disturbance of the CT machine did not allow us to exactly detect the position of the LV lead. Individual local electromechanical delays are described in Table 3. The electromechanical delays of the two “paced segments” were identical in 2 pts only. For them, the simultaneous BiV pacing was predicted to be optimal. In all the remaining pts, the electromechanical delays of segments paced by the LV lead were longer than those paced by the RV lead (mean difference 15; range 3 - 33 ms). In these pts, the sequential BiV pacing with pre-activation of the LV lead by the difference in electromechanical delays of the two “paced segments” was predicted to be optimal. The segments with the earliest onset of myocardial deformation were those paced by the RV lead in 14 pts and the basal septal segments activated by the intrinsic conduction system in 2 pts. In these two patients the AV delay was shortened as described previously. The mean onset of deformation of these early contracting/deforming segments was 54 (20 to 87) ms. The mean onset of deformation of LV segments with the most delayed onset of deformation was 194 (107 - 380) ms. Thus, a significant LV contractile asynchrony still persisted even after BiV pacing.

Comparison of functional parameters measured at various V-V interval configurations

The “optimal V-V intervals A and B” were predicted and tested in 15 and 14 pts, respectively. In one pt the disturbance of the CT did not allow us to exactly detect the position of LV lead for the prediction of the “optimal V-V interval A”. The “optimal V-V interval B” was not tested in 2 pts. In the first pt the PM (Atlas+ HF) did not allow pre-activation of the left ventricle by 10 ms. In the second pt the V-V interval could not be predicted because of the inability to record the pulmonary flow.

Table 1 demonstrates the functional parameters measured at predicted optimal V-V intervals A and B and in the other experimental variants. In both methods tested, the setting of the predicted optimal V-V interval provided a significantly greater cardiac output than the other experimental V-V intervals. The dP/dt as a marker of LV contractility was significantly improved only under the application of method A. There were no significant changes in PCWP under the V-V intervals tested.

Comparison of methods A and B in the prediction of “optimal V-V interval”

Table 2 compares the effectiveness of methods A and B in achieving optimal functional parameters. The “optimal V-V interval” predicted by method A allowed us to obtain a significantly greater cardiac output and dP/dt than were those predicted by method B. The average “optimal V-V interval A” was 15.4 ± 10.7 (ranged 0-30, median 18) ms. The “optimal V-V interval A” correctly predicted the delay providing the maximal cardiac output in 73 % of the pts (11 of the 15 pts), in remaining 4 pts POVV was approximately the same as in POVV +20 ms or POVV -20 ms. The average “optimal V-V interval B” was 30.8 ± 24.8 (ranged 8-80, median 22,5) ms. The “optimal V-V interval B” correctly predicted the delay

providing the maximal cardiac output in only 43 % of the pts (6 of the 14 pts). The absolute values of optimal V-V delays are given in Table 4.

Discussion

To quantify intra-ventricular asynchrony, several echocardiographic methods have been applied including M-mode echocardiography (Pitzalis *et al.* 2002), Doppler tissue imaging (Sogaard *et al.* 2004, Bax *et al.* 2003, Bax *et al.* 2004, Yu *et al.* 2004, Yu *et al.* 2005, Notabartolo *et al.* 2004), and strain-rate echocardiography (Yu *et al.* 2004). Of them, only Doppler tissue imaging (DTI) and strain-rate imaging are able to determine the onsets of contraction/deformation of the individual LV myocardial segments. However, strain rate has the advantage of reflecting primarily myocardial deformation without the confusing effect of overall heart motion in the chest cavity (Breithard *et al.* 2003).

The most important finding of our study is the proposal and verification of a new non-invasive method based on strain rate echocardiography which allows predicting the optimal V-V interval for the achievement of the maximal effectiveness of sequential BiV pacing. In concordance with literature (Bader *et al.* 2004, Verbeek *et al.* 2003, Fauchier *et al.* 2002, Bordachar *et al.* 2004) we show that the determination of such a delay requires the optimization of intra- rather than inter-ventricular synchrony. Longer electromechanical delays were very consistent for LV segments and correspond with the activation pattern of epicardially applied impulses which do not penetrate the conduction system and thus need longer time to activate the myocardium.

Shortening of AV delay in case of spontaneous AV conduction activated basal segments too early (2 patients of our group) may lead to A wave truncation and filling limitation. We did not reevaluated mitral flow in these two patients. Betablocker dose increase may be beneficial in such patients.

As echo based optimization is time-consuming and impractical for optimizing all patients, St. Jude Medical developed and implemented new algorithm (QuickOpt™) for V-V delay optimization in latest models of dual-chamber and biventricular ICDs. This algorithm optimizes AV and VV interval in about a minute and is clinically-proven to correlate with echo based methods. The algorithm measures intrinsic interventricular delay, conduction speed from right to left and from left to right and counts optimal VV delay (Porterfield *et al.* 2006). This algorithm is based on measurements of electrical activity. On contrary our method is based on mechanical deformation and takes into account the electromechanical delay. The comparison of these two methods would be interesting.

The main limitation of our study was the fact that we were unable to identify the position of the tip of LV lead with echocardiography. To do so we had to use CT, which increased the cost of investigation and prolonged its duration. The application of new LV pacing electrodes accentuating echo reflections could overcome this limitation. The strain-rate analysis may be influenced by a suboptimal alignment of the ultrasound beam with the direction of the longitudinal motion of LV walls. However, this fact affects the absolute values of peak strain rate or the strain rather than the onset of deformation evaluated in our study.

Another limitation of our study is the fact that described method is quite time- and resource-consuming. In addition we are not sure whether the electromechanical delay does not change during time especially in the relation to reverse remodelling of left ventricle and whether another measurements and V-V delay rechange would be necessary in the future.

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Abbreviations

BiV – biventricular, V-V interval - left and right ventricular pacing interval delay, POVV-A or -B - predicted optimal V-V interval A or B, HF - heart failure, pt – patient, pts – patients, RV - right ventricle, LV - left ventricle, NYHA – New York Heart Association (Classification of dyspnoea into 4 classes), LBBB - left bundle branch block, AV - atrio-ventricular, CT - computed tomography, PM – pacemaker, PCWP - pulmonary capillary wedge pressure

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Table 1

Functional parameters measured at predicted optimal V-V pacing intervals A and B and at the other experimental variants. (Data are presented as mean \pm standard deviation).

	Method A			Method B		
	POVV	POVV +20ms	POVV -20ms	POVV	POVV +20ms	POVV -20ms
CO [l.min ⁻¹]	4.6 \pm 0.3** ₊₊	4.3 \pm 0.3	4.3 \pm 0.3	4.4 \pm 0.2** ₊₊	4.2 \pm 0.2	4.3 \pm 0.2
dP/dt [mm Hg.s ⁻¹]	818 \pm 68* ₊	717 \pm 51	681 \pm 49	727 \pm 58	724 \pm 50	683 \pm 38
PCWP [mm Hg]	9.6 \pm 2.1	9.9 \pm 1.6	10.8 \pm 1.8	9.7 \pm 1.8	10.1 \pm 1.8	10.3 \pm 1.7

POVV = predicted optimal V-V pacing interval, CO = cardiac output, PCWP = pulmonary capillary wedge pressure.

* p<0.05 vs POVV plus 20ms, ** p<0.01 vs POVV plus 20ms, + p<0.05 vs POVV minus 20ms, ++ p<0.01 vs POVV minus 20ms

Table 2

Comparison of the effectiveness of methods A and B in identifying the optimal V-V stimulation delay

Parameter ¹	Method	Mean \pm SD	Pairwise difference of original values ²	p value
CO [l.min ⁻¹]	Method A	4.6 \pm 0.3	0.2 \pm 0.1	0.014
	Method B	4.4 \pm 0.2		
dP/dt [mm Hg.s ⁻¹]	Method A	818 \pm 68	91 \pm 31	0.005
	Method B	727 \pm 58		
PCWP [mm Hg]	Method A	9.6 \pm 2.1	-0.1 \pm 0.6	0.897
	Method B	9.7 \pm 1.8		

¹Both methods, A and B, measured at predicted optimal V-V stimulation delays,

²pairwise difference (method A – method B): mean \pm standard deviation (SD).

Other abbreviations as in Table 1.

Table 3

Average electromechanical delays [ms] in particular segments paced by left ventricle lead. Values are expressed as average \pm standard deviation. (Number of patients in brackets).

segment	posterior	lateral	anterior
basal	63 (n=1)	79 \pm 25 (n=3)	58 \pm 11 (n=2)
mid		73 \pm 27 (n=6)	63 (n=1)
apical			60 (n=1)

Table 4

Absolute values of optimal V-V delay [ms] in individual patients using method A and B.

Pt. No	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Method A	20	20	10	30	20	0	30	10	0	16	0	30	10	20
Method B	30	10	10	60	48	70	80	10	10	8	20	25	40	10

Figure 1
Sources of left ventricle activation
in biventricular pacing

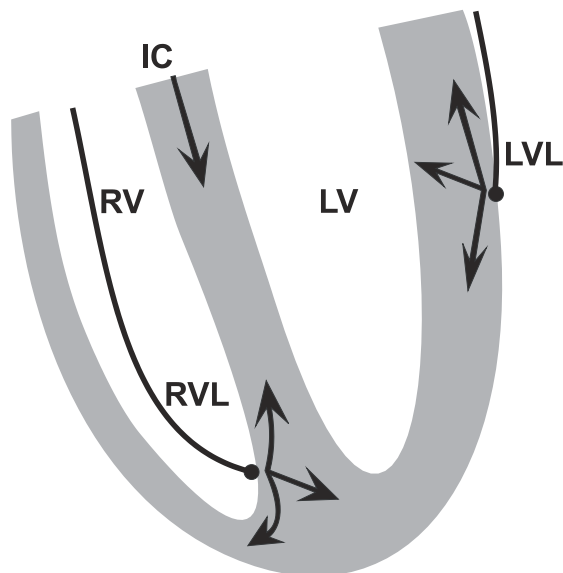


Figure 1 legend.

A scheme of three potential sources of LV activation in pts after implantation of BiV PM. The contribution of the intrinsic conduction system depends on AV delay setting. The maximum intra-ventricular synchronization is achieved by cancelling the differences in the onsets of myocardial contraction/deformation of segments initially activated by LV and RV leads and by the intrinsic conduction system, respectively.

LV = left ventricle, RV = right ventricle, RVL = right ventricular lead, LVL = left ventricular lead, IC = intrinsic conduction system.