

An electrographic AV optimization for the maximum integrative atrioventricular and ventricular resynchronization in CRT

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Abstract

Background:

Atrioventricular (AV) delay could affect AV and ventricular synchrony in cardiac resynchronization therapy (CRT). Strategies to optimize AV delay according to optimal AV synchrony (AV_{opt-AV}) or ventricular synchrony (AV_{opt-V}) would potentially be in discordant. This study aimed to explore a new AV delay optimization algorithm guided by electrograms to get the maximum integrative effects of AV and ventricular resynchronization (opt-AV).

Methods:

Forty-nine patients with CRT were enrolled. AV_{opt-AV} was measured through the Ritter method. AV_{opt-V} was obtained by yielding the narrowest QRS. The opt-AV was considered to be AV_{opt-AV} or AV_{opt-V} when their difference was $<20ms$, and to be the AV delay with the maximal aortic velocity-time integral between AV_{opt-AV} and AV_{opt-V} when their difference was $>20ms$.

Results:

The results showed sensing/pacing AV_{opt-AV} ($SAV_{opt-AV}/PAV_{opt-AV}$) were correlated with atrial activation time (P_{end-As}/P_{end-Ap}) ($P=0.05$). Sensing/pacing AV_{opt-V} (SAV_{opt-V}/PAV_{opt-V}) were correlated with the intrinsic AV conduction time (As-Vs/Ap-Vs) ($P=0.01$). The percentages of patients with more than 20ms differences between $SAV_{opt-AV}/PAV_{opt-AV}$ and SAV_{opt-V}/PAV_{opt-V} were 62.9% and 57.1%, respectively. Among them, the opt-AV were linearly correlated with $SAV_{opt-AV}/PAV_{opt-AV}$ and SAV_{opt-V}/PAV_{opt-V} . The sensing opt-AV (opt-SAV) = $0.1 \times SAV_{opt-AV} + 0.4 \times SAV_{opt-V} + 70ms$ ($R^2=0.665$, $P<0.01$) and the pacing opt-AV (opt-PAV) = $0.25 \times PAV_{opt-AV} + 0.5 \times PAV_{opt-V} + 30ms$ ($R^2=0.560$, $P<0.01$).

Conclusion:

The $SAV_{opt-AV}/PAV_{opt-AV}$ and SAV_{opt-V}/PAV_{opt-V} were correlated with the atrial activation time and the intrinsic AV conduction interval respectively. Almost half of patients had a $>20ms$ difference between $SAV_{opt-AV}/PAV_{opt-AV}$ and SAV_{opt-V}/PAV_{opt-V} . The opt-AV could be estimated based on electrogram parameters.

Background

Cardiac resynchronization therapy (CRT) is a milestone therapy in advanced congestive heart failure for its ability in decreasing symptoms, improving quality of life and exercise capacity, and reducing hospitalization and mortality in selected patients with heart failure^{1,2}. However, up to 30% – 45% of patients do not respond to CRT therapy^{1,3}. Among them, almost 50% cases have suboptimal atrioventricular (AV) timing⁴.

The AV interval can affect AV and ventricular synchrony simultaneously. However, improving AV and ventricular dyssynchrony is the underlying therapeutic mechanism of CRT. To obtain the optimal AV synchrony, an AV interval is required to ensure that the left ventricle (LV) only contracts after completion of left atrial (LA) contraction⁵. At this time, the optimal AV interval is subject to the atrial activation time. If there is inter/intra-atrial conduction delay, a relatively long AV interval is required for delayed LA contraction. Furthermore, ventricular resynchronization is maximally achieved through the narrowest QRS, which is obtained by optimal fusion between intrinsic atrioventricular activation and paced activation^{6,7}. Therefore, the optimal AV interval should coincide with the intrinsic AV conduction interval for obtaining optimal ventricular synchrony.

As a result, in some cases, the optimal AV delay for maintaining AV synchrony may be quite different from that for maintaining ventricular synchrony. For example, in patients with a long PR interval but normal atrial conduction, optimal ventricular resynchronization (the narrowest QRS) would require a longer AV delay, while this might lead to sub-optimal AV resynchronization since a normal atrial conduction required a relatively short AV delay.

In this study, the AV intervals were optimized according to optimal AV synchrony (AV_{opt-AV}) and optimal ventricular synchrony (AV_{opt-V}). The relationships between AV_{opt-AV} and the atrial activation time, AV_{opt-V} and the intrinsic AV interval, AV_{opt-AV} and AV_{opt-V} were further investigated. The aim was to study the difference between AV_{opt-AV} and AV_{opt-V} , and propose a novel AV optimized algorithm only guided by the intrinsic AV interval and atrial activation time to obtain the maximal integrative effects of AV and ventricular resynchronization.

Methods

Study population

This was a multicenter, nonrandomized study, which enrolled patients aged 18 or older, who had been implanted with CRT defibrillators for at least 1 month with standard criteria (NYHA classes II-IV; ejection fraction $\leq 35\%$; sinus rhythm; left bundle branch block with QRS ≥ 130 ms). Patients were excluded from the study if they had congenital heart diseases, valve repairment or replacement surgeries, atrial tachyarrhythmias or frequent atrial or ventricular ectopy, and second/third degree of AV block. The protocol of the study was approved by the institutional review boards of the participating hospitals, and all patients gave written informed consent.

Study procedures

General data

Clinical data, such as demographics (age, gender, etc.), etiology, heart failure status before CRT device implantation (NYHA classes, left ventricular end-diastolic diameter, left ventricular end-systolic diameter,

ejection fraction), medications, CRT device data (model number and date of implant), and the location of the right atrium and LV electrodes were collected before the study procedure.

Electrocardiogram and device electrograms

The patient's intrinsic electrocardiogram (ECG) was recorded after the device marker recording showed atrial sensing (As) and ventricular sensing (Vs) by programming the lower rate to 50/40 bpm and sensed AV delay to 300/350 ms. Heart rate, QRS duration, PR interval, the device-recorded intrinsic AV conduction interval (As-Vs), and atrial activation time (duration from As to the end of the P wave [$P_{\text{end-As}}$]) were sequentially measured. Then the lower rate was programmed to 10 bpm more than the intrinsic heart rate. The intervals from atrial pacing (Ap) to Vs (Ap-Vs), and the duration from Ap to the end of the P wave ($P_{\text{end-Ap}}$) were also measured sequentially for at least 10 times (Fig. 1).

Measurement of AV delay according to optimal atrioventricular synchrony

The Ritter method was originally developed for AV delay setting to achieve optimal AV synchrony in patients with complete AV block and preserved LV function⁸. Its aim was to maximize LV filling (including maximizing the role of LA contraction) and minimize pre-systolic mitral regurgitation by ensuring that left ventricular contraction starts soon after the completion of the left atrial contraction. Then it and its analogue became the gold standard for AV delay optimization in CRT⁹. In this study, we used the Ritter method to optimize $AV_{\text{opt-AV}}$. In brief, mitral flow velocity and surface ECG were simultaneously recorded. A short and a long AV delay ($AV_{\text{short}}/AV_{\text{long}}$) were programmed, and the relevant intervals from the pacing spike (Q) to the end of the Doppler mitral inflow A wave ($QA_{\text{short}}/QA_{\text{long}}$) were measured. $AV_{\text{opt-AV}}$ was calculated as follows: $AV_{\text{opt-AV}} = AV_{\text{long}} + QA_{\text{long}} - QA_{\text{short}}$ ^{8, 10}. In this study, the VV intervals were always kept in 0 ms.

Measurement of AV delay according to optimal ventricular synchrony

The narrower the QRS duration was, the more synchronous the ventricle was. Simultaneous 12-lead ECGs were recorded when the sensing/pacing AV delays (SAV/PAV) were programmed to values from 70 ms to an AV delay of 40 ms less than the intrinsic As-Vs/Ap-Vs by 10-ms steps in random order. The durations of QRS were automatically calculated by the built-in software in the ECG machine. The SAV/PAV delays with the narrowest QRS duration were considered sensing/pacing $AV_{\text{opt-V}}$ ($SAV_{\text{opt-V}}/PAV_{\text{opt-V}}$) (Fig. 2).

Determination of the optimal AV delay

When sensing/pacing $AV_{\text{opt-AV}}$ ($SAV_{\text{opt-AV}}/PAV_{\text{opt-AV}}$) with $SAV_{\text{opt-V}}/PAV_{\text{opt-V}}$ were compared, if the difference in values (D-values) was <20 ms, $SAV_{\text{opt-AV}}/PAV_{\text{opt-AV}}$ and $SAV_{\text{opt-V}}/PAV_{\text{opt-V}}$ were regarded as not different^{11, 12}, and were considered as the optimal sensing/pacing AV delay (opt-SAV/opt-PAV). If the D-values were ≥ 20 ms, the aortic velocity-time integral (AoVTI) was measured by continuous wave Doppler recordings from $SAV_{\text{opt-AV}}/PAV_{\text{opt-AV}}$ to $SAV_{\text{opt-V}}/PAV_{\text{opt-V}}$ by 10-ms steps. SAV/PAV with the

maximum AoVTI were considered as the opt-SAV/opt-PAV. All measurements of echocardiographic data were averaged from nine to 12 consecutive cardiac beats.

Statistical analysis

Continuous variables that were normally distributed are shown as mean \pm standard deviation. Non-normally distributed variables are shown as median and interquartile range. The data were analyzed with IBM SPSS software version 20.0 for Windows (IBM Inc., Armonk, NY, USA). The paired-samples t-test or two related-samples Wilcoxon rank sum tests were used in between-group statistical analysis according to evaluation of a normal distribution. Regression analysis and Pearson's correlation coefficient were performed to evaluate correlations. The theoretical frequency $P < 0.05$ was defined as statistically significant.

Results

Patients population

A total of 49 patients were enrolled in the study from three hospitals (the First Affiliated Hospital of Sun Yat-Sen University, Sun Yat-Sen Memorial Hospital of Sun Yat-Sen University, and Nanfang Hospital of Nanfang Medical University) from July 2017 to May 2020. The clinical characteristics of the patients are shown in Table 1. The majority of patients (35/49) were men. The mean intrinsic PR interval and QRS duration were 185.88 ± 38.20 (115–275) ms and 166.29 ± 21.34 (146–237) ms. The atrial electrodes were placed in the right atrial appendage in all patients.

Table 1
Clinical characteristics of the patients involved in the study

Age, years	67.25 ± 9.37
Male/female	35/14
Etiology, n (%)	
Ischemic heart disease	20 (40.8)
Dilated cardiomyopathy	24 (49.0)
Noncompaction of ventricular myocardium	4 (8.2)
Other	1 (2.0)
NYHA class, n (%)	
I	13 (28.9)
II	29 (64.4)
III	4 (8.9)
Medication, n (%)	
Beta-blocker	42 (93.3)
ACEI/ARB	27 (60.0)
MRA	44 (97.8)
ARNI	18 (40.0)
I _f -channel inhibitor	3 (6.7)
Diuretics	4 (8.9)
Digitalis	3 (6.7)
UCG	
LV EF (%)	28.66 ± 4.94
LVEDD (mm)	70.42 ± 10.29
LVESD (mm)	59.13 ± 10.94

NYHA: New York heart association; ACEI: Angiotensin-converting-enzyme inhibitor; ARB: Angiotensin II receptor antagonist; MRA: Aldosterone receptor antagonist; ARNI: Angiotensin receptor-neprilysin inhibitor; I_f: Funny current; UCG: Ultrasonic cardiogram; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; PA: Pulmonary artery; ECG: Electrocardiogram; As-Vs: Intrinsic atrioventricular conduction time at the time of atrial sensing; Ap-Vs: Intrinsic atrioventricular conduction time at the time of atrial pacing; P_{end-As}: Atrial activation time at the time of atrial sensing; P_{end-Ap}: Atrial activation time at the time of atrial pacing.

Age, years	67.25 ± 9.37
PA pressure (mmHg)	38.45 ± 6.98
Diastolic mitral regurgitation, n (%)	31 (68.9)
ECG characteristics	
Intrinsic heart rate (bpm)	68.21 ± 11.76
PR interval (ms)	185.88 ± 38.20
QRS duration (ms)	166.29 ± 21.34
Location of LV lead, n (%)	
Short axis	
Lateral/posterolateral	32 (65.3)
Anterolateral	13 (25.5)
Posterior	4 (8.2)
Anterior	0
Long axis	
Basic	16 (32.7)
Middle	33 (67.3)
Apical	0
Device electrogram characteristics	
As-Vs (ms)	200.02 ± 34.26
Ap-Vs (ms)	258.33 ± 45.46
P _{end-As} (ms)	86.08 ± 22.68
P _{end-Ap} (ms)	136.84 ± 23.92

NYHA: New York heart association; ACEI: Angiotensin-converting-enzyme inhibitor; ARB: Angiotensin II receptor antagonist; MRA: Aldosterone receptor antagonist; ARNI: Angiotensin receptor-neprilysin inhibitor; I_f: Funny current; UCG: Ultrasonic cardiogram; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; PA: Pulmonary artery; ECG: Electrocardiogram; As-Vs: Intrinsic atrioventricular conduction time at the time of atrial sensing; Ap-Vs: Intrinsic atrioventricular conduction time at the time of atrial pacing; P_{end-As}: Atrial activation time at the time of atrial sensing; P_{end-Ap}: Atrial activation time at the time of atrial pacing.

Relationship between AV_{opt-AV} and atrial activation time

AV_{opt-AV} was successfully determined in 35 patients by the Ritter method. Regression analysis showed that SAV_{opt-AV} was significantly correlated with P_{end-As} ($SAV_{opt-AV}=0.80\times P_{end-As}+50$ ms, $R^2 = 0.467$, $P < 0.01$). A similar result was also found between PAV_{opt-AV} and P_{end-Ap} ($PAV_{opt-AV}=0.70\times P_{end-Ap}+70$ ms, $R^2 = 0.221$, $P < 0.05$).

Relationship between AV_{opt-V} and intrinsic AV conduction and QRS duration

The SAV_{opt-V}/PAV_{opt-V} was achieved through the narrowest QRS duration in all 49 patients.

SAV_{opt-V}/PAV_{opt-V} were significantly correlated with As-Vs/Ap-Vs ($SAV_{opt-V}=0.60\times As-Vs + 15$ ms, $R^2 = 0.456$, $P < 0.01$; $PAV_{opt-V}=0.60\times Ap-Vs + 40$ ms, $R^2 = 0.417$, $P < 0.01$), but there was no significant correlation with the intrinsic QRS duration (both $P > 0.5$).

Difference between AV_{opt-AV} and AV_{opt-V}

In the 35 patients, in which $SAV_{opt-AV}/PAV_{opt-AV}$ and SAV_{opt-V}/PAV_{opt-V} were successfully directly measured simultaneously, no significant correlations were found between SAV_{opt-AV} and SAV_{opt-V} , and between PAV_{opt-AV} and PAV_{opt-V} (both $P > 0.05$). If > 20 -ms D-values between $SAV_{opt-AV}/PAV_{opt-AV}$ and SAV_{opt-V}/PAV_{opt-V} were considered as meaningful differences, 22/35 (62.9%) patients had a > 20 -ms difference in SAV and 20/35 (57.1%) had a > 20 -ms difference in PAV. Among them, 17/35 (48.6%) patients had a > 20 -ms difference in both SAV and PAV. Moreover, if $SAV_{opt-AV}/PAV_{opt-AV}$ and SAV_{opt-V}/PAV_{opt-V} were obtained by calculation according to their relationship with P_{end-As}/P_{end-Ap} and As-Vs/Ap-Vs, respectively, > 20 -ms D-values were found in 22/49 (44.9%) patients in SAV, in 29/49 (59.2%) patients in PAV, and in 17/49 (34.7%) patients in both SAV and PAV (Table 2).

Table 2

The percentage of patients with more than 20ms differences between AV_{opt-AV} and AV_{opt-V}

	Patients with directly measured AV (n = 35)	Patients with calculated AV* (n = 49)
SAV	22(62.9%)	22(44.9%)
PAV	20(57.1%)	29(59.2%)
SAV and PAV	17(48.6%)	17(34.7%)
*the Sensing/Pacing AV_{opt-AV} and AV_{opt-V} were calculated according to the following formulae:		
$SAV_{opt-AV} = 0.80 \times P_{end-As} + 50 \text{ ms}$		
$SAV_{opt-V} = 0.60 \times As-Vs + 15 \text{ ms}$		
$PAV_{opt-AV} = 0.70 \times P_{end-Ap} + 70 \text{ ms}$		
$PAV_{opt-V} = 0.60 \times Ap-Vs + 40 \text{ ms}$		

Relationships of opt-SAV/opt-PAV with $SAV_{opt-AV}/PAV_{opt-AV}$ and SAV_{opt-V}/PAV_{opt-V}

Opt-SAV/opt-PAV was considered according to the maximum AoVTI when the D-values between $SAV_{opt-AV}/PAV_{opt-AV}$ and SAV_{opt-V}/PAV_{opt-V} were > 20 ms. Regression analysis showed that opt-SAV = $0.1 \times SAV_{opt-AV} + 0.4 \times SAV_{opt-V} + 70 \text{ ms}$ ($R^2 = 0.665$, $P < 0.01$) and that opt-PAV = $0.25 \times PAV_{opt-AV} + 0.5 \times PAV_{opt-V} + 30 \text{ ms}$ ($R^2 = 0.560$, $P < 0.01$).

Echocardiographic evaluation of opt-SAV/opt-PAV

The difference of hemodynamics was evaluated by echocardiographic measurement of AoVTI. In the cases with > 20 ms D-values between SAV_{opt-AV} and SAV_{opt-V} , the AoVTI on opt-SAV was significantly greater than the AoVTI on SAV_{opt-V} (opt-SAV - $SAV_{opt-V} = 1.52 \pm 0.22 \text{ cm}$, $P < 0.001$), and was not less than that on SAV_{opt-AV} (opt-SAV - $SAV_{opt-AV} = 0.89 \pm 0.82 \text{ cm}$, $P = 0.290$). Furthermore, the AoVTI on opt-PAV was also significantly greater than that on PAV_{opt-AV} (opt-PAV - $PAV_{opt-AV} = 2.47 \pm 0.80 \text{ cm}$, $P = 0.006$) and PAV_{opt-V} (opt-PAV - $PAV_{opt-V} = 0.76 \pm 0.30 \text{ cm}$, $P = 0.021$), respectively.

Discussion

AV delay has effects on both AV and ventricular resynchronization simultaneously in CRT, and could be optimized according to the optimal AV and ventricular synchrony respectively. This study showed that $SAV_{opt-AV}/PAV_{opt-AV}$ were related to the atrial activation time (P_{end-As}/P_{end-Ap}), and SAV_{opt-V}/PAV_{opt-V} were related to the intrinsic atrioventricular conduction interval ($As-Vs/Ap-Vs$). However, nearly 50% of

patients showed a significant difference between $SAV_{opt-AV}/PAV_{opt-AV}$ and SAV_{opt-V}/PAV_{opt-V} (D-values > 20 ms). At this time, opt-SAV/opt-PAV optimized according to the maximal AoVTI were linearly correlated with $SAV_{opt-AV}/PAV_{opt-AV}$ and SAV_{opt-V}/PAV_{opt-V} , and had significantly improved hemodynamics. Therefore, the optimal AV delay in CRT could be considered as $SAV_{opt-AV}/PAV_{opt-AV}$ or SAV_{opt-V}/PAV_{opt-V} if the D-values were < 20 ms, or it could be achieved by formulas (opt-SAV = $0.1 \times SAV_{opt-AV} + 0.4 \times SAV_{opt-V} + 70$ ms; opt-PAV = $0.25 \times SAV_{opt-AV} + 0.5 \times SAV_{opt-V} + 30$ ms) if the D-values were > 20 ms. The AV optimized algorithm with the maximal integrative effects of AV and ventricular resynchronization was shown in Fig. 3.

Optimal atrioventricular synchrony is a mechanical status in which the onset of LV contraction only coincides with the end of LA contraction and yields the longest diastolic filling time and a fully active filling phase. This is also the principle based on the Ritter method and its analogues for optimization of AV delay⁹. Previous studies have shown that this type of AV delay is related to the atrial conduction time¹³. In this study, we defined this AV delay for optimal atrioventricular synchrony as AV_{opt-AV} . Using the duration from As/Ap to the relevant end of the P wave (P_{end-As}/P_{end-Ap}) as the atrial activation time, the results showed that $SAV_{opt-AV}/PAV_{opt-AV}$ were linearly correlated with P_{end-As}/P_{end-Ap} . Similar results were also found by Jones et al¹⁴ who suggested that $SAV = P_{end-As} + 40$ ms and $PAV = P_{end-Ap} + 30$ ms. We did not find any significant differences when compared these two equations with our formulas (both $P > 0.05$, data not shown).

The duration of QRS is a marker of ventricular synchrony. Many studies have shown that the extent of a decrease in QRS duration is related to clinical improvement and reverse remodeling of the LV in CRT^{7, 15, 16}. Achieving the narrowest QRS duration was first applied in VV optimization^{17, 18}. This was further used in AV optimization to maximize LV global contractile function^{12, 13, 19} because the narrowest QRS duration could be obtained by maximal fusion between intrinsic atrioventricular activation and paced activation.^{6, 7} Therefore, AV delay for optimal ventricular synchrony according to the narrowest QRS duration should be correlated with the intrinsic AV conduction interval. In this study, we defined AV delay for the narrowest QRS as SAV_{opt-V}/PAV_{opt-V} , and found that they were correlated with intrinsic AV conduction (As-Vs/Ap-Vs).

However, in patients with CHF, the intrinsic AV conduction interval and the atrial activation time are not always proportional. In our patients, we could not find a significant correlation between As-Vs/Ap-Vs and P_{end-As}/P_{end-Ap} (data not shown). Therefore, AV delay optimized according to maximal AV synchrony, which was correlated with the atrial activation time, did not always coincide with AV delay optimized according to maximal ventricular synchrony, which was correlated with intrinsic AV conduction. In this study, no significant correlations were found between $SAV_{opt-AV}/PAV_{opt-AV}$ and SAV_{opt-V}/PAV_{opt-V} , and almost 50% of patients showed > 20-ms differences between $SAV_{opt-AV}/PAV_{opt-AV}$ and SAV_{opt-V}/PAV_{opt-V} . These findings indicated the AV delay optimized only according to optimal AV synchrony or ventricular synchrony was not optimal in approximately half of the patients with CRT. In

fact, some studies showed that the narrowest QRS complex in CRT was not always associated with maximal improvement of cardiac contractive function¹³. Sometimes the AV delay optimized by the Ritter method is not as useful as other methods (e.g., Doppler-derived AoVTI)^{2, 18, 20}. This further indicates that the optimization of AV delay only according to either optimal AV or ventricular synchrony is not sufficient in CRT. Therefore, optimal AV delay with maximal hemodynamic improvement should be the AV interval that produces maximal integration of atrioventricular and ventricular synchrony. In this study, we found that the optimal AV delay with maximal AoVTI was linearly correlated with $SAV_{opt-AV}/PAV_{opt-AV}$ and SAV_{opt-V}/PAV_{opt-V} when the D-values between them were > 20ms. The AoVTIs on opt-AV were either significantly greater or not less than that on AV_{opt-AV} and AV_{opt-V} . These indicated that the AV optimization according to the maximal integrative effects of AV and ventricular resynchronization was significantly more effective than the AV interval determined by either optimal AV or ventricular synchrony alone.

There are several limitations to our study. Firstly, we only enrolled 49 patients with CRT. This relatively small number of cases might have affected the accuracy of the regression formula, although the current equation was statistically significant. Secondly, the atrial electrodes were all placed in the right atrial appendages in our patients. The sites of atrial electrodes could affect measurement of the atrial activation time ($As-P_{end}/Ap-P_{end}$) and the intrinsic AV conduction time ($As-Vs/Ap-Vs$). Therefore, the formulas that were used in our study might not be appropriate for other CRT patients whose atrial electrodes placed in different sites. Additionally, we only focused on the optimal AV delay in the condition of biventricular simultaneous pacing but did not study the situation of only LV pacing. However, when or how to select the pacing mode of only LV pacing is still controversial. AV and ventricular synchrony are also required to be considered simultaneously when the AV delay is optimized in only LV pacing mode.

Conclusions

AV delay could affect atrioventricular and ventricular synchrony in CRT. AV delay optimized according to optimal atrioventricular synchrony or optimal ventricular synchrony is correlated with the atrial activation time or the intrinsic AV conduction interval, respectively. However, almost half of the patients show a significant difference between AV_{opt-AV} and AV_{opt-V} . Optimal AV delay is the maximal integration of atrioventricular and ventricular synchrony, and could be considered as $SAV_{opt-AV}/PAV_{opt-AV}$ or SAV_{opt-V}/PAV_{opt-V} if the D-values were < 20 ms, or be obtained by formulas that linearly correlated with AV_{opt-AV} and AV_{opt-V} when the D-values were > 20 ms.

Abbreviations

CRT

cardiac resynchronization therapy

SAV

sensing atrioventricular delay

PAV

pacing atrioventricular delay

AV_{opt-AV}

AV delay with optimal atrioventricular synchrony

AV_{opt-V}

AV delay optimal ventricular synchrony

opt-AV

the optimal AV delay with the maximum integrative effects of AV and ventricular resynchronization

As

atrial sensing

Ap

atrial pacing

Vs

ventricular sensing

As-Vs

the interval from As to Vs

Ap-Vs

the interval from Ap to Vs

P_{end-As}

atrial activation time (duration from As to the end of the P wave)

P_{end-Ap}

atrial activation time (duration from Ap to the end of the P wave)

AoVTI

aortic velocity-time integral

Declarations

Ethics approval and consent to participate: The protocol of the study was approved by Medical Ethics Committee at Sun Yat-Sen University and Nanfang Hospital of Nanfang Medical University, respectively. All patients gave written informed consents.

Consent for publication: All authors have reviewed and agree with the content of the article for publication.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: JL, YW, JM and SC were major contributor in the tests on the patients directly. ML and CS corresponded for the statistics of data. XC, HH, YM, CF, JJ, Jun Liu assisted the tests and data collection. JH, AT, YD and XH assisted the design and interpreted the patients. YC and LW corresponded the design and writing the manuscript. All authors read and approved the final manuscript.

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Figures

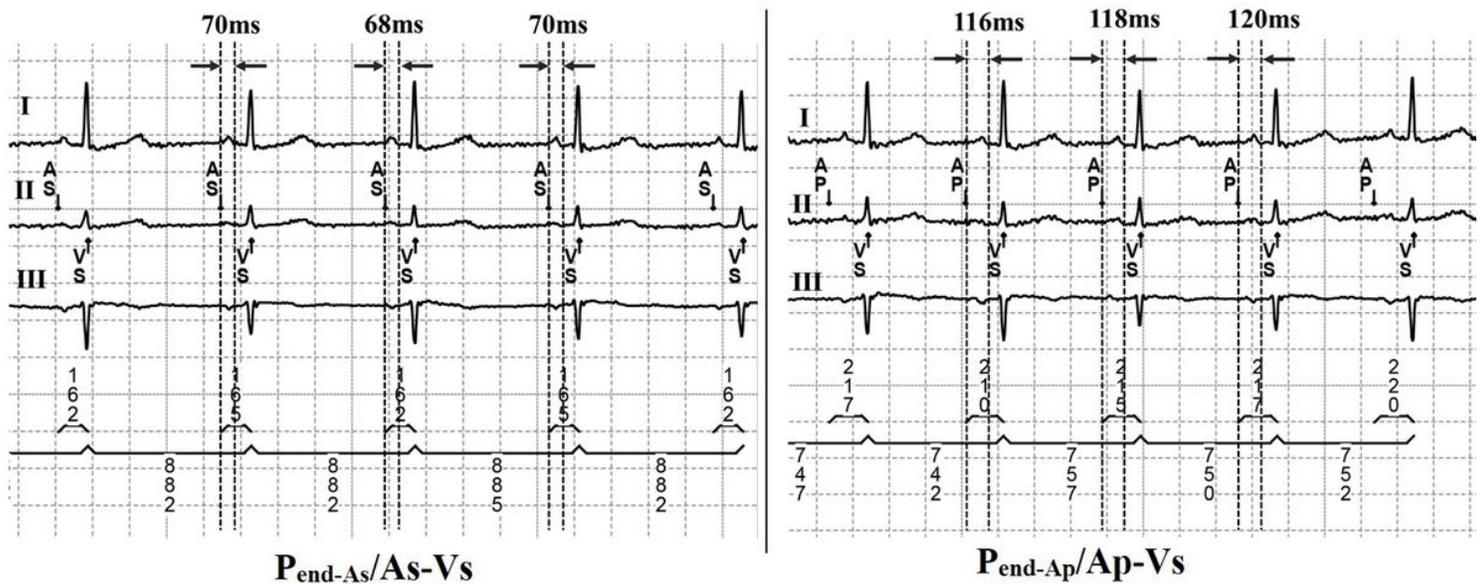


Figure 1

Measurement of atrial activation and intrinsic atrioventricular conduction time Left panel: atrial activation time ($P_{\text{end-As}}$) and intrinsic atrioventricular conduction time (As-Vs) at the time of atrial sensing. Right panel: atrial activation time ($P_{\text{end-Ap}}$) and intrinsic atrioventricular conduction time (Ap-Vs) at the time of atrial pacing. AS: atrial sensing; AP: atrial pacing; VS: ventricular sensing.

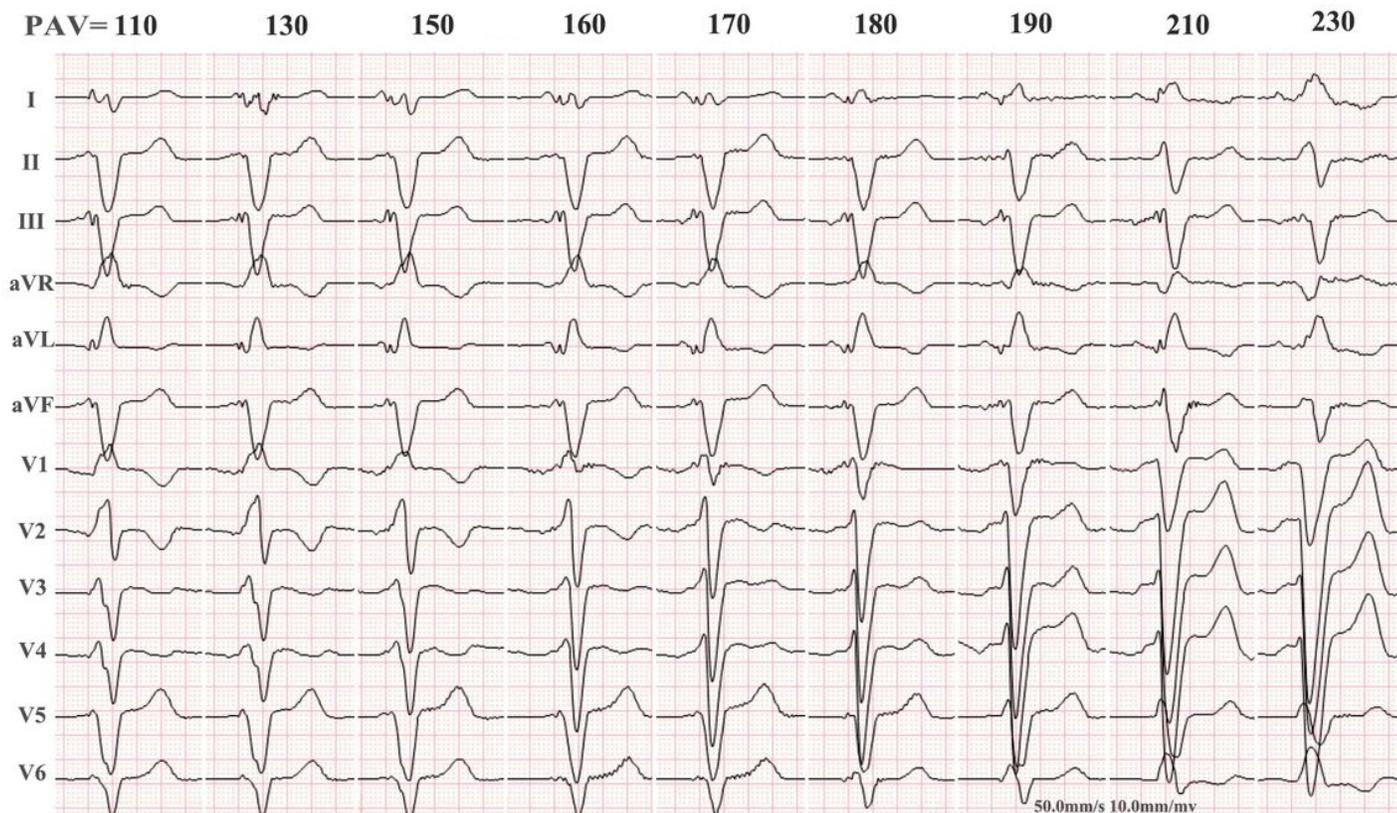


Figure 2

Measurement of atrioventricular delay according to optimal ventricular resynchronization. A representative electrocardiographic series shows measurement of pacing atrioventricular delay for optimal ventricular resynchronization. Ap-Vs=260 ms, pacing rate=90 bpm. The numbers shown on the top of the electrocardiograms are values (ms) of PAV. The narrowest QRS (128 ms) occurred at the PAV of 170 ms. Ap-Vs: the intrinsic atrioventricular conduction time at the time of atrial pacing. PAV: pacing AV delay.

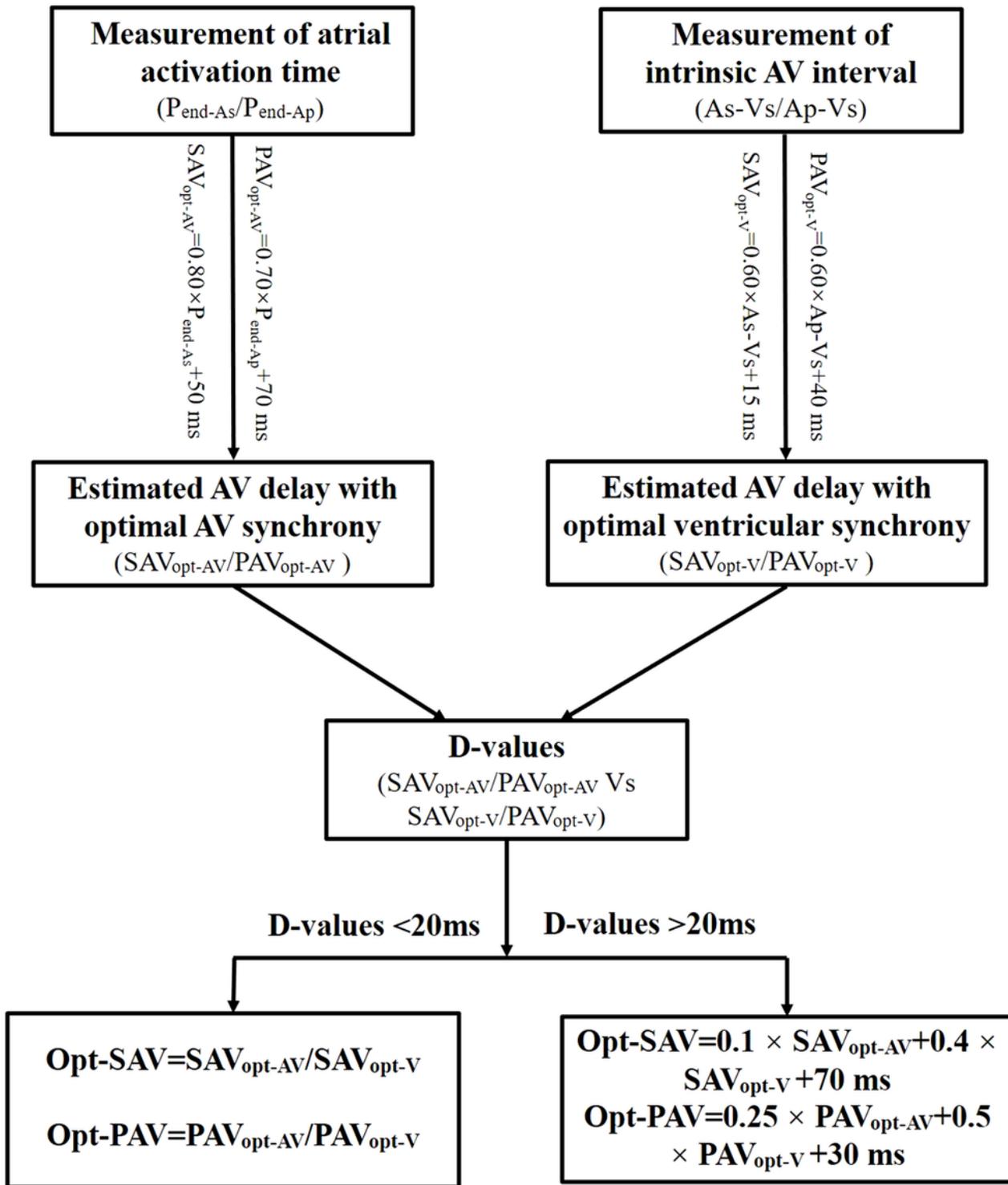


Figure 3

The optimizing algorithm of the optimal AV delay P_{end-As}/P_{end-Ap} : atrial activation time at atrial sensing/ pacing; AV: atrioventricular; $As-Vs/Ap-Vs$: intrinsic atrioventricular conduction time at atrial sensing/pacing; $SAV_{opt-AV}/PAV_{opt-AV}$: sensing/pacing AV delay optimized according to optimal AV synchrony; SAV_{opt-V}/PAV_{opt-V} : sensing/pacing AV delay optimized according to optimal ventricular

synchrony; D-values: different values; opt-SAV/opt-PAV: the optimal sensing/pacing AV delay with the maximal integrative AV and ventricular resynchronization.