Prospective comparison of echocardiographic atrioventricular delay optimization methods for cardiac resynchronization therapy

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BACKGROUND Atrioventricular (AV) delay optimization can be an important determinant of the response to cardiac resynchronization therapy (CRT) in patients with medically refractory heart failure and a ventricular conduction delay.

OBJECTIVES The purpose of this study was to compare two Doppler echocardiographic methods of AV delay optimization after CRT.

METHODS Forty consecutive patients (age 59 ± 12 years) with severe heart failure, New York Heart Association class 3.1 ± 0.4, QRS duration 177 ± 23 ms, and left ventricular ejection fraction 26% ± 6% referred for CRT were studied using two-dimensional Doppler echocardiography. In each patient, the acute improvement in stroke volume with CRT in response to two methods of AV delay optimization was compared. In the first method, the AV delay that produced the largest increase in the aortic velocity time integral (VTI) derived from continuous-wave Doppler (aortic VTI method) was measured. In the second method, the AV delay that optimized the timing of mitral valve closure to occur simultaneously with the onset of left ventricular systole was calculated from pulsed Doppler mitral waveforms at a short and long AV delay interval (mitral inflow method).

RESULTS The optimized AV delay determined by the aortic VTI method resulted in an increase in aortic VTI of 19% ± 13% compared with an increase of 12% ± 12% by the mitral inflow method ($P < .001$). The optimized AV delay by the aortic VTI method was significantly longer than the optimized AV delay calculated from the mitral inflow method (119 ± 34 ms vs 95 ± 24 ms, $P < .001$). There was no correlation in the AV delay determined by the two methods ($r = 0.03$).

CONCLUSION AV delay optimization by Doppler echocardiography for patients with severe heart failure treated with a CRT device yields a greater systolic improvement when guided by the aortic VTI method compared with the mitral inflow method.

KEYWORDS Heart failure; Cardiac resynchronization therapy; Doppler echocardiography

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Introduction

A subset of patients with heart failure and left ventricular (LV) systolic dysfunction have a significant intraventricular conduction delay and ventricular dyssynchrony.[1–6] Cardiac resynchronization therapy (CRT) is an adjunct treatment of heart failure in these patients.[7–9] The improvement in LV systolic performance and the clinical response to CRT can be influenced by atrioventricular (AV) delay optimization.[10–12] AV delay optimization protocols that utilize Doppler echocardiography are widely used. However, whether AV delay optimization for CRT by Doppler echocardiography is best determined by measurements of LV diastolic filling time intervals or indices of LV systolic function has not been compared. We prospectively evaluated patients who received a CRT device to determine each

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patient's response to AV delay optimization using two Doppler echocardiographic methods: (1) measurement of the continuous-wave Doppler-derived aortic velocity time integral (VTI) as an estimate of stroke volume (aortic VTI method), and (2) calculation of the AV delay interval from pulsed Doppler measurement of the timing of mitral valve closure at a short and long AV delay setting (mitral inflow method).[13–15] The primary outcome measurement was improvement in the Doppler-derived aortic VTI.

Methods

Patient characteristics

Patients referred for CRT implantation were asked to participate in the study, and informed consent was obtained from all patients. The protocol was approved by the Washington University Human Studies Committee. All participants underwent CRT device implantation between January 1, 2002 and January 1, 2003. Inclusion criteria were a history of stable, medically refractory heart failure symptoms despite an optimized medical regimen for heart failure for at least 1 month, sinus rhythm, QRS duration $>.15$ seconds, LV enlargement determined by a two-dimensional echocardiographic end-diastolic diameter >6.0 cm, and LV ejection fraction $<35\%$. Exclusion criteria were symptomatic bradyarrhythmias, or medically refractory atrial arrhythmias.

CRT device implantation

CRT device implantation was performed by a single operator via a transvenous approach. In all cases, the LV stimulation site was targeted to the mid-lateral wall if an appropriate coronary sinus branch was present. Alternative LV stimulation sites in the anterolateral or posterolateral venous branches were used when a mid-lateral branch was either absent or unacceptable because of phrenic nerve stimulation or high stimulation threshold. All devices were programmed to "inactive" ventricular demand pacing (VVI, 40 ppm) at the time of device implantation. CRT was not initiated until after the baseline echocardiographic study.

Two-dimensional Doppler echocardiography

Two-dimensional and Doppler echocardiography were performed within 24 hours after CRT device implantation. LV ejection fraction was determined by the biplane method of discs according to American Society of Echocardiography guidelines.[16] Continuous-wave Doppler was performed in the apical five-chamber view for measurements of aortic VTI. Pulsed wave–derived transmitral velocities were obtained at the mitral leaflet tips. Diastolic filling time was determined as the time interval from onset of transmitral valve flow to mitral valve closure. Doppler-derived aortic and transmitral indices were measured by an experienced echocardiographer in at least four consecutive cardiac cycles and averaged.

Aortic VTI method for AV delay optimization

Immediately after the baseline echocardiographic study, continuous-wave Doppler was performed to record the aortic flow velocity envelope. The CRT device was programmed to atrial synchronous ventricular pacing (VDD) mode at an initial AV delay of 200 ms or the longest AV delay that resulted in biventricular excitation. The AV delay was decreased in 20-ms increments after 20 cardiac cycles to a minimum AV delay of 60 ms. Aortic VTI was measured after 10 cardiac cycles at each of the programmed AV delay intervals. The optimized AV delay was determined as the AV delay that resulted in the greatest increase in aortic VTI from baseline (Figure 1). The average time for acquiring the Doppler aortic velocities and performing measurements was approximately 10 minutes.

Mitral inflow method for AV delay optimization

After AV delay optimization by the aortic VTI method, an optimized AV delay was calculated by the mitral inflow method in each patient. With this method, the AV delay that synchronizes the termination of late diastolic transmitral flow velocity to the onset of isovolumic LV contraction is calculated to optimize LV filling. The mitral inflow method requires measurements derived from recordings of the pulsed Doppler mitral inflow velocity at long and short AV delay intervals.[14,15] AV delay intervals used in this study were 160 ms (long AV delay) and 60 ms (short AV delay). All patients were biventricular paced at both intervals. The optimized AV delay by the mitral inflow method is determined by the time difference between ventricular activation and the termination of the mitral A wave at a long AV delay (interval "a" measured in Figure 2A). Measurement of LV electromechanical delay is defined by the measured time difference between LV stimulation and closure of the mitral valve at a short AV delay (time interval "b" shown in Figure 2B). In the theoretical case of no LV electromechanical delay, a long AV delay would have to be shortened by interval "a" to achieve an optimized AV delay. In the presence of an LV electromechanical delay, the long AV delay is further adjusted by interval "b" to yield an optimized AV delay determined by the calculation: $160 - (b - a)$. The time to acquire the mitral inflow velocities at the two AV delays and perform the measurements was approximately 5 minutes.

Statistical analysis

Continuous variables are presented as mean $\pm$ SD. Differences between the two Doppler methods were compared

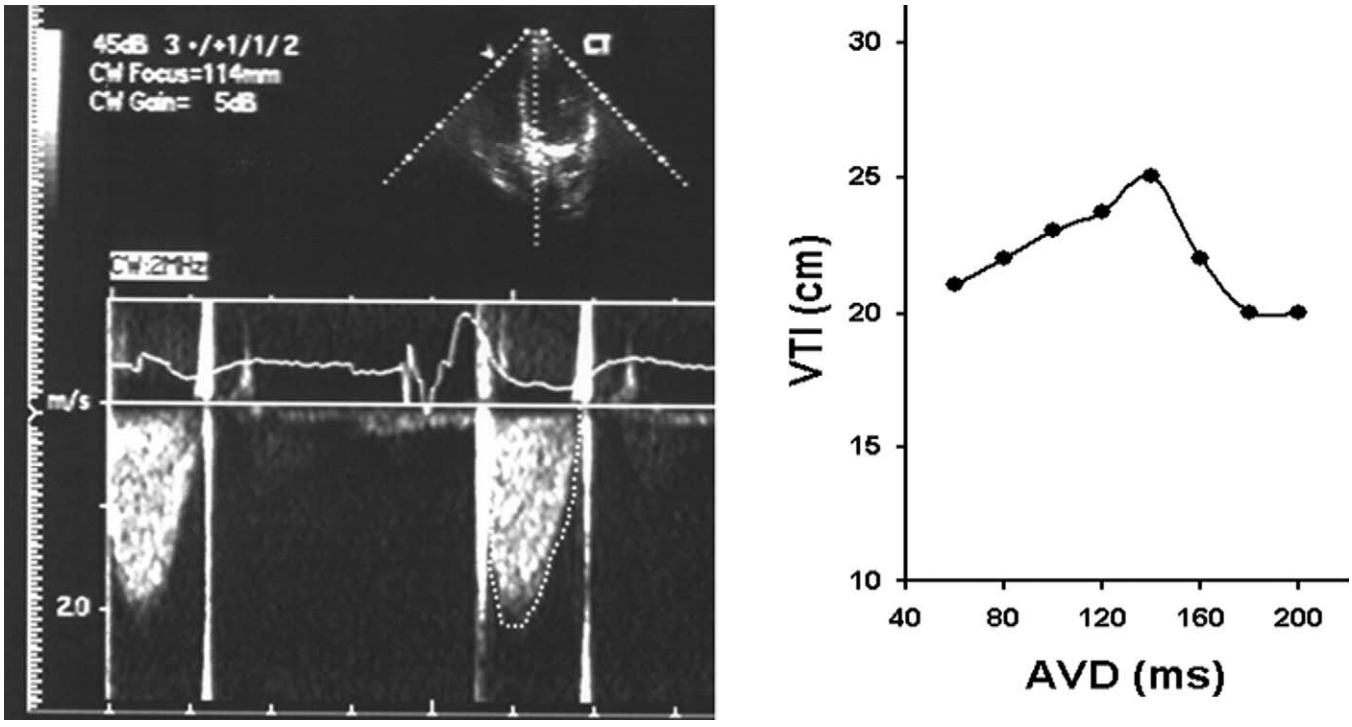

Figure 1 Aortic velocity time integral (VTI) method for atrioventricular delay (AVD) optimization. In this patient, the AV delay was programmed to a series of values from 200 to 60 ms in 20-ms decrements. At each AV delay, the aortic Doppler waveform was recorded and VTI calculated **(A)** after 10 cardiac cycles. A plot of the average VTI values **(B)** demonstrated the AV delay associated with the greatest VTI (140 ms in this example).

using a paired or unpaired two-tailed Student's t-test, as appropriate. Linear regression analysis was performed to compare the results of the two methods of AV delay optimization.

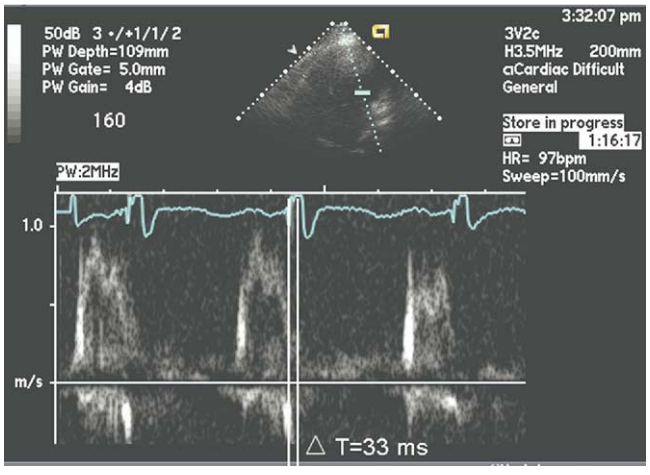

Figure 2 Mitral inflow method for AV delay optimization. **A:** A long AV delay (AVLong) program results in premature mitral valve closure, prior to the paced QRS. The time interval "a" is measured from the termination of the mitral A wave to the onset of the paced QRS. **B:** A short AV delay results in closure of the mitral valve due to the onset of left ventricular systolic contraction. The electromechanical delay, time interval "b," is measured from the onset of the paced QRS to the termination of the mitral A wave. The optimal AV delay is calculated by the equation AVLong − (b − a).

Results

The clinical characteristics of the study population (n = 40) are given in Table 1. The majority of patients were male (65%). The etiology of heart failure was primarily nonischemic (63%), and nearly all patients had heart failure symptoms consistent with New York Heart Association (NYHA) class III or IV at the time of CRT device implantation (95%). All patients had successful implantation of the LV lead, and no lead dislodgments occurred prior to echocardiographic evaluation. LV lead placement was mid-lateral in 21 patients (53%), mid-posterolateral in 12 (30%), mid-anterolateral in 6 (15%), and anterior in 1 (2%).

AV delay optimization and Doppler methods

The beat-to-beat variability of the Doppler-derived aortic VTI at each of the programmed AV delay intervals was ≤3

Table 1 Baseline characteristics

Variable	Study group (n = 40)
Age (yr)	59 ± 12
Male gender (%)	65
Ischemia (%)	38
New York Heart Association class	3.1 ± 0.4
PR interval (ms)	203 ± 31
QRS interval (ms)	177 ± 23
Left ventricular ejection fraction (%)	25.7 ± 5.6

Values are given as mean ± SD or percentage.

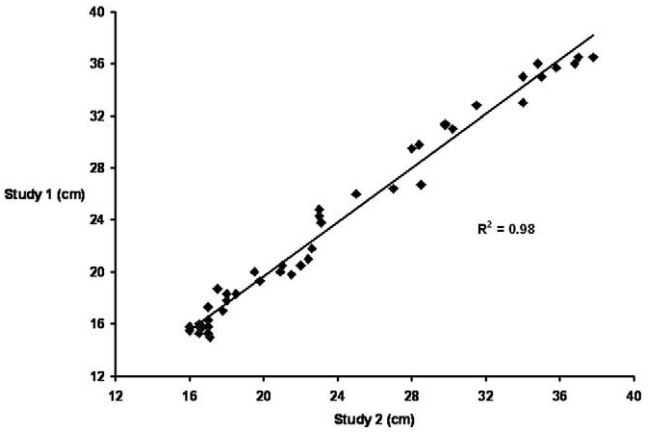

Figure 3 Intraobserver variation in measurement by the aortic velocity time integral (VTI) method. The reliability of measurement of aortic VTI was estimated by one observer in eight randomly selected patients by measurement of the average aortic VTI for each programmed AV delay on two occasions. The results of each measurement are plotted in coordinate pairs in the figure. There was an excellent correlation of the measurements between trials.

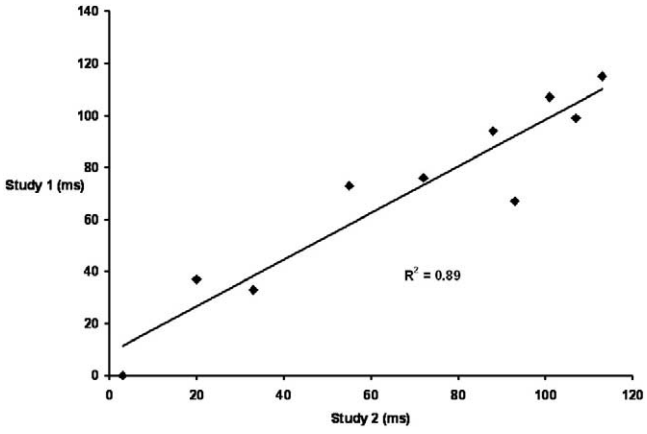

Figure 4 Intraobserver variation in measurement by the mitral inflow method. The reliability of measurements used to calculate the optimal AV delay in the mitral inflow method was estimated by one observer for two separate measurements of interval "b" measured at the short AV delay (part A) and interval "a" measured at the long AV delay (part B) in eight patients. Both measurements demonstrated an excellent correlation between trials.

cm. This corresponded to a standard error of the mean <1 cm for average VTI measurements used in this analysis. The intraobserver reproducibility of aortic VTI measurement, determined in 8 of 40 randomly selected patients, was excellent (r = 0.99, Figure 3). With a criterion for significance of a change in VTI compared with baseline greater than the standard error of the mean, AV delay optimization with the aortic VTI method resulted in a significant increase in the continuous-wave Doppler-derived aortic VTI in 39 of 40 patients after CRT, with an average improvement relative to the baseline aortic VTI of 19.4% ± 13.4% (P <.001 vs baseline). The optimized AV delay was 119 ± 34 ms, with a wide variability of optimized AV delay intervals (60–180 ms) among the patient cohort. A value ≥120 ms was determined in 24 (60%) of 40 patients.

The mitral inflow method of AV delay optimization significantly increased the aortic VTI in 37of 40 patients (12.3% ± 12.2%, P <.001 vs baseline). The optimal AV delay determined by the mitral inflow method (95 ± 24 ms) was significantly shorter compared with the aortic method (P <.001). There was a wide range of optimized AV delay intervals among the patient cohort (43–143 ms), and 11 (28%) of 40 were ≥120 ms. The variability of mitral valve closure time intervals at either long and short programmed AV delay interval was ≤20 ms. Intraobserver reproducibility determined in 10 of 40 randomly selected patients was excellent (r = 0.95 and 0.99 at long and short AV delay interval, respectively, Figure 4).

The aortic VTI method produced a greater improvement in LV stroke volume, estimated by the relative change in the aortic VTI, compared with the mitral inflow method in 36 of 40 patients. In the remaining four patients, there was an equivalent change in the relative stroke volume, with CRT achieved using either method of AV delay optimization (Figure 5). There was no correlation of the AV delay values predicted by the two methods of AV delay optimization (r = 0.03). The difference in optimal AV delay predicted by the two methods was >40 ms in nearly half (19/40) of the patient cohort. LV diastolic filling time significantly increased by 17% ± 16% and 15% ± 10% with AV delay

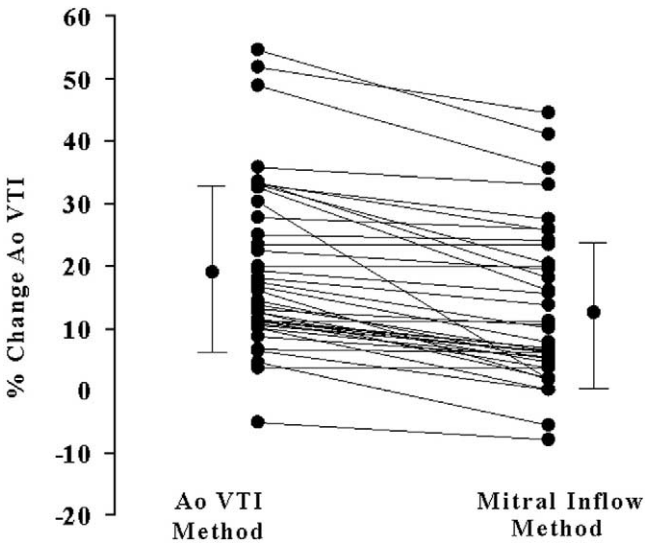

Figure 5 Individual responses to AV delay optimization by the aortic velocity time integral (VTI) and mitral inflow methods. The percent change in aortic VTI after cardiac resynchronization therapy, compared with baseline, at the optimal AV delay determined by the aortic VTI method and the mitral inflow method is plotted for each patient. The aortic VTI method produced a larger improvement than the mitral inflow method (19% ± 13% vs 12% ± 12%, P <.0001). The percent increases by each method are connected by lines among individual patients. The aortic VTI method produced a larger increase in relative stroke volume in 36 of 40 patients compared with that achieved by the mitral inflow method.

optimized CRT by either the aortic VTI or mitral inflow method, respectively (both $P < .001$ vs pre-CRT). There was no significant difference in the magnitude of the change in diastolic filling time achieved with either method.

Discussion

This study demonstrates that in patients with severe heart failure who receive CRT, optimization of AV delay by the continuous-wave Doppler aortic VTI method yields a greater increase in LV stroke volume compared with that achieved by a mitral inflow method that optimized diastolic filling time. Our findings differ form prior observations in patients with complete heart block treated with dual-chamber pacing.[14] In that report, AV delay optimization by either an aortic VTI method or the mitral inflow method yielded equal improvement in the echocardiographic-determined stroke volume with similar optimized AV delay intervals. A second study, also performed in patients with heart block treated with dual-chamber pacing, reported that AV delay optimization with the mitral inflow method improved stroke volume compared with a fixed AV delay interval.[17] Based upon these reports, the mitral inflow method has been widely applied in clinical trials of CRT.[7,8] The present study was performed to directly compare the results of AV delay optimization in individual heart failure patients treated with CRT to determine if noninvasive measurement of stroke volume (i.e., aortic VTI) is a better guide for AV delay optimization compared with the mitral inflow method. Our results demonstrate that the aortic VTI method is superior to the mitral inflow method, with a 58% larger relative improvement in LV stroke volume with initiation of CRT compared with the mitral inflow method.

There are important differences between the present investigation and prior studies that included patients with complete heart block who received dual-chamber right ventricular pacing.[14,15] This study included patients with intact AV nodal conduction and simultaneous right and left ventricular pacing. Therefore, the pattern of LV electrical excitation is very different in our study. Second, the prior studies did not comment on the degree of LV systolic dysfunction and likely included patients with preserved LV function. All of the patients in this investigation had severe LV systolic dysfunction, and many had concomitant LV diastolic dysfunction. As a result, the impact of programmed AV delay on LV filling and stroke volume could be fundamentally different.

The mitral inflow method of AV delay optimization has been proposed to optimize diastolic filling of the LV and eliminate premature closure of the mitral valve that often occurs when the PR interval is prolonged. Diastolic filling subsequently improves, and diastolic mitral regurgitation, if present, can be abolished. This investigation revealed that the increases in diastolic filling time were not significantly different whether the AV delay was optimized by the aortic VTI method or the mitral inflow method.

The larger improvement in stroke volume observed in this study with the aortic VTI method, compared with the mitral inflow method, likely is explained by the direct assessment of systolic performance provided by measurement of relative changes in LV stroke volume. Although the maximal improvement in LV systolic performance with CRT has been reported to be steeply dependent on optimal timing of LV mechanical systole to occur at the peak of the LV pressure pulse due to left atrial contraction, this relationship is independent of changes in LV end-diastolic pressure.[11] Therefore, the benefits due to CRT do not result from optimization of LV preload alone. Our data support the prior finding[11] that the timing of LV systolic contraction is an important determinant of the clinical benefit of CRT independent of preload optimization. There are several possible mechanistic explanations for this observation. For example, potential energy stored in the elastic recoil of the LV in response to atrial systole may be converted back to kinetic energy for ejection. If true, the efficiency of this conversion would be critically dependent on the timing of systolic contraction to match the oscillation of the LV "spring." A second possibility is that the contraction sequence of the LV in the presence of native conduction is critically affected by AV delay timing. In other words, the degree of fusion of activation wavefronts from native AV conduction through the AV node–His–right bundle branch and activation by the right and left ventricular leads may vary significantly with AV delay timing. The optimal contraction sequence then would be independent of preload but critically dependent on AV timing. A third possibility in patients with mitral regurgitation is that the mitral regurgitant volume is affected by AV delay timing with a reciprocal relationship to stroke volume. The superiority of the aortic VTI method for AV delay optimization may result from its sensitivity to these potential systolic mechanisms as well as preload optimization.

The effects of CRT on stroke volume and the optimal programmed AV delay vary among heart failure patients as shown in this study. In addition, clinical benefits from CRT are primarily linked to improvement in systolic performance, whereas the effects on diastolic function are variable.[5,6,8] Therefore, an AV delay optimization method that directly measures improvements in LV systolic performance (i.e., aortic VTI) is predictably preferable to AV delay optimization methods that optimize LV filling parameters to maximize the benefit of CRT.

Study limitations

Invasive measurements of stroke volume and cardiac output, or LV pressures to determine dP/dt, pulse pressure, and/or LV end-diastolic pressure, were not performed in this study. Instead, a noninvasive approach to estimate relative changes in LV stroke volume was used based upon measurement of the continuous-wave Doppler-derived aortic VTI. Variations in the aortic VTI from cardiac cycle to cycle may have influenced this method for estimating

changes in the stroke volume during AV delay optimization. However, the VTI measurements were averaged over four consecutive cardiac cycles and had excellent intraobserver reproducibility.

Several potential limitations of the mitral inflow method for AV delay optimization may have compromised the performance of this method. For example, the influence of loading conditions may significantly alter LV filling patterns.[18] In addition, the mitral inflow method is critically dependent on visualizing mitral A-wave truncation as a result of premature mitral valve closure with a very short AV delay. In patients with LV diastolic dysfunction, a common occurrence in heart failure patients, the mitral A wave may be severely attenuated or abbreviated by early mitral valve closure. Therefore, performance of the mitral inflow method may be compromised in these patients. A different method for optimizing the AV delay has been reported in patients with significant mitral regurgitation.[19] The onset of the mitral regurgitation Doppler signal can be used to determine the onset of LV contraction and calculate LV electromechanical delay. However, mitral regurgitation may not be detected in all patients with heart failure and was present in only 70% of our study patients.

The similar increase in LV diastolic filling time with either AV delay optimization method evaluated in this investigation suggests that optimizing LV filling was not directly related to maximal improvement in stroke volume. In fact, a study from our laboratory has demonstrated that diastolic function determined by the pre-CRT mitral inflow pattern may potentially impact the acute effects of CRT.[20] Whether the observed difference in improvements of LV stroke volume between the two methods may have influenced functional and/or clinical outcomes was not addressed in the study design. In addition, the utility of aortic VTI or mitral inflow methods for AV delay optimization in CRT patients with QRS intervals of 120 to 150ms was not evaluated in the present study.

Conclusion

Doppler echocardiographic methods for optimizing AV delay in patients who receive a CRT device vary substantially in performance. The presence of variability of AV delay that maximizes stroke volume suggests an empiric programmed AV delay interval for CRT devices is not optimal in many patients. Our results demonstrate that the continuous-wave Doppler-derived aortic VTI method for AV delay optimization is associated with a larger systolic enhancement from CRT, as determined by increases in stroke volume, than the mitral inflow method in heart failure patients treated with CRT.

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