Randomized prospective trial of atrioventricular delay programming for cardiac resynchronization therapy

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OBJECTIVES The purpose of this study was to determine if AV delay optimization with continuous-wave Doppler aortic velocity-time integral (VTI) is clinically superior to an empiric program in patients treated with cardiac resynchronization therapy (CRT) for severe heart failure.

BACKGROUND The impact of AV delay programming on clinical outcomes associated with CRT is unknown.

METHODS A randomized, prospective, single-blind clinical trial was performed to compare two methods of AV delay programming in 40 patients with severe heart failure referred for CRT. Patients were randomized to either an optimized AV delay determined by Doppler echocardiography (group 1, n = 20) or an empiric AV delay of 120 ms (group 2, n = 20) with both groups programmed in the atriosynchronous biventricular pacing (VDD) mode. Optimal AV delay was defined as the AV delay that yielded the largest aortic VTI at one of eight tested AV intervals (between 60 and 200 ms). New York Heart Association (NYHA) functional classification and quality-of-life (QOL) score were compared 3 months after randomization.

RESULTS Immediately after CRT initiation with AV delay programming, VTI improved by 4.0 ± 1.7 cm vs 1.8 ± 3.6 cm ($P < .02$), and ejection fraction (EF) increased by 7.8 ± 6.2% vs 3.4 ± 4.4% ($P < .02$) in group 1 vs group 2, respectively. After 3 months, NYHA classification improved by 1.0 ± 0.5 vs 0.4 ± 0.6 class points ($P < .01$), and QOL score improved by 23 ± 13 versus 13 ± 11 points ($P < .03$) for group 1 vs group 2, respectively.

CONCLUSIONS Echocardiography-guided AV delay optimization using the aortic Doppler VTI improves clinical outcomes at 3 months compared to an empiric AV delay program of 120 ms.

KEYWORDS Cardiac resynchronization therapy; Heart failure; Atrioventricular delay

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Introduction

Cardiac resynchronization therapy (CRT) improves hemodynamic and echocardiographic parameters of cardiac function, congestive heart failure (CHF) symptoms, and functional status in patients with medically refractory CHF associated with prolonged QRS duration.[1–4] Although the majority of patients treated with CRT show a significant clinical benefit, up to 30% of patients have either no change or deterioration in New York Heart Association (NYHA) functional classification after initiation of CRT.[1,5] Optimal AV delay programming may play an important role in the hemodynamic and clinical response to CRT because suboptimal AV delay programming can result in as much as a 15% decline in optimal cardiac output.[6]

Currently, there is no standard for AV delay programming in CRT. Clinical trials of CRT have used various methods for guiding AV delay programming by optimizing either systolic function or diastolic filling with invasive or noninvasive techniques.[1,4] In addition, the importance of AV delay optimization in patients with severe heart failure has been questioned because high left ventricular (LV) filling pressures typical for these patients may minimize the preload contribution of atrial systole. Therefore, an AV delay near 120 ms for atrial synchronous ventricular pacing (VDD) has been suggested as a reasonable empiric AV delay program in patients receiving CRT.[7]

We conducted a prospective, randomized, single-blind clinical trial to test the hypothesis that AV delay optimization guided by the aortic Doppler velocity-time integral

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(VTI) as a surrogate for stroke volume[8,9] leads to improved clinical outcomes compared to an empiric AV delay program of 120 ms.

Methods

Patient selection

Patients undergoing implantation of a CRT device for treatment of medically refractory CHF symptoms were enrolled in the study. The protocol was overseen by the Washington University Human Studies Committee, and all patients provided written informed consent.

Inclusion criteria were NYHA class III or IV, age >18 years, LV ejection fraction less than 35%, QRS duration >150 ms, and standard medical therapy for heart failure including an angiotensin-converting enzyme inhibitor or angiotensin-II receptor blocker, a diuretic, digoxin, and spironolactone (Aldactone) if not contraindicated. Patients taking beta-blockers were required to be taking a stable dose for more than 1 month. Exclusion criteria were symptomatic bradyarrhythmias, medically refractory atrial arrhythmias, pregnancy, myocardial infarction or coronary intervention within 3 months of enrollment, or a significant comorbid illness defined as severe obstructive pulmonary disease requiring chronic supplementation of oxygen, serum creatinine >2.5, malignancy, or medically refractory anginal symptoms.

Study protocol

Patients meeting entry criteria underwent a baseline evaluation prior to CRT that included NYHA functional classification, quality-of-life (QOL) assessment with the Minnesota Living with Heart Failure Questionnaire, and a 6-minute walk measurement. After baseline evaluation, a CRT device was implanted and programmed to an inactive ventricular demand (VVI) mode with the lower rate limit set at 40 bpm. All leads were implanted transvenously. The LV lead was targeted, when possible, to an epicardial site on the mid-lateral LV wall through a branch of the coronary sinus.

The day after device implantation, all patients underwent a comprehensive two-dimensional (2D) Doppler echocardiographic study (Sequoia ultrasound system, Acuson-Siemens, Mountain View, CA, USA) prior to initiation of CRT. Measurements included LV ejection fraction, calculated by the biplane method of disks, and aortic Doppler VTI in accordance with the American Society of Echo guidelines.[10,11] The CRT device was programmed to the VDD mode, and all patients underwent echocardiographic analysis at varying AV delays. Measurement of continuous-wave aortic Doppler flow velocities was done in the apical five-chamber view at eight AV intervals: 200, 180, 160, 140, 120, 100, 80, and 60 ms. After 20 cardiac cycles at each AV delay, measurements were made on the final three to four cardiac cycles. Aortic Doppler VTI calculations were made after all AV intervals had been measured. The optimal AV delay was defined as the AV delay associated with the largest average aortic Doppler VTI. After AV delay evaluation, patients were randomized by order of enrollment. Half of the patients were programmed to the aortic Doppler VTI optimized AV delay setting (odd numbered enrollment, group 1, n = 20); the other half of patients were programmed to an empiric AV delay setting of 120 ms (even numbered enrollment, group 2, n = 20). The 2D Doppler echocardiographic study was repeated 10 minutes after AV delay programming in all patients.

Patients returned for follow-up 3 months after programming, at which time clinical parameters (NYHA classification, QOL score, 6-minute walk) were evaluated, and 2D Doppler echocardiographic evaluation was performed. In a subset of patients, optimization of AV delay by measurement of the aortic Doppler VTI was repeated at 3 months with the same protocol described earlier.

Statistics

Baseline characteristics in each group were compared for significant differences, as were differences in echocardiographically derived LV ejection fraction and aortic Doppler VTI after AV delay programming and in clinical outcomes at 3 months. A Chi-square test was used for dichotomous variables, and the Student's t-test (unpaired, two-tailed, alpha = .05) was used for continuous variables. All continuous variables are expressed as mean ± SD. The correlation coefficient r was calculated using linear regression.

Results

Patient characteristics

The baseline characteristics of the patients are shown in Table 1. There were no significant differences between the two groups among the measured characteristics. Forty patients (average age 59.8 ± 12.1 years, NYHA class 3.1 ± 0.5, ejection fraction 25.6 ± 5.4%, QRS duration 176 ± 22 ms, PR interval 202 ± 30 ms) were enrolled. The majority of patients in the trial were men (70%) with a nonischemic cardiomyopathy (55%). Successful implantation of a transvenous CRT system was accomplished in all patients enrolled in the study. There was no significant difference in the anatomic location of the LV lead between groups. LV lead locations were in the mid-lateral LV wall in 55% of patients, mid-posterolateral wall in 23%, and mid-anterolateral in 17%.

Optimal AV delay

The average aortic Doppler VTI optimized AV delay for the study population was 119 ± 34 ms; however, the range

Table 1 Baseline characteristics of the patient population

Characteristic	All patients (n = 40)	Group 1 (n = 20)	Group 2 (n = 20)	*P* value*
Age (yr)	59.8 ± 12.1	59.3 ± 13.1	59.6 ± 11.0	.95
Male sex	28 (70%)	15 (75%)	13 (65%)	.49
History CAD	18 (45%)	9 (45%)	9 (45%)	1.00
Tobacco use	14 (35%)	7 (35%)	7 (35%)	1.00
Diabetic	16 (40%)	7 (35%)	9 (45%)	.52
LBBB	35 (88%)	18 (90%)	17 (88%)	.64
NYHA class	3.1 ± 0.5	3.1 ± 0.5	3.1 ± 0.5	1.00
QOL score	71 ± 17	72 ± 18	70 ± 16	.67
Distance walked in 6 min (m)	242 ± 92	258 ± 83	225 ± 100	.40
EF (%)	25.6 ± 5.4	25.3 ± 5.8	25.9 ± 5.1	.74
Aortic VTI (cm)	19.8 ± 5.7	20.5 ± 6.6	19.1 ± 4.7	.44
QRS interval (ms)	176 ± 22	175 ± 20	176 ± 24	.83
PR interval (ms)	202 ± 30	202 ± 20	202 ± 40	.98
ACEI/ARB	40 (100%)	20 (100%)	20 (100%)	1.00
Diuretic	40 (100%)	20 (100%)	20 (100%)	1.00
Digitalis	26 (65%)	14 (70%)	12 (60%)	.51
Aldactone	28 (70%)	13 (65%)	15 (75%)	.49
β-Blocker	31 (78%)	15 (75%)	16 (80%)	.71

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CAD = coronary artery disease; EF = ejection fraction; LBBB = left bundle branch block; NYHA = New York Heart Association; QOL = quality of life; VTI = velocity-time integral.
*Group 1 vs group 2.

of optimal AV delays was broad, with a minimum value of 60 ms and a maximum value of 200 ms (Figure 1). A subset of patients (n = 32) underwent the AV delay optimization protocol again at 3 months. This evaluation demonstrated a good correlation with the optimal AV delay determined at initial programming (r = 0.7; Figure 2).

AV delay optimization

Immediately after AV delay programming, group 1 (optimized AV delay) had significantly larger improvements in aortic Doppler VTI and LV ejection fraction compared to group 2 (AV delay of 120 ms). Aortic Doppler VTI improved by 4.0 ± 1.7 cm vs 1.8 ± 3.0 cm ($P < .02$), and LV ejection fraction increased by 7.8 ± 6.2% vs 3.4 ± 4.4% ($P < .02$) in group 1 vs group 2.

The average improvement in aortic Doppler VTI after initiation of CRT with AV delay programming was 3.0 ± 2.3 cm (Figure 3); however, not all patients had a significant change in VTI in response to CRT. Three patients in group 1 versus eight patients in group 2 had a less than 2-cm improvement in aortic Doppler VTI immediately after final AV delay programming ($P = .08$).

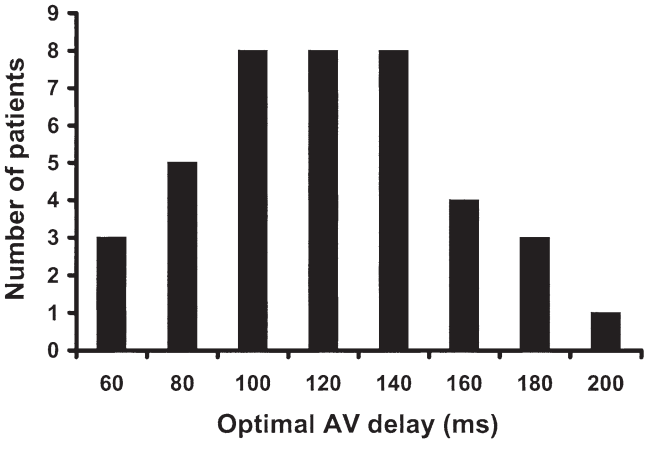

Figure 1 Distribution of optimal AV delays. The acutely optimized AV delays measured in all patients are plotted in the bar graph. All patients were programmed in the VDD mode. The number of patients with optimal augmentation of the aortic Doppler velocity-time integral are plotted for each of the eight tested AV intervals: 60, 80, 100, 120, 140, 160, 180, and 200 ms (n = 40).

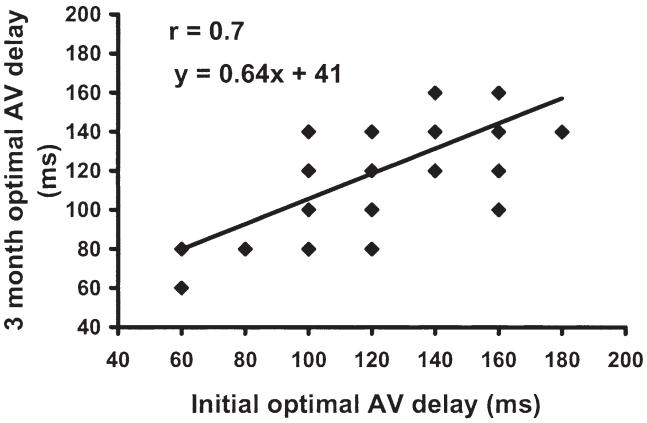

Figure 2 Consistency of optimized AV delay over time. The correlation for the optimal AV delay determined initially with that determined at 3 months (n = 32) is plotted. Linear regression was used to calculate the correlation coefficient r displayed on the graph.

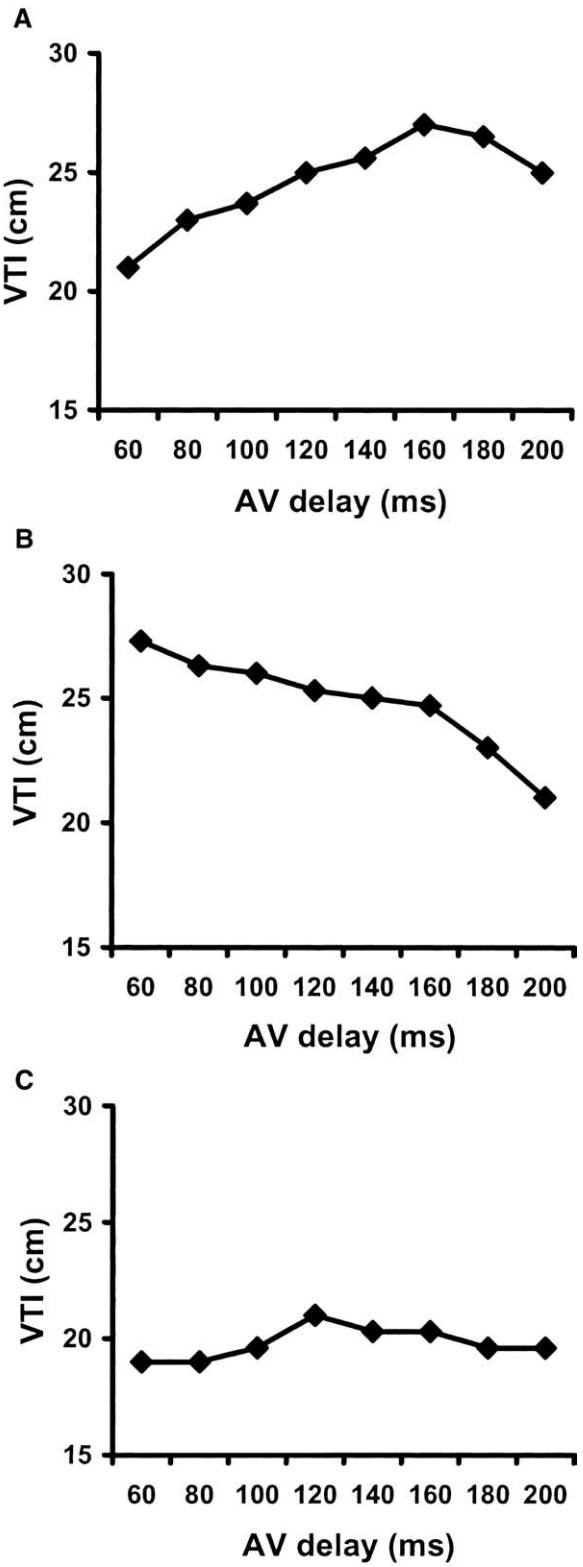

Figure 3 Representative data from three patients showing varying responses to cardiac resynchronization therapy (CRT) with adjustment of AV delay. **A:** Patient 5 had an optimal AV delay response at 160 ms. Aortic velocity-time integral (VTI) improved from 21 to 27 cm at optimal AV delay programming. **B:** Patient 17 had an optimal response at the shortest tested AV delay of 60 ms. C: Patient 29 showed a less than 2-cm change in VTI with CRT.

Clinical outcomes

At 3-month follow-up, group 1 had a larger improvement in NYHA class points (1.0 ± 0.5 vs 0.4 ± 0.6, $P < .01$) compared to group 2. Seventy-five percent of patients in group 1 improved by at least one NYHA functional classification, whereas only 40% of patients in Group 2 improved by one NYHA functional class ($P < .03$). Group 1 patients also had a significantly larger improvement in QOL score (23 ± 13 vs 13 ± 11 points, $P < .03$). The change in 6-minute walk distance between the two groups was not significantly different; however, there was a significant improvement in 6-minute walk distance above baseline values in the study cohort (all patients) after 3 months of active CRT (Table 2).

Events

All patients had successful implantation of a CRT device and underwent randomization. After implantation, two patients required revision of the LV lead. Both patients were included using intention-to-treat analysis. One patient originally enrolled in the trial later was excluded due to death before the 3-month follow-up period. This patient died from cancer that was not diagnosed at the time of enrollment and device implantation. There were no other deaths during the follow-up period.

Six patients in group 1 were hospitalized during the follow-up period versus nine patients in group 2 ($P = .3$). There were two implantable cardioverter-defibrillator shocks in group 2 versus none in group 1. Two patients in group 1 were on continuous IV ionotropic support (dobutamine) at the time of enrollment and were weaned off of the ionotropes during the study period. No patients in group 2 were on IV ionotropic support at any time during the study.

Stability of AV delay optimization

Among patients who underwent redetermination of optimal AV delay at 3 months, eight patients (two from group 1 and six from group 2) had an AV delay program that differed by $\geq$40 ms from the optimally determined AV delay. Only 2 (25%) of these 8 patients improved by one NYHA functional classification during the course of this study compared with 23 (72%) of the 32 patients in the rest of the study cohort ($P < .02$). In addition, at 3 months, LV ejection fraction in these eight patients improved by only $3.3 \pm 2.3\%$ compared with an $8.4 \pm 6.2\%$ improvement in LV ejection fraction in the rest of the study cohort ($n = 32$; $P < .05$).

Predictive value of acute response to CRT

To evaluate the predictive value of the acute response to CRT on clinical outcomes at 3 months, patient data was reclassified based on the clinical response to CRT irrespec-

Table 2 Clinical and echocardiographic outcomes at 3 months

Characteristic	All patients	Group 1	Group 2	*P* value (group 1 vs group 2)
NYHA class baseline	3.1 ± 0.5	3.1 ± 0.5	3.1 ± 0.5	1.00
NYHA class at 3 months	2.4 ± 0.6*	2.1 ± 0.5*	2.7 ± 0.7	.01
Quality-of-life score baseline	71 ± 17	72 ± 18	70 ± 16	.67
Quality-of-life score at 3 months	52 ± 23*	48 ± 21*	56 ± 25*	.03
6-min walk baseline (m)	219 ± 94	236 ± 83	201 ± 108	.51
6-min walk at 3 months (m)	288 ± 111*	310 ± 100*	266 ± 122*	.21
Ejection fraction (%) baseline	25.6 ± 5.4	25.3 ± 5.8	25.9 ± 5.1	.74
Ejection fraction (%) at 3 months	33.7 ± 10.4*	35.6 ± 10.9*	31.8 ± 10.0*	.28
LVEDV (mL) baseline	238 ± 104	242 ± 107	234 ± 103	.83
LVEDV (mL) at 3 months	211 ± 92*	208 ± 101*	214 ± 86	.85
LVESV (mL) baseline	181 ± 88	181 ± 90	180 ± 89	.98
LVESV (mL) at 3 months	148 ± 85*	142 ± 93*	154 ± 78*	.7

NYHA = New York Heart Association. LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume.
*$P < .05$ vs baseline.

tive of the initial treatment assignment. "Responders" were defined as patients who improved by at least one NYHA functional class (n = 25) at 3-month follow-up. "Nonresponders" were defined as patients with less than one NYHA functional class improvement (n = 15) at 3-month follow-up. This analysis demonstrated that the acute response to CRT measured by the aortic Doppler VTI was strongly predictive of the clinical response at 3 months (Figure 4). With a cutoff of a 10% improvement in the aortic Doppler VTI measured acutely after initiation of CRT, 23 of 25 responders were predicted compared to 0 of 15 nonresponders.

Discussion

This prospective, randomized clinical trial of AV delay programming in CRT is the first to compare the clinical response of an empiric AV delay program to a noninvasively determined optimal AV delay. Our results demonstrate that AV delay optimization with continuous-wave aortic Doppler VTI yields better echocardiographic and clinical outcomes compared to an empiric AV delay program of 120 ms in patients being treated with CRT for severe heart failure. The average optimized AV delay program in the study cohort (119 ms) was very close to the empiric AV delay program (120 ms) that was used in this trial. Thus, individual patient variation likely accounted for the observed differences in outcomes between groups. Due to the large range of optimal AV delay programs that was observed (60–200 ms), many patients in the empiric AV delay arm of the trial received an AV delay program that was significantly different than their optimized AV delay. These outliers showed the least improvement from CRT over the course of this study. AV delay optimization reduced the nonresponse rate to CRT with regard to both acute hemodynamic improvement (improvement in aortic Doppler VTI) and improvement in NYHA functional classification at 3 months.

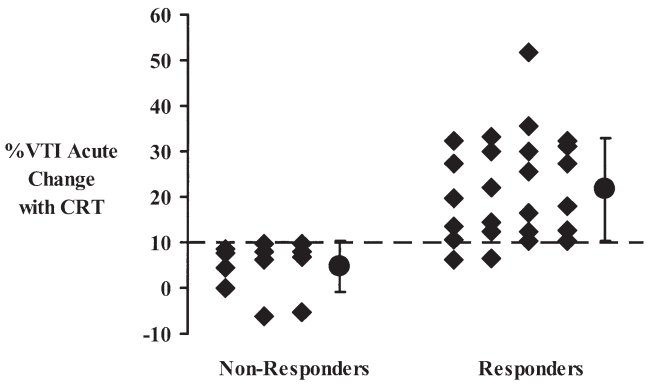

Figure 4 Predictive value of the acute change in the aortic Doppler velocity-time integral (VTI). Patients were defined as "responders" if their New York Heart Association (NYHA) functional class improved by one class point (n = 25). "Nonresponders" had no change in NYHA classification (n = 15). The plot demonstrates that an acute improvement of 10% in the aortic Doppler VTI was highly predictive of clinical improvement after 3 months of cardiac resynchronization therapy as indicated by NYHA functional classification.

AV delay optimization has been shown to improve the acute hemodynamic response to CRT. Optimized patients have demonstrated improved long-term clinical outcomes from CRT.[3,4] However, in these trials, no comparison was made to patients with non–"AV optimized" CRT; therefore, the extent to which device programming played a role in the observed chronic benefit from CRT is unclear. In addition, the invasive method of AV delay optimization used (evaluation of the maximum rate of change in LV pressure and aortic pulse pressure) limits its adoption in routine clinical practice. Other clinical trials of CRT have used a noninvasive echocardiography-guided AV delay optimization protocol based on Doppler evaluation of transmitral filling patterns.[1,2] This method attempts to optimize late LV filling with the presumption that maximal filling yields the maximum increase in stroke volume. However, the pulsed-Doppler mitral inflow method of AV delay optimization has only been tested in dual-chamber pacing in patients with

high-degree AV block[12] and has not been validated in CRT. We previously reported that this method yields a significantly smaller response to CRT compared to that associated with an aortic Doppler VTI optimized AV delay program.[13]

Our data are consistent with previous trials of CRT with regard to the observed improvements in ejection fraction, NYHA class, QOL score,[1] aortic VTI,[14] and average optimal AV delay.[7] Our data confirm that individual AV delay optimization improves acute hemodynamics and long-term clinical outcomes; however, the best AV delay optimization method remains to be determined. Characteristics of an optimal method for AV delay optimization include ease of performance, patient comfort, and accuracy of the method. Our experience with AV delay optimization using the aortic Doppler VTI is consistent with this description. The method is relatively easy to perform (the optimization protocol can be done in $<$10 minutes), and the optimal AV delay determined with this method stays relatively consistent over time. We believe that routine use of the aortic Doppler VTI to optimize the AV delay is beneficial for patients receiving CRT who have intact sinus node function. An alternative clinical approach that may be useful is using aortic Doppler VTI to optimize the AV delay in patients who previously received a nonoptimized CRT device and have not had a favorable clinical response.

Study limitations

The limitations of this trial include its small size and relatively short 3-month follow-up period. In addition, the patients included in this study had intact sinus and AV nodal function. The applicability of aortic Doppler VTI AV delay optimization in CRT patients with sick sinus syndrome requiring atrial pacing or in patients with heart block remains to be determined. Although patients were blinded to their treatment assignment in this clinical trial, a double-blind design was not utilized. Therefore, we cannot eliminate the potential for bias affecting these results.

Another potential source of bias is the observation that the study population included a slight majority (55%) of patients with a nonischemic cardiomyopathy. The trial design did not include a selection bias for nonischemic cardiomyopathy patients. Therefore, this observation reflects either a slight referral bias or a phenomenon of chance from sampling a large population. As there is currently no compelling evidence suggesting a differential response to CRT in nonischemic versus ischemia cardiomyopathy patients, the response to AV delay optimization likely would not differ between these two patient groups.

Conclusion

AV delay optimization using the continuous-wave aortic Doppler VTI as a surrogate for stroke volume improves LV ejection fraction immediately following initiation of CRT compared to an empiric AV delay program. The acute hemodynamic improvements observed with individual AV delay optimization translate into improved NYHA functional classification and QOL at 3 months relative to an empiric AV delay program. Longer follow-up will determine whether this benefit is sustained.

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