JACC: CARDIOVASCULAR IMAGING VOL. 4, NO. 7, 2011

ISSN 1936-878X/$36.00

PUBLISHED BY ELSEVIER INC.

DOI:10.1016/j.jcmg.2011.02.019

ORIGINAL RESEARCH

Influence of Atrial Function and Mechanical Synchrony on LV Hemodynamic Status in Heart Failure Patients on Resynchronization Therapy

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OBJECTIVES The aim of this study was to evaluate atrial and ventricular function in patients undergoing cardiac resynchronization therapy (CRT).

BACKGROUND Right atrial pacing (AP) in CRT induces delays in electrical and mechanical activation of the left atrium. The influence of atrial sensing (AS) versus AP on ventricular performance in CRT and the mechanisms underlying the differences between AS and AP in CRT have not been fully elucidated.

METHODS Fifty-five patients with heart failure undergoing CRT for 9 ± 12.5 months and 22 control subjects without heart failure were enrolled. Conventional and tissue Doppler echocardiography was performed to examine atrial and ventricular mechanics and hemodynamic status.

RESULTS The optimal atrioventricular interval was shorter in AS compared with AP mode (126 ± 19 ms vs. 155 ± 20 ms, $p < 0.0001$). Left ventricular (LV) outflow tract time-velocity integral (22 ± 7 cm vs. 20 ± 7 cm, $p < 0.001$), diastolic filling period (468 ± 124 ms vs. 380 ± 93 ms, $p < 0.001$), and global strain (−32 ± 24% vs. −27 ± 22%, $p = 0.001$) were greater in AS compared with AP mode. Atrial strain was higher in AS compared with AP mode in the right atrium (−28.2 ± 8.6% vs. −22.6 ± 7.6%, $p = 0.0007$), interatrial septum (−17.1 ± 6.5% vs. −13.2 ± 5.4%, $p = 0.002$), and left atrium (−16.4 ± 11.0% vs. −13.6 ± 8.5%, $p = 0.02$). There was no difference in intraventricular dyssynchrony but significantly lower atrial dyssynchrony in AS compared with AP mode (31 ± 19 ms vs. 42 ± 24 ms, $p = 0.0002$).

CONCLUSIONS AS is associated with preserved atrial contractility and atrial synchrony, resulting in optimal LV diastolic filling, stroke volume, and LV systolic mechanics. This pacing mode maximizes LV performance and the hemodynamic benefit of CRT in patients with heart failure. (J Am Coll Cardiol Img 2011;4:691–8) © 2011 by the American College of Cardiology Foundation

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Manuscript received January 14, 2011; revised manuscript received February 16, 2011, accepted February 24, 2011.

JACC: CARDIOVASCULAR IMAGING, VOL. 4, NO. 7, 2011
JULY 2011:691–8

Cardiac resynchronization therapy (CRT) alleviates symptoms, improves functional capacity, induces reverse remodeling, and extends survival in patients with heart failure with electrocardiographic evidence of conduction abnormalities, low ejection fractions, and advanced symptoms despite optimal medical therapy (1,2). In CRT, both ventricles are paced at a certain atrioventricular (AV) interval after atrial sensing (AS) or atrial pacing (AP). Hemodynamic studies in patients with conduction disease, with and without CRT, have demonstrated that there is a finite range of AV delays during which cardiac output and left ventricular (LV) performance is optimal (3,4). Although differences in interventricular (VV) activation can be modified through device programming, interatrial mechanical delays are not adjustable and can significantly affect left-sided AV filling and consequentially LV stroke volume. Right atrial (RA) pacing in CRT induces delays in electrical and mechanical activation of the left atrium (5–9). However, the influence of AS versus AP on ventricular performance in CRT remains unclear. Furthermore, the mechanisms underlying the differences between AS and AP in CRT have not been fully elucidated. Right ventricular pacing induces LV dyssynchrony and dysfunction, but it is plausible that a similar mechanism exists in the atria (10). To better clarify the implications of AS versus AP in CRT, we prospectively examined atrial and ventricular mechanics and hemodynamic status, and AV coupling, using standard Doppler indexes and tissue Doppler strain Z in patients undergoing CRT after the optimization of AV and VV delays. We hypothesized that AS allows superior LV hemodynamic status and performance by at least affecting atrial mechanics.

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ABBREVIATIONS AND ACRONYMS

AP = atrial pacing
AS = atrial sensing
AV = atrioventricular
CRT = cardiac resynchronization therapy
LA = left atrial
LV = left ventricular
LVOT = left ventricular outflow tract
RA = right atrial
TVI = time-velocity integral
VV = interventricular

METHODS

All participants provided informed consent for this study, which was approved by the institutional review board. Seventy-two consecutive patients who had undergone the implantation of a CRT device and been referred for echocardiography-based optimization were enrolled. We excluded patients with permanent atrial fibrillation or poor image quality (n = 17), and analysis was performed on 55 subjects. We also enrolled 21 patients with dual-chamber pacemakers but without heart failure as a control group.

Echocardiography. A Vivid 7 cardiac ultrasound machine (GE Healthcare, Milwaukee, Wisconsin) with a 3.5-MHz transducer was used. Echocardiographic examinations were performed with patients in the left lateral decubitus position. At each programmed AV interval of the optimization procedure (described in the following), an apical 4-chamber view with tissue Doppler imaging and mitral pulsed-wave Doppler examination using a sample volume at the mitral leaflet tip and annulus level was obtained. Pulsed Doppler of the LV outflow tract (LVOT) was acquired from an apical 5-chamber view.

Optimization protocol. All subjects underwent optimization of the AV delay and VV delay. The LVOT time-velocity integral (TVI) was used as the primary end point for optimization. For sensed AV optimization (AS mode), the AV delay was initially programmed to 250 ms and reduced by 30 ms until truncation of mitral Doppler inflow A-wave was noted. At each stage, LVOT TVI, total transmitral inflow TVI, and the mitral late diastolic inflow velocity A-wave TVI were measured. The optimal AV delay was defined as that which yielded completely paced beats (i.e., without evidence of ventricular fusion) and the maximal LVOT TVI. For paced AV optimization (AP mode), the AP rate was set 10 beats/min higher than the intrinsic atrial rate, and the AV delay was initially programmed to 300 ms. The optimization process was repeated as described earlier. The pacemaker settings were then adjusted to the optimal AS and AP settings. We then performed VV optimization at the optimal sensed and paced AV intervals. The imaging sequence was repeated with the following VV settings: simultaneous (offset 0 ms), right ventricle pre-activated by 30 and 60 ms, and left ventricle pre-activated by 30 and 60 ms. The ideal VV delay was that which yielded the maximal LVOT TVI. All parameters were measured after 2 min of pacing at each programmed VV interval.

Hemodynamic status. We assumed that the mitral annular and LVOT diameters were unchanged during the study. Thus, changes in LVOT TVI were considered reflective of changes in stroke volume. The total transmitral inflow TVI at the annulus was used to assess LV diastolic filling. In addition to LVOT TVI, LV ejection fraction and global longitudinal strain were used to assess LV

global systolic function. The diastolic filling period was defined from the onset of transmitral inflow to the subsequent R-wave in this study and was expressed as a percent of the entire cardiac cycle.

Cardiac mechanics. Tissue Doppler and strain echocardiography have been extensively validated as accurately depicting regional myocardial motion and deformation, respectively. Strain has been demonstrated as being superior to tissue velocity in the assessment of regional and global function (1,11–13). Absolute strain values were used to assess regional and global ventricular function (14). For the purposes of this study, global strain was defined as the sum of systolic strain in the lateral and septal walls in the apical 4-chamber view and used to assess LV global function (13).

We have previously shown that strain echocardiography can be used to evaluate atrial systolic function (15). Atrial strain and strain rate were measured in the RA free wall, atrial septum, and left atrial (LA) free wall. The atrial strain rate tracing (Fig. 1) comprises 3 waves. The systolic wave coincides with ventricular systole, the early diastolic wave coincides with passive atrial filling, and the late diastolic wave is produced by active atrial contraction. Late diastolic atrial strain rate reflects atrial contractility. The atrial mechanical activation time was defined as the time from the peak of the atrial contraction wave to the subsequent R-wave. We used the electrocardiographic R-wave as the reference point of electric activity, because the R-wave is more easily recognized than the P-wave. Atrial synchrony was defined as the time difference between atrial mechanical activation times at the RA and LA free walls and the interatrial septum. Ventricular synchrony was assessed by tissue Doppler imaging and strain echocardiography. Intra-atrial and interatrial, AV, and intraventricular mechanical synchrony were defined as the time difference between atrial walls, atrial and ventricular walls, and ventricular walls, respectively.

Strain echocardiography was analyzed using strain (offset) distances of 8 mm in the ventricles and 6 mm in the atria. Mean temporal resolution was 10 ms. Only tracings with clear systolic and diastolic peaks were analyzed.

All time delays were corrected for heart rate using the Bazett formula (time delay in milliseconds normalized to the square root of the RR interval in seconds).

Statistical analysis. Data are expressed as mean ± SD or as frequencies. Paired *t* tests or Wilcoxon signed rank tests, depending on distribution, were used to compare data between AS and AP modes. A p value <0.05 was considered statistically significant.

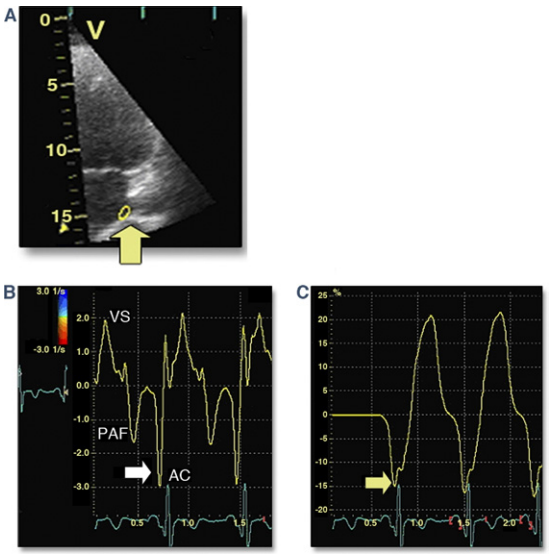

Figure 1. Atrial Strain Echocardiography

Representative atrial strain rate tracing obtained from the left atrial free wall **(A, yellow arrow)** depicting ventricular systole (VS), passive atrial filling (PAF), and atrial contraction (AC) **(B, white arrow)**. Integration of the atrial contraction wave in strain rate yields atrial strain **(C, yellow arrow)**. Atrial strain rate and strain reflect atrial contractility.

RESULTS

We analyzed 55 of 72 enrolled patients with heart failure who had adequate-quality images and were not in atrial fibrillation (mean age 63.8 ± 13.3 years; 35 men). The mean duration of CRT was 9.0 ± 12.5 months at the time of enrollment.

Table 1 details the baseline echocardiographic characteristics of CRT patients in the AS and AP settings. The mitral late diastolic inflow velocity A-wave TVIs were comparable between the two modes. The optimal AV interval was significantly shorter in AS compared with AP mode (126 ± 19 ms vs. 155 ± 20 ms) (mean difference 29 ± 17 ms, $p < 0.0001$). The optimal AV delay observed with AP was ≥30 ms longer than optimal AV delay with AS in 65% of the patients. Almost all Doppler-based measures of ventricular hemodynamic performance were better in AS compared with AP mode. The total transmitral inflow TVI (20.6 ± 6.5 cm vs. 17.5 ± 5.1 cm, $p < 0.001$), LVOT TVI (21.9 ± 7.0 cm vs. 20.0 ± 6.7 cm, $p < 0.001$), diastolic filling period (468 ± 124 ms vs. 380 ± 93 ms, p <

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Table 1. Baseline Echocardiographic Characteristics in CRT

Variable	AS Mode	AP Mode	p Value
AV delay (ms)	126 ± 19	155 ± 20	<0.0001
Mitral late diastolic inflow velocity A-wave TVI (cm)	8.6 ± 3.0	8.6 ± 3.1	0.98
Total transmitral inflow TVI (cm)	20.6 ± 6.5	17.5 ± 5.1	<0.001
LVOT TVI (cm)	21.9 ± 7.0	20.0 ± 6.7	<0.001
MV-R time (ms)	468 ± 124	380 ± 93	<0.001
Diastolic filling time (%)	49 ± 9	43 ± 9	<0.0001
LA EF (%)	52 ± 17	50 ± 16	0.19
LV EF (%)	27 ± 10	26 ± 10	0.02
Global LV strain (%)	−32.3 ± 24.2	−26.8 ± 22.2	0.001
LV post-systolic strain (%)	−37.0 ± 23.2	−32.4 ± 21.3	0.0013

Values are mean ± SD.
AP = atrial pacing; AS = atrial sensing; AV = atrioventricular; CRT = cardiac resynchronization therapy; EF = ejection fraction; LA = left atrial; LV = left ventricular; LVOT = left ventricular outflow tract; MV-R time = onset of mitral inflow to the subsequent R-wave; TVI = time-velocity integral.

0.001), and global strain (−32.3 ± 24.2% vs. −26.8 ± 22.2%, p = 0.001) were greater in AS compared with AP mode. Differences in LV ejection fraction (0.27 ± 0.1 vs. 0.26 ± 0.1, p = 0.02) were statistically significant but numerically very close.

To further investigate potential mechanisms underlying these hemodynamic differences, we evaluated atrial mechanics, including atrial contractility and synchrony. Active atrial strain (reflecting atrial contractility) was significantly higher in AS compared with AP mode in the right atrium (−28.2 ± 8.6% vs. −22.6 ± 7.6%, p = 0.0007), interatrial septum (−17.1 ± 6.5% vs. −13.2 ± 5.4%, p = 0.002), and left atrium (−16.4 ± 11.0% vs. −13.6 ± 8.5%, p = 0.02). In the control group, active atrial strain was significantly higher in AS mode as well (Table 2).

We subsequently assessed AV mechanical synchrony using atrial and ventricular strain signals. No significant differences were noted in the mechanical delay between the right atrium and right ventricle (p = 0.85), the interatrial septum and interventricular septum (p = 0.62), and the left atrium and left ventricle (p = 0.70). Similarly, there was no difference in the degree of intraventricular dyssynchrony using either time to peak strain (p = 0.80) or time to peak systolic velocity (p = 0.39) (Table 3).

Table 2. Atrial Mechanics: Regional Active Atrial Strain

Region	AS Mode	AP Mode	p Value
CRT			
Right atrium (%)	−28.2 ± 8.6	−22.6 ± 7.6	0.0007
Interatrial septum (%)	−17.1 ± 6.5	−13.2 ± 5.4	0.002
Left atrium (%)	−16.4 ± 11	−13.6 ± 8.5	0.02
Control group			
Right atrium (%)	−29.0 ± 6.4	−25.6 ± 6.3	<0.0001
Interatrial septum (%)	−16.0 ± 4.8	−13.6 ± 4.2	0.0025
Left atrium (%)	−15.2 ± 6.1	−13.6 ± 5.4	0.0258

Values are mean ± SD.
Abbreviations as in Table 1.

In contrast, there were significant differences in intra-atrial mechanical synchrony, measured using the atrial strain rate signal, between AS and AP modes. In the right atrium, the time delay from the RA free wall to the interatrial septum was shorter in AS compared with AP mode (27 ± 18 vs. 41 ± 26 ms, p < 0.001). Similarly, in the left atrium, the time delay from the interatrial septum to the LA free wall was shorter in AS compared with AP mode (31 ± 19 ms vs. 42 ± 24 ms, p = 0.0002). The time delay from the RA to the LA free wall (interatrial synchrony) was shorter in AS compared with AP mode (56 ± 34 ms vs. 80 ± 45 ms, p < 0.0001). In the control group, there were significant differences in intra-atrial and interatrial mechanical synchrony in AP mode as well (Table 4).

Interobserver and intraobserver variability showed good agreement (Fig. 2) in the measurement of time delay (93% and 92%, respectively) and strain (97% and 96%, respectively). The limits of agreement for interobserver and intraobserver variability in time delay ranged from 14.9 to −18.3 ms and from 11.4 to −12.6 ms, respectively. The limits of agreement for interobserver and intraobserver variability in strain ranged from 7.9% to −9.7% and from 6.2% to −6.2%, respectively.

DISCUSSION

Our study clarifies multiple mechanical and hemodynamic issues that have a direct impact on the management of CRT device programming. First, we demonstrate that most patients (65%) have a difference of ≥30 ms in the optimal AV interval between AS and AP modes. We also demonstrate, for the first time, the presence of atrial mechanical dysfunction and dyssynchrony in AP mode in CRT patients, using strain echocardiography. Last, we present hemodynamic and mechanical evidence indicating that these atrial mechanical abnormalities result in reduced transmitral filling and consequentially lower ventricular stroke volume and global ventricular systolic strain in AP mode. These multiple lines of evidence suggest that AS-based pacing in CRT provides a more favorable mechanical and hemodynamic profile compared with AP.

Table 3. AV and Intraventricular Mechanics

Variable	AS Mode	AP Mode	p Value
Delay in time to peak strain rate (ms)			
RA to RV	302.2 ± 53.8	298.6 ± 49.7	0.85
IAS to IVS	301.6 ± 54.4	304.5 ± 51.9	0.62
LA to LV	279.7 ± 62.9	277.9 ± 54.7	0.70
Delay in time to peak strain (ms)			
LV, septal to lateral wall	18.0 ± 62.5	27.3 ± 91.5	0.8
Delay in time to peak systolic velocity (ms)			
LV, septal to lateral wall	−4.6 ± 71.2	5.4 ± 66.1	0.39

Values are mean ± SD.
IAS = interatrial septum; IVS = interventricular septum; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle; other abbreviations as in Table 1.

Cardiac resynchronization corrects the mechanical inefficiency of delayed lateral wall contraction in a remodeled and dyssynchronous heart, thereby increasing ventricular stroke volume. In heart failure, remodeling develops not only in the ventricles but also in the atria (16). Traditional pacing algorithms are such that only the right atrium is sensed and paced in CRT. It is well known that pacing the RA appendage significantly worsens interatrial conduction delay, as reflected by the prolonged P-wave duration on the surface electrocardiogram and interatrial conduction time on intracardiac electrograms (5–8). Camous et al. (17) showed that there was a close positive correlation between paced and spontaneous interatrial conduction times. Interatrial conduction block is thought to be a marker of LA contractile dysfunction, with a linear relationship between the degree of electrical delay and the extent of LA dysfunction (18). Cha et al. (9) recently showed an increased latency period of RA stimulation to LA contraction in the AP pacing mode.

Doppler and M-mode echocardiography have previously shown that RA pacing significantly increases interatrial mechanical delay (6,19). Given that Doppler signals are the result of net pressure gradients between the atrium and the ventricle, the timing of Doppler signals does not necessarily correspond to the timing of mechanical activation. Similarly, M-mode echocardiography also has its limitations, because it can interrogate only a limited number of ventricular and/or atrial walls despite its high temporal resolution (19). In contrast, tissue Doppler and strain imaging have high temporal (>200 frames/s) and spatial resolution and depict regional mechanical events in real time in virtually any segment of the heart. Tissue velocity imaging has been used to demonstrate a significant increase in intra-atrial and interatrial asynchrony in patients with heart failure in sinus rhythm, compared with normal controls (20). Also, a time delay of peak strain in atrial segments, suggestive of atrial dyssynchrony, has been documented during RA appendage pacing (5).

Our study used previously validated and sophisticated noninvasive techniques to compare atrial and AV mechanics and hemodynamic parameters in 2 common modes of pacing in CRT. Our data indicate significant atrial contractile abnormalities and intra-atrial and interatrial mechanical delays in AP compared with AS mode. Furthermore, Doppler data indicate that these atrial mechanical abnormalities result in suboptimal AV filling and stroke volume.

The significance of LA contribution to LV filling and overall LV performance has been previously noted in animal and clinical studies. Goyal and Spodick (18) found an inverse correlation between P-wave duration and LA ejection fraction. Furthermore, AP reduced LV stroke volume without significant differences in regional LV strain in an animal study (21). In our study, AP resulted in a reduction of LV filling and stroke volume as re-

Table 4. Intra-Atrial and Interatrial Mechanics

Variable	AS Mode	AP Mode	p Value
	Delay in Time to Atrial Contraction by Strain Rate (ms)		
CRT			
RA to IAS	27 ± 18	42 ± 26	<0.001
RA to LA	56 ± 34	80 ± 45	<0.0001
IAS to LA	31 ± 19	42 ± 24	0.0002
Control group			
RA to IAS	26 ± 15	34 ± 11	0.0286
RA to LA	59 ± 24	78 ± 25	0.0003
IAS to LA	33 ± 14	44 ± 21	0.003

Values are mean ± SD.
Abbreviations as in Tables 1 and 3.

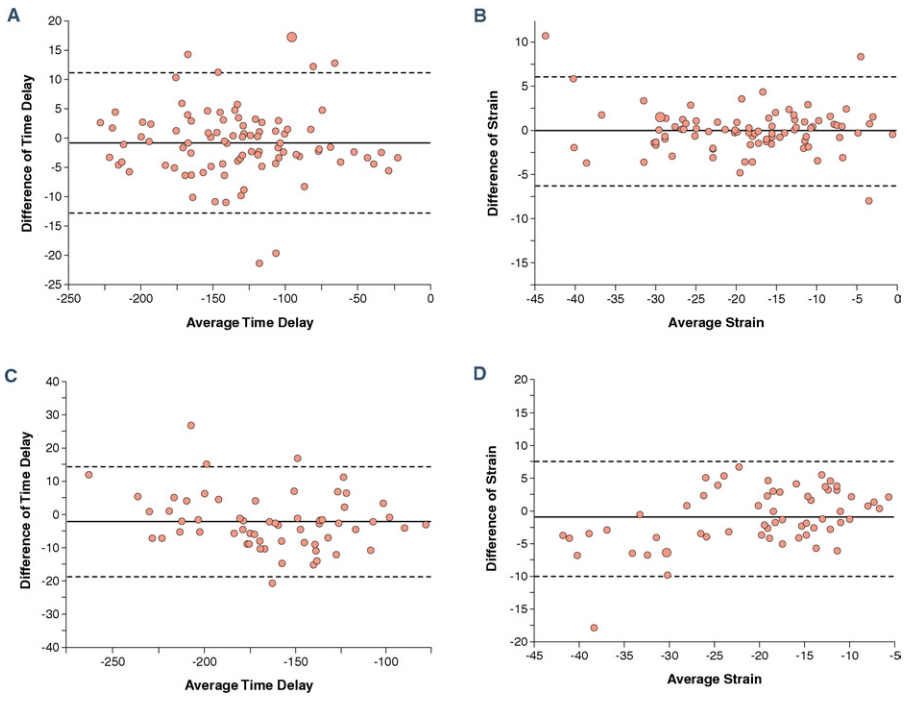

Figure 2. Intraobserver and Interobserver Variability

Bland-Altman plots of intraobserver **(A, B)** and interobserver **(C, D)** variability in the measurement of time delay and peak strain. The **solid line** indicates the mean value of the difference, and the **dashed line** indicates mean ± 2 SDs.

flected by lower total transmitral inflow TVI and LVOT TVI, respectively. A recent study by Bernheim et al. (22) involving a small number of patients suggested that AP is suboptimal in CRT, because it induces intraventricular dyssynchrony. Although our study supports the contention that AS mode is superior to AP mode, our data are not fully concordant with this previous study, especially with regard to the possible mechanisms underlying the superiority of AS mode. For example, Bernheim et al. (22) reported intraventricular dyssynchrony with AP. This finding seems counterintuitive given that all patients were on CRT and that their settings were optimized before the study. In contrast, our study demonstrated synchronous ventricular contraction, by tissue Doppler imaging and strain methods, in AS and AP modes. All patients were treated with CRT, and AV and VV timings were optimized before evaluation. One potential reason for this discrepancy could be the difference in the method of optimization. We determined the optimal AV interval in either mode on the basis of maximal LVOT TVI, whereas Bernheim et al. (22) used a fixed "pace compensation" of 40 ms plus the optimal AV interval in AS mode as the optimal AV delay in AP mode. Therefore, there is a possibility of fusion activation of the left ventricle between intrinsic and biventricular paced rhythms because of an inappropriately "long" AV interval, resulting in a loss of LV synchronization in AP mode in the study by Bernheim et al. (22).

Our data are somewhat divergent from those of Gold et al. (23), who reported a mean AS to AP offset of 75 ms, compared with about 30 ms in our study. Also their data suggested that AP resulted in superior hemodynamic results compared with AS mode in CRT. The use of different end points (percent change in LV dP/dt in their study vs. stroke volume by echocardiography in ours) may partially explain these differences. Others have demonstrated that LV dP/dt and cardiac output measurements do not agree in heart failure models (24). The mean difference in optimal AV delay in AS and AP modes in our study is concordant with other studies (25). The additional mechanistic evaluation in our study supports our observation that AS mode is superior to AP mode, which agrees with that reported by Bernheim et al. (22).

Although LV ejection fractions were statistically lower in the AP group, suggesting lower global LV systolic function, the absolute mean

difference of 1% between the 2 pacing modes is not clinically meaningful. However, the more sensitive strain measurements demonstrate larger, statistically significant differences, indicating that LV systolic function is indeed lower in AP mode. Our data indicate that this difference in LV function is related to significant atrial systolic dysfunction and dyssynchrony, causing decreased atrial emptying and consequently reduced LV preload. In a failing human heart, the Frank-Starling mechanism is well preserved in the isolated whole heart and an isolated muscle strip. However, the myocardium is considerably stiffer in heart failure compared with the normal heart (26). Thus, the failing heart may be more sensitive to small changes in LV preload such as those induced by the atrial mechanical abnormalities and dyssynchrony noted in our study, suggesting that AS is the preferred pacing mode in CRT.

Study limitations. This study was performed with patients at rest, and its findings may not hold true during activity. Because of time constraints, global LV strain was acquired in 6 representative segments in the 4-chamber view rather than all 16 segments of the left ventricle. Our global strain data, however, closely track changes in stroke volume and ejection fraction in our population. Although our data suggest AS as the preferred mode of pacing in CRT patients, sinus node dysfunction in heart failure may necessitate the use of AP (27). There is a small theoretical possibility that some of the changes in atrial or ventricular performance can be attributed to the 10 beats/min difference in heart rate between the 2 pacing modes. We used the Bazett formula to adjust for any differences in heart rate between the 2 modes, realizing that the heart rate dependence of AV delays may not be well described by this formula.

CONCLUSIONS

Intrinsic atrial activation during AS mode in CRT is associated with preserved atrial contractility and atrial synchrony, resulting in better LV diastolic filling, stroke volume, and LV systolic mechanics. This mode maximizes LV performance and the hemodynamic benefit of CRT in patients with heart failure. Our data suggest that AS is the optimal mode of pacing in CRT.

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Key Words: atrial function ■ cardiac resynchronization therapy ■ strain echocardiography.