

FOCUS ISSUE: CARDIAC RESYNCHRONIZATION THERAPY

Diastolic Function and Resynchronization

Improvements in Left Ventricular Diastolic Function After Cardiac Resynchronization Therapy Are Coupled to Response in Systolic Performance

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OBJECTIVES	To determine the short-term effects of cardiac resynchronization therapy (CRT) on measurements of left ventricular (LV) diastolic function in patients with severe heart failure.
BACKGROUND	Cardiac resynchronization therapy improves systolic performance; however, the effects on diastolic function by load-dependent pulsed-wave Doppler transmitral indices has been variable.
METHODS	Fifty patients with severe heart failure were evaluated by two-dimensional Doppler echocardiography immediately prior to and 4 ± 1 month after CRT. Measurements included LV volumes and ejection fraction (EF), pulsed-wave Doppler (PWD)-derived transmitral filling indices (E- and A-wave velocities, E/A ratio, deceleration time [DT], diastolic filling time [DFT], and isovolumic relaxation time). Tissue Doppler imaging was used for measurements of systolic and diastolic (Em) velocities at four mitral annular sites; mitral E-wave/Em ratio was calculated to estimate LV filling pressure. Color M-mode flow propagation velocities were also obtained.
RESULTS	After CRT, LV volumes decreased significantly ($p < 0.001$) and LVEF increased $>5\%$ in 28 of 50 patients (56%) and were accompanied by reduction in PWD mitral E-wave velocity and E/A ratio (both $p < 0.01$), increased DT and DFT (both $p < 0.01$), and lower filling pressures (i.e., E-wave/Em septal; $p < 0.01$). Patients with LVEF response $\leq 5\%$ after CRT had no significant changes in measurements of diastolic function; LV relaxation (i.e., Em velocities) worsened in this group.
CONCLUSIONS	In heart failure patients receiving CRT, improvement in LV diastolic function is coupled to the improvement in LV systolic function. (J Am Coll Cardiol 2005;46:2244–9) © 2005 by the American College of Cardiology Foundation

Cardiac resynchronization therapy (CRT) can be an adjunctive treatment in patients with medically refractory heart failure symptoms, severe left ventricular (LV) systolic dysfunction, and an interventricular conduction delay. Clinical trials of CRT have consistently demonstrated improvement in heart failure symptoms and a reduction in recurrent hospitalizations for heart failure exacerbation (1–3). CRT has been shown to decrease ventricular volumes and improve LV ejection fraction (LVEF) (4). The effects of CRT on LV diastolic function are not well characterized.

The LV diastolic function is physiologically coupled to LV systolic performance and is an important determinant of symptoms and outcomes in patients with LV systolic

dysfunction (5–7). Prior studies that have used pulsed-wave Doppler (PWD)-derived transmitral indices to characterize diastolic function have reported that CRT consistently increases diastolic filling time, but salutary effects on LV filling velocities (i.e., E-wave, E/A ratio) and deceleration time (DT) have been variable (8–15). These inconsistent findings in LV diastolic filling parameters after CRT may reflect the influence of preload alterations and/or systolic performance on these PWD-derived transmitral indices (16–17).

Tissue Doppler imaging (TDI) early diastolic annular (Em) and color M-mode flow propagation (FP) velocities have been established as relatively preload-independent measurements of LV relaxation and the ratios of PWD-derived mitral E-wave/Em and E/FP velocities reflect LV filling pressures (18–24). These newer methods to assess LV diastolic function have not been extensively reported in patients after CRT. This investigation tested the hypothesis that patients who had reduction in LV volumes and improvement in LVEF after CRT would demonstrate improvement in LV diastolic function.

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Abbreviations and Acronyms

CRT	= cardiac resynchronization therapy
DT	= deceleration time
DFT	= diastolic filling time
Em	= early diastolic mitral annular velocity
FP	= flow propagation
IVRT	= isovolumic relaxation time
LVEF	= left ventricular ejection fraction
NYHA	= New York Heart Association
PWD	= pulsed-wave Doppler
Sm	= systolic mitral annular velocity
TDI	= tissue Doppler imaging

METHODS

Patient population. All consecutive patients scheduled to receive implantation of a CRT device were asked to participate in the study. Inclusion criteria were a history of medically refractory heart failure symptoms, an optimized medical regimen for heart failure for at least three months, sinus rhythm with a QRS duration >0.13 s, LV enlargement (LV diastolic diameter >6.0 cm) and LVEF $<35\%$. Exclusion criteria included prior atrioventricular sequential dual-chamber pacemaker, medically refractory atrial fibrillation, symptomatic sinus node dysfunction, or unwillingness to participate in follow-up studies. The protocol was approved by the Human Studies Committee of Washington University.

Clinical and hemodynamic measurements. Functional assessment included New York Heart Association (NYHA) functional class and quality of life scores (Minnesota Living With Heart Failure Questionnaire) and a 6-min walk distance (in patients who were able to perform the test). Clinical outcomes included hospital admission for heart failure. Heart rate, systolic and diastolic blood pressures, and pulse pressure (systolic minus diastolic blood pressures) were obtained in the supine position after 10 min of rest at the time of echocardiography.

CRT device implantation. CRT device implantation included pacemaker-only and -defibrillator CRT devices. 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 (i.e., anterolateral or posterolateral) were used when a mid-lateral branch was either absent or unacceptable because of phrenic nerve stimulation or high stimulation threshold. After implantation, all devices were programmed to VVI mode, with a lower rate of 40 beats/min, and echocardiography was performed within 24 h after implant. CRT was initiated in the VDD mode with atrial synchronous ventricular pacing. The atrioventricular delay was programmed by use of continuous-wave Doppler measurements of aortic time velocity integral as previously described (25).

Echocardiography. A commercially available ultrasound system was used (Sequoia C256; Acuson-Seimens, Mountain View, California) for the echocardiography studies.

Two-dimensional (2D) measurements included LV volumes at end-diastole and end-systole from the apical four- and two-chamber views (method of discs), LVEF calculated by the biplane method, and LV mass determined by the area-length method and indexed for body surface area (26). Left atrial diameter was measured in the parasternal long axis view.

The PWD-derived transmitral velocities were obtained at the mitral leaflet tips according to American Society of Echocardiography guidelines (27). Measurements included the early diastolic (E) and atrial (A) wave velocities, the E/A ratio, the durations of the E- and A-wave (in ms), and the E-wave DT. Diastolic filling time (DFT) was determined as the time interval (ms) from the onset of diastolic flow to mitral valve closure. Isovolumic relaxation time (IVRT) was measured from the closure of the aortic valve to opening of the mitral valve. Continuous-wave Doppler of the mitral regurgitant jet velocity was performed to derive the mean rate of LV pressure decline, as a semiquantitative measurement of $-dP/dt$, in patients with a well defined jet envelope (28). Both 2D echocardiographic and Doppler-derived transmitral indices were measured by one observer in three to five consecutive cardiac cycles and averaged.

Pulsed-wave TDI was performed in the apical four- and two-chamber views by placement of a 3-mm sample volume at the lateral, septal, anterior, and inferior mitral annulus for measurements of the systolic (Sm) and early diastolic (Em) velocities (27). The time interval from Q-wave to peak Sm at each annular site and the maximal difference between sites was derived to determine the extent of intraventricular dyssynchrony (29,30). Em velocity was determined at each annular site and averaged (Em global). The PWD-derived mitral E-wave/TDI-derived Em velocity ratio was calculated (lateral, septal, and global) to determine LV filling pressure. Additional indices of LV relaxation included the time from the end of Sm to onset of Em velocity. Color M-mode FP was obtained in the apical four-chamber view by positioning an M-mode cursor to measure the slope (cm/s) of the early diastolic velocities from the mitral leaflets to a distance of 4 cm into the LV chamber; the ratio of mitral E-wave/FP velocity was determined as an estimation of LV filling pressure (27). Measurements of TDI and FP velocities were the average of three to five consecutive cardiac cycles.

At the four-month follow-up, patients were grouped according to their LVEF response to CRT (29, 30). Responders were those who increased LVEF $>5\%$, and nonresponders had a LVEF response $\leq 5\%$.

Statistical analysis. All statistical analysis was performed using SPSS software (version 11.0, SPSS Inc., Chicago, Illinois); continuous variables are expressed as mean \pm one standard deviation. A comparison of the clinical and echocardiographic variables prior to and after CRT was performed using paired and unpaired Student *t* test and Pearson correlations as appropriate. Statistical significance was determined as a *p* value of <0.05 .

Table 1. Clinical and Hemodynamic Variables After CRT

Variable	Responders (n = 28)		Nonresponders (n = 22)	
	Pre-CRT	Post-CRT	Pre-CRT	Post-CRT
NYHA functional class	3.1 ± 0.4	2.3 ± 0.5*	3.1 ± 0.5	2.5 ± 0.8‡
Heart failure score	66 ± 18	42 ± 21*	69 ± 25	42 ± 33‡
Six-min walk distance (feet)	672 ± 271	995 ± 270*	688 ± 333	966 ± 362‡
Heart rate (beats/min)	77 ± 13	70 ± 14‡	75 ± 10	75 ± 15
Systolic blood pressure (mm Hg)	114 ± 18	121 ± 17	107 ± 16	117 ± 17‡
Diastolic blood pressure (mm Hg)	68 ± 10	71 ± 9	64 ± 9	70 ± 9
Pulse pressure (mm Hg)	45 ± 13	51 ± 11‡	42 ± 12	48 ± 15‡

Responders defined as increase in left ventricular ejection fraction >5% after CRT. Variables are expressed as mean ± SD; *p ≤ 0.001; †p ≤ 0.01; ‡p ≤ 0.05 vs. pre-CRT.

CRT = cardiac resynchronization therapy; NYHA = New York Heart Association.

RESULTS

Of the 53 consecutive patients who enrolled in the study, three were excluded owing to inadequate echocardiographic images for two and one death from heart failure prior to four-month follow-up. The remaining 50 patients (age 60 ± 11 years) were predominantly male (74%), and the etiology of heart failure was primarily nonischemic (72%). Medications included angiotensin-converting enzyme inhibitors in 98%, diuretics in 84%, beta-blockers in 86%, digoxin in 73%, and potassium-sparing diuretics in 61%. The PR interval was 200 ± 20 ms and QRS duration was 180 ± 20 ms. There were no complications from CRT device implantation; two patients required LV lead repositioning during follow-up. The LV pacing lead was placed in a mid-lateral or posteriolateral vein in the majority of patients (84%), and the programmed atrioventricular delay was 118 ± 25 ms.

Functional and hemodynamic parameters after CRT based on LVEF response. Fifty patients were restudied at a mean of 4 ± 1 month after CRT; 28 (56%) were responders (i.e., increase in LVEF >5%). There were no significant differences between responders and nonresponders by their age, gender, medications for heart failure, follow-up time, etiologies of LV systolic dysfunction, LV

pacing site, PR interval, QRS duration, or programmed atrioventricular delay. The programmed atrioventricular delay remained unchanged during the follow-up interval.

As shown in Table 1, both groups had significant improvement in functional measurements after CRT as shown by decreases in NYHA functional classification, heart failure questionnaire scores, and increases in walk distance. The NYHA functional class improved by at least one class after CRT in both responders and nonresponders (71% vs. 64%, respectively); Quality-of-life scores decreased by >15% in 24 of 28 (75%) in responders compared to 11 of 22 (50%) nonresponders. Hospital readmission for heart failure occurred in 1 of 28 (4%) responders and in 5 of 22 (23%) nonresponders. Heart rate decreased (p = 0.01) and the pulse pressure increased (p = 0.04) significantly in responders. Systolic and pulse pressure increased significantly after CRT in nonresponders (p = 0.05 and 0.01, respectively), but the heart rate was unchanged.

Echocardiographic measurements and LVEF response after CRT. As shown in Table 2, LV end-diastolic and end-systolic volumes and LV mass decreased significantly in the responder group. LV volumes were significantly greater in nonresponders prior to CRT (p < 0.05). The PWD-

Table 2. Echocardiographic and Doppler Variables After CRT

Variable	Responders (n = 28)		Nonresponders (n = 22)	
	Pre-CRT	Post-CRT	Pre-CRT	Post-CRT
LV end diastolic volume (ml)	216 ± 70	174 ± 81*	270 ± 110	256 ± 91
LV end systolic volume (ml)	161 ± 57	109 ± 49*	209 ± 95	194 ± 83‡
LVEF (%)	26 ± 5	39 ± 10*	24 ± 6	26 ± 7†
LV mass index (g/m ²)	156 ± 30	142 ± 36‡	164 ± 46	170 ± 43
Left atrial diameter (cm)	4.5 ± 0.8	4.3 ± 0.7	4.7 ± 1.1	4.8 ± 0.8
Mitral E velocity (cm/s)	77 ± 34	56 ± 21*	88 ± 34	83 ± 38
Mitral E duration (ms)	172 ± 51	227 ± 82*	171 ± 48	191 ± 39
Mitral A velocity (cm/s)	63 ± 25	73 ± 16	73 ± 25	72 ± 28
Mitral A duration (ms)	131 ± 38	152 ± 17†	135 ± 34	142 ± 31
Mitral E/A velocity ratio	1.5 ± 1.1	0.8 ± 0.3*	1.4 ± 1.1	1.5 ± 1.2
Deceleration time (ms)	190 ± 56	228 ± 64†	165 ± 38	174 ± 31
Diastolic filling time (ms)	337 ± 96	427 ± 129*	345 ± 82	370 ± 106
Isovolumic relaxation time (ms)	119 ± 34	142 ± 27†	102 ± 33	114 ± 30‡
Mitral regurgitant jet (-) dP/dt	536 ± 99	599 ± 126‡	425 ± 109	491 ± 85

Responders defined as increase in LVEF >5% after CRT. Variables expressed as mean ± SD; *p ≤ 0.001, †p ≤ 0.01, ‡p ≤ 0.05 vs. pre-CRT.

CRT = cardiac resynchronization therapy; LV = left ventricular; LVEF = left ventricular ejection fraction.

Table 3. Tissue Doppler and Color M-Mode Variables by LVEF Response After CRT

Variable	Responders (n = 28)		Nonresponders (n = 22)	
	Pre-CRT	Post-CRT	Pre-CRT	Post-CRT
Q-Sm difference (ms)	66 ± 26	41 ± 25*	59 ± 29	64 ± 34
Em lateral (cm/s)	9.8 ± 3.6	7.7 ± 3.0*	9.3 ± 1.9	7.7 ± 2.7‡
Mitral E/Em lateral	8.1 ± 3.8	7.7 ± 3.2	9.7 ± 4.1	11.8 ± 6.0‡
Em septal (cm/s)	6.2 ± 2.3	6.3 ± 1.4	6.1 ± 1.6	5.5 ± 1.5
Mitral E/Em septal	13.2 ± 6.0	9.2 ± 3.4*	15.3 ± 7.4	15.3 ± 6.3
Em global (cm/s)	7.7 ± 2.4	7.1 ± 2.1	7.5 ± 1.3	6.8 ± 1.8‡
Mitral E/Em global	10.1 ± 3.7	7.7 ± 2.3*	11.7 ± 4.4	12.3 ± 4.6
Relaxation time lateral (ms)	137 ± 49	145 ± 54	128 ± 54	135 ± 54
Relaxation time septal (ms)	191 ± 53	167 ± 52	175 ± 50	171 ± 48
Relaxation time global (ms)	169 ± 46	148 ± 40	146 ± 52	148 ± 41
Flow propagation velocity (cm/s)	38 ± 9	38 ± 11	36 ± 10	37 ± 8

Responders defined as increase in left ventricular ejection fraction >5% after CRT. Variables expressed as mean ± SD; *p ≤ 0.001, †p ≤ 0.01, ‡p ≤ 0.05 vs. pre-CRT.

CRT = cardiac resynchronization therapy; LVEF = left ventricular ejection fraction.

derived parameters of diastolic function improved significantly (i.e., decreased E-wave velocity and E/A ratio; increased E-wave duration, DT, and DFT) in the responder group; IVRT and $-dp/dt$ also increased significantly. In contrast, in the nonresponder group there were no significant changes in any of these Doppler-derived transmitral inflow parameters. Therefore, only those patients who had significant decreases in LV end-diastolic volume and increases in LVEF after CRT demonstrated improvement in PWD-derived diastolic filling indices.

As shown in Table 3, the maximal Q-Sm difference between the four annular sites decreased significantly only in responders. The TDI-derived Em velocities at the lateral mitral annulus decreased significantly in both groups, and Em global decreased significantly in nonresponders. The mitral E-wave/Em septal decreased significantly only in responders, and the E-wave/Em lateral significantly increased in nonresponders. The TDI-derived myocardial relaxation time intervals and color M-mode FP velocities were unchanged regardless of LVEF response. Thus, the lack of change in the relatively load-independent indices (i.e., Em and FP) suggests that CRT does not significantly improve regional or global LV relaxation, even in patients who show improvement in LV systolic performance. The TDI-derived LV filling pressures decreased only in responders.

DISCUSSION

This study demonstrates that reductions in LV volumes and improvement in LVEF at four months after CRT are accompanied by improvement in PWD-derived indices of diastolic filling. Those patients who did not increase LVEF after CRT demonstrated no improvement in LV diastolic indices. LV relaxation remained unchanged or worsened regardless of the LVEF response after CRT. Functional measurements, including NYHA functional classification, quality-of-life scores, and six-minute walk distance, improved after CRT in most patients regardless of their LVEF response. However, clinical outcomes differed, with a lower

rate of hospital readmission for heart failure in responders compared to nonresponders (4% vs. 23%).

Effects of CRT on LV diastolic filling. Prior studies that have evaluated the effects of CRT on LV diastolic function by use of PWD-derived transmitral filling parameters have reported variable results (8–15). It is well established that LV diastolic filling time increases after CRT (8,9,12–14). However, the mitral E-wave velocity or E/A ratio may not be significantly altered (9,11,13). Other investigations have reported that the PWD-derived E-wave velocity decreases after CRT (12,14). In the present study some of these inconsistencies are clarified: CRT decreases the mitral E-wave velocity and the E/A ratio only in those patients who exhibit significant decreases in LV volumes and significant improvements in LVEF. These results are consistent with the preload-dependency of PWD-derived mitral inflow parameters (16–17). Similarly, increases in mitral E-wave DT after CRT have been observed in some studies (11,14) but not in others (9,12,13). These results are likely due in part to increase in DFT and the decrease in LV filling pressures after CRT, as shown by reduction in the TDI-derived E-wave/Em septal velocity. The increase in DT was observed primarily in those patients who demonstrated significant reduction in LV volume and/or an increase in LVEF >5%. It may also be postulated that increases in DT after CRT may reflect improvements in LV compliance (31–32).

Effects of CRT on LV relaxation. Despite the benefits observed in LV diastolic filling and lower LV filling pressures after CRT, measurements of global or regional LV relaxation were not favorably altered. The increases in continuous-wave Doppler-determined IVRT and $-dp/dt$ observed after CRT were likely due to decreases in preload because neither measurement was significantly altered in the nonresponder group. There were no changes after CRT in the relatively load-independent measurements of TDI-derived Em and color M-mode FP velocities, regardless of the response in LV volumes or LVEF. These results were unexpected, because minor improvements in LV systolic

performance have been shown to improve LV relaxation in patients with heart failure (5). Therefore, the results of this study extend previous acute observations in animal and human studies that have demonstrated that LV pacing has no beneficial effect on LV relaxation (33-35). These short-term observations may be secondary to lack of changes in LV mass, residual LV dyssynchrony and/or LV systolic dysfunction after CRT (4,36). It is also possible that recovery of LV relaxation is delayed after CRT and thus not yet evident at a short-term follow up of four months.

Study limitations. Invasive measurements of LV diastolic function were not obtained in patients; LV diastolic function was characterized using only echocardiographic parameters. However, prior investigations that have assessed changes in LV systolic and diastolic function after CRT at short-term follow-up have used similar methods (8-15). Suitable recordings of pulmonary venous velocities were not possible in many of the patients for analysis to assess potential changes in LV end-diastolic pressures. TDI-derived velocities obtained from the apical views reflect longitudinal diastolic function and are subject to translational motion of the LV. However, measurements of Em velocities were made at the mitral annulus to minimize translation artifact (26). The nonresponse rate in this study may be due to a lack of significant dyssynchrony prior to CRT, as reported by others. (37) The fact that functional outcomes improved after CRT in the nonresponder group may be related to the small but statistically significant decrease in end-systolic volumes, improved efficacy of pharmacologic therapy, or changes in other measurements of diastolic function (i.e., LV end-diastolic pressure) not directly assessed in the study.

CONCLUSIONS

Cardiac resynchronization therapy improves LV diastolic filling and lowers LV filling pressure, and these changes are coupled to reductions of LV volumes and increases in LVEF. Left ventricular relaxation does not improve following CRT, regardless of the response in systolic performance.

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