Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 53, No. 7, 2009
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2008.08.079

Persistent Hemodynamic Benefits of Cardiac Resynchronization Therapy With Disease Progression in Advanced Heart Failure

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Objectives Our aim was to determine the potential hemodynamic contributions of cardiac resynchronization therapy (CRT) in patients admitted for advanced decompensated heart failure.

Background CRT restores synchrony of the heart resulting in hemodynamic support that can facilitate the reversal of left ventricular (LV) remodeling in some patients.

Methods A total of 40 consecutive patients with advanced decompensated heart failure and CRT implanted >3 months, admitted due to hemodynamic derangements, underwent simultaneous comprehensive echocardiographic and invasive hemodynamic evaluation under different CRT settings.

Results All patients (mean LV ejection fraction 22 ± 7%, LV end-diastolic volume 323 ± 140 ml, 40% ischemic) had experienced progressive cardiac remodeling despite adequate LV lead positions and continuous biventricular pacing. A significant worsening of hemodynamics was observed immediately when CRT was programmed OFF in the majority (88%) of patients (systolic blood pressure: 105 ± 12 mm Hg to 98 ± 13 mm Hg; pulmonary capillary wedge pressure: 17 ± 6 mm Hg to 21 ± 7 mm Hg; cardiac output: 4.6 ± 1.4 l/min·m^2 to 4.0 ± 1.1 l/min·m^2; all $p < 0.001$). Worsening of hemodynamics coincided with reappearance of significant electrical (QRS width 161 ± 29 ms to 202 ± 39 ms, $p < 0.001$) and intraventricular mechanical dyssynchrony (15 ± 26 ms to 57 ± 41 ms, $p < 0.001$), together with a significant reduction in diastolic filling time (377 ± 138 ms to 300 ± 118 ms, $p < 0.001$).

Conclusions Despite progressive cardiac remodeling and decompensation, chronic CRT continues to provide hemodynamic augmentation in the failing heart in most patients. Our data suggest that disease progression may not be explained by diminished beneficial hemodynamic contributions of successful resynchronization. (J Am Coll Cardiol 2009;53:600–7) © 2009 by the American College of Cardiology Foundation

Cardiac resynchronization therapy (CRT) restores the coordination of contraction and relaxation among cardiac chambers, leading to a better survival in patients with advanced heart failure and evidence of ventricular conduction delay (1–3). The primary contribution of CRT is thought to be the restoration of hemodynamic support from a coordinated heart that might facilitate the reversal of pathophysiologic processes. While the extent of hemodynamic improvement is only an indicator of early response, reversal of basal dyssynchrony by CRT has proven to be a better indicator of chronic response and cardiac remodeling (reduction in left ventricular [LV] volumes, and improvement in LV ejection fraction) (4–9). However, as with any effective therapy for patients, responses are often heterogeneous and patients may not see any improvement in clinical status and/or reversal of cardiac remodeling after 3 to 6 months of CRT (2,10–13). Therefore, one might postulate that "nonresponders" may experience a diminished hemodynamic benefit by CRT over time. Although discordance between clinical and echocardiographic response to CRT has been observed in prior studies, the degree of hemodynamic response in the absence of a robust echocardiographic

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Manuscript received May 5, 2008; revised manuscript received August 29, 2008, accepted August 31, 2008.

remodeling to long-term CRT has not been explored (14). Herein, we aim to examine the contributions of biventricular pacing to the clinical, hemodynamic, and echocardiographic profiles of patients admitted with advanced heart failure and evidence of disease progression despite long-term CRT therapy.

Methods

Study population. We prospectively enrolled 40 consecutive patients who had received a CRT plus defibrillator device for at least 3 months, and were subsequently admitted to the Cleveland Clinic heart failure intensive care unit between October 1, 2007, and February 20, 2008, due to hemodynamic compromise. The CRT device was always implanted because of stable but advanced heart failure (New York Heart Association [NYHA] functional class III or IV) despite optimal medical therapy, including angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker, beta-blocking agent, and spironolactone, for at least 3 months, a depressed LV ejection fraction (≤35%), and prolonged QRS duration (≥120 ms). Exclusion criteria included: 1) patients on artificial ventilation; and 2) status after cardiac transplantation or congenital heart disease. The Cleveland Clinic Institutional Review Board approved this research project, which is part of the standard clinical evaluation tailored for patients admitted to our heart failure intensive care unit.

CRT optimization protocol. Data reported were collected during a CRT optimization protocol as part of standard evaluation within 24 h of admission to the heart failure intensive care unit. Briefly, an electrocardiogram and anterior-posterior and lateral chest X-ray were performed to ensure biventricular pacing and adequate positions of the right atrial, right ventricular, and LV leads (basal or midlateral/posterior position). A comprehensive device interrogation was then performed including assessment of battery status, lead impedances and thresholds, heart rate and activity histograms, percentage of atrial and ventricular pacing, and presence of atrial and ventricular tachyarrhythmias.

Hemodynamic and echocardiographic data were then simultaneously collected with nominal settings of the CRT device ("CRT-ON"). Next, the CRT device was programmed into a nonfunctional pacing mode (VVI, backup 40 beats/min) for 10 min, after which collection of hemodynamic and echocardiographic data were repeated ("CRT-OFF"). No changes in intensive medical therapy were made during the entire pacing protocol. If the patient had no underlying atrial rhythm or a total atrioventricular (AV) nodal block, the pacemaker could be programmed in an AAI or DDD mode, respectively, at similar heart rates as the nominal settings (only 2 patients of study population, 1 in AAI and 1 in DDD). After completion, the device was reprogrammed in a CRT mode, and the AV interval was optimized using conventional Doppler echocardiography (15,16). The optimal AV interval was assessed by pulsed-wave Doppler at the mitral valve leaflet tips and corresponded to the shortest AV interval that dissociated the E- and A-wave but did not interrupt the end of the A-wave (15,16). Afterwards, patients were scheduled for long-term clinical follow-ups and device checks. Appropriate actions would be taken, such as identifying cases of inadequate lead position, inappropriate device programming, arrhythmias, or improvement of hemodynamics in those with CRT-OFF.

Abbreviations and Acronyms

AV = atrioventricular
CO = cardiac output
CRT = cardiac resynchronization therapy
CVP = central venous pressure
LV = left ventricle/ventricular
NYHA = New York Heart Association
PCWP = pulmonary capillary wedge pressure

Hemodynamic evaluation. Hemodynamic data, including systemic blood pressure, central venous pressure (CVP), pulmonary artery pressures, and pulmonary capillary wedge pressure (PCWP) (wedge position was verified by fluoroscopy and phasic changes in pressure waveforms), represent the average of 5 cycles, and with balanced transducers (0 level at the midaxillary line). The CVP, pulmonary artery pressures, and PCWP were assessed at end-expiration with a balloon-tipped catheter at steady state with the patient in a supine position by an investigator unaware of the echocardiographic measurements. Cardiac output (CO) was determined using the Fick equation through averaging of 2 samples of a mixed central venous blood gas taken in the pulmonary artery while assuming standard metabolic rates. Systemic blood pressures were measured noninvasively by an automatic cuff sphygmomanometer at scheduled intervals.

Transthoracic echocardiography. A comprehensive 2-dimensional echocardiographic exam was performed with a commercially available system (Vingmed, System VII, General Electric, Horton, Norway) by a cardiologist highly experienced in echocardiography. Images were acquired in the left lateral decubitus position using a phased array transducer in the standard parasternal and apical views. Standard 2-dimensional and Doppler data, triggered to the QRS complex, were digitally stored in a cine-loop format. Individuals experienced with echocardiographic measurements without prior knowledge of clinical or hemodynamic data performed the analysis offline.

All reported echocardiographic measurements were averaged from at least 3 consecutive cycles. LV volumes, LV ejection fraction, diastolic filling parameters (mitral E, deceleration time, diastolic filling time, Q-A time), transmitral, and LV outflow velocity time integral were assessed as recommended by the American Society of Echocardiography (17). Interventricular mechanical dyssynchrony was assessed as the difference between the pre-ejection intervals from QRS onset to the beginning of ventricular ejection at the pulmonary and aortic valve levels using pulsed-wave Doppler (1,2). Intraventricular mechanical dyssynchrony was assessed from regional

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Table 1 Subject Characteristics (n = 40)

Demographics	
Age (yrs)	62 (53–67)
Men (%)	71
Weight (kg)	88 (70–103)
Comorbidities (%)	
Hypertension	68
Hyperlipidemia	71
Diabetes	24
Heart failure etiology (%)	
Idiopathic dilated	60
Ischemic	40
Medications (%)	
ACE inhibitors/ARB	60
Beta-blockers	72
Spironolactone	60
Loop diuretic	92
Digoxin	36
Hydralazine	42
Isosorbide dinitrate	44
Sodium nitroprusside	50
Inotropic drugs	32
Laboratory data	
Hemoglobin (g/dl)	11.6 (10.4–13.6)
Creatinine (mg/dl)	1.4 (1.0–2.2)
B-type natriuretic peptide (pg/ml)	580 (269–1,469)

Values are median (interquartile range) or %.
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker.

time intervals between the onset of the QRS complex and the peak of the systolic myocardial velocity (Ts) in 4 basal segments of the LV (septal, lateral, anteroseptal, posterior) using color tissue Doppler imaging (7).

Statistical analysis. All data were expressed as mean ± SD for continuous data (median and interquartile range for nonparametric data), and as a ratio for categorical data. Univariate comparisons of these variables were performed between the same patients with CRT-ON and CRT-OFF, using SPSS for Windows, release 13.0 (SPSS Inc., Chicago, Illinois). A paired *t* test for continuous data was used for appropriate comparisons. Statistical significance was set at a 2-tailed probability level of <0.05.

Table 2 Biventricular Pacemaker Diagnostics (n = 40)

Sinus rhythm (%)	86
DDD configuration (%)	94
VVIR configuration (%)	6
Lower rate (beats/min)	60 ± 10
Upper rate (beats/min)	125 ± 15
Pacing mode	
ASVS	4
ASVP	66
APVS	0
APVP	30
Paced AV interval (ms)	130 (120–160)
Sensed AV interval (ms)	120 (100–130)
VV timing (ms)	0 (0–4)

Values are %, mean ± SD, or median (interquartile range).
APVP = atrial pacing ventricular pacing; APVS = atrial pacing ventricular sensing; ASVP = atrial sensing ventricular pacing; ASVS = atrial sensing ventricular sensing; AV = atrioventricular; DDD = atrial and ventricular pacing and sensing; VVIR = ventricular pacing and sensing only; VV timing = interventricular timing interval.

Results

Patient characteristics. Baseline characteristics and treatment during admission of the 40 patients are summarized in Table 1. All patients were classified as NYHA functional class III (14%) or IV (86%), with a mean LV ejection fraction of 22 ± 7% and mean LV end-diastolic volume of

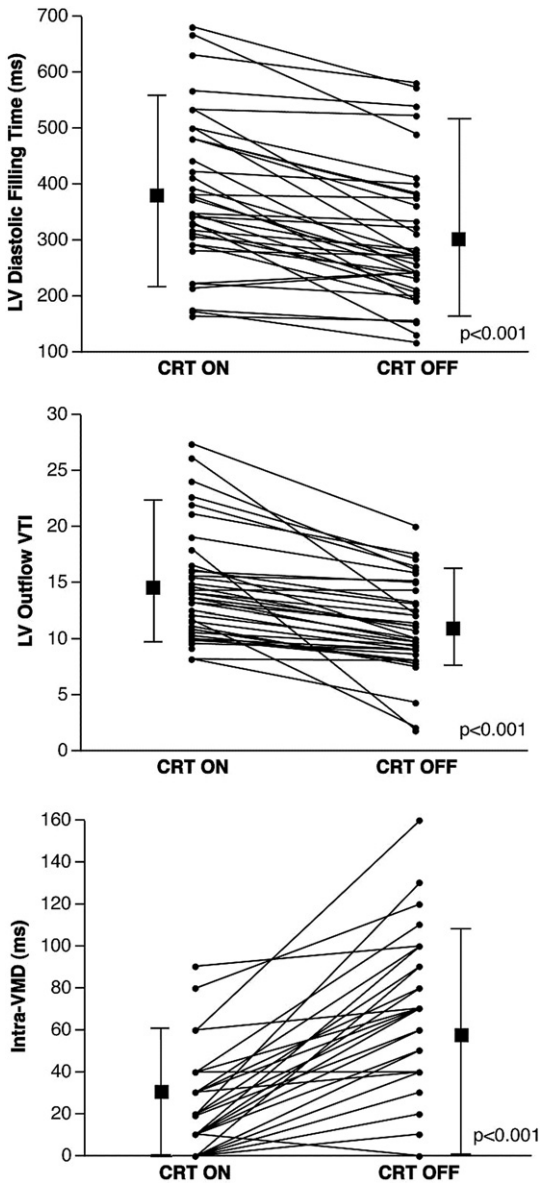

Figure 1 Selected Echocardiographic Changes in Patients With CRT-ON and CRT-OFF

CRT = cardiac resynchronization therapy; LV = left ventricle; VMD = ventricular mechanical dyssynchrony; VTI = velocity time integral.

Table 3 Hemodynamic and Echocardiographic Changes in Patients With CRT-ON and CRT-OFF (n = 40)

Variable	CRT-ON	CRT-OFF	p Value
Heart rate (beats/min)	69 ± 34	67 ± 38	NS
Systolic blood pressure (mm Hg)	105 ± 12	98 ± 13	<0.001
Central venous pressure (mm Hg)	9 ± 7	11 ± 7	<0.001
Systolic pulmonary artery pressure (mm Hg)	44 ± 13	49 ± 15	<0.001
Diastolic pulmonary artery pressure (mm Hg)	22 ± 8	25 ± 9	<0.001
Pulmonary capillary wedge pressure (mm Hg)	17 ± 6	21 ± 7	<0.001
Cardiac output (l/min)	4.6 ± 1.4	4.0 ± 1.1	<0.001
QRS width (ms)	161 ± 29	202 ± 39	<0.001
Mitral valve regurgitation (scale 0–4/4)	1.9 ± 0.8	2.1 ± 1	<0.001
Mitral valve E velocity (cm/s)	96 ± 26	108 ± 37	<0.001
Mitral valve E deceleration time (ms)	178 ± 63	159 ± 59	<0.001
LV diastolic filling time (ms)	377 ± 138	300 ± 118	<0.001
Onset QRS until end of A-wave time (ms)	69 ± 47	19 ± 31	<0.001
LV inflow velocity time integral	19 ± 6	16 ± 5	<0.001
LV outflow velocity time integral	14 ± 5	11 ± 4	<0.001
Interventricular mechanical dyssynchrony (ms)	22 ± 15	45 ± 25	<0.001
Intraventricular mechanical dyssynchrony (ms)	15 ± 26	57 ± 41	<0.001

Values are mean ± SD.
CRT = cardiac resynchronization therapy; LV = left ventricle.

323 ± 140 ml. Device and lead implantation were successful in all patients without major complications, on average 574 ± 410 days before enrollment into the study. Seventy-five percent of patients had experienced a subjective improvement in ≥1 NYHA functional class at 3 months post-implant. However, at the time of study enrollment, 1.2 hospitalizations for heart failure exacerbation per patient had occurred. Reliable serial LV end-diastolic volumes (and diameters) could be retrieved in 29 (72.5%) patients, and were found to be 266 ± 128 ml (6.8 ± 1.2 cm) pre-implant, 272 ± 141 ml (6.8 ± 1.3 cm) at 3 months post-implant ($p = 0.2$ vs. pre-implant), and 309 ± 133 ml (7.1 ± 1.2 cm) ($p < 0.01$ vs. pre-implant and 3 months) at the time of study enrollment.

Device interrogation was successful in all patients (Table 2). All patients had a lead in the right atrium, right ventricle, and coronary sinus, including 14% of patients that were in atrial fibrillation at enrollment. No lead dislodgement was detected, and in 35 (87.5%) patients, the LV lead was deemed to be in a satisfactory lateral or posterolateral position. Patients were being paced in a biventricular mode 96% of the time, predominantly in an atrial sensing-ventricular pacing mode. Heart rates at time of study enrollment, with CRT-ON and CRT-OFF, were also similar (69 ± 34 beats/min vs. 67 ± 38 beats/min, p = NS).

Impact of biventricular pacing on echocardiographic variables. Acute changes in echocardiographic indexes in different settings of CRT programming are illustrated in Figure 1 and Table 3. Overall, compared with CRT-ON, native conduction (i.e., CRT-OFF) was associated with acute worsening of LV diastolic filling, as evidenced by a significant reduction in diastolic filling time, mitral valve deceleration time, and time between QRS onset and end of A-wave. Also, acutely, the mitral valve velocity time integral (as a surrogate of the total volume of blood that entered the LV) and corresponding estimated LV stroke volume was reduced with CRT-OFF compared with that seen with CRT-ON. Furthermore, the amplitude of mitral E-wave and severity of mitral regurgitation increased. There was

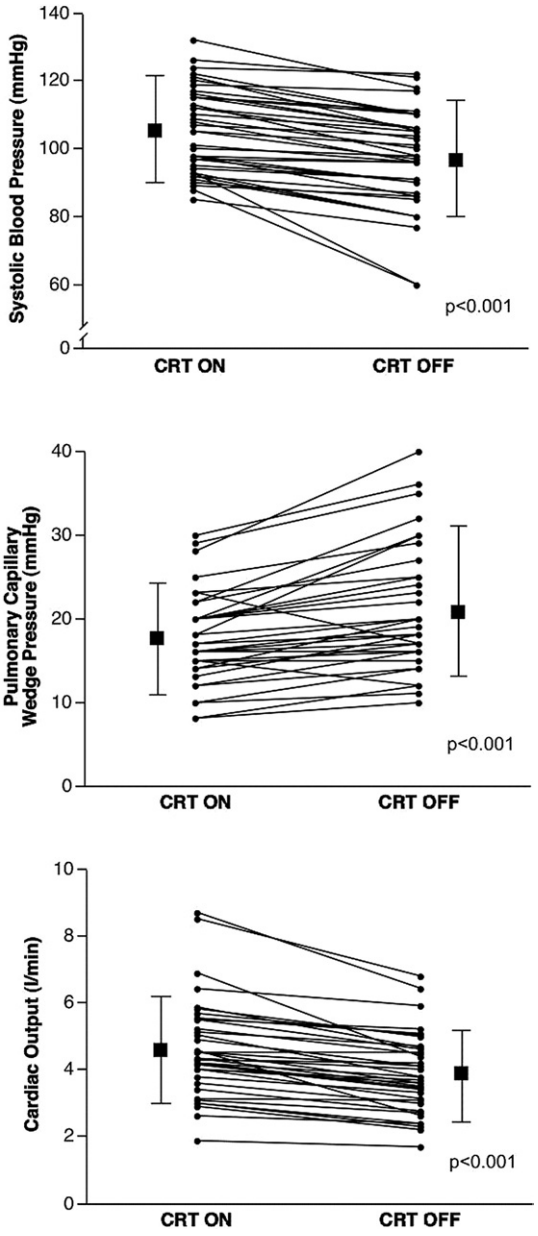

Figure 2 Selected Hemodynamic Changes in Patients With CRT-ON and CRT-OFF

CRT = cardiac resynchronization therapy.

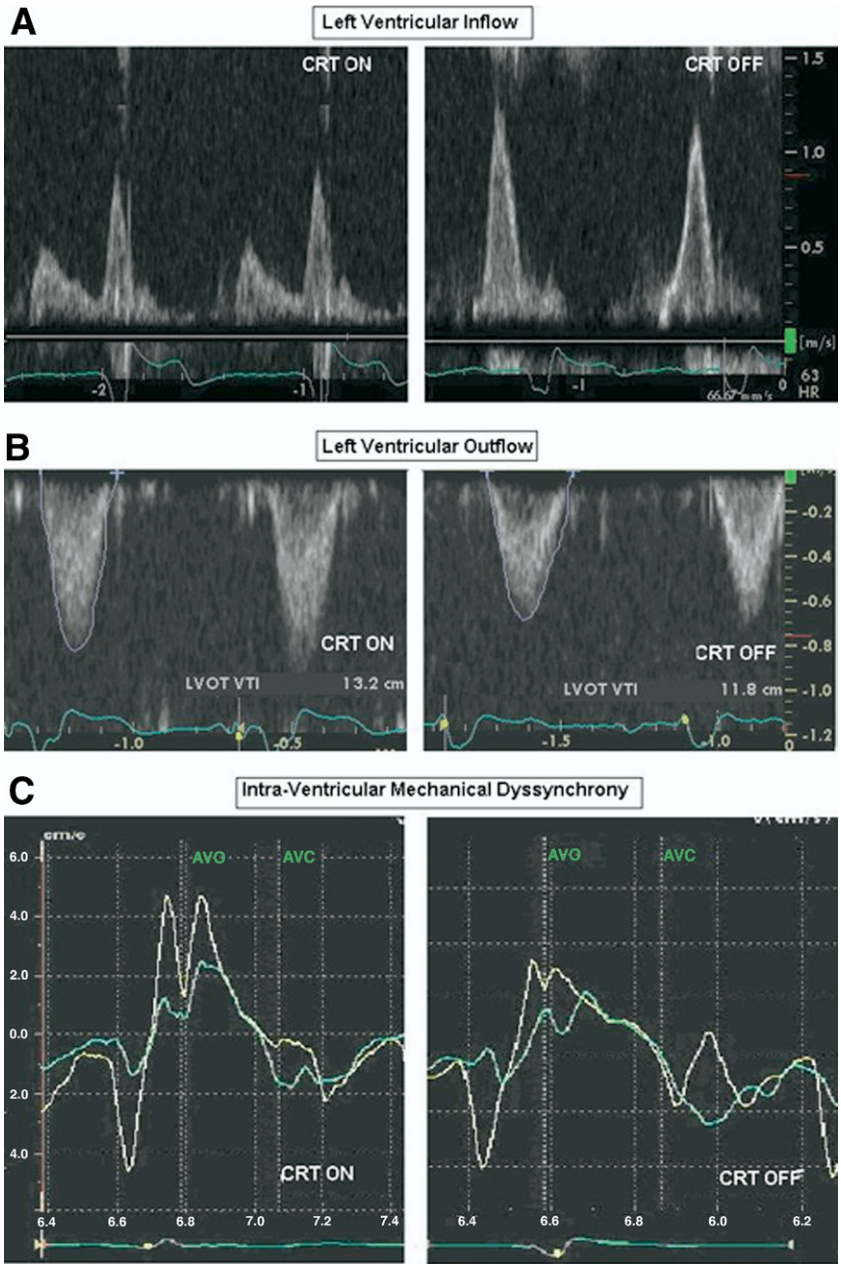

Figure 3 **Example of Hemodynamic Changes During CRT-ON and CRT-OFF**

(A) Left ventricular inflow using pulsed-wave Doppler at the mitral valve leaflet tips. Programming cardiac resynchronization therapy (CRT)–OFF leads to fusion of early (E-wave) and late (A-wave) filling shortens left ventricular diastolic filling time, deceleration time, and time between onset of QRS and end of A-wave (QA-time), and reduces mitral valve velocity time integral: all indicative of worse diastolic function. **(B)** Left ventricular outflow using pulsed-wave Doppler at left ventricular outflow tract. Programming CRT-OFF leads to increased left ventricular pre-ejection times (onset QRS to start of left ventricular ejection) and reduces the left ventricular outflow tract velocity time integral, indicative of worse left ventricular contractile performance. **(C)** Intraventricular dyssynchrony using color tissue Doppler echocardiography. Color tissue Doppler sample placed at basal part of the septum **(yellow)** and lateral wall **(green)** in an apical 4-chamber view. Septal-to-lateral wall motion delay is measured as the maximal time difference between onset of QRS and peak of regional velocities of myocardial systolic shortening between different walls. Note the appearance of a septal-to-lateral wall motion delay as an indicator of intraventricular mechanical dyssynchrony when CRT-OFF. AVC = aortic valve closing; AVO = aortic valve opening. *Continued on next page.*

also evidence of increased electrical dyssynchrony (i.e., QRS width) as well as inter- and intraventricular mechanical dyssynchrony with CRT-OFF compared with that of CRT-ON.

Impact of biventricular pacing on hemodynamic variables. CRT-OFF was associated with acute worsening of LV contractile performance, indicated by a statistically significant drop in CO (−13%) and systemic systolic blood

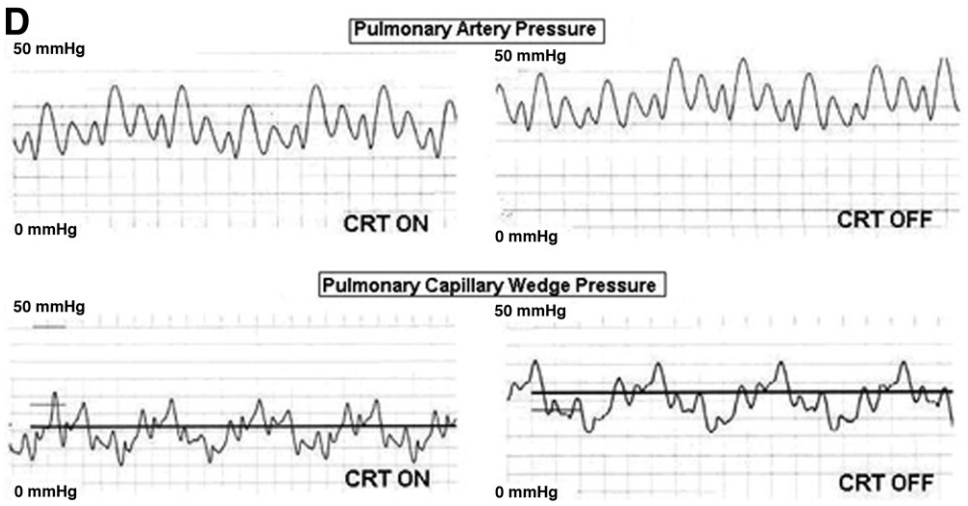

Figure 3 Continued

(D) Pulmonary artery catheter tracings in pulmonary artery and pulmonary capillary wedge position. Note the increase in pulmonary artery pressure and pulmonary capillary wedge pressure when CRT is programmed OFF.

pressure (−7%), as well as a statistically significant increase in CVP (+22%), systolic (+12%) and diastolic (+14%) pulmonary artery pressure, and PCWP (+24%, all $p < 0.001$) (Fig. 2, Table 3). Figure 3 shows a typical example of the detrimental hemodynamic changes assessed by echocardiography and invasive hemodynamic measurement when CRT was programmed from ON to OFF.

Subanalysis of patients implanted with a CRT device for more than 6 months (n = 26) versus between 3 to 6 months (n = 14) revealed similar detrimental effects of hemodynamic measurements when CRT was programmed OFF, regardless of implant duration. Also, the magnitude of deterioration of hemodynamic parameters during CRT-OFF was similar in patients with LV end-diastolic volumes above or below the mean (assessed at moment of CRT implant or at study enrollment), and between patients with ischemic or nonischemic etiology (data not shown).

Three patients had a significant and sustained improvement of their hemodynamic (systolic blood pressure [+8%], CVP [−17%], PCWP [−17%], and CO [+15%]) (Table 4) and echocardiographic measurements in CRT-OFF, rather than in CRT-ON. In all 3 patients, the CRT was programmed in a permanent VVI back-up mode. Two patients had an inadequate anterolateral LV lead position and were scheduled for revision of their LV lead. The other patient had a QRS complex of 114 ms, and it was decided to keep the CRT device in a back-up pacing mode.

Discussion

This mechanistic observational study provides detailed echocardiographic and invasive hemodynamic measurements to determine the relative contributions of biventricular pacing in patients with decompensation of their advanced heart failure despite chronic CRT therapy. The key finding is that long-term CRT continues to provide hemodynamic augmentation in a patient population typically categorized as clinical and echocardiographic "nonresponders" to CRT. These observations challenge the prevailing belief that patients with symptomatic disease progression have not derived benefit from CRT and are "nonresponders." In a subset of patients with serial measurements of LV volumes, we observed that improvement of hemodynamic derangements through successful resynchro-

Table 4 Selected Hemodynamic Changes in Patients Who Improved With CRT-OFF

	Systolic Blood Pressure (mm Hg)		Central Venous Pressure (mm Hg)		Pulmonary Capillary Wedge Pressure (mm Hg)		Cardiac Output (l/min)	
	CRT-ON	CRT-OFF	CRT-ON	CRT-OFF	CRT-ON	CRT-OFF	CRT-ON	CRT-OFF
Patient #1	86	92	13	11	13	11	4.5	5.0
Patient #2	93	95	16	13	16	13	3.6	4.8
Patient #3	106	123	11	9	11	9	3.9	4.0

CRT = cardiac resynchronization therapy.

nization therapy itself is not always sufficient to avert progressive LV remodeling.

The present study is the first to investigate the effects of chronic CRT on invasive hemodynamics in patients who did not exhibit beneficial reverse remodeling at a time period long after implantation. Importantly, invasive hemodynamic and echocardiographic assessments were performed with CRT-ON and CRT-OFF in close temporal proximity, providing a more accurate measure of the extent of acute hemodynamic deterioration in the absence of biventricular pacing support, with a minimized likelihood for time-dependent changes in factors such as pre-load or heart rate to confound the analysis. The improvement in diastolic filling is largely dependent on the restoration of a more physiologic AV interval. Additionally, improvement in CO can be achieved through restoration of contractile coordination, which subsequently leads to reduction in LV filling pressures. These benefits were lost acutely when CRT was programmed OFF. This relative "inotropic" effect can be achieved at reduced oxygen demand (18), and the hemodynamic benefits appear to be consistent with previous reports from patients shortly after their device implantation (4,5).

The focus on achieving reversal of LV remodeling with CRT stems from the wide acceptance that "resynchronized" electrical-mechanical coupling results in changes in cardiac structure and performance, which are primarily responsible for changing the disease course in patients with heart failure. Indeed, prevention of cardiac remodeling improves prognosis in heart failure, and numerous studies have shown chronic CRT to be linked with reverse remodeling (2,3,10,19–21). Though the clinical and echocardiographic responses to CRT may vary significantly among individuals and heart failure etiology, this does not always appear to translate into a greater effect on clinical outcomes. Also, patients with nonischemic heart disease derive more improvement in ventricular function and seem to exhibit a greater improvement in survival after CRT (22–25). Therefore, it is important to recognize that like any effective drug or device therapy for patients with heart failure, response to therapy can be heterogeneous. In the case of CRT, various factors that may affect the efficiency of resynchronization include (but are not limited to) extent and location of scar tissue and viable myocardium, the appropriateness of lead positioning, inadequate delivery of LV pacing, the presence of concomitant rhythm abnormalities, suboptimal device programming, or absence of myocardial contractile reserve (4,16,26,27). While many of these factors may directly influence the ability of CRT to provide beneficial hemodynamic effects, patients in our study population had fulfilled standard inclusion criteria including significant electrical dyssynchrony (QRS duration) for CRT at the time of implantation, and the aforementioned standard reasons for lack of response could not account for the lack of reverse remodeling.

It is, therefore, likely that unrecognized contributors of disease progression (e.g., progressive myocyte dysfunction, apoptosis, chamber size, and geometry) that may be independent of hemodynamic derangements may directly influence the clinical and echocardiographic responses to CRT. Such contributors may also affect responses to any therapeutic intervention. Hence, lack of clinical or echocardiographic responses despite successful resynchronization should not directly imply lack of acute or chronic hemodynamic benefits from CRT. Instead, the appropriate interpretation for our "nonresponder" population should consider the possibility that the hemodynamic augmentation after successful resynchronization by CRT may not be sufficient to warrant a persistent meaningful change in the natural history of heart failure disease progression but rather may slow down the disease progression. In fact, our group and others have suggested that the presence of alterations in molecular expression of myocardial contractile genes after CRT is more predictive of clinical and echocardiographic responses than effective reduction in baseline dyssynchrony or contractile reserve (20,28). In addition, lead position and its incumbent role in any evaluation for suboptimal responses to CRT remains an unknown until precise mechanisms of CRT are elucidated.

Study limitations. It is important to recognize that this is not a randomized comparison, even though echocardiographic analyses were made independent of any knowledge of clinical or hemodynamic data. Our observations do not exclude the possibility of improving response by lead repositioning, although >87% of LV leads were deemed to be in an appropriate position and significant reduction in electrical and mechanical dyssynchrony were observed in our population. We also cannot exclude the possibility that early hemodynamic changes during CRT-OFF might not reflect more long-term ones and that optimization of AV and ventriculo-ventricular timings at the time of implantation may have provided better clinical and echocardiographic responses leading to fewer patients with disease progression, although that strategy has yet to be proven. No acute post-implant hemodynamic data were gathered though early clinical improvement in NYHA functional class, and stabilization of LV volumes suggests at least some early benefits of CRT. However, despite continuous hemodynamic support, patients had experienced progressive LV remodeling at the time of study enrollment. Despite the goal to reach maximally tolerated, guideline-recommended medical therapy as specified in the Methods section, the challenge of up-titration in this patient population with advanced heart failure (32% inotropic agents during hospitalization) is apparent to most practicing physicians. However, at the time of CRT implant, all patients were on optimal, stable medical therapies. Although the echocardiographic techniques used in this study have been widely considered as relatively robust measures, the gold standard for defining and quantifying dyssynchrony is still being debated and is currently undergoing prospective validation.

Conclusions

Despite adverse cardiac remodeling and heart failure decompensation, CRT continues to provide persistent hemodynamic augmentation in the failing heart. Our data show that detrimental disease progression may not be explained solely by diminishing beneficial hemodynamic contributions of successful resynchronization. Our data also illustrate that a lack of clinical and/or echocardiographic response should not be interpreted as a failure to deliver hemodynamic benefits from successful CRT.

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Key Words: heart failure ■ hemodynamics ■ pacing ■ remodeling.