Journal of the American College of Cardiology
© 2009 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 53, No. 9, 2009
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2008.11.024

Insights From a Cardiac Resynchronization Optimization Clinic as Part of a Heart Failure Disease Management Program

Wilfried Mullens, MD, Richard A. Grimm, DO, FACC, Tanya Verga, RN, Thomas Dresing, MD, Randall C. Starling, MD, MPH, FACC, Bruce L. Wilkoff, MD, FACC, W. H. Wilson Tang, MD, FACC
Cleveland, Ohio

Objectives Our aim was to determine the feasibility and value of a protocol-driven approach to patients with cardiac resynchronization therapy (CRT) who did not exhibit a positive response long after implant.

Background Up to one-third of patients with advanced heart failure do not exhibit a positive response to CRT.

Methods A total of 75 consecutive ambulatory patients with persistent advanced heart failure symptoms and/or adverse reverse remodeling and CRT implanted >6 months underwent a comprehensive protocol-driven evaluation to determine the potential reasons for a suboptimal response. Recommendations were made to maximize the potential of CRT, and adverse events were documented.

Results All patients (mean left ventricular [LV] ejection fraction 23 ± 9%, LV end-diastolic volume 275 ± 127 ml) underwent evaluation. Eighty-eight percent of patients had significantly better echocardiographic indexes of LV filling and LV ejection with optimal setting of their CRT compared with a temporary VVI back-up setting. Most patients had identifiable reasons for suboptimal response, including inadequate device settings (47%), suboptimal medical treatment (32%), arrhythmias (32%), inappropriate lead position (21%), or lack of baseline dyssynchrony (9%). Multidisciplinary recommendations led to changes in device settings and/or other therapy modifications in 74% of patients and were associated with fewer adverse events (13% vs. 50%, odds ratio: 0.2 [95% confidence interval: 0.07 to 0.56], p = 0.002) compared with those in which no recommendation could be made.

Conclusions Routine protocol-driven approach to evaluate ambulatory CRT patients who did not exhibit a positive response is feasible, and changes in device settings and/or other therapies after multidisciplinary evaluation may be associated with fewer adverse events. (J Am Coll Cardiol 2009;53:765–73) © 2009 by the American College of Cardiology Foundation

Cardiac resynchronization therapy (CRT) restores the coordination of contraction and relaxation among cardiac chambers, leading to improved exercise tolerance, cardiac remodeling (reduction in left ventricular [LV] volumes and improvement in LV ejection fraction), and a better survival in patients with advanced heart failure and evidence of ventricular conduction delay (1–3). However, up to one-third of patients may not experience any improvement in clinical status and/or reversal of cardiac remodeling after CRT based on current selection criteria (2,4–7).

The literature regarding post-implantation management of CRT is sparse, particularly long after device implantation. While the extent of the response can be heterogeneous, most studies have focused primarily on refining pre-implantation patient selection to predict favorable response (such as detecting evidence of basal dyssynchrony) (8–13). However, a variety of post-implant issues besides patient selection can also contribute to suboptimal responses, although less is known about their prevalence and impact. There has been a paucity of data to systematically evaluate how to best manage patients with CRT after their implantation, and to troubleshoot their settings post-implant in order to maximize the potential of the resynchronization therapy. In particular, the feasibility and value of a systematic, post-implantation, protocol-driven, multidisciplinary approach to diagnose potential contributors for a suboptimal response and to optimize or titrate CRT in these patients is unknown.

From the Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, Ohio. Dr. Mullens was supported by a fellowship training grant sponsored by Boston Scientific and St. Jude. Drs. Starling, Dresing, and Tang are consultants for Medtronic. Drs. Dresing and Tang are consultants for Boston Scientific. Dr. Dresing is a consultant for St. Jude. Dr. Grimm is a consultant/advisory board member for Medtronic, St. Jude, and GE Healthcare. Dr. Wilkoff is a consultant and receives research support from Medtronic, Boston Scientific, and St. Jude. Dr. Wilkoff is a consultant for LifeWatch. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the paper as written.

Manuscript received August 13, 2008; revised manuscript received November 10, 2008, accepted November 12, 2008.

JACC Vol. 53, No. 9, 2009
March 3, 2009:765–73

Abbreviations and Acronyms

AV = atrioventricular

CRT = cardiac resynchronization therapy

LV = left ventricle/ventricular

The aim of this pilot study is to describe the feasibility of a multidisciplinary protocol-driven approach of ambulatory CRT patients who did not experience clinical or echocardiographic improvement (or improved only transiently) after CRT implantation. We aim to identify potential clinical or device-related contributors associated with suboptimal responses and to estimate the requirements and potential clinical impact if such a strategy were to be incorporated in a heart failure disease management program.

Methods

Study population. We evaluated 75 consecutive ambulatory patients between April 1, 2007, and April 1, 2008, who were referred to the CRT optimization clinic for comprehensive evaluation. All had received a CRT plus defibrillator device for at least 6 months (54% implanted at our own institution) but experienced persistent advanced heart failure symptoms (New York Heart Association functional class III or IV symptoms), and/or continuation (or lack of reversal) of adverse cardiac remodeling. The CRT device was implanted because of stable but advanced heart failure despite optimal medical therapy, an impaired LV ejection fraction (≤35%), and prolonged QRS duration (≥120 ms). The Cleveland Clinic Institutional Review Board approved this research project.

CRT optimization clinic protocol. The CRT optimization clinic protocol has been established as part of a multidisciplinary approach incorporated in a heart failure disease management program accessible to any referring cardiologist (Fig. 1). Briefly, on the day of the clinic visit, a heart failure nurse recorded an electrocardiogram with and without CRT pacing to ensure biventricular pacing, and the patient performed a 6-min walk test to objectively assess his/her exercise tolerance. An anterior-posterior and lateral chest X-ray were performed to ensure adequate positions of the right atrial, right ventricular, and LV lead (basal or midlateral and posterior position), and routine laboratory tests were obtained (including standard electrolyte and renal panel, complete blood count, and B-type natriuretic peptide) to detect occult anemia and metabolic derangements. Afterward, a physician performed a careful clinical evaluation and data review, and a comprehensive device interrogation was performed including assessment of battery status, lead impedances and thresholds, heart rate and activity histograms, percentage of atrial and ventricular pacing, and the presence of atrial and ventricular tachyarrhythmia.

Next, a comprehensive 2-dimensional echocardiographic examination was performed (Vingmed, System VII, General Electric, Horton, Norway) with nominal settings of the CRT device. All reported echocardiographic measurements were averaged from at least 3 consecutive cycles as recommended by the American Society of Echocardiography (14). Interventricular mechanical dyssynchrony was assessed as the difference between the pre-ejection intervals from QRS onset to the beginning of ventricular ejection at the pulmonic and aortic valve levels using pulsed-wave Doppler (1,2). Intraventricular mechanical dyssynchrony was assessed from regional time intervals between the onset of the QRS complex to the peak of the systolic myocardial velocity in 4 basal segments of the LV (septal, lateral, anteroseptal, posterior) using color tissue-Doppler imaging (11). Then, an effort was always made to optimize the LV diastolic filling (if other than stage I) by altering atrioventricular (AV) timing using conventional Doppler echocardiography. The optimal AV interval was determined by sampling mitral inflow with pulsed-wave Doppler and corresponded to the shortest AV interval that dissociated the E- and A-wave but did not interrupt the end of the A-wave (15–17). Next, the CRT device was programmed into a nonfunctional pacing mode (VVI, backup 40 beats/min) for 10 min, after which collection of echocardiographic data was repeated to ensure that CRT pacing itself was not detrimental. If the patient had no underlying atrial rhythm or a total AV nodal block, the pacemaker was programmed in an AAI or DDD mode, respectively, at heart rates similar to the nominal settings.

Multidisciplinary hypothesis and recommendations. Based upon the findings of the CRT optimization clinic, a working hypothesis for the lack of optimal response was formulated, and a multidisciplinary recommendation was proposed to the patient and referring cardiologist based on consensus of a designated electrophysiologist, cardiac imaging, and heart failure specialist to maximize or improve the potential of the CRT. These recommendations were not mutually exclusive, and such changes were made only upon agreement by the patient and referring cardiologist after a discussion of risks, benefits, and alternatives of the interventions. Appropriate actions can be categorized as repositioning of the LV lead in the case of inappropriate lead position, a change in device programming in the case of suboptimal device programming (mostly AV timing), treatment of arrhythmias either medically or invasively, adding and up-titrating of medical therapy, as well as nonpharmacologic interventions (such as recommendations of diet and fluid restriction). The option of programming the CRT device to a back-up mode (VVI 40 beats/min) was considered in the case of an absence of underlying electrical dyssynchrony and improvement of hemodynamics without CRT as assessed by echocardiographic parameters of global LV function. Finally, patients were scheduled for long-term clinical follow-up and device checks.

End points. Since interventions performed can vary widely, we also established a dichotomous grading scheme ("favorable" vs. "neutral" intervention) to capture and qualitatively assess the subjective impression of the multidisciplinary team with regard to the propensity of subsequent clinical improvement based on the implemented recommendation. These data were docu-

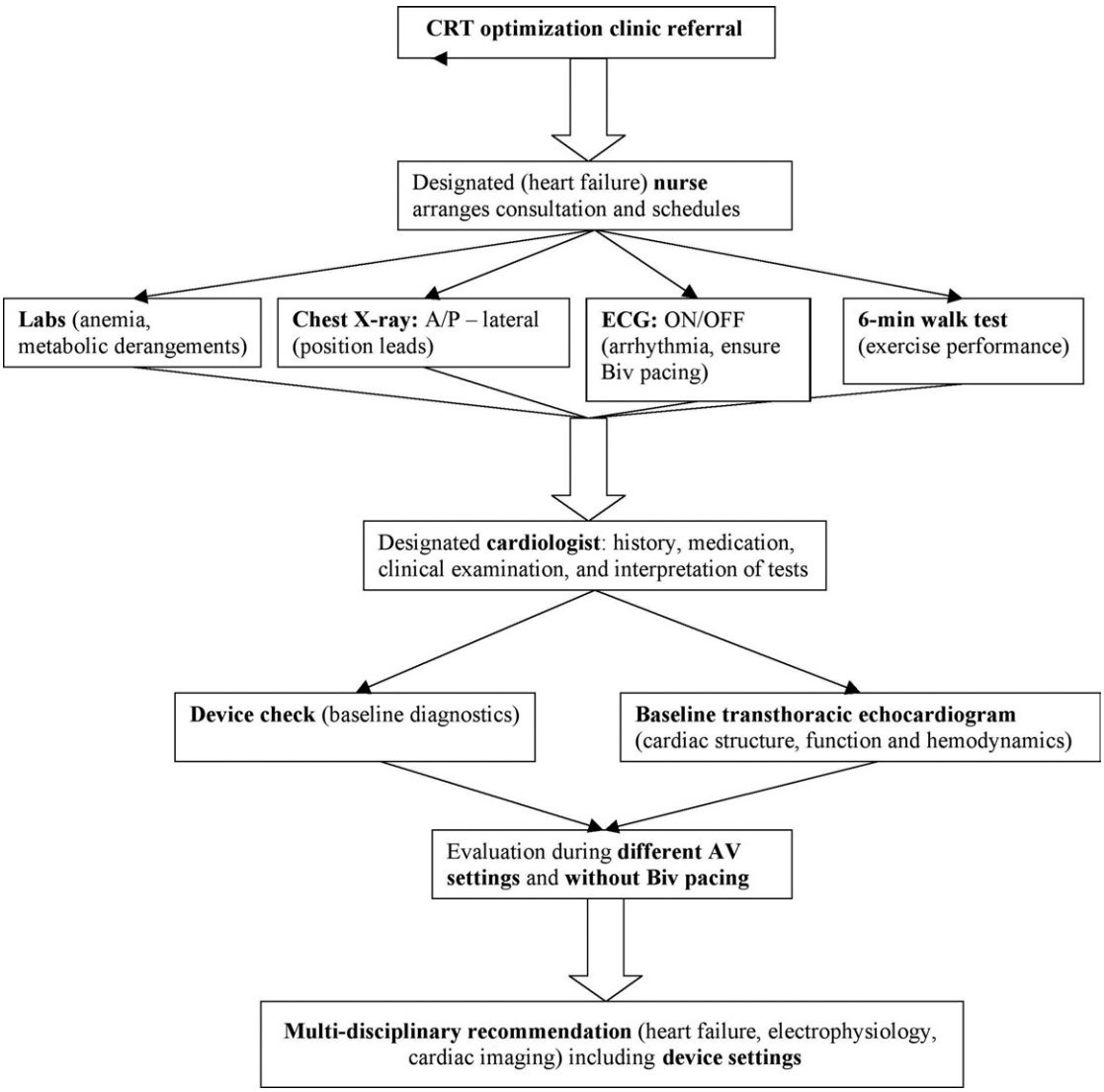

Figure 1 CRT Optimization Clinic Flow Chart

A/P = antero/posterior; AV = atrioventricular; Biv = biventricular; CRT = cardiac resynchronization therapy; ECG = electrocardiogram.

mented at the conclusion of the CRT optimization session after the recommendation was made and implemented.

We pre-specified the primary end point for this analysis as the time to first occurrence of any of the following outcomes followed up to July 31, 2008: all-cause mortality, cardiac transplantation, ventricular assist device implantation, and/or first readmission for heart failure after the CRT optimization clinic visit. Death was determined using data documented in the medical record and confirmed by the Social Security Death Index. These end points were collected independently from the aforementioned grading scheme.

Statistical analysis. All data were expressed as mean ± SD for continuous data and as a ratio for categorical data. Univariate comparisons of these variables were performed between patients with "favorable" intervention versus those with "neutral" intervention. The Cox proportional hazards regression model was used to determine if patients with a favorable intervention had a reduction in the combined end point during the follow-up period compared with patients with neutral intervention. Kaplan-Meier survival curves were constructed for the combined end point for patients with and without a favorable intervention. Statistical significance was set at a 2-tailed probability level of <0.05. All statistical analyses were performed using SPSS for Windows, version 13.0 (SPSS Inc., Chicago, Illinois).

Results

Patient characteristics. Tables 1 and 2 summarize the baseline characteristics of the study population. All patients

JACC Vol. 53, No. 9, 2009
March 3, 2009:765–73

Table 1 Baseline Demographics (n = 75)

Age (yrs)	62 ± 12
Men (%)	77
Weight (kg)	90 ± 23
Body mass index (kg/m^2)	29 ± 8
Hemoglobin (g/dl)	12.5 ± 1.7
Creatinine (mg/dl)	1.3 ± 0.4
B-type natriuretic peptide (pg/ml)	557 ± 574
New York Heart Association functional class III/IV (%)	75/25
Hypertension (%)	74
Hyperlipidemia (%)	61
Diabetes (%)	34
Idiopathic dilated (%)	60
Ischemic (%)	40
Beta-blockers (%)	89
ACE inhibitors/ARBs (%)	84
Spironolactone (%)	66
Loop diuretic (%)	96
Digoxin (%)	42
Hydralazine (%)	19
Isosorbide dinitrate (%)	24
Dobutamine (%)	6

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker.

were classified as experiencing New York Heart Association functional class III or IV symptoms, with a mean LV ejection fraction of 23 ± 9% and mean LV end-diastolic volume of 275 ± 127 ml. Device and lead implantation were successful in all patients without major complications, on average 24 ± 22 months before enrollment in the study.

Potential clinical contributors to suboptimal response. Patients presented with low normal systemic blood pressures and mildly elevated jugular venous pressure (Fig. 2, Table 2). Up to 24% of patients were not prescribed an evidence-based drug therapy despite having no noticeable contraindications (this does not imply that they have never been prescribed, only that at the time of evaluation they were found not to be taking them). Another 8% of patients were identified to be noncompliant with regard to medication or fluid/diet intake after careful interview. In addition, 41% of patients had a body mass index of ≥30 kg/m^2, and 16% qualified as being morbidly obese (body mass index ≥40 kg/m^2). Finally, 30% of patients experienced anemia (defined as hemoglobin <11 g/dl for female subjects/<12 g/dl for male subjects), although only 3 patients (4%) had hemoglobin <10 g/dl. One patient had primary right ventricular dysfunction without LV dysfunction.

Potential electromechanical related issues to suboptimal response. All patients had a lead in the right atrium, right ventricle, and on the LV, either via the coronary sinus (95%) or epicardially (5%) (Fig. 2). No lead dislodgement was detected, but 21% of patients had their LV lead placed in an inappropriate position (Fig. 3, Patient #1), mostly anteriorly. The mean QRS width was 152 ± 44 ms for the overall patient cohort at the time of evaluation at the CRT optimization clinic. An underlying narrow QRS (<130 ms) was detected in 9% of patients, and another 16% of patients had persistent significant mechanical dyssynchrony with biventricular pacing (11% interventricular mechanical dyssynchrony and 9% intraventricular mechanical dyssynchrony). Finally, inefficient LV filling due to suboptimal programming of AV timings was found in 47% of patients.

Potential electrophysiological and device-related issues to suboptimal response. Device interrogation was successful in all patients (Fig. 2). All were being paced in a biventricular mode on average 90% of the time, predominantly in an atrial sensing-ventricular pacing mode (Table 3). No battery depletion, lead threshold/impedance problem, or lack of rate response was noted (all but 2 patients were programmed in DDDR/VVIR mode with adequate heart rate histograms). Underlying arrhythmias were common, with 15% of patients being in permanent atrial fibrillation and another 17% of patients demonstrating a significant amount of supraventricular and ventricular ectopy (Fig. 3, Patient #3), contributing to an insufficient percentage of biventricular pacing (<90% of time).

Multidisciplinary recommendation and actions. All patients and referring physicians agreed to follow the outlined recommendations (average 1.6 recommendations per patient) with the exception of LV lead replacement (which is dependent on patient preferences) (Table 4). In 53% of the patients, appropriate clinical measures were recommended at the time of the visit to improve patient compliance to diet, fluid restriction, and medication adherence, including initiation and up-titration of neurohormonal blockade to guideline-recommended doses whenever possible. Patients with obesity were scheduled to see a nutritional therapist as well. All patients with inappropriate LV lead positions were advised to replace their LV leads. However, only 7 of 16 patients (9% of total) opted to do so because they either felt better with other instituted measures (5 of 16) or were deemed too sick by their referral cardiologist to undergo the procedure (4 of 16). AV timings could be optimized (stepwise changes by ≥30 ms), resulting in improved LV filling, in 45% of patients with conventional Doppler echocardiography (Fig. 3, Patient #2). The arrhythmia

Table 2 Clinical and Echocardiographic Parameters (n = 75)

6-min walk test (ft)	1,022 ± 378
Heart rate (beats/min)	75 ± 9
Systolic blood pressure (mm Hg)	110 ± 16
Diastolic blood pressure (mm Hg)	68 ± 11
Jugular venous pressure (mm Hg)	8 ± 4
QRS width (ms)	152 ± 44
LV ejection fraction (%)	23 ± 9
LV end-diastolic volume (ml)	275 ± 127
Diastolic function (scale 1 to 3)	1.9 ± 0.8
Mitral valve regurgitation (scale 0 to 4/4)	2.0 ± 0.9
Tricuspid valve regurgitation (scale 0 to 4/4)	1.4 ± 0.8
Interventricular mechanical dyssynchrony (ms)	11 ± 20
Intraventricular mechanical dyssynchrony (ms)	14 ± 26

LV = left ventricular.

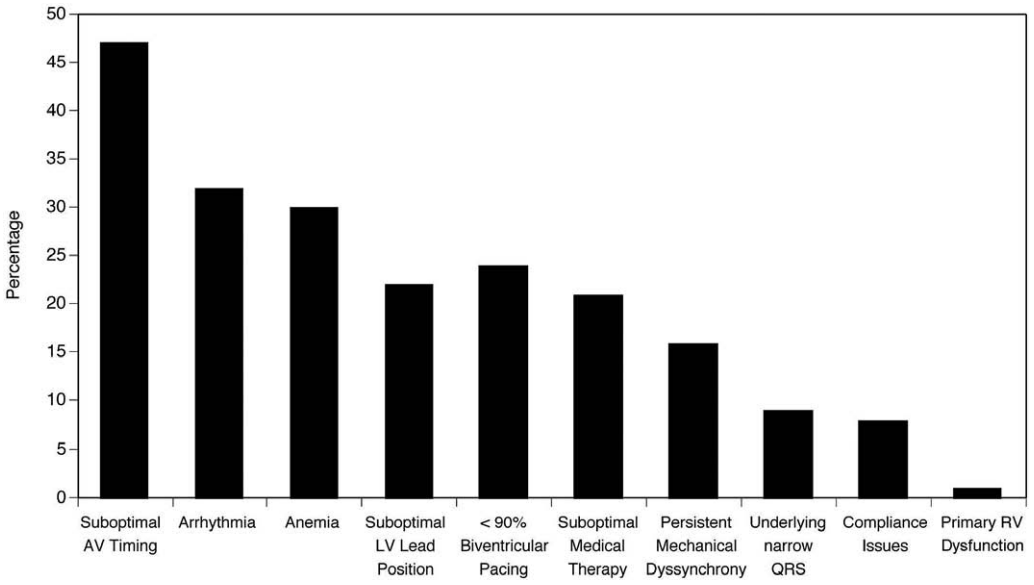

Figure 2 **Potential Reasons for Suboptimal Response**

AV = atrioventricular; LV = left ventricular; RV = right ventricular.

burden was successfully reduced, leading to biventricular pacing in >90% of all patients with institution of medical therapy, although 3 patients also underwent invasive electrophysiological procedures.

Eighty-eight percent of patients had significantly better echocardiographic indices of LV filling and LV function with optimal setting of their CRT compared with a temporary VVI back-up setting. However, 9 patients (12%) had an immediate improvement in their hemodynamics when the CRT was turned off. Overall, baseline characteristics were similar between patients who improved or deteriorated when CRT was temporarily withheld. In 7 patients, the CRT was programmed in a permanent VVI back-up mode. Five of the 7 had an underlying narrow QRS complex (<130 ms) without any mechanically significant dyssynchrony. One other patient had an inadequate anterolateral LV lead position and was scheduled for revision of the LV lead, and the other patient had an AV nodal tachycardia, which was successfully ablated after which CRT pacing was resumed. The 2 remaining patients had a QRS width between 120 to 130 ms, and the CRT was kept on.

Feasibility and outcomes. Mean clinic visit duration was 75 min with involvement of a designated nurse (75 min) and cardiologist (60 min). At the end of the follow-up period (mean follow-up duration 6.1 months), 23% of the patients had either died, undergone cardiac transplantation, were hospitalized for decompensated heart failure, or underwent implantation of an LV assist device. As shown in Table 4, patients categorized as being in the favorable intervention group (n = 55, 73%) had more changes in device settings including AV timing reprogramming (20% vs. 69%, p < 0.001) and LV lead repositioning (0% vs. 9%, p = 0.006) compared with those in the neutral intervention group (n = 20, 27%). Baseline characteristics between the 2 groups were similar, other than a more impaired LV ejection fraction (19 ± 8% vs. 24 ± 10%, p = 0.03) in the neutral intervention group. However, even corrected for LV ejection fraction, the favorable intervention group was associated with a lower adverse event rate during follow-up (13% vs. 50%, odds ratio: 0.2 [95% confidence interval: 0.07 to 0.56], p = 0.002) (Fig. 4). Importantly, within the favorable intervention group, the potential to optimize AV timings indicated a group with fewer adverse events during follow-up (Fig. 4).

Discussion

We present our clinical experience in a multidisciplinary, protocol-driven CRT optimization clinic as part of a heart failure disease management program for ambulatory patients with persistent symptoms and/or disease progression long after their implantation. Using an algorithm with standard equipment and testing that can be reproduced in any outpatient cardiology clinic, we identified suboptimal medical treatment, LV lead position, and uncontrolled arrhythmias to be associated most often with a suboptimal response. The remaining changes that resulted from a perceived favorable intervention by the multidisciplinary team commonly involved optimization of AV timing interval titrating to the best LV filling efficiency based on transmitral Doppler flow. Although hypothesis generating, our data suggest that like any interventions, optimal titra-

JACC Vol. 53, No. 9, 2009
March 3, 2009:765–73

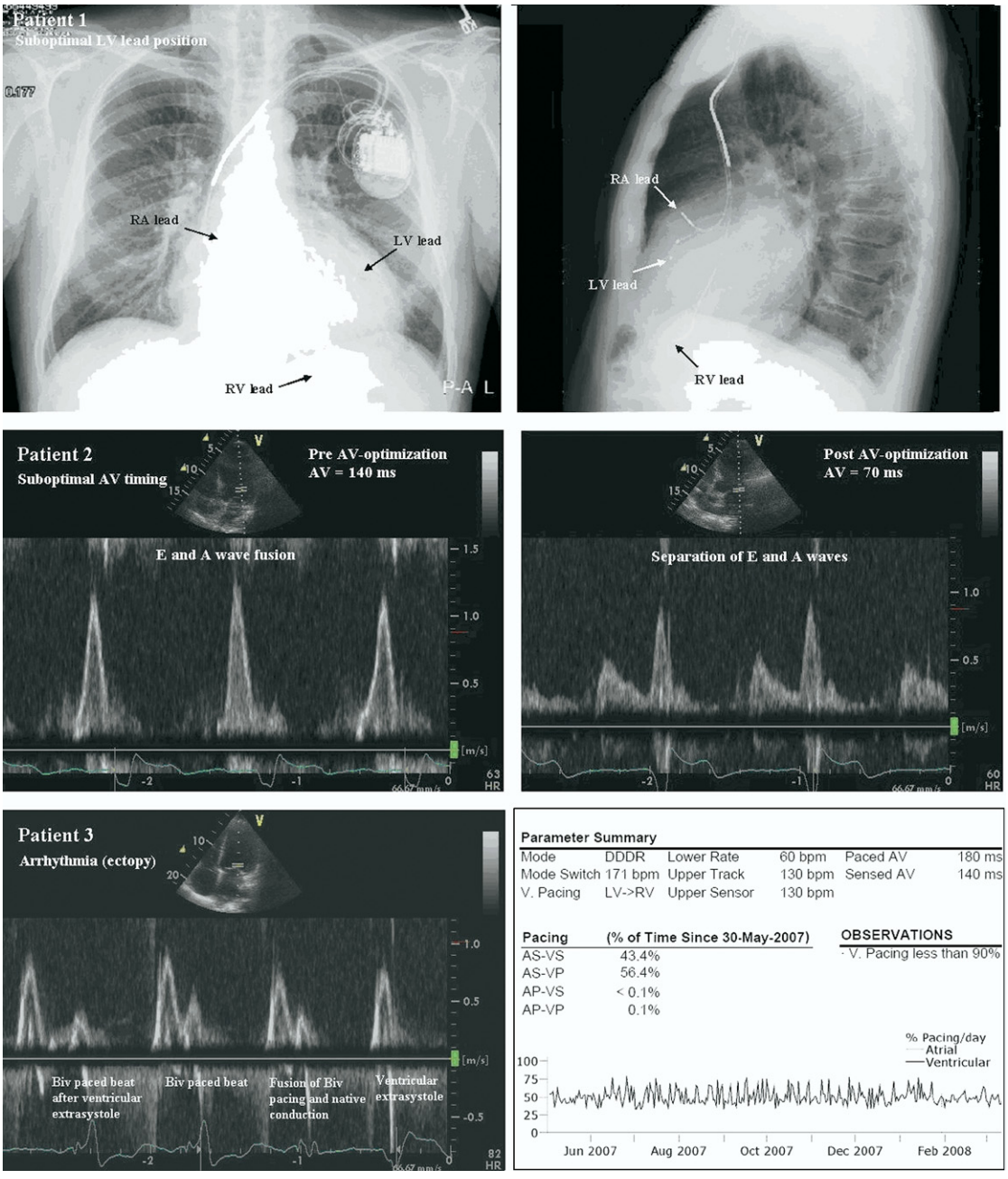

Figure 3 **Patient Examples**

Suboptimal LV lead positioning (Patient #1), suboptimal AV-interval timing (Patient #2), and the presence of arrhythmia (Patient #3). AP = atrial pacing; AS = atrial sensing; Biv = biventricular; bpm = beats/min; RA = right atrium; V. Pacing = ventricular pacing; VP = ventricular pacing; VS = ventricular sensing; other abbreviations as in Figure 2.

tion should be considered to maximize the benefits of CRT in those who lack optimal or sustained responses (i.e., a "nonresponder" can improve if optimal adjustments can be identified, and some may be perceived to have favorable expectations).

The design of our CRT optimization clinic protocol in ambulatory patients who did not exhibit a beneficial clinical response and/or reverse remodeling at a time period long after implantation is unique in several aspects. First, it utilized a combination of a comprehensive clinical and device-based evaluation, as well as an echocardiographic examination embedded in a single centralized multidisciplinary outpatient evaluation without additional appointments for the patient to visit, thus allowing a comprehensive

Table 3 Biventricular Pacemaker Diagnostics (n = 75)

Time after implant (months)	23.7 ± 21.8
Sinus rhythm (%)	85
DDDR configuration (%)	94
VVIR configuration (%)	6
Lower rate (beats/min)	60 ± 10
Upper rate (beats/min)	127 ± 10
Biventricular pacing (%)	90 ± 23
AS-VS (%)	8
AS-VP (%)	66
AP-VS (%)	2
AP-VP (%)	24
Paced AV interval (ms)	153 ± 37
Sensed AV interval (ms)	123 ± 33
VV timing (ms)	5 ± 9

AP = atrial pacing; AS = atrial sensing; AV = atrioventricular; VP = ventricular pacing; VS = ventricular sensing.

evaluation of the impact of CRT on cardiac structure, function, and hemodynamics, as well as on electromechanical events, which is universally available to all physicians. Second, the multidisciplinary approach including input of electrophysiological and cardiac imaging expertise, coupled with a heart failure disease management strategy, allowed the CRT optimization clinic to provide insights into reasons for a suboptimal response to long-term CRT above and beyond the standard of care. Third, by classifying these cases individually, a management strategy of titrating resynchronization therapy could be prospectively validated.

The clinical and echocardiographic responses to CRT may vary significantly among individuals, and it is important to recognize that like any effective drug or device therapy for patients with heart failure, response to therapy can be heterogeneous. This report is the first to explore the potential reasons for suboptimal response to CRT in patients with ongoing disease progression and/or persistent (or returning) symptoms at a time period long after implantation. Although various reversible device-related issues that may affect the efficacy of resynchronization therapy were anticipated, the prevalence at which they occurred was higher than expected. Issues including inappropriate lead positioning (21%), the presence of rhythm abnormalities (32%) with concomitant inadequate delivery of biventricular pacing, and suboptimal device programming (47%) were surprisingly high, especially since these patients were implanted on average 2 years before enrollment into the study. These observations highlight the notion that current post-implant approaches to longitudinal monitoring may overlook treatable problems. Finally, a subset of patients clearly demonstrated an improvement of their hemodynamics without biventricular pacing, either secondary to lack of underlying dyssynchrony or inappropriate lead positioning.

Importantly, the multidisciplinary design of the clinic also potentially impacted the clinical condition of more than two-thirds of the patients. Despite the challenge of up-titration guideline-recommend medical therapy in this patient population with advanced heart failure, we

Table 4 Recommendations

Recommendation (%)	All Patients (n = 75)	Neutral Intervention (n = 20)	Favorable Intervention (n = 55)	p Value Favorable vs. Neutral
Better with CRT-ON	88	85	89	NS
AV changes (>30 ms)	45	20	69	<0.001
Unchanged device settings	36	65	25	0.003
Arrhythmia intervention	31	30	31	NS
LV lead revision	9	0	9	0.006
CRT-OFF	9	10	9	NS
Other (compliance, medication, diet, and so on)	53	40	58	NS

AV = atrioventricular; CRT = cardiac resynchronization therapy; LV = left ventricular.

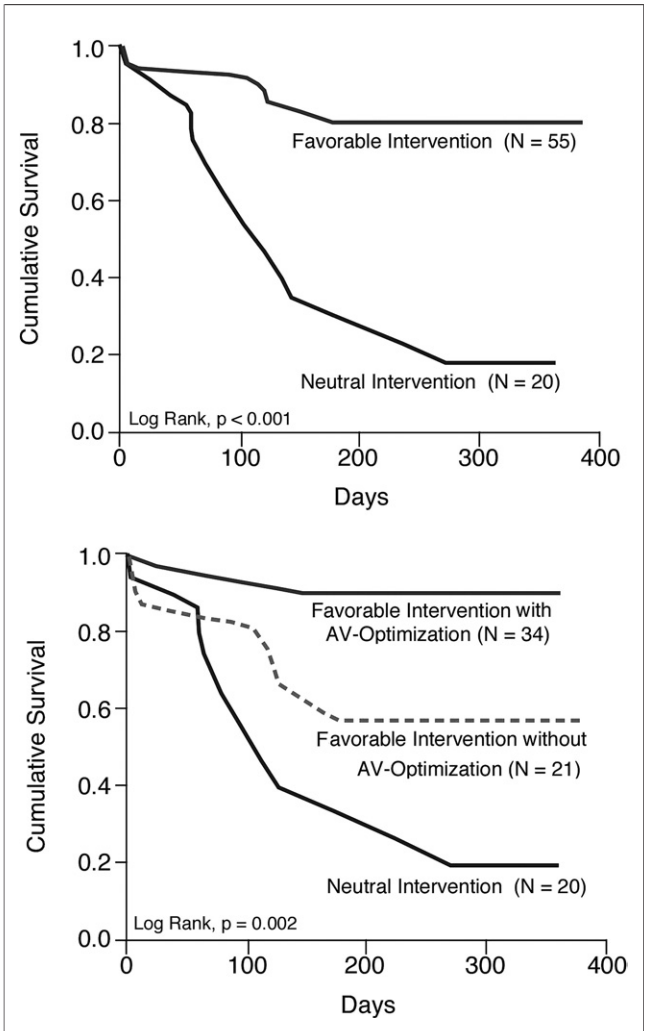

Figure 4 Clinical Outcomes of "Favorable" Versus "Neutral" Interventions With or Without AV Optimization

Kaplan-Meier curves for patients deemed to be successfully optimized ("favorable" intervention) with/without atrioventricular (AV) optimization versus those that could not be significantly optimized ("neutral" intervention) after the cardiac resynchronization therapy optimization clinic.

were able to modify the medical regimen in more than one-half of the cases, in addition to providing standard patient education materials by a heart failure disease management clinic. Device-related issues such as replacement of the LV lead or device reprogramming of the AV interval based on a simple echocardiographic protocol were also prevalent and under-recognized. Indeed, AV optimization has been shown to be safe, feasible, and associated with reduced filling pressures and improved cardiac output, thereby creating a more favorable hemodynamic profile, which might be associated with reduced adverse events (18–21). The fact that this benefit was mostly observed in patients without overt mechanical ventricular dyssynchrony (but with symptomatic disease progression) lends credence to the suggestion that combining heart failure disease management measures and optimization of the AV interval may have been synergistic.

Clinical implications. There might be a reluctance of physicians to use a dedicated CRT optimization clinic protocol as part of their routine follow-up of patients with CRT who experience ongoing disease progression. The lack of data to illustrate the incremental benefit (in the form of clinical outcomes), the lack of resources to support such an ambitious venture, or the impression that one might be able to also detect subtle inefficiencies of CRT programming without a dedicated protocol may all contribute to physicians' lack of enthusiasm in establishing such a process. In addition, there might be realistic concerns that such an approach might lead to an increased workload, unnecessary treatments based on inaccurate information, and even costs incurred due to excessive investigations and/or procedures. It is, therefore, reassuring to observe in our "real-life" experience that a routine protocol-driven approach, without using complex, expensive additional testing or invasive procedures, resulted in the identification of mostly clear-cut easily correctable reasons for suboptimal response in more than two-thirds of patients. By combining the imaging, heart failure, and electrophysiology evaluation within 1 centralized outpatient visit, total cost could be contained. It is conceivable that this approach can be performed by any practicing cardiologist interested in maximizing the potential of CRT in patients with advanced heart failure who lacked optimal responses. In our protocol, we adopted many commonly available tools that can be scalable for adoption by any multispecialty cardiology practice. As in our experience, a multidisciplinary clinic is perhaps the most direct path to getting the appropriate care and cross-training among subspecialties, although it is conceivable that this approach can be performed by any number of practicing cardiologists knowledgeable and interested in maximizing the potential of CRT in patients with advanced heart failure who lacked optimal responses. It is reassuring that the time commitment is likely acceptable as part of any heart failure disease management program, and these data illustrate the inadequacy of management regarding current approaches to post-implant care that warrant further investigations.

Study limitations. It is important to recognize that this is not a randomized comparison between optimization versus no optimization and that referral of patients was based on the referring physicians' clinical impression of "nonresponse," which might have introduced some bias toward referral of patients who were less sick and, therefore, more prone to be successfully optimized. Although some patients might have experienced an immediate or short-term (3 to 6 months) response to CRT, the design of our protocol focused on long-term (>6 months) response, which is more representative of the true clinical impact of the therapy. Although optimal AV intervals were assessed at rest and not during exercise, we were still able to demonstrate a significant benefit from AV optimization based on a standard, clinically applicable echocardiographic approach without extensive post-imaging data processing. Improved LV filling (Fig. 3, Patient #2) surely led to improved hemodynamics in certain cases. We did not optimize ventriculo-ventricular timings since there is no reliable methodology to do so in the clinical setting, and we cannot exclude the possibility that optimization of ventriculo-ventricular timings may have provided better clinical and echocardiographic responses. Finally, patients were not routinely scheduled for a follow-up CRT optimization clinic visit, so any effect of optimization on reverse remodeling or clinical improvement could not be demonstrated in this analysis.

Conclusions

A multidisciplinary protocol-driven approach to ambulatory CRT patients who did not exhibit a positive response long after implant may uncover potential contributors to a suboptimal response, may potentially maximize the potential of CRT, and may be associated with a reduction in adverse events.

Reprint requests and correspondence: Dr. W. H. Wilson Tang, Section of Heart Failure and Cardiac Transplantation Medicine, Department of Cardiovascular Medicine, Cleveland Clinic, 9500 Euclid Avenue, Desk J3-4, Cleveland, Ohio 44195. E-mail: tangw@ccf.org.

REFERENCES

1. Leclercq C, Kass DA. Retiming the failing heart: principles and current clinical status of cardiac resynchronization. J Am Coll Cardiol 2002;39:194–201.
2. Cleland JG, Daubert JC, Erdmann E, et al., for the Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539–49.
3. Linde C, Leclercq C, Rex S, et al. Long-term benefits of biventricular pacing in congestive heart failure: results from the MUltisite STImulation in Cardiomyopathy (MUSTIC) study. J Am Coll Cardiol 2002;40:111–8.
4. St John Sutton MG, Plappert T, Abraham WT, et al. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. Circulation 2003;107:1985–90.
5. Yu CM, Fung WH, Lin H, Zhang Q, Sanderson JE, Lau CP. Predictors of left ventricular reverse remodeling after cardiac resyn-

chronization therapy for heart failure secondary to idiopathic dilated or ischemic cardiomyopathy. Am J Cardiol 2003;91:684–8.
6. Pitzalis MV, Iacoviello M, Romito R, et al. Cardiac resynchronization therapy tailored by echocardiographic evaluation of ventricular asynchrony. J Am Coll Cardiol 2002;40:1615–22.
7. Vanderheyden M, Mullens W, Delrue L, et al. Myocardial gene expression in heart failure patients treated with cardiac resynchronization therapy responders versus nonresponders. J Am Coll Cardiol 2008;51:129–36.
8. Tournoux FB, Alabiad C, Fan D, et al. Echocardiographic measures of acute haemodynamic response after cardiac resynchronization therapy predict long-term clinical outcome. Eur Heart J 2007;28:1143–8.
9. Stellbrink C, Breithardt OA, Franke A, et al., PATH-CHF (PAcing THerapies in Congestive Heart Failure) Investigators, CPI Guidant Congestive Heart Failure Research Group. Impact of cardiac resynchronization therapy using hemodynamically optimized pacing on left ventricular remodeling in patients with congestive heart failure and ventricular conduction disturbances. J Am Coll Cardiol 2001; 38:1957–65.
10. Kass DA, Chen CH, Curry C, et al. Improved left ventricular mechanics from acute VDD pacing in patients with dilated cardiomyopathy and ventricular conduction delay. Circulation 1999;99:1567–73.
11. Bax JJ, Bleeker GB, Marwick TH, et al. Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy. J Am Coll Cardiol 2004;44:1834–40.
12. Suffoletto MS, Dohi K, Cannesson M, et al. Novel speckle-tracking radial strain from routine black-and-white echocardiographic images to quantify dyssynchrony and predict response to cardiac resynchronization therapy. Circulation 2006;113:960–8.
13. Gorcsan J 3rd, Tanabe M, Bleeker GB, et al. Combined longitudinal and radial dyssynchrony predicts ventricular response after resynchronization therapy. J Am Coll Cardiol 2007;50:1476–83.
14. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two dimensional echocardiography: American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 1989;2:358–67.
15. Gorcsan J 3rd, Abraham T, Agler DA, et al. Echocardiography for cardiac resynchronization therapy: recommendations for performance and reporting—a report from the American Society of Echocardiography Dyssynchrony Writing Group endorsed by the Heart Rhythm Society. J Am Soc Echocardiogr 2008;21:191–213.
16. Mullens W, Tang WH, Grimm RA. Using echocardiography in cardiac resynchronization therapy. Am Heart J 2007;154:1011–20.
17. Grimm R. Non-responders and patient selection from an echocardiographic perspective. In: Sutton J, editor. Cardiac Resynchronization Therapy. London, UK: Informa UK, 2007:251–61.
18. Auricchio A, Stellbrink C, Block M, et al. Effect of pacing chamber and atrioventricular delay on acute systolic function of paced patients with congestive heart failure: the Pacing Therapies for Congestive Heart Failure Study Group: the Guidant Congestive Heart Failure Research Group. Circulation 1999;99:2993–3001.
19. Kedia N, Ng K, Apperson-Hansen C, et al. Usefulness of atrioventricular delay optimization using Doppler assessment of mitral inflow in patients undergoing cardiac resynchronization therapy. Am J Cardiol 2006;98:780–5.
20. Porciani MC, Dondina C, Macioce R, et al. Echocardiographic examination of atrioventricular and interventricular delay optimization in cardiac resynchronization therapy. Am J Cardiol 2005;95:1108–10.
21. Sawhney NS, Waggoner AD, Garhwal S, Chawla MK, Osborn J, Faddis MN. Randomized prospective trial of atrioventricular delay programming for cardiac resynchronization therapy. Heart Rhythm 2004;1:562–7.

Key Words: heart failure ■ cardiac resynchronization ■ optimization ■ disease management.