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 dys synchrony) (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.
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) 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 reposi-}

Abbreviations and Acronyms

- **AV** = atrioventricular
- **CRT** = cardiac resynchronization therapy
- **LV** = left ventricle/ventricular

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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
41% of patients had a body mass index of 30 kg/m², and another 16% 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 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).
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-
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

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.
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 postimplant 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.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Biventricular Pacemaker Diagnostics (n = 75)</th>
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<tbody>
<tr>
<td>Time after implant (months)</td>
<td>23.7 ± 21.8</td>
</tr>
<tr>
<td>Sinus rhythm (%)</td>
<td>85</td>
</tr>
<tr>
<td>DDDR configuration (%)</td>
<td>94</td>
</tr>
<tr>
<td>VVIR configuration (%)</td>
<td>6</td>
</tr>
<tr>
<td>Lower rate (beats/min)</td>
<td>60 ± 10</td>
</tr>
<tr>
<td>Upper rate (beats/min)</td>
<td>127 ± 10</td>
</tr>
<tr>
<td>Biventricular pacing (%)</td>
<td>90 ± 23</td>
</tr>
<tr>
<td>AS-VS (%)</td>
<td>8</td>
</tr>
<tr>
<td>AS-VP (%)</td>
<td>66</td>
</tr>
<tr>
<td>AP-VS (%)</td>
<td>0</td>
</tr>
<tr>
<td>AP-VP (%)</td>
<td>24</td>
</tr>
<tr>
<td>Paced AV interval (ms)</td>
<td>153 ± 37</td>
</tr>
<tr>
<td>Sensed AV interval (ms)</td>
<td>123 ± 33</td>
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</table>

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendation (%)</td>
<td>All Patients (n = 75)</td>
</tr>
<tr>
<td>Better with CRT-ON</td>
<td>88</td>
</tr>
<tr>
<td>AV changes (&gt;30 ms)</td>
<td>45</td>
</tr>
<tr>
<td>Unchanged device settings</td>
<td>36</td>
</tr>
<tr>
<td>Arrhythmia intervention</td>
<td>31</td>
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<tr>
<td>LV lead revision</td>
<td>9</td>
</tr>
<tr>
<td>CRT-OFF</td>
<td>9</td>
</tr>
<tr>
<td>Other (compliance, medication, diet, and so on)</td>
<td>53</td>
</tr>
</tbody>
</table>

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

\[AV = \text{atrioventricular; CRT = cardiac resynchronization therapy; LV = left ventricular.}\]
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 a 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.

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