Introduction and objectives. Little is known about how responses to cardiac resynchronization therapy (CRT) are affected by the nature of the underlying cardiopathy. The aim of this study was to investigate how cardiopathy etiology influences the effect of CRT on reverse left ventricular remodeling.

Methods. The study included 106 patients with left ventricular systolic dysfunction and left bundle branch block (LBBB) who were receiving CRT. Clinical and echocardiographic investigations were performed at baseline before implantation and at 6 and 12 month follow-up to determine left ventricular diameter, volume, and systolic function, and to quantify mitral regurgitation.

Results. During follow-up, it was observed that CRT reduced left ventricular volume and diameter, increased left ventricular ejection fraction (LVEF), and reduced mitral regurgitation severity irrespective of the etiology of the cardiopathy. In patients with ischemic dilated cardiomyopathy, LVEF increased by 34% and end-diastolic and end-systolic volumes decreased by 4% and 12%, respectively; in those with idiopathic dilated cardiomyopathy, LVEF increased by 38% and end-diastolic and end-systolic volumes decreased by 13% and 19%, respectively (P=NS for ischemic vs non-ischemic disease). Nor were differences observed between the groups in clinical outcome: 74% of the ischemic group responded compared with 62% of the non-ischemic group (P=NS).

Conclusions. At 12-month follow-up, patients with left ventricular systolic dysfunction and LBBB treated by CRT showed clinical improvements and demonstrated reverse ventricular remodeling, irrespective of the etiology of their cardiopathy.

Key words: Echocardiography. Imaging. Pacemaker. Ventricular remodeling.

Influencia de la cardiopatía subyacente en la respuesta a la terapia de resincronización cardiaca

Introducción y objetivos. La influencia del tipo de cardiopatía en la respuesta a la terapia de resincronización cardíaca (TRC) es poco conocida. El objetivo de este estudio fue analizar el efecto de la TRC en el remodelado, en función de la etiología de la cardiopatía subyacente.

Métodos. Se incluyó a 106 pacientes con disfunción sistólica del ventrículo izquierdo (VI) y bloqueo de rama izquierda del haz de His (BRIHH) tratados con TRC. Se les realizó una evaluación clínica y ecocardiográfica para estudiar los diámetros, los volúmenes y la función sistólica del VI y cuantificar la insuficiencia mitral, antes del implante y a los 6 y 12 meses de seguimiento.

Resultados. La TRC indujo un incremento de la fracción de eyectorción del VI (FEVI) y una reducción de los volúmenes telediastólico y telesistólico en el 34% y 38% de los pacientes con cardiopatía isquémica (MCD-CI) y en el 37% y 34% de los pacientes con cardiopatía no isquémica (MCD), respectivamente (P=NS). No se encontraron diferencias en la respuesta clínica: el 74% de los pacientes con MCD-CI y el 62% de los pacientes con MCD no respondedores clínicos (P=NS).

Conclusiones. A los 12 meses de seguimiento, los pacientes con disfunción sistólica del VI y BRIHH tratados con TRC presentaron mejora clínica y un remodelado ventricular inverso independientemente de la etiología de su cardiopatía.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is an effective treatment for patients with advanced heart failure and left bundle branch block (LBBB). It improves their symptoms and reduces mortality. In addition, it causes reverse ventricular remodeling, with a progressive reduction of ventricular diameters and volumes, which is more evident in patients who respond clinically to CRT.

However, this benefit is not observed in all patients and all series report a lack of response in 30% of the cases. A range of echocardiographic and clinical variables have been proposed as possible markers of non-response, including the etiology of the underlying heart disease of the patient. It is still a point of discussion whether the ischemic origin of the disease is a predictor of non-response, as the few studies on the subject are inconclusive.

In view of this lack of information, the main aim of this study was to analyze whether there were any differences in clinical response and the extent of ventricular remodeling according to the etiology of the underlying heart disease in our series of patients treated with CRT.

METHODS

We included 106 consecutive patients with ischemic dilated cardiomyopathy (IDCM) or nonischemic dilated cardiomyopathy (DCM) treated with CRT (between June 2003 and December 2005). The etiology of the heart disease was considered ischemic when significant disease was found (stenosis $\geq 50\%$) in 1 or more epicardial arteries in a recent coronary angiogram (performed $< 6$ months earlier).

The criteria for the indication of CRT were as follows: 
1. functional class III-IV heart failure according to the New York Heart Association (NYHA) classification despite medical treatment or NYHA class II failure if the patient had covered $< 350$ m in the 6-minute walk test and met criteria b and c;  
2. left ventricular ejection fraction (LVEF) $\leq 35\%$; and  
3. QRS $> 120$ ms regardless of cardiac rhythm. Patients were excluded on the following grounds:  
   a. treatable heart disease;  
   b. heart transplantation scheduled within 6 months; or  
   c. short life expectancy.

The study was approved by the ethics committee and informed consent was obtained from all patients.

Study Design and Objectives

The study protocol included a baseline evaluation of the patient by transthoracic echocardiography to analyze left ventricular (LV) morphology and function; a clinical evaluation to determine the functional class according to the NYHA classification, the distance covered in the 6-minute walk test; and the patient’s quality of life with the Minnesota Living With Heart Failure questionnaire for assessing the well-being of such patients (lower score, higher quality of life) translated into Spanish and duly validated were also performed. The same echocardiographic study was repeated between 24 and 72 hours after device placement and at 6 and 12 months of follow-up. The same clinical assessment was also undertaken at 6 and 12 months. Patients were considered as clinical responders if they were alive without having received a heart transplant and had increased the distance covered in the 6-minute walk test by at least 10%. Reverse remodeling was considered to have occurred when LVEF increased by 5 points ($\Delta 5\%$) and/or end-systolic volume decreased by 15%.

Device Placement

Each patient received a 3-chamber pacemaker with or without defibrillator in line with the clinical indication according to the current guidelines. One electrode was placed in the right atrium if the patient was in sinus rhythm, 1 at the apex of the right ventricle, and 1 in a posterolateral branch through the coronary sinus.

Echocardiography

Echocardiographic studies were done with a conventional commercially available device (Vivid 7; General Electric-Vingmed, Milwaukee, Wisconsin, USA). In each study, the same variables were assessed: LV end-diastolic and end-systolic diameters were measured with M mode in the long axis parasternal view; LVEF and volumes were quantified with the Simpson method in the 4- and 2-chamber apical view, and cardiac load was calculated using quantitative Doppler technique in accordance with the recommendations of the American Society of Echocardiography. If the patient showed mitral regurgitation (MR), this was quantified with the proximal isovelocity surface area method, and if tricuspid regurgitation allowed an atrioventricular gradient to be obtained by quantitative Doppler measurement, the
systolic pressure in the pulmonary artery was estimated. Likewise, we studied whether interventricular asynchrony was present with pulsed Doppler techniques, calculating the difference between the pulmonary and aortic preejection times. Intraventricular asynchrony was also assessed with M mode, by measuring the time elapsed from maximum septal contraction to peak contraction of the posterior wall.21

Inter- and intraobserver variations in our laboratory for measurement of different cardiac dimensions were 4.6% (2.8%-5.3%) and 3.5% (2%-4.5%), respectively. All studies were stored in digital format and analyzed off-line by experienced echocardiographers who, not being involved in the clinical follow-up of the patient, were unaware of whether the patients were clinical responders to CRT or not.

Statistical Analysis
A general descriptive analysis was undertaken. Quantitative variables were expressed as mean (SD) and qualitative ones as absolute frequencies, and percentages. For comparison of the echocardiographic variables before and after starting CRT, a Student t test was used for paired data with a Bonferroni correction when multiple comparisons were made. Qualitative variables were compared with the χ² test. The functional class before and after CRT was analyzed with the Wilcoxon test. A P value less than .05 was considered significant. Data were analyzed with the SPSS software package, version 11.0.

RESULTS
Baseline Clinical and Echocardiographic Characteristics
In total, 106 consecutive patients treated with CRT were prospectively included (age, 69 [8] years; 84 [78%] were men). Eleven patients (10%) were in atrial fibrillation. The patients completed 12 months of follow-up. Baseline echocardiography showed a severe systolic dysfunction with a mean LVEF of 23 [7]%—and severe LV dilatation (end-systolic and end-diastolic diameters, 73 [8] mm and 60 [9] mm, respectively). Mitral regurgitation was reported in 44 (41%) patients. Significant (nontrivial) regurgitation was considered when the regurgitant volume was 10 mL/beat. Overall, 71 patients (67%) were in NYHA functional class II; 10 (9%) in functional class IV; and 25 (23%) in functional class II. Of those in functional class II, all covered less than 350 m in the 6-minute walk test. Patients covered on average 309 [139] m in the 6-minute walk test. The baseline characteristics are shown in Table 1.

43 (40%) patients had IDC and 63 (60%) had nonischemic DCM. The baseline clinical and echocardiographic characteristics of the 2 groups are shown in Tables 2 and 3, respectively. Among the patients with IDC, 39 (90%) had a history of myocardial infarction with no other clinically significant differences compared to patients with IDC (Table 2). In addition,
patients with DCM had significantly larger ventricular volumes than those patients with IDCm (Table 3).

During follow-up, devices with programming capability became available. Therefore, in the last 31 patients in the series (18 with DCM and 13 with IDCm; \(P=\text{NS}\)) programming of the device was carried out using echocardiographic optimization. The study of the transmitral flow with pulsed Doppler was used for the A V interval optimization and the assessment of the intraventricular asynchrony with tissue Doppler techniques were used for the interventricular interval (VV) optimization; this programming was not modified during follow-up.

**Echocardiographic Evolution**

At 6 and 12 months of follow-up, there was an overall reverse ventricular remodeling, with the reduction of both left ventricular diameters and volumes, as well as a progressive increase in LVEF. There was also a reduction in the severity of mitral regurgitation, with a decrease of the mitral regurgitation orifice and regurgitant volume, although there were no significant changes in the severity of pulmonary hypertension (Table 1).

### TABLE 2. Clinical Differences in Baseline and Follow-Up Variables According to the Etiology of the Underlying Heart Disease

<table>
<thead>
<tr>
<th></th>
<th>Dilated Cardiomyopathy (n=63)</th>
<th>Ischemic Dilated Cardiomyopathy (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline OFF</td>
<td>Baseline ON</td>
</tr>
<tr>
<td>Age</td>
<td>69 (8)</td>
<td>69 (7)</td>
</tr>
<tr>
<td>QRS, ms</td>
<td>154 (29)</td>
<td>140 (28)</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>7 (11%)</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>History of AMI, %</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NYHA FC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td></td>
<td></td>
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<tr>
<td>III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-minute walk test, m</td>
<td>290 (140)</td>
<td>416 (164)</td>
</tr>
<tr>
<td>Quality-of-life score, points</td>
<td>42 (19)</td>
<td>26 (21)</td>
</tr>
<tr>
<td>ACEI or ARA-II, %</td>
<td>52 (83%)</td>
<td>33 (78%)</td>
</tr>
<tr>
<td>β-Blockers, %</td>
<td>40 (64%)</td>
<td>29 (68%)</td>
</tr>
</tbody>
</table>

NYHA FC indicates New York Heart Association Functional Class; AMI, acute myocardial infarction; ACEI or ARA-II, angiotensin converting enzyme inhibitor or angiotensin II receptor antagonists.

### TABLE 3. Differences in Baseline and Follow-Up Echocardiographic Variables According to the Etiology of the Underlying Heart Disease

<table>
<thead>
<tr>
<th></th>
<th>Dilated Cardiomyopathy (n=63)</th>
<th>Ischemic Dilated Cardiomyopathy (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline OFF</td>
<td>Baseline ON</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>22 (8)</td>
<td>25 (6)</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>76 (9)</td>
<td>74 (8)</td>
</tr>
<tr>
<td>LVESD, mm</td>
<td>61 (9)</td>
<td>60 (9)</td>
</tr>
<tr>
<td>LVEDV, mL</td>
<td>232 (100)</td>
<td>234 (100)</td>
</tr>
<tr>
<td>LVESEL, mL</td>
<td>181 (81)</td>
<td>179 (86)</td>
</tr>
<tr>
<td>LVCL, L/min</td>
<td>3.6 (1)</td>
<td>3.6 (1.2)</td>
</tr>
<tr>
<td>Mitral RO, mm²</td>
<td>36 (19)</td>
<td>20 (15)</td>
</tr>
<tr>
<td>Mitral RV, mL/beat</td>
<td>51 (25)</td>
<td>32 (24)</td>
</tr>
<tr>
<td>PAP, mm Hg</td>
<td>38 (9)</td>
<td>33 (12)</td>
</tr>
<tr>
<td>s-pw, ms</td>
<td>159 (98)</td>
<td>130 (84)</td>
</tr>
<tr>
<td>IV-D, ms</td>
<td>54 (28)</td>
<td>29 (28)</td>
</tr>
<tr>
<td>Echo resp., %</td>
<td>45 (72%)</td>
<td>32 (74%)</td>
</tr>
</tbody>
</table>

LVEDD indicates left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; LVCL, left ventricular cardiac load; RO, regurgitation orifice; PAP, pulmonary artery systolic pressure; Echo resp., echocardiographic responder; 5-point increase in LVEF and/or 15% decrease in LVESV; IV-D, interventricular delay; s-pw, distance between the septum and posterior wall; RV, regurgitation volume; LVEDV, left ventricular end-diastolic volume; LVESEL left ventricular end-systolic volume.

\(P<.05\) compared with baseline OFF.

\(P<.05\) in baseline OFF of IDCm versus baseline OFF of DCM.
When the extent of LV remodeling was analyzed according to the etiology of the underlying heart disease, we found a reduction in LV volumes and an increase in LVEF after CRT in both groups of patients (Table 3). Although ischemic patients tended to present less reverse remodelling than non-ischemic patients, there were no statistically significant differences between the groups with IDCM and DCM. Thus, after 12 months follow-up, patients with IDCM presented an absolute reduction of 4% and 12% in the LV end-diastolic and end-systolic volumes whereas the corresponding reduction was 13% and 19%, respectively, in patients with DCM (with no significant differences between IDCM and DCM in either case). Likewise, LVEF increased 34% in the IDCM group compared to 38% among patients with DCM (P=NS) (Figure 1).

From the echocardiographic point of view, 77 patients (73%) in the overall group showed a response to CRT (increase of 5 points of LVEF and/or decrease of 15% in LV end-systolic volume) after 12 months follow-up; 69 patients (65%) showed a 5-point increase in LVEF, 43 (40%) showed a 15% decrease in LV end-systolic volume, and 35 (33%) showed both. The proportion of echocardiographic responders was similar in both groups: 32 (74%) in the IDCM group and 45 (72%) in the DCM group (P=NS). Likewise, the proportion of patients with a decrease in LV end-systolic volume of more than 15% was 72% in the IDCM group and 67% in the DCM group (P=NS). Finally, the percentage of patients with a 5-point increase in LVEF after 12 months follow-up was also similar for both groups: 38% in the IDCM patients and 40% in the DCM patients (P=NS).

**Clinical Evolution**

At 6 months follow-up, 76 patients (72%) had responded clinically to CRT and 30 (28%) had not. Of those who failed to respond, 2 had received a heart transplant and 5 had died; the remaining patients (23) were considered nonresponders because the distance covered in the 6-minute walk test had not increased by at least 10%. At 12 months, a further 2 patients had received a transplant and another 3 patients died. There was still a group of 23 patients who could not walk 10% further in the 6-minute walk test. In general, therefore, clinical response to CRT at 12 months follow-up was favorable in 71 patients (67%), whereas there was no response in the remaining 35 (33%) in accordance with our previously described criterion. Furthermore, after 12 months, 60 patients (64%) were in NYHA functional class I or II, whereas only 33 (35%) remained in functional class III and 1 (1%) was in functional class IV. Similarly, the distance covered in the 6-minute walk test increased and the score on the quality-of-life questionnaire improved (Table 1).

Analysis of the clinical response to CRT in the 2 groups of patients divided according to etiology of the underlying heart disease also failed to reveal significant differences:
after 12 months follow-up, of the 63 patients with DCM, 39 (62%) had responded to CRT and 24 (38%) had not, compared to 32 (74%) and 11 (26%), respectively, in the population with IDCM (DCM vs IDCM, \(P=\text{NS}\)) (Figure 2). There were no significant differences between the 2 groups in the increase in the distance covered in the 6-minute walk test: after 12 months the patients with DCM walked 143 (183) m further than at baseline and the patients with IDCM walked 175 (144) m further (\(P=\text{NS}\)) (Table 2). With regard to the quality-of-life questionnaire, the patients with DCM showed a 12-point improvement in the score on the test and the patients with IDCM showed a 15-point improvement after 12 months follow-up (\(P=\text{NS}\)).

**DISCUSSION**

The present study shows the clinical benefit of treating patients with CRT. It also points to the reverse ventricular remodeling that occurs with this therapy, with a progressive and sustained decrease in LV size, increase in LVEF, and decrease of the severity of mitral valve regurgitation. In addition, this study shows that the clinical and echocardiographic benefit occurs in patients with DCM as well as in patients with IDCM.

**CRT and Ventricular Remodeling**

It is hypothesized that the neurohormonal activation induced by heart failure is the main mechanism favoring LV remodeling and that this mechanism is the target for both medical treatments and CRT.\(^{22,23}\) It is likely that CRT favors reverse remodeling by several different mechanisms which act both on improving the synchrony of contraction of the different myocardial segments and on normalization of LV diastolic filling time, which tends to normalize the neurohormonal profile.\(^{24-28}\) CRT acts by producing changes in LV morphology and these changes confer a hemodynamic benefit that translates into a clinical improvement of the patient.\(^{29,30}\)

If there is limited information on how exactly CRT acts in the pathophysiology of LV remodeling, there is still less information on whether the patient’s heart disease etiology can determine or limit the extent of the benefit obtained with this therapy. Thus, it is not yet clear whether this morphological change that should hypothetically provide clinical benefit in patients treated with CRT occurs to the same extent in hearts with substantial scars as sequelae of a previous infarction.

**CRT and Etiology of the Underlying Heart Disease**

Previous studies, such as the SCARS registry,\(^7,8\) show that having a dilated cardiomyopathy of ischemic origin, particularly if advanced and associated with a severely dilated left ventricle and severe mitral valve regurgitation, is a predictor of poorer response to CRT. Likewise, Sutton et al\(^10\) showed in a population of 228 patients included in the Multicenter Insync Randomized Clinical Evaluation that reverse ventricular remodeling after CRT implantation occurred mainly in nonischemic patients and the authors attributed the differences to progression of ischemic disease. Contrary to those findings, Molhoek et al,\(^9\) comparing a population of 74 patients, 34 with ischemic heart disease and 40 with DCM, over a 2-year follow-up, did not find any significant differences.\(^{31-33}\)

In our series, we also failed to find any differences in the extent of clinical or echocardiographic response between patients with IDCM and those with DCM. However, patients with DCM had significantly higher baseline LV volumes than ischemic patients (Table 3), a factor which is associated with worse prognosis.\(^7,8\) Despite this, we found a similar proportion of clinical
and echocardiographic responders among patients with DCM or with ischemic etiology. This could indicate that the extent of reverse remodeling is greater in patients with DCM than in ischemic patients, in agreement with the results of Sutton et al.\textsuperscript{10} Probably, the response to CRT is limited by large regions of scar tissue in patients with a history of infarction, an observation which serves to highlight the growing interest in undertaking viability studies to better select patients with IDCM who might respond to CRT.\textsuperscript{34,35}

**Limitations**

The last 31 patients of the series received an optimization of the AV and VV intervals although there were no significant differences in the number of optimized patients in each group. However, the programming was not subsequently reviewed, and this could have influenced the subsequent evolution of these patients.

The definition of IDCM according to the presence of at least one lesion >50% in one artery can be debated as a sole cause of cardiomyopathy, and in fact this continues to be the object of discussion in the literature.\textsuperscript{12} In our case, we decided to follow what has been widely accepted in recent years and published in studies similar to our own.\textsuperscript{9}

**CONCLUSIONS**

CRT is an effective alternative therapy in patients with dilated heart disease whether of ischemic or nonischemic origin, although the echocardiographic response in terms of reverse remodeling tends to be slightly lower in ischemic patients. Therefore, at present, no patient should be ruled out of CRT due to the etiology of the cardiopathy.

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