Cardiac Resynchronization Therapy and Valvular Cardiomyopathy After Corrective Surgery

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Cardiac resynchronization therapy (CRT) has been shown to have clinical benefits in certain groups of patients with advanced heart failure (HF). However, patients with valvular cardiomyopathy are underrepresented in randomized clinical studies. The aim of this study was to assess the medium-term (ie, at 6 months) effects of CRT in patients with HF exclusively due to valvular disease. The study included 40 consecutive patients who underwent CRT device implantation. At 6 months, there were improvements in functional class, left ventricular remodeling, and intraventricular dyssynchrony parameters in treated patients. In this particular subgroup of patients, the benefits of CRT were similar to those observed in patients with HF due to other etiologies.

Key words: *Cardiac resynchronization therapy. Heart failure. Valvular heart disease.*

Terapia de resincronización cardiaca y miocardiopatía valvular tras cirugía correctora

La terapia de resincronización cardiaca (TRC) ha mostrado utilidad terapéutica en un determinado grupo de pacientes con insuficiencia cardiaca avanzada. Sin embargo, los pacientes con diagnóstico de miocardiopatía de origen valvular están infrarrepresentados en los estudios clínicos aleatorizados. El objetivo del estudio fue evaluar el efecto de la TRC en pacientes con insuficiencia cardiaca de etiología exclusivamente valvular a medio plazo (6 meses). Se incluyó a 40 pacientes consecutivos a quienes se implantó un dispositivo de resincronización cardiaca. A los 6 meses de seguimiento, se produjo una mejora de la clase funcional, el remodelado ventricular izquierdo y los parámetros de asincronía intraventricular en los pacientes tratados. En este subgrupo de pacientes, la TRC muestra un beneficio similar al obtenido en pacientes con insuficiencia cardiaca de otra etiología.

Palabras clave: *Terapia de resincronización cardiaca. Insuficiencia cardiaca. Valvulopatías.*

INTRODUCTION

Cardiac resynchronization therapy (CRT) has been clinically demonstrated to improve functional class and quality-of-life, reduce hospital admissions and increase survival in patients with heart failure.[1]

Current guidelines give CRT a class I indication for patients in NYHA functional class III or IV, with QRS complex $\geq$120 ms and left ventricular ejection fraction (LVEF) $\leq$35%.[2] However, the vast majority of the >4000 patients included in randomized clinical studies of CRT have cardiomyopathy of ischemic or idiopathic etiology. Little data is available about the usefulness of CRT in heart failure due to other etiologies, like congenital heart disease or valvular heart disease.

The objective of this study is to describe the mid-term (6 months) clinical efficacy and effect of CRT on left ventricular remodeling in patients with advanced heart failure of valvular etiology.

METHOD

We included 40 consecutive patients diagnosed with valvular cardiomyopathy and with classic indications for CRT.

In diagnosing valvular cardiomyopathy, we included patients with a history of mitral valve disease and/or aortic valve surgery, documented previously or post-surgical left ventricular dysfunction, and heart failure with no other obvious etiology. All patients had undergone surgery at least 6 months prior to device implantation

and ischemic heart disease had been ruled out by coronary angiography (coronary arteries without angiographic lesions >50%). No patient had a history of myocardial infarction or angina. We excluded patients undergoing surgery for a diagnosis of severe mitral valve failure secondary to mitral ring dilatation due to non-ischemic dilated cardiomyopathy.

At baseline and 6-month follow-up, we recorded the clinical history of all patients and results of physical examination, electrocardiogram (ECG), 6 minute walking test, quality-of-life test (Minnesota Living with Heart Failure Quality of Life Score), echocardiogram, and study of aerobic functional capacity with metabolic analysis of exhaled gases.

By echocardiography, we determined EF using Simpson's rule, ventricular diameters and volumes, E/E' ratio (tissue E wave), aortic flow integral, systolic pulmonary artery pressure (sPAP), Tei index, and parameters of interventricular and ventricular dyssynchrony (septo-posterior and septo-lateral wall delay by tissue Doppler) using previously described techniques.[3] Using tissue Doppler, septo-lateral delay was calculated as the difference in milliseconds between QRS complex onset and maximum systolic velocity for each ventricular region on the apical 4-chamber axis.

Patients in atrial fibrillation (AF) were discharged with the right ventricle trigger algorithm activated and at 1 month we checked the percentage of pacing. If it was <85%, we indicated an atrioventricular node (AVN) ablation.

We considered patients non-CRT responders if they met one or more of the following criteria at 6-month follow-up: a) cardiac death; b) inclusion on a heart transplantation waiting list; and c) <10% increase in 6 minute walking test distance.

Numerical results are expressed as mean (SD). Qualitative variables were tested with χ^2 and quantitative variables with Student's t test. A P value less than .05 was considered significant.

RESULTS

Patient clinical and demographic characteristics are in Table 1.

The left ventricular electrode was successfully deployed in 37 (92.5%) patients. Implantation failure was caused by the inability to cannulate the coronary sinus (CS) in 2 patients and the inability to advance the guiding catheter due to the severe angle of the ostium in 1 (Figure 1). Final CS electrode position was lateral region in 22 patients; posterolateral, 8; anterior, 4; and anterolateral, 3.

Three major complications occurred (8.1%): 1 substantial hematoma, 1 early CS electrode displacement, and 1 transitory ischemic event.

At 6-month follow-up, we considered 31 (83.7%) patients had responded to CRT. Of the 6 non-responders,

TABLE 1. Clinical and Demographic Characteristics

Age, mean (SD), y	67 (10)
Men, n (%)	31 (77.5)
Etiology, n	
Aortic	25
Mitral	12
Mitroaortic	3
NYHA functional class, n (%)	
III	33 (82.5)
IV	7 (17.5)
Medical treatment, %	
ACE inhibitors/ARB-II	97.5
Diuretics	100
Beta-blockers	60
Antialdosterone therapy	40
IAD, n (%)	25 (62.5)
LBBB, n (%)	38 (95)
QRS, mean (SD), ms	161.5 (30.3)
PR, mean (SD), ms	189.5 (50.1)
AF, n (%)	23 (57.5)
6 Minute walking test, mean (SD), m	244 (119)
Quality-of-life score, mean (SD)	44 (16)
Surgery-implantation time, mean (SD), d	1318 (478)

ACE indicates angiotensin converting enzyme; AF, atrial fibrillation; ARB-II, angiotensin II receptor blockers; IAD, implantable automatic defibrillator; LBBB, left bundle branch block.

2 died of terminal heart failure, and 2 received transplants. Moreover, 5 had sPAP >50 mm Hg. Among those who responded to CRT, 1 died suddenly 4 months after pacemaker implantation.

At the end of the follow-up, NYHA functional class (3.2 [0.7] vs 2.1 [0.8]; P=.01), quality-of-life (44 [16] vs 20 [12]; P=.03) and 6 minute walking test distance (244 [119] vs 413 [54] m; P=.001) had improved. The metabolic study identified increased maximum oxygen consumption (Figure 2).

Of 20 patients in AF, 7 (35%) underwent AVN ablation. Among patients without ablation, 91% (6%) received pacing. Rates of responders in AF (16/20 patients) and in sinus rhythm (15/17 patients) were 80% and 88.2%, respectively (P=.125).

Effects of CRT on electrocardiographic parameters and parameters of dyssynchrony appear in Table 2 and Figure 3, respectively.

DISCUSSION

The present study describes the clinical efficacy of CRT in patients with valvular cardiomyopathy and advanced heart failure, a subpopulation underrepresented in randomized studies, as demonstrated by the CARE-HF study, in which valvular cardiomyopathy was the etiology in only 19 (2%) of 813 patients.[4]
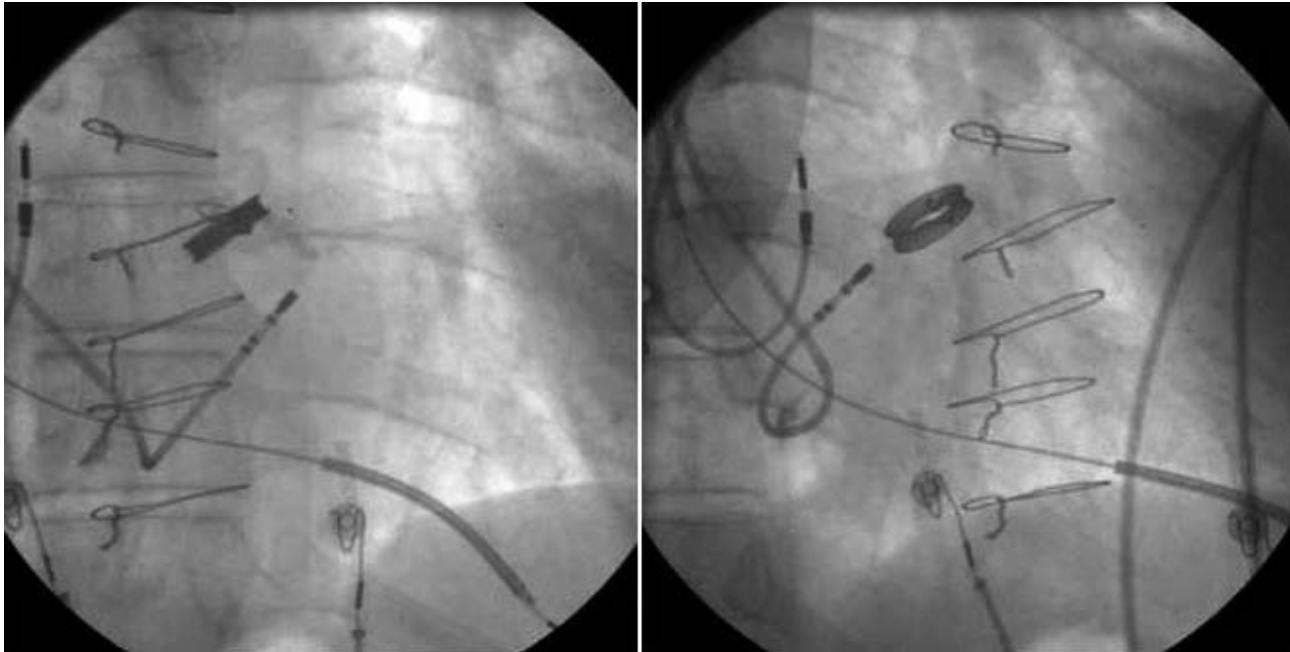
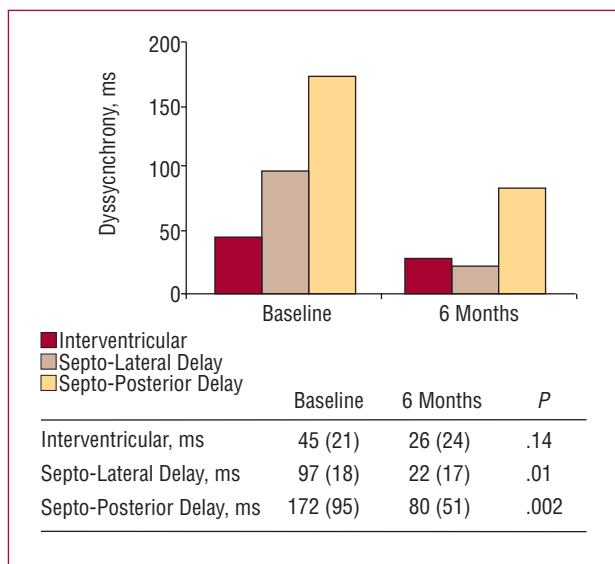**Figure 1.** Severe angle of coronary sinus ostium (2 projections) that prevents the guide catheter from advancing.

	Baseline	6 Months	P
Interventricular, ms	45 (21)	26 (24)	.14
Septo-Lateral Delay, ms	97 (18)	22 (17)	.01
Septo-Posterior Delay, ms	172 (95)	80 (51)	.002

Figure 2. Parameters of interventricular and ventricular dyssynchrony prior to implantation and at 6 months.

TABLE 2. **Hemodynamic and Ventricular Remodeling Parameters Determined by Echocardiography**

	Baseline	6 Months	P
EF, %	24.2 (8.8)	36.1 (6.5)	.01
EDD, mm	67 (12)	60 (7)	.02
ESD, mm	55 (10)	46 (9)	.04
EDV, mL	204 (85)	172 (65)	.02
ESV, mL	150 (70)	103 (67)	.02
E/E'	18.3 (3.6)	12.4 (4.8)	.03
Tei index	0.65 (0.03)	0.49 (0.05)	.02
Ao integral	16.1 (4.8)	19.7 (3.9)	.01
sPAP, mm Hg	48 (14)	34 (12)	.03

Ao indicates aorta; EDD, end-diastolic diameter; EDV, end-diastolic volume; E/E', mitral ring E wave ratio and tissue E wave; EF, ejection fraction; ESD, end-systolic diameter; ESV, end-systolic volume; sPAP, systolic pulmonary artery pressure.

In valvular heart disease, ventricular dysfunction is generally due to the absence of ventricular remodeling regression after corrective surgery.[5] Frequently, behavior disorders develop—often causing mechanical dyssynchrony—and contribute to the situation. However, at present, some aspects of this type of cardiomyopathy—eg, incidence of sudden death or response to resynchronization, which are better defined for other types of cardiomyopathy—remain unknown. The clinical efficacy of CRT in our patients is clearly reflected in improved classical parameters and substantially increased maximum oxygen consumption—a more objective parameter that is less likely to be subject to a hypothetical placebo effect. Moreover, the rate of CRT responders, close to 84%, is in consonance with these findings and similar to that found in patients with idiopathic dilated cardiomyopathy.[6] In our study, this also clearly demonstrates the effect of CRT on ventricular remodeling, with improvements in EF and ventricular diameters and volumes, as well as in noninvasive hemodynamic parameters (Tei index, aortic flow integral, and E/E' ratio), comparable to data on CRT in other cardiomyopathies.[7]
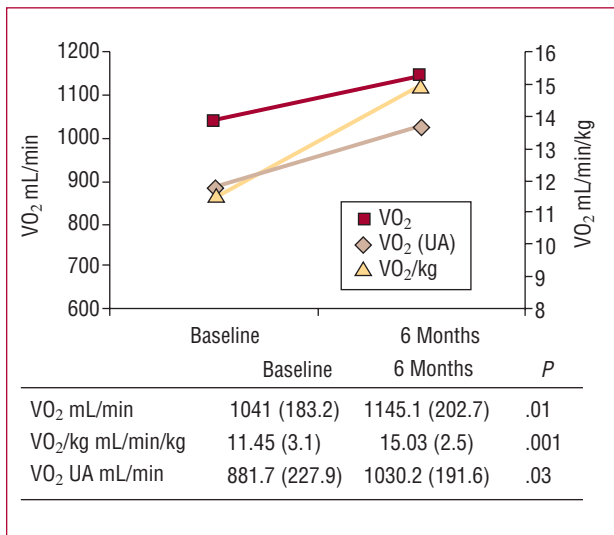
	Baseline	6 Months	P
VO$_2$ mL/min	1041 (183.2)	1145.1 (202.7)	.01
VO$_2$/kg mL/min/kg	11.45 (3.1)	15.03 (2.5)	.001
VO$_2$ UA mL/min	881.7 (227.9)	1030.2 (191.6)	.03

Figure 3. Maximum oxygen consumption obtained at baseline and at the end of the follow-up. AT indicates anaerobic threshold; VO$_2$, oxygen consumption.

As in earlier studies, parameters of ventricular dyssynchrony became practically normal after device implantation but interventricular delay was not modified. Essentially, this may be explained by the limited interventricular dyssynchrony observed in our patients (45 [21] ms; cutoff at 40 ms), and the lengthened pulmonary preejection period in patients with pulmonary hypertension that is prevalent (87.5%) in our study.[8]

Finally, our study indicates that management of this subpopulation of patients has its own peculiarities. The greater incidence of AF and substantial atrial dilatation that are usually present can prejudice the implantation success rate.[9] However, precise management of antithrombotic treatment is vitally important due to the possible appearance of surgical hematomas and high risk of embolic events that the change of anticoagulants favor.

In conclusion, this study indicates important mid-term beneficial effects derive from CRT both clinically and in terms of ventricular remodeling in patients with advanced heart failure secondary to valvular cardiomyopathy. In the absence of randomized clinical studies, these beneficial effects can be similar to those obtained by CRT in patients with left ventricular dysfunction of other origin.

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