BRIEF REPORT

Evolution of Severe Mitral Regurgitation After Optimization of Pharmacological Therapy in Non-Ischemic Dilated Cardiomyopathy

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In dilated cardiomyopathy, severe functional mitral regurgitation (MR) is associated with a poor prognosis. In 112 consecutive clinically stable patients with non-ischemic dilated cardiomyopathy, echocardiography identified 15 (14%) patients who had severe MR (age, 53±12 years; 80% male; left ventricular ejection fraction, 26±8%). Existing medical treatment with ACE inhibitors and beta-blockers was increased up to the maximum tolerated doses. At 6 months, MR decreased by at least one grade in 13 (87%) patients (*P*=.001), as did the effective regurgitant orifice area (from 0.41 [0.05] mm^2 to 0.20 [0.15] mm^2; *P*< .001) and the jet area (from 13.6 [2.1] cm^2 to 7.4 [4.5] cm^2; *P*<.001). These changes correlated with an increase in left ventricular ejection fraction (from 26 [8]% to 35 [10]%, *P*=.009; *r*=0.60, *P*=.01) and a decrease in end-diastolic volume (from 168 [46] mL to 142 [72] mL, *P*=.04; *r*=0.59, *P*=.02). An improvement in New York Heart Association class was observed (from 2.7 [0.5] to 1.9 [0.7]; *P*< .001). The severity of functional MR decreased after medical treatment was maximized. The decrease correlated with improvements in left ventricular systolic function.

Key words: *Mitral regurgitation. Dilated cardiomyopathy. Pharmacology. Echocardiography.*

Evolución de la insuficiencia mitral severa tras optimización del tratamiento médico en la miocardiopatía dilatada no isquémica

En la miocardiopatía dilatada, la insuficiencia mitral (IM) funcional grave se asocia con una peor situación clínica y pronóstica. De 112 pacientes consecutivos con miocardiopatía dilatada no isquémica, 15 (14%) presentaban IM grave funcional por ecocardiografía (53 ± 12 años, 80% varones, FEVI 26 ± 8%). Se optimizó el tratamiento previo hasta dosis máximas toleradas de un inhibidor de la enzima de conversión de la angiotensina (IECA) y un bloqueador beta. A los 6 meses disminuyó el grado de insuficiencia en 13 pacientes (87%) (p = 0,001), el área del orificio regurgitante efectivo (0,41 ± 0,05 frente a 0,20 ± 0,15 mm^2; p < 0,001) y del *jet* (13,6 ± 2,1 frente a 7,4 ± 4,5 cm^2; p < 0,001). Estos cambios se correlacionaron con una mayor FEVI (26 ± 8 frente a 35 ± 10%; p = 0,009; r = 0,60, p = 0,01) y un menor volumen telesistólico (168 ± 46 frente 142 ± 72 ml; p = 0,04; r = 0,59, p = 0,02). Se observó una mejoría de la clase NYHA (2,7 ± 0,5 frente a 1,9 ± 0,7; p < 0,001). La IM funcional grave evolucionó hacia la mejoría tras la optimización máxima de IECA y bloqueadores beta, lo que parece correlacionar con una mejora de la función sistólica.

Palabras clave: *Insuficiencia mitral. Miocardiopatía dilatada. Farmacología. Ecocardiografía.*

INTRODUCTION

Functional mitral regurgitation (MR) can occur even in a structurally normal valve as a consequence of left ventricular systolic dysfunction.[1] In non-ischemic dilated cardiomyopathy, severe functional MR is associated with deterioration of the patient's clinical and hemodynamic status, and a poorer prognosis.[2] Despite the high prevalence of this condition on echocardiography,[3] functional MR is often clinically silent,[4] a fact that makes its detection and clinical management difficult. The pathogenesis of functional MR is multifactorial and still uncertain. Several factors are involved in the loss of valve coaptation, including ring dilation, imbalance of the traction forces, local papillary remodeling, and a reduced transvalvular pressure gradient resulting from contractile dysfunction.[5-7]

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TABLE 1. **Baseline Characteristics of Patients With Dilated Cardiomyopathy, With or Without Severe Mitral Failure***

	Non-Severe MR (n=97)	Severe MR (n=15)	*P*
Age, mean±SD, years	52±14	53±12	.78
Males	72 (74%)	12 (80%)	.75
Etiology			
Idiopathic	59 (61%)	9 (60%)	.51
Familiar	6 (6%)	2 (13%)	
Hypertensive	11 (11%)	2 (13%)	
Alcoholic	12 (12%)	2 (13%)	
Miscellaneous	9 (9%)	0 (0%)	
Diabetes mellitus	20 (21%)	3 (20%)	.89
NYHA class, mean±SD	2.7±0.5	2.3±0.5	.004
Systolic blood pressure, mean±SD, mm Hg	113±14	112±14	.87
Heart rate, mean±SD, bpm	71±8	77±3	.19
Sinus rhythm	71 (73%)	11 (73%)	.90
Complete bundle branch block	36 (37%)	8 (53%)	.24
LVEF, mean±SD, %	24±8	26±8	.55
LVEDV, mean±SD, mL	215±102	225±51	.85
LA, mean±SD, mm	49±8	52±8	.18
ACEI	82 (85%)	12 (80%)	.85
Beta-blockers	39 (40%)	5 (33%)	.57
Digitalis	52 (54%)	8 (53%)	.98
Diuretics	55 (57%)	10 (67%)	.47

*ACEI indicates angiotensin-converting enzyme inhibitor; LA, left atrium; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

In recent years the interest on this type of valve disease has increased, with the main therapeutic options being surgical techniques[8] and biventricular resynchronization therapy.[9] Apart from these approaches, the current role of medical treatment for the management of functional MR has not been established or assessed.

PATIENTS AND METHODS

Population and Design

The study included 112 consecutive patients referred for advanced heart failure between January 2002 and January 2003. All had non-ischemic, dilated myocardial disease consisting of left ventricular dilation with diffuse hypokinesia and no segmental abnormalitis or history of artery disease, confirmed by coronary angiography in 76 patients (68%). We selected the patients with severe functional mitral regurgitation (MR) and no organic valvular involvement on echocardiography, who were stable and had no changes in therapy or decompensation of the disease over the previous month. The patients' medical treatment was optimized to reach the maximum tolerated dose (maximum recommended or associated with adverse effects). Therapy consisted of an angiotensin-converting enzyme inhibitor (ACEI) or, in cases of intolerance, an angiotensin II type 2 receptor antagonist (ARA-II) plus a beta-blocker (BB). Patients were followed-up and at 6 months a new echocardiography study was performed. this was assessed on a blind basis with respect to the baseline study.

TABLE 2. **Optimized Therapy at 6 Months**

	Baseline Treatment	Final Treatment	*P*
ACEI/ARA-II			.001
Maximum doses	3 (20%)	15 (100%)	
Intermediate doses	8 (60%)	–	
Low doses	3 (20%)	–	
No	–	–	
Beta-blockers			<.001
Maximum doses	1 (7%)	3 (20%)	
Intermediate doses	2 (14%)	10 (66%)	
Low doses	2 (14%)	1 (7%)	
No	10 (66%)	1 (7%)	
Furosemide, mean±SD, mg/day	57±12	45±11	.21

*ACEI indicates angiotensin-converting enzyme inhibitor; ARA-II, angiotensin II receptor agonists; SD, standard deviation. Maximum doses were: ramipril 10 mg/day, enalapril 40 mg/day, losartan 100 mg/day, carvedilol 50 mg/day, bisoprolol 10 mg/day. Low doses were: ramipril 2.5 mg/day, enalapril 10 mg/day, losartan 25 mg/day, carvedilol 12.5 mg/day, bisoprolol 2.5 mg/day. Intermediate doses were between the high and low doses.

Echocardiography

Echocardiographic studies were performed by one blinded technician, using a Sonos 5500 instrument

TABLE 3. **Changes at 6 Months***

	Baseline	Final	*P*
SBP, mean±SD, mm Hg	113±14	107±10	.008
HR, mean±SD, beats/min	77±13	66±6	.002
NYHA, mean±SD	2.7±0.5	1.9±0.7	<.001
MR grade			
3 or severe	15	2	<.001
2 or moderate	0	5	
1 or mild	0	6	
0 or absent	0	2	
EROA, mean±SD, mm^2	0.41±0.05	0.20±0.15	<.001
Jet MR, mean±SD, cm^2	13.6±2.1	7.4±4.5	<.001
LVEF, mean±SD, %	26±8	35±10	.009
LVESV, mean±SD, mL	168±46	142±72	.04
LVEDV, mean±SD, mL	225±51	210±87	.19
LA, mean±SD, cm	52±8	49±10	.2

*EROA indicates effective regurgitant orifice area; HR, heart rate; LA, left atrium; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; NYHA, New York Heart Association; SBP, systolic blood pressure.

(Hewlett-Packard) and acquiring standardized views and measurements. The grade of MR was established as mild (1), moderate (2), or severe (3) according to the following parameters:[10] *1*) maximum area of the jet: mild <4 cm^2, moderate 4-10 cm^2, severe >10 cm^2; *2*) proximal isovelocity surface area (PISA) with calculation of the effective regurgitant orifice area (EROA): mild <20 mm^2, moderate 20-40 mm^2, severe >40 mm^2; *3*) pulmonary venous flow pattern: inversion of the systolic wave in severe grade; and *4*) mitral filling pattern: dominant E wave in severe grade.

Statistics

Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as a number (%). Between-group comparisons were performed with the χ^2 test (categorical variables) and Student's *t* test (quantitative variables). Student's *t* test for related samples was used for comparing the variables before and after medical treatment. Correlations between the observed changes were determined by Pearson's (*r*) and Spearman's (r_s) bivariate correlations.

RESULTS

Among 112 consecutive patients, 15 (13.4%) presented severe MR. Coronary arteriography had been performed in 13 of these patients (87%) and none of the studies showed coronary disease. Baseline characteristics are shown in Table 1; patients with severe MR presented a poorer NYHA functional class. Drug therapy optimization consisted of a significant increase in the doses of ACEI (or ARA-II) and BB administered, with no changes in the dose of diuretics (Table 2).

At 6 months, MR grade had decreased in 13 (87%) patients, as did the area of the jet and the EROA (Table 3). This reduction was associated with an improvement in NYHA functional class and a reduction in the end-systolic volume. The end-diastolic volume and left atrial diameter showed no differences.

The decrease in MR grade correlated weakly with the rise in LVEF (*P*=.03; r_s=0.56) and the reduction in end-systolic volume (*P*=.03; r_s=0.55), but not with the end-diastolic volume or atrial diameter. The reduction in EROA correlated with the decrease in LVEF and the end-diastolic volume (*P*=.01 and *r*=0.62 for both), whereas the area of the jet additionally correlated with the left atrial diameter (*P*=.03; *r*=0.56). The changes recorded in blood pressure and heart rate showed no significant correlations.

DISCUSSION

Functional MR is sometimes silent and in severe cases is associated with greater clinical deterioration.[2-4] In our population of patients with non-ischemic left ventricular systolic dysfunction, the prevalence of MR was 13.4%, and the condition was associated with a poorer NYHA functional class.

The first related studies, published more than a decade ago in patients with heart failure, showed that the reduction in functional MR was associated with a more favorable response to vasodilator and diuretic treatment.[11,12] The decrease in postload obtained with nitroprusside or hydralazine achieved an acute reduction in MR and an increase in cardiac output, that was more apparent in patients with severe MR.[12] In 1991, Hamilton et al[13] found that the acute improvement persisted at 6 months of oral vasodilator treatment. Few studies have been performed on the response of MR to medical treatment since that time. One study conducted in 1998 by Rosario et al[14] investigating 14 patients with severe MR (6 ischemic and 8 non-ischemic) found that intravenous therapy with vasodilators and diuretics was associated with a reduction in both the regurgitant volume and EROA.

In recent years there has been increasing interest in this condition, mainly from the perspective of surgery and biventricular resynchronization.[8,9] In contrast to the earlier research with hydralazine and captopril, our study considers this subject in the light of more extensive current pharmacological options, including BB and ARA-II. The present study is the first to show that maximum optimization of ACEI/ARA-II and BB doses is associated with a significant improvement in the MR grade at middle term.

Correction of MR is based on its functional character, but little is known about the mechanism implicated in the reduction of MR with medical treatment. Rosario et al[14] reported a correlation between the decrease in MR and reductions in the diastolic ventricular volume, mitral ring diameter, and right atrial diameter, suggesting a mechanism

related to changes in the valvular geometry. Nevertheless, Otsuji et al[5] have shown that dilation of the ring alone does not suffice to cause severe MR. Schwammenthal et al[15] demonstrated that the EROA presents a dynamic pattern that responds to changes in the loading conditions. In addition, Hung et al[6] found that the dynamic changes in the EROA are mainly determined by the transmitral gradient and not by changes in the valvular geometry. These findings are in keeping with the results of our study, in which the improvement in contractile function and the reduction in systolic volume, determinants of an increase in transmitral pressure, correlated with the reduction in MR grade and EROA. Although the present study does not measure the direct effect on ventricular preload and postload, it does suggest, together with the studies cited, that beyond interventions to reduce the mitral ring, severe functional MR can respond to therapies that reduce the loading conditions and improve cardiac function. Assessment of severe functional MR can be useful as a guide to the therapeutic and prognostic guide.

Limitations

The small number of patients included and the lack of a control group are the two main limitations of the study. Consequently, we cannot rule out that there may have been some influence of uncontrolled factors on the evolution of MR. In addition, it was not possible to establish causal relationships between the pharmacological optimization carried out and the changes observed in the parameters studied.

CONCLUSION

In this small series of patients with non-ischemic dilated cardiomyopathy and severe functional MR, optimization of ACEI, and BB therapy at the maximum tolerated doses resulted in an improvement of MR and echocardiographic parameters of left ventricular systolic function.

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