

## Clinical Outcome and Reversibility of Systolic Dysfunction in Patients With Dilated Cardiomyopathy Due to Hypertension and Chronic Heart Failure

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**Introduction and objectives.** There is little information on the clinical and functional course of patients with heart failure secondary to dilated cardiomyopathy due to hypertension. The objectives of our study were to assess the clinical and functional course of these patients, and to identify possible predictors of prognosis.

**Patients and method.** We evaluated a series of 49 patients with this condition diagnosed in our hospital from 1994 to 2003. Mean age was 63 (11) years, and 40% were women. Left ventricular ejection fraction was 30.1 (4.8)%. Follow-up was 45 (23) months (median, 41 months).

**Results.** Four-year survival was 0.84, the 4-year rate of hospitalization due to heart failure was 0.12, and likelihood of readmission-free survival was 0.80 at 4 years. Left ventricular ejection fraction increased from 30.1 (4.8)% to 57.6 (13.5)% ( $P < .001$ ). An unfavorable clinical and functional outcome at 4 years (death, readmission for heart failure or persistence of dilated cardiomyopathy) was recorded in only in 40% of the patients. Multivariate analysis with the Cox model showed appropriate control of blood pressure to be the only independent predictor of a favorable clinical outcome (absence of death or readmission for heart failure) (hazard ratio = 4.58; 95% CI, 1.32-9.83;  $P = .032$ ).

**Conclusions.** The course of patients with severe dilated cardiomyopathy due to hypertension was favorable in 60% of cases. Adequate control of blood pressure was the only independent predictor of a favorable clinical outcome.

**Key words:** Heart failure. Systemic hypertension. Dilated cardiomyopathy.

### Evolución clínica y reversibilidad de la disfunción sistólica en pacientes con miocardiopatía dilatada hipertensiva e insuficiencia cardíaca crónica

**Introducción y objetivos.** Hay poca información sobre la evolución clínica y funcional de los pacientes con insuficiencia cardíaca secundaria a miocardiopatía dilatada de origen hipertensivo. Los objetivos de nuestro trabajo son estudiar la evolución clínica y funcional de estos pacientes, así como identificar los posibles factores predictores de esta evolución.

**Pacientes y método.** Para ello, hemos evaluado a una serie de 57 pacientes diagnosticados en nuestro centro entre 1994 y 2003 con dicho problema. La edad media de los pacientes fue de  $63 \pm 11$  años, y el 40% eran mujeres. La fracción de eyección ventricular izquierda era del  $30,1 \pm 4,8\%$ . El tiempo de seguimiento fue de  $45 \pm 23$  meses (mediana, 41 meses).

**Resultados.** La supervivencia a los 4 años fue 0,84, la tasa de reingresos por insuficiencia cardíaca, 0,12 y la supervivencia libre de reingresos, 0,80. La fracción de eyección aumentó desde el  $30,1 \pm 4,8\%$  hasta el  $57,6 \pm 13,5\%$  ( $p < 0,001$ ). En conjunto, sólo el 40% de los pacientes presentó mala evolución clínica y/o funcional (muerte, reingreso por insuficiencia cardíaca, persistencia de miocardiopatía dilatada) al final del seguimiento. En el estudio multivariable (modelo de Cox), el adecuado control de la presión arterial fue el único predictor independiente de buena evolución clínica (ausencia de muerte y/o reingreso por insuficiencia cardíaca; razón de riesgo = 4,58; intervalo de confianza del 95%, 1,32-9,83;  $p = 0,032$ ).

**Conclusiones.** La evolución de los pacientes con miocardiopatía dilatada hipertensiva severa es buena en el 60% de los casos. El control de la presión arterial fue el único predictor independiente de buena evolución clínica.

**Palabras clave:** Insuficiencia cardíaca. Hipertensión arterial. Miocardiopatía dilatada.

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Received November 13, 2003.  
Accepted for publication May 27, 2004.

## INTRODUCTION

Hypertension (HT) is a major cause of heart failure resulting from either diastolic or systolic dysfunction. Although the first mechanism is more frequent, the second tends to accompany ischemic heart dis-

**ABBREVIATIONS**

BP: blood pressure.  
 CHF: congestive heart failure.  
 DCM: dilated cardiomyopathy.  
 HT: hypertension.  
 LVEF: left ventricular ejection fraction.  
 LVM: left ventricular mass.  
 LVMI: left ventricular mass index.  
 RWT: relative wall thickness.

ease and appear in more advanced stages of the process. Cases of isolated hypertensive systolic dysfunction with no disease of the large coronary arteries have been reported, although the pathogenic mechanisms for this condition may include microvascular ischemia.<sup>1</sup>

Perhaps because this "pure" form of ventricular dysfunction has a low prevalence, the literature contains little information on the history and effect of treatment in hypertensive dilated cardiomyopathy (DCM), with differing results obtained in small series.<sup>2,3</sup>

The present study was designed to establish the clinical evolution and changes in ventricular function of patients with hypertensive DCM in whom other factors to explain the dysfunction have been ruled out, particularly epicardial coronary disease. An additional aim of the study was to identify potential predictive factors of clinical evolution in this entity.

**PATIENTS AND METHODS**

Between January 1994 and June 2003, we conducted a prospective study including 57 patients admitted to our hospital for New York Heart Association (NYHA) functional class III or IV heart failure who met the following inclusion criteria: *a*) history of prior poorly controlled HT with systolic blood pressure (BP) >160 mm Hg; *b*) evidence of left ventricular dilation and ejection fraction <40%; and *c*) history of chronic heart failure of at least one year's duration.

Patients with any of the following characteristics were not included: *a*) myocardial ischemia visualized according to a study protocol based on perfusion myocardial scintigraphy and coronary angiography; *b*) proven myocardial infarction; *c*) valve disease; *d*) regular consumption of alcohol; *e*) congenital heart diseases explaining the ventricular dysfunction; *f*) clinically suspected acute myocarditis; *g*) endocrine and metabolic alterations possibly explaining the systolic abnormality; and *h*) secondary HT.

**Study Protocol**

Blood pressure was measured using a mercury blood pressure monitor, in accordance with the usual recommendations.

The echocardiography studies were performed by two specialists from our department, using Aloka SSD 830 and Acuson Sequoia units. The tracings were analyzed using previously recorded tapes. In the echocardiography study, the end-diastolic diameters (EDD), normalized diastolic diameters and end-systolic diameters were measured, as well as posterior wall (PW) thickness, and interventricular septal thickness (IVS) during diastole. These measurements were then used in the Penn-convention formula to calculate left ventricular mass (LVM, in grams =  $0.8 \times 1.04 \times \{ [EDD + IVS + PW]^3 - EDD^3 \} - 13.6$ ) and normalized for height to give the left ventricular mass index (LVMI). Left ventricular ejection fraction (LVEF) was calculated according to the Teichholz method. The relative wall thickness (RWT) was calculated from the formula:

$$RWT = 2 \times \text{posterior wall} / \text{left ventricular diastolic diameter}$$

Pulsed-wave Doppler ultrasound was used with the sample volume placed at the tip of the mitral leaflets, to calculate the peak E wave velocity, peak A wave velocity and isovolumic relaxation time. The following patterns were established from these measurements: *a*) normal or pseudonormal pattern: E:A ratio between 1 and 2.5 and isovolumic relaxation time between 60 and 100 ms; *b*) abnormal relaxation pattern: E:A ratio <1 and isovolumic relaxation time >100 ms; and *c*) altered distensibility pattern: E:A ratio >2.5 and isovolumic relaxation time <60 ms. Because it is hard to differentiate between a normal pattern and one observed when an abnormal relaxation pattern progresses to a distensibility alteration (pseudonormal pattern), we made no distinction between the two types of tracing. In the case of atrial fibrillation, we considered Doppler estimation of ventricular filling to be "nonassessable."

**Myocardial Ischemia Study Protocol**

Once adequate clinical control was achieved, each patient underwent a myocardial perfusion study with radioactive isotopes. However, coronary angiography was performed directly if the initial clinical suspicion of coronary disease was high. When scintigraphy showed severe, multiple or extensive perfusion defects, cardiac catheterization was performed in order to diagnose and treat possible high-risk coronary disease. If there were perfusion defects but no severity data, the patient was not included in the study. Patients

were included only if the myocardial perfusion scintigraphy was normal and/or no significant lesions (diameter loss >50% of the reference value for the arterial segment being studied) were visualized on coronary angiography.

The radioactive isotope study was done using single photon emission computed tomography (SPECT), and was interpreted by a specialist in nuclear medicine. If the patient's physical condition allowed, a treadmill stress test was performed according to the Bruce protocol. If exercise was difficult for the patient, intravenous adenosine was used.

**Follow-up**

During the follow-up, 2 of the cardiologists authoring this article saw the patients every 6 months in the outpatient service of our hospital; adequate blood pressure control was defined as BP <140/90 mm Hg. Therapy was adjusted according to the patient's clinical condition and blood pressure control. Normalization of LVEF was considered to have occurred when the LVEF had risen to ≥55%.<sup>4</sup> There were no losses during follow-up.

**Statistical Study**

SPSS for Windows was used for the statistical analysis. Results are expressed as a percentage for qualitative variables or as mean ± standard deviation (SD) for quantitative variables.

The χ<sup>2</sup> or Fisher's exact test (when the expected frequency was <5) were used to compare qualitative variables. Student's *t* test was used to compare the mean values. To verify changes in a variable, Student's *t* test for paired data or χ<sup>2</sup> was used. Actuarial probabilities were calculated according to Kaplan-Meier. The multivariate study of the prognostic influence of various parameters on the clinical evolution of patients (death and/or rehospitalization for congestive heart

failure [CHF]) and normalization of LVEF was done by Cox regression analysis.

**RESULTS**

**Baseline Characteristics**

During the inclusion period for the study, 1385 patients were discharged from our cardiology department with a principal diagnosis of CHF, or a mean of about 154 per year. Pure hypertensive DCM accounted for only 4% of all cases of CHF seen by our department. The predominant etiology was ischemic (45%), followed by valve disease (27%) and idiopathic or alcoholic DCM (20%). Other, less frequent causes accounted for the remaining 4%.

The baseline clinical and electrocardiographic characteristics of the series are shown in Table 1. All patients experienced significant symptomatic improvement with the therapy started during hospitalization, and systolic BP figures were brought to levels below 140/90 mm Hg in 50 (87%) of the 57 patients prior to discharge.

At the time cardiomyopathy was diagnosed, LVEF was 30.1±4.8% (range, 20%-40%). In 10 (17%) patients, LVEF was less than 25%. The baseline systolic and diastolic diameters, wall thicknesses and left ventricular RWT are shown in Table 2.

The predominant left ventricular filling pattern was an abnormal relaxation pattern, occurring in 23 (41%) cases. Sixteen percent (9 patients) had an altered distensibility pattern, the same percentage as patients considered to have normal or pseudonormal filling. The remaining 27% (16 patients) had atrial fibrillation.

Coronary angiography was performed in 18 (32%) patients. Four of these patients had positive scintigraphy, with extensive perfusion defects requiring catheterization. In another 14, the test was performed directly because of high initial clinical suspicion. The presence of myocardial ischemia was ruled out in the remaining 39 (68%) patients based on normal findings in the perfusion scintigraphy.

All patients were discharged from the hospital with diuretics. Angiotensin-converting enzyme (ACE) inhibitors were used in 52 patients (91%), beta-blockers in 30 (52%), digoxin in 18 (34%), dihydropyridine calcium antagonists in 15 (26%), spironolactone in 21 (37%), alpha blockers in 13 (22%), and losartan, an angiotensin II receptor antagonist, in 5 (8%) patients. The doses of the most commonly used drugs were: enalapril, 27±7 mg/day; carvedilol, 21±6 mg/day; spironolactone, 31±8 mg/day; amlodipine, 8±2 mg/day, and losartan, 45±9 mg/day. Multidrug therapy was common, with 3 drugs used in 31 (54%) patients, 4 drugs in 8 (14%) and 5 drugs in 10 (18%). Only 8 patients were discharged with 2 hypotensive drugs.

**TABLE 1. Baseline Clinical and Electrocardiographic Characteristics of Patients With Dilated Cardiomyopathy of Hypertensive Origin\***

Age, years	63.2±11.2
Sex, female	23 (40%)
Diabetes mellitus	12 (21%)
Atrial fibrillation	16 (27%)
Left bundle-branch block	23 (41%)
Time of HT evolution, years	9.2±5.4
Time of CHF evolution, years	3.6±3.1
Initial systolic BP, mm Hg	179.2±19.7
Initial diastolic BP, mm Hg	106.1±9.7
Initial pulse pressure, mm Hg	73.1±15.1
BP control during admission	50 (87%)

\*HT indicates hypertension; CHF, congestive heart failure; BP, blood pressure.

**TABLE 2. Evolution of Ventricular Echocardiographic Values in Patients With Dilated Cardiomyopathy of Hypertensive Origin**

Variable	Initial	Final	P
LV diastolic diameter, mm	64.3±6.1	57.1±8.2	<.0001
Diastolic diameter index, mm/m	37.9±3.3	33.9±5.1	<.005
Systolic diameter, mm	51.2±6.3	41.4±10.3	<.0001
Estimated LV mass, g	349.1±103.8	282.9±77.4	<.0001
Ventricular mass index, g/m	204.8±58.9	167.9±45.2	<.0001
Septal thickness, mm	10.4±1.9	10.3±2.5	.89
Posterior wall thickness, mm	10.6±2	10.2±2.4	.85
Relative wall thickness	0.33±0.06	0.37±0.09	<.0001
Left ventricular ejection fraction, %	30.1±4.8	57.6±13.5	<.0001
LVIRT, s	0.12±0.04	0.11±0.02	.24
E:A ratio	1.5±1.1	1.1±0.6	.045
Filling pattern, %			
Normal/pseudonormal	9 (16%)	16 (27%)	
Abnormal relaxation	23 (41%)	29 (51%)	
High distensibility	9 (16%)	2 (4%)	
Nonassessable	16 (27%)	10 (18%)	.037

\*LVIRT indicates left ventricular isovolumic relaxation time; LV, left ventricle

## Progress

After a mean follow-up of 45±23 months (median, 41 months), systolic BP decreased from 179.2±19.7 to 124.6±15.8 mm Hg and diastolic BP from 106.1±9.7 to 80.2±7.8 mm Hg. By the end of follow-up, 90% (51 patients) of the patients had a systolic BP <140 mm Hg.

Table 2 shows the changes in echocardiographic values between the time of inclusion and completion of the study. A significant decrease was observed in LVMI due to the decrease in systolic and diastolic diameters. Patients with normalized left ventricular diameter were 51% (29) of the total. Normalization of LVEF was achieved in 60% of the cases (34 patients) during the study period. The E:A ratio decreased significantly. The altered distensibility pattern was reduced at the expense of an increase in patients with abnormal relaxation or normal/pseudonormal pattern.

During the follow-up, 5 patients died, 2 of them due to sudden death (at 22 and 47 months of follow-up), 2 from progressive pump failure (at 20 and 48 months from discharge) and 1 from pleural mesothelioma (at 37 months from discharge). The probability of survival was 1.00 at 1 year, 0.96 at 2 years, 0.92 at 3 years and 0.84 at 4 years. Rehospitalization for heart failure occurred in four patients (at 3, 18, 24, and 48 months of follow-up, respectively) and the probability of no rehospitalization for CHF was 0.96 at 1 year, 0.93 at 2 years, 0.90 at 3 years and 0.88 at 4 years. Therefore, the probability of no rehospitalization for CHF in patients from our series was 0.96 at 1 year, 0.92 at 2 years, 0.86 at 3 years and 0.80 at 5 years. At the time of the last follow-up, 7 patients were functional class III and it was common to find no normalization of left

ventricular ejection fraction or diameter. The remaining patients persisted in Class I or II. No cardiac ischemic events were recorded. As a whole, only 37% of our patients presented unfavorable clinical and/or functional evolution (i.e., death, readmission for CHF and/or persistence of left ventricular systolic dysfunction).

## Prognostic Factors

Table 3 contains the bivariate analysis results with or without normalization of LVEF (LVEF>55%) during follow-up. Normalization of LVEF was associated with younger age, shorter clinical history of HT, smaller baseline diastolic diameter, higher baseline relative wall thickness and adequate control of BP. Cox multivariate analysis showed that adequate control of BP (risk ratio [RR]=3.98; 95% confidence interval [CI], 1.28-7.34; *P*=.038) and higher baseline relative wall thickness (RR=2.65; 95% CI, 1.13-6.89; *P*=.091) were independent predictors of normalization of LVEF.

Table 4 lists the factors implicated in the bivariate analysis when death and/or rehospitalization due to CHF occurred in our patients. Patients who had any event during the follow-up presented greater left ventricular dilation in the first echocardiographic study and worse final systolic function. In terms of BP figures, clearly poorer control was observed in patients with unfavorable clinical progress (Table 4). In the Cox model, poor blood pressure control continued to be the only independent predictor of death or rehospitalization for CHF (RR=4.58; CI 95%, 1.32-9.83; *P*=.091).

**TABLE 3. Factors Related to Normalization of Left Ventricular Ejection Fraction in Patients With Hypertensive Dilated Cardiomyopathy at the End of Follow-up (Bivariate Analysis)\***

Variable	LVEF>55%	LVEF<56%	P
Initial diastolic diameter, mm	62.4±5.8	65.2±6.1	.66
Initial systolic diameter, mm	50.6±5.9	53.6±6.5	.18
Initial LVEF, %	31.5±4.8	30.5±5.3	.35
Age, years	59.4±10.8	65.2±8.5	.045
Time of HT evolution, years	6.8±3.2	11.1±5.7	.039
Time of CHF evolution, years	2.8±2.9	4.2±3.2	.23
Initial systolic BP, mm Hg	179.2±17.1	180.9±23.1	.75
Initial diastolic BP, mm Hg	107.1±10.4	104.6±8.8	.78
Initial pulse pressure, mm Hg	72.1±10.6	76.3±19.6	.56
Initial DDI, mm/m	36.5±3.2	38.7±2.9	.043
Posterior wall, mm	10.9±1.7	9.8±1.2	.03
Ventricular mass index, g/m	208.2±53.9	200.3±64.8	.81
Initial RWT	0.35±0.6	0.3±0.7	.86
Final systolic BP, mm Hg	124.6±8.3	136.3±7.4	.006
Final diastolic BP, mm Hg	76.4±7.8	86.1±9.5	.005
Controlled BP at end of study	33 (96%)	14 (60%)	.007
Male sex	15 (62%)	12 (54%)	.54
Left bundle-branch block	11 (32%)	11 (47%)	.55
Atrial fibrillation	7 (21%)	8 (35%)	.42
Diabetes mellitus	7 (23%)	4 (17%)	.48
Filling pattern			.59
Normal/pseudonormal	7 (23%)	2 (8%)	
Abnormal relaxation	9 (28%)	10 (43%)	
Abnormal distensibility	6 (16%)	4 (17%)	

\*DDI indicates diastolic diameter index; LVEF, left ventricular ejection fraction; RWT, relative wall thickness; HT, hypertension; CHF, congestive heart failure; BP, blood pressure.

**DISCUSSION**

A history of hypertension is present in most patients with heart failure among the general population. In the Framingham study, 75% of the patients presented elevated blood pressure figures.<sup>5</sup> A similar percentage can be observed among patients followed up in outpatient clinics by general practitioners or cardiologists in Spain,<sup>6</sup> as well as among hospitalized patients.<sup>7</sup> However, when invasive methods are used for assessment the importance of hypertension per se drops dramatically and the diagnosis of coronary heart disease increases.<sup>8-11</sup> Left ventricular dilation with hypocontractility is the most infrequent form of hypertensive heart disease, affecting hearts with severe long-term overload and generally associated with heart failure.<sup>1,12</sup> As a result, the number of patients with hypertensive DCM in the reported series is small.<sup>2,12,13</sup>

The use of scintigraphy as a diagnostic tool for coronary disease in DCM has not been extensively investigated, although it is known that perfusion studies in hypertensive patients show a high sensitivity and negative predictive value with an elevated proportion of false positives. Glamman et al<sup>14</sup> performed ventricu-

**TABLE 4. Factors Related to Death or Hospitalization for Congestive Heart Failure in Patients With Dilated Cardiomyopathy of Hypertensive Origin During Follow-up. Bivariate Analysis**

Variable	Death/Hospitalization		P
	Yes	No	
Initial DDI, mm/m	39.4±1.4	37.7±3.2	.043
Final ejection fraction, %	43.6±12.3	54.1±13.3	.045
Final systolic BP, mm Hg	138.7±19.4	129.1±13.2	.045
Controlled BP	21 (46%)	6 (87%)	.035
Final diastolic BP, mm Hg	82.8±15.7	81.4±8.3	.005
Pulse pressure, mm Hg	56.3±12.9	47.8±8.4	.44
Initial systolic diameter	54.7±5.6	52.1±6.5	.49
Initial LV mass index	226.4±73.1	200.3±56.2	.12
Initial RWT	0.33±0.09	0.33±0.07	.86
Initial ejection fraction	29.9±3.3	30.2±5.3	.86
Initial relative wall thickness	10.4±2.7	10.4±1.5	.92
LVIRT, ms	0.11±0.02	0.11±0.04	.91
E:A ratio	1.3±0.1	1.6±0.2	.045
Final DDI, mm/m	34.4±5.1	33.3±4.9	.56
Age, years	63.1±10.1	62.7±10.2	.34
Time of HT evolution, years	9.2±3.7	8.7±5.6	.039
Time of CHF evolution, years	3.6±2.9	3.9±3.3	.23
Female sex, %	16 (32%)	4 (50%)	.32
LBBS His, %	33 (68%)	3 (37%)	.24
Atrial fibrillation, %	16 (32%)	2 (25%)	.67
Diabetes mellitus, %	5 (11%)	2 (25%)	.61
Filling pattern, %			
Normal/pseudonormal	5 (11%)	2 (25%)	
Abnormal relaxation	22 (46%)	3 (37%)	.78
High distensibility	5 (11%)	2 (25%)	
Nonassessable	17 (32%)	1 (13%)	

\*LBBS His indicates left bundle-branch block of the bundle of His; DDI, diastolic diameter index; RWT, relative wall thickness; HT, hypertension; CHF, congestive heart failure; LVIRT, left ventricular isovolumic relaxation time; LV, left ventricle.

lography on 75 patients with DCM and no obstructive lesions on coronary angiography. The authors found regional contractility alterations in 48% of patients. Seventeen of these cases were studied by thallium scintigraphy, and myocardial perfusion abnormalities were observed in 94%. The proposed causes of the fixed defects were fibrosis, thinning of the ventricular wall or prior infarctions due to embolization. Reversible defects would occur as the result of alterations in the coronary reserve or defects in the integrity of the myocyte membrane.<sup>14</sup> Several studies have shown the high negative predictive value of myocardial perfusion scintigraphy to rule out coronary disease in the angiography in patients with hypertension.<sup>15-18</sup> Therefore, we chose this technique to initially exclude ischemic heart disease and used coronary angiography only for cases with a high initial probability of ischemic heart disease or positive scintigraphy. The absence of ischemic events during follow-up in our se-

ries indicates the safety of this protocol when screening for coronary disease.

Among the 6 patients included in the series of Dall'Aglío et al,<sup>2</sup> reversal to normal in ventricular diameters and fractional shortening occurred during a follow-up period of 11 to 39 months. In contrast, no significant improvement was observed in the 8 patients described by Hamada et al<sup>3</sup> during a mean follow-up of 16 months, despite a significant decrease in BP. It should be taken into consideration, however, that thallium scintigraphy showed heterogeneous distribution of the tracer in these patients; therefore, the absence of coronary disease is inconclusive.

Various mechanisms have been proposed to explain the origin of systolic dysfunction in hypertensive heart disease. In addition to the structural changes implicated in hypertrophy, interstitial fibrosis, apoptosis phenomena and myocardial ischemia,<sup>19</sup> a prolonged increase of ventricular afterload can lead to ventricular dilation as a "preload reserve" mechanism.<sup>2</sup> Fibrosis and myocyte loss caused by apoptosis and ischemic necrosis might have contributed to the absence of parietal thickening observed in our patients, who presented a pattern of eccentric left ventricular hypertrophy, with increased LVM but no increase in wall thicknesses. Wall stress is inversely related to the ventricular mass/volume ratio, and it is precisely in patients with DCM where wall stress is greatest. Moreover, the type of hypertrophy determines the capacity for tolerating hypertensive emergencies and recovering after hypotensive therapy: more benefit from a specific decrease in afterload is obtained in a dilated heart than in a heart with concentric hypertrophy. Conversely, the same increase in blood pressure would imply greater oxygen consumption and deterioration of systolic function in DCM.<sup>12</sup>

The long-term survival of patients with hypertensive DCM in our experience is notably higher than that reported other series of patients with heart failure and systolic dysfunction. In the series of McAlister et al<sup>9</sup>, 3-year survival was 62%, regardless of etiology, and 70% when nonischemic disease was considered.<sup>9</sup> In the Framingham study, 5-year survival of patients with depressed LVEF was 36%, in comparison with 78% in the control subjects.<sup>20</sup> However, the Framingham study was a population study, whereas McAlister's patients were managed in a specialized clinic. Additionally, the mean patient age is higher in the Framingham study. Survival in our series was very high, 84% at 4 years, with a very low proportion of rehospitalizations for CHF (12%).

This great dissimilarity between the reports found in the literature, even the most recent clinical trials, and our results have no clear explanation. Various factors have been implicated in the reversal of adverse remodeling in patients with systolic dysfunction. Kawai et al<sup>21</sup> studied 78 patients with idiopathic DCM and

found higher systolic BP and a lower pulmonary arterial wedge pressure to be predictive factors of remodeling. The authors speculated that patients with a ventricle in better condition would maintain higher systolic pressures due to greater contractility.<sup>21</sup> Another recent study found that patients who experienced an improvement in systolic function presented a shorter duration of symptoms, were younger and more frequently had a prior history of HT.<sup>22</sup>

In our series, the patients with normalization of LVEF during follow-up showed a higher initial RWT, probably because ventricles with a higher mass/volume ratio present higher wall stress, and lower oxygen consumption than hearts that tend more toward a pattern of dilation with a thin wall.<sup>12</sup> The decrease and adequate control of blood pressure were also shown to be independent predictors of both normalization of LVEF and good clinical progress, without death or rehospitalization for CHF. Systolic BP is one of the determining factors for wall stress, and decreased systolic BP leads to improved function. Moreover, antihypertensive therapy itself can have direct effects on the myocardial structure. ACE inhibitors, beta-blockers, calcium antagonists, diuretics, and angiotensin receptor antagonists have all been shown to be effective in achieving reversal of hypertrophy.<sup>23-25</sup>

In addition, the decrease in LVM results in an improvement in both "conventional" fractional shortening<sup>26</sup> and midwall fractional shortening. Using enalapril, González-Juanatey et al<sup>27</sup> have shown that the improvement is maintained despite discontinuation of therapy. The significant improvement in ejection fraction observed among our patients after normalization of BP may be related to the decreased afterload, similar to what occurs in patients with severe aortic stenosis and ventricular dysfunction after the stenosis is corrected by valve replacement.

In the Steimle et al<sup>28</sup> series of patients referred for pretransplant assessment, the patients showing improvement in LVEF presented considerably higher transplant-free survival, as in our series. In the study by Kawai et al,<sup>21</sup> 100% of patients with favorable remodeling were free from rehospitalization for CHF at 2 years, as compared to 81% of the group without recovery of systolic function. Likewise, in the Cicoira et al<sup>22</sup> study, all the patients with improved function survived with no need for transplantation during a minimum period of 12 months, compared to 63% of patients who experienced no improvement. The absolute and indexed ventricular diameters were also predictive in patients with CHF.<sup>29</sup>

In our experience, blood pressure control during follow-up was the only independent predictor of survival without rehospitalization for heart failure. In other articles addressing the clinical evolution of patients with DCM, patients with worse clinical progress had lower BP.<sup>21,30,31</sup> It has been speculated that persistent deterior-

ration of ventricular contractility is the origin of lower systemic pressure in these patients,<sup>21</sup> rather than the result. We believe that the better prognosis in the group with "controlled" BP cannot be explained merely by improved ventricular function. A decrease in systolic BP is critical in patients with DCM of hypertensive origin, in terms of oxygen consumption and the capacity of systolic function to respond in situations of acute stress.

Although the above mechanisms could have played a part in the favorable prognosis of our hypertensive DCM patients, selection bias cannot be ruled out. The characteristics of our patients (absence of coronary disease, improvement of LVEF with therapy) might have resulted in a group having a favorable prognosis. Adequate control of blood pressure was important, since almost 90% of the patients were discharged with adequate BP control, a situation that improved even during follow-up. Therapy was appropriate in terms of both the drugs and the dosages. Only 13% of the patients at discharge and 10% at the end of follow-up had not achieved blood pressure figures below 140/90 mm Hg, despite intensive therapy. Control of HT was an independent predictor of both clinical evolution and LVEF improvement.

### Limitations of the Study

Various technical and methodological aspects of our work should be taken into consideration before drawing conclusions. The number of individuals included in the study was low. The selection criteria were strict and because of the low frequency of this form of hypertensive heart disease, our series is actually one of the largest to date. It was not possible to compare our results with those obtained from subsets of hypertensive DCM patients included in larger series and clinical trials, since the specific evolution of this subgroup was not indicated in these studies.

Catheterization in all patients would have been desirable in our study, since coronary angiography is the gold standard for detecting significant arteriosclerotic disease and hemodynamic studies provide important information. However, this tool is an invasive technique with questionable benefits, limiting its use as a routine test.

Blood pressure figures are single measurements that often do not reflect the patient's actual blood pressure control, as shown by studies using ambulatory monitoring. However, the "clinical" BP is widely used in daily practice and more accessible for the physician.

### CONCLUSIONS

Taking into account the above limitations, our study indicates that the clinical progress of patients with DCM of hypertensive origin and severe heart

failure is favorable at the short and medium-term in almost two-thirds of cases, with low mortality and re-hospitalization for congestive heart failure as well as normalization of LVEF in a high percentage of patients. Blood pressure control and several echocardiographic parameters, such as initial relative wall thickness, were independent predictors of this clinical progress.

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