Prognostic Determinants of Patients with Chronic Systolic Heart Failure Secondary to Systemic Arterial Hypertension

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Abstract

Background: Systemic arterial hypertension (SAH) is an important cause of chronic systolic heart failure (CHF) in underdeveloped countries. It would be desirable to know predictors of mortality for patients with this condition in order to provide proper scientific treatment.

Objective: To determine risk factors for all-cause mortality in patients with CHF secondary to SAH in the current era of heart failure therapy for left ventricular systolic dysfunction.

Methods: All patients routinely and prospectively followed at the Cardiomyopathy Clinic of our Institution from January, 2000 to April, 2008 with the diagnosis of CHF secondary to SAH were screened for the study. Cox proportional hazards model was used to establish independent predictors of all-cause mortality.

Results: One hundred thirty patients were included; 74 (57%) were male. Thirty one (24%) patients died, 5 (4%) underwent heart transplantation, and 94 (72%) were alive at study end. Survival probability at 12, 24, 36, 48, and 60 months was 96%, 93%, 84%, 79%, and 76%, respectively. Age (Hazard Ratio=1,05, 95% Confidence Interval 95% 1,01 to 1,08, p value=0,01), left ventricular diastolic dimension (Hazard Ratio=1,08; 95% Confidence Interval 1,02 to 1,09; p value=0,003), and B-Blocker therapy (Hazard Ratio=0,41; 95% Confidence Interval 0,19 to 0,86; p value=0,02) were found to be independent predictors of mortality.

Conclusion: Age, left ventricular diastolic dimension and underuse of Beta-Blocker therapy were independent predictors of mortality for patients with CHF secondary to SAH in the population studied. (Arq Bras Cardiol 2012;98(1):76-83)

Keywords: Heart failure, systolic, hypertension, prognosis, ventricular remodeling, survival.

Introduction

It has long been recognized that systemic arterial hypertension is a precursor of chronic heart failure in up to 75% of cases[1], mainly when systolic arterial hypertension is present[2]. In underdeveloped countries, systemic arterial hypertension is the leading cause of chronic heart failure associated to coronary artery disease[3]. Chronic heart failure associated with systemic arterial hypertension may be due to left ventricular systolic dysfunction or left ventricular diastolic dysfunction[4]. Chronic left ventricular systolic dysfunction associated with systemic arterial hypertension is still one of the leading causes of chronic heart failure in underdeveloped countries[5].

The mechanism by which systemic arterial hypertension leads to chronic systolic heart failure is multifactorial, and the association with underlying coronary artery disease has been claimed to play a pivotal role[6]. Therefore, it is necessary to rule out concomitant coronary artery disease if one wishes to establish outcome and prognostic determinants for patients with chronic heart failure secondary to systemic arterial hypertension.

The clinical course of chronic systolic heart failure has been established in different types of cardiomyopathy, including Idiopathic Dilated Cardiomyopathy[7,8], Ischemic Cardiomyopathy[9], and Chagas' cardiomyopathy[10]. By contrast, little is known about outcome and predictors of mortality in patients with chronic systolic heart failure secondary to systemic arterial hypertension in the absence of coronary artery disease.

Three previous longitudinal studies[11-13] performed in the developed world have addressed this question. Another study carried out in Brazil also examined the clinical course of patients with systolic heart failure and systemic arterial hypertension; however, in that study no patient received B-Blocker therapy[14], an essential component of chronic systolic heart failure therapy in hypertensive patients[15]. Therefore, no previous study has evaluated the clinical course of chronic systolic heart failure secondary to systemic arterial hypertension in underdeveloped countries in the current era of heart failure therapy.

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Accordingly, this study aimed at determining noninvasive predictors of all-cause mortality and outcome of patients with chronic systolic heart failure secondary to systemic arterial hypertension in the absence of concomitant coronary artery disease in a single-center Brazilian cohort.

Methods

Patients

All patients routinely and prospectively followed at the Cardiomyopathy Clinic of our Institution from January 2000 to April 2008 diagnosed with chronic systolic heart failure secondary to systemic arterial hypertension were screened for the study. To be included in the study, patients had to have: 1) systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg on admission; 2) documented medical history of past systemic arterial hypertension if blood pressure was normal at presentation and patients were given antihypertensive medications; 3) previous history and/or treatment of systemic arterial hypertension determined at the time of presentation by investigators on the basis of patient interview when systemic arterial pressure was normal upon physical examination[13]; 4) left ventricular ejection fraction smaller than or equal to 55% on Doppler-echocardiography or < 50% on Radionuclide Ventriculography; 5) Obstructive Coronary Artery Disease ruled out by either coronary arteriogram or myocardial scintigraphy when patients refused or were unable to undergo the procedure; 6) absence of any other disease which could induce heart disease by itself.

Patients underwent history-taking and physical examination on admission, followed by standard laboratory tests, 12-lead electrocardiogram, and Dopplerechocardiogram. On admission, the severity of Heart Failure was graded according to the New York Heart Association Functional Class, and Systemic Arterial Pressure and Heart Rate were noted.

All patients were given furosemide to alleviate congestive symptoms. Digoxin was given to patients in the New York Heart Association class III or IV and to patients on New York Heart Association Class II with left ventricular ejection fraction < 30%. Spironolactone was given to patients in the New York Heart Association Functional Class III or IV. Angiotensin Converting Enzyme Inhibitors (Captopril: target dose, 75-150 mg/day; Enalapril: target dose: 20 mg/day) or Losartan (target dose: 50 mg/day) were given to all patients. Patients were also given carvedilol (target dose: 50 mg/day) or metoprolol succinate (target dose: 200 mg/day).

Until 2005, patients classified in New York Heart Association Class I/II received angiotensin converting enzyme inhibitors before Beta-Blocker therapy. From 2006 onwards, following the publication of CIBIS III trial[16], patients in New York Heart Association Class I/II were given Beta-Blocker therapy before angiotensin converting enzyme inhibitors/angiotensin receptor blocker. Patients in New York Heart Association class III/IV always received angiotensin converting enzyme inhibitors/angiotensin receptor blockers before B-Blockers.

Statistical Analysis

Parametric data are shown as mean ± standard deviation, whereas nonparametric data are presented as median (25% percentile, 75% percentile).

The Cox proportional hazards model was used to establish independent predictors of all-cause mortality. Explanatory variables known to be of prognostic importance for patients with chronic systolic heart failure were entered into the univariate model. The variables entered in this model were as follows: age, sex, New York Heart Association Functional Class, previous hospitalization, concomitant diabetes mellitus, heart rate, systolic blood pressure, diastolic blood pressure, need of inotropic support; atrial fibrillation, artificial pacemaker, Implantable Cardioverter-Defibrillator, left bundle branch block, right bundle branch block, left anterior fascicular block, low QRS complex, ventricular premature contractions on electrocardiography; left ventricular diastolic dimension, left ventricular systolic dimension, left ventricular ejection fraction, right ventricular dimension, and segmental wall motion abnormalities on echocardiography; sodium serum levels, potassium serum levels, creatinine serum levels, hemoglobin; use of diuretics, angiotensin converting enzyme inhibitors/ angiotensin receptor block, Beta-Blockers, spironolactone.

Variables with p value <0.05 on univariate analysis were entered into the multivariate stepwise analysis with a forward approach. Continuous variables significant in the univariate analysis were tested for correlation by the Spearman test. Among the correlated variables selected for the multivariate analysis, only that one with the highest Wald coefficient was included. C statistic was used to select the best cut-off point of a continuous variable to predict mortality by constructing a ROC curve. An area under the curve >0.50 was considered statistically significant.

The Kaplan-Meier survival curve was constructed to estimate survival over time. Patients were censored at time of transplantation, death or spontaneous withdrawal from the study. The log-rank sum test was used to compare survival according to dichotomization of variables with independent power to predict mortality. In all circumstances, differences at a p value < 0.05 were considered of statistical significance.

Results

One hundred thirty patients fulfilled the inclusion criteria and were entered in the investigation. Table 1 shows baseline characteristics of the study population, whereas Table 2 shows electrocardiographic, echocardiographic and laboratory tests data. Results of univariate and multivariate analysis by Cox regression model are given in Table 3. Mean follow-up was 39±26 months. Thirty one (24%) patients died, 5 (4%) underwent heart transplantation, and 94 (72%) were alive at study end. Survival probability at 12, 24, 36, 48, and 60 months was 96%,

Table 1 - Baseline characteristics of study population (n = 130)

Variable	Data
Age (years)	59 ± 13
Male	74 (57%)
NYHA Class I/II	92 (69%)
NYHA Class III/IV	40 (31%)
Previous Hospitalization	71 (55%)
Inotropic Support	15 (11%)
Heart Rate (beats per minute)	78 ± 14
Systolic Blood Pressure (mmHg)	130.8 ± 22.5
Diastolic Blood Pressure (mmHg)	83 ± 17,2
Diabetes Mellitus	34 (26%)
Digoxin (0.20 ± 0.01 mg/day)	80 (61%)
Amiodarone (188 ± 33.2 mg/day)	25 (19%)
ACEI/ARB	125 (96%)
Enalapril (19.9± 9.8 mg/day)	34 (26%)
Captopril (114.6 ± 43.3 mg/day)	58 (45%)
Losartan (59.4 ± 30 mg/day)	32 (25%)
Beta-Blockers	96 (74%)
Carvedilol (34.8 ± 19.6 mg/day)	73 (56%)
Metoprolol Succinate (144.3±65.4 mg/day)	23 (18%)
Diuretics	121 (91%)
Furosemide (75 ± 50.1 (mg/day)	108 (83%)
Spironolactone (26.6 ± 8.9 mg/day)	91 (70%)

NYHA - New York Heart Association; ACEI - Angiotensin Converting Enzyme Inhibitors; ARB - Angiotensin Receptor Blocker.

93%, 84%, 79%, and 76%, respectively, as shown in Figure 1. Figure 2 shows survival probability according to age. Figure 3 shows survival probability according to left ventricular diastolic dimension on echocardiography, and Figure 4 shows survival probability according to Beta-Blocker therapy.

Discussion

This study clearly shows that age, left ventricular diastolic dimension on echocardiography, and B-Blocker therapy are independent predictors of mortality of patients with chronic systolic heart failure secondary to systemic arterial hypertension in the absence of obstructive coronary artery disease.

Age was associated with mortality in this investigation. A similar result was observed in the study by Carvalho Frimm et al[14]. It is well known that age has been associated with left ventricular hypertrophy[17] and myocardial fibrosis[18] in patients with systemic arterial hypertension and left ventricular systolic dysfunction. This association leads to ventricular remodeling process over time, which is characterized by left ventricular dilatation and thinning of ventricular walls, as detected in the echocardiographic study performed in our patients. Not surprisingly, therefore, age was a prognostic determinant in our study.

Table 2 - Electrocardiographic, echocardiographic, and laboratory tests at baseline of the study population (n = 131)

Variable	Data
12-lead ECG parameters	
Left Bundle Branch Block	61 (47%)
Premature Ventricular Contractions	24 (18%)
Atrial Fibrillation	23 (18%)
Left Anterior Fascicular Block	20 (15%)
Pacemaker	5 (4%)
Right Bundle Branch Block	3 (2%)
Low voltage of QRS complex	2 (1%)
Echocardiographic parameters	
Left ventricular diastolic dimension (mm)	67.4 ± 10.1
Left ventricular systolic dimension (mm)	55.6 ± 10.6
Right ventricular (mm)	22.9 ± 6.3
Left ventricular ejection fraction (%)	35.7 ± 9.7
Segmental wall motion abnormalities	19 (15%)
Laboratory tests	
Na (mEq/L)	142.3 ± 4.2
K (mEq/L)	4.4 ± 0.5
Creatinine (mg]dL)	1.3 ± 0.6

Table 3 - Univariate and Multivariate analysis by Cox proportional hazards model

Variable	Hazard Ratio	95% CI	p value
		Univariate	
Age	1.04	1.01 to 1.08	0.005
LVDD	1.05	1.01 to 1.08	0.01
LVSD	1.04	1.01 to 1.08	0.02
Beta-Blocker	0.36	0.17 to 0.71	0.004
NYHA	2.35	1.07 to 5.14	0.03
		Multivariate	
age	1.05	1.01 to 1.08	0.01
LVDD	1.06	1.02 to 1.09	0.003
B-Blocker	0.41	0.19 to 0.86	0.02

LVDD - Left ventricular diastolic dimension; LVSD - Left ventricular systolic dimension; NYHA - New York Heart Association class.

Left ventricular diastolic dimension was another independent predictor of mortality in this investigation. This finding has not previously been reported in the setting of chronic systolic heart failure secondary to systemic arterial hypertension. This anatomic abnormality is thought to represent the final pathway of the left ventricular remodeling process and can negatively impact the survival of patients with this condition. In fact, left

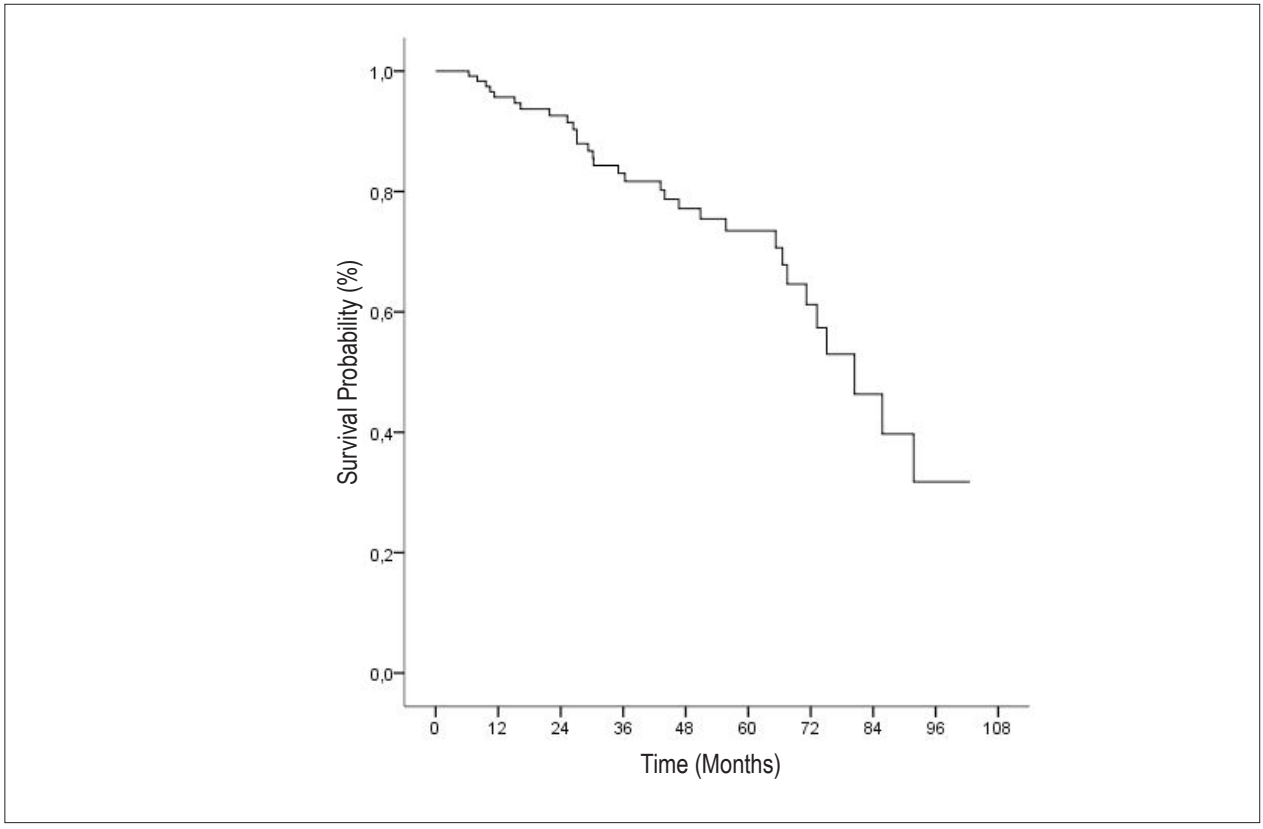

Figure 1 - *Survival probability for a cohort of patients with chronic systolic heart failure secondary to systemic arterial hypertension in the absence of concomitant obstructive coronary artery disease (n = 130).*

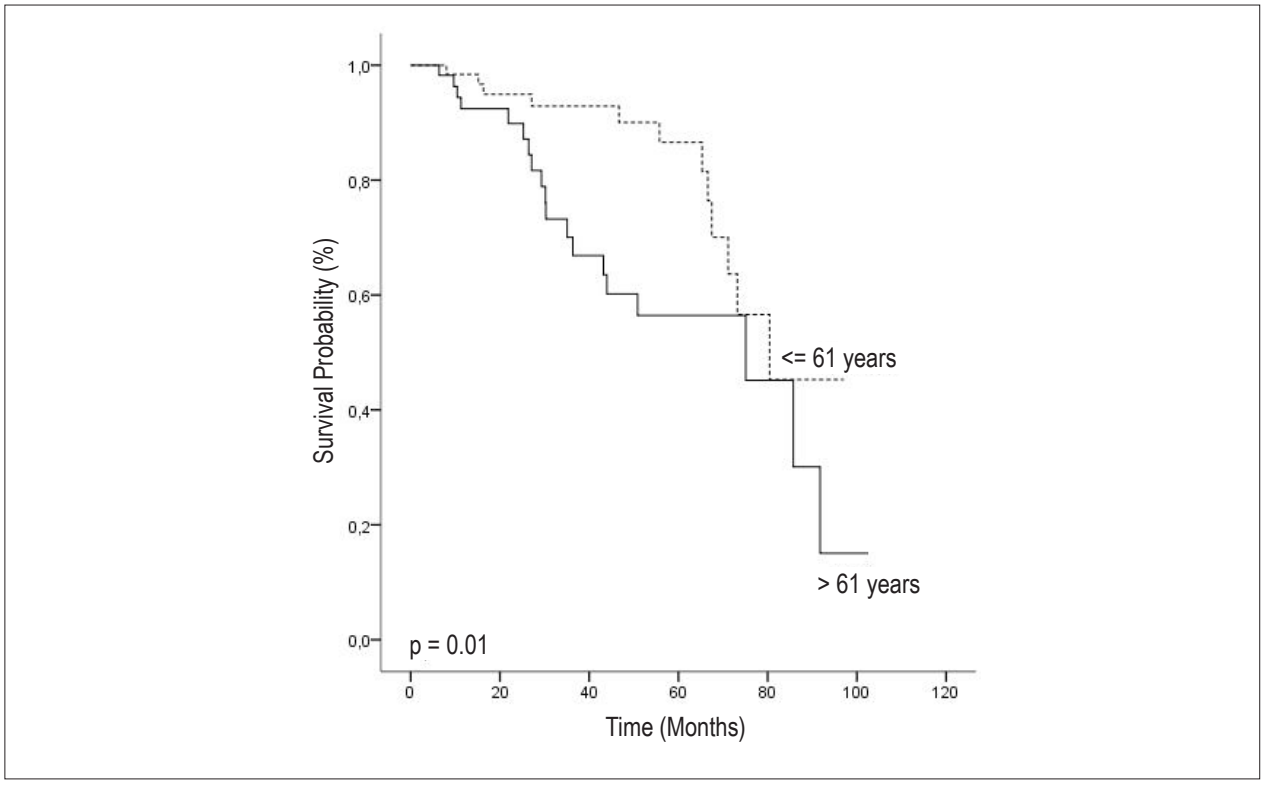

Figure 2 - *Probability of survival according to patients' age dichotomized according to the best cutoff point obtained in a ROC curve.*

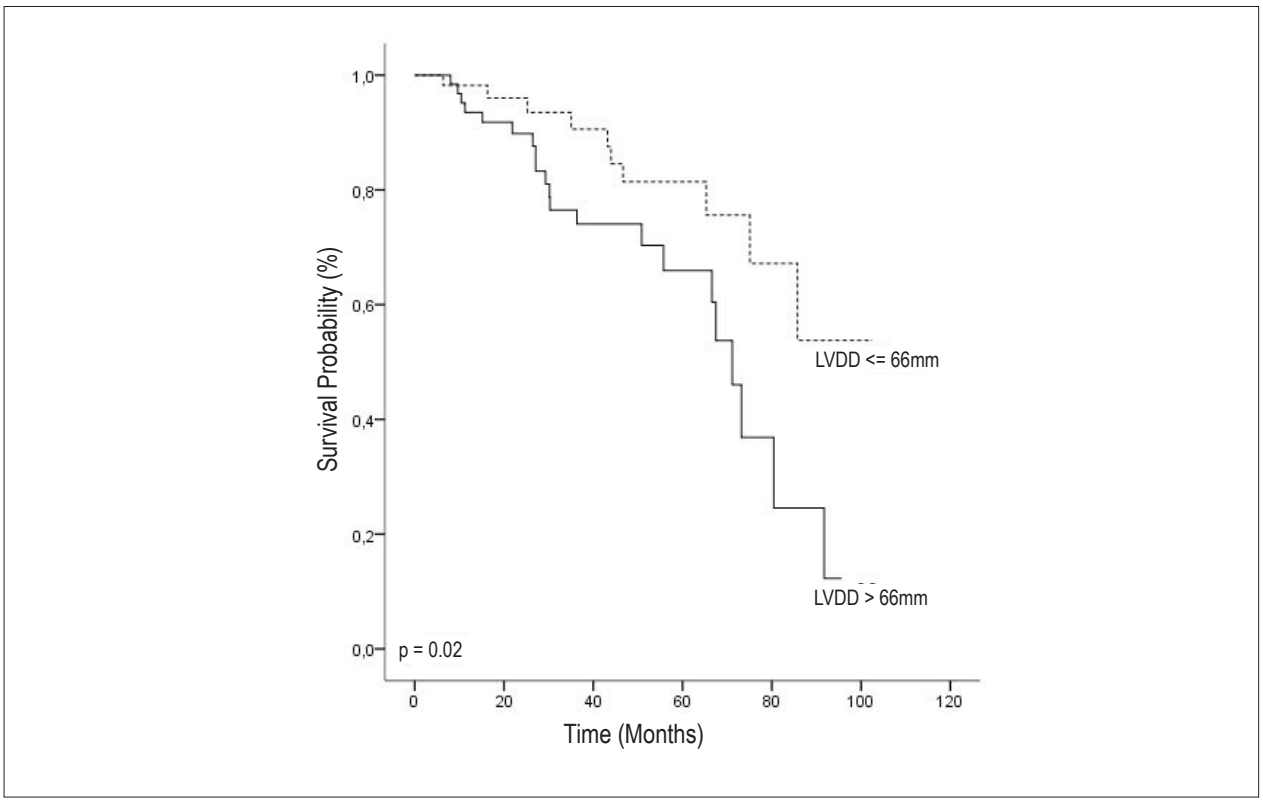

Figure 3 - *Probability of survival according to left ventricular diastolic dimension dichotomized according to the best cutoff point obtained in a ROC curve.*

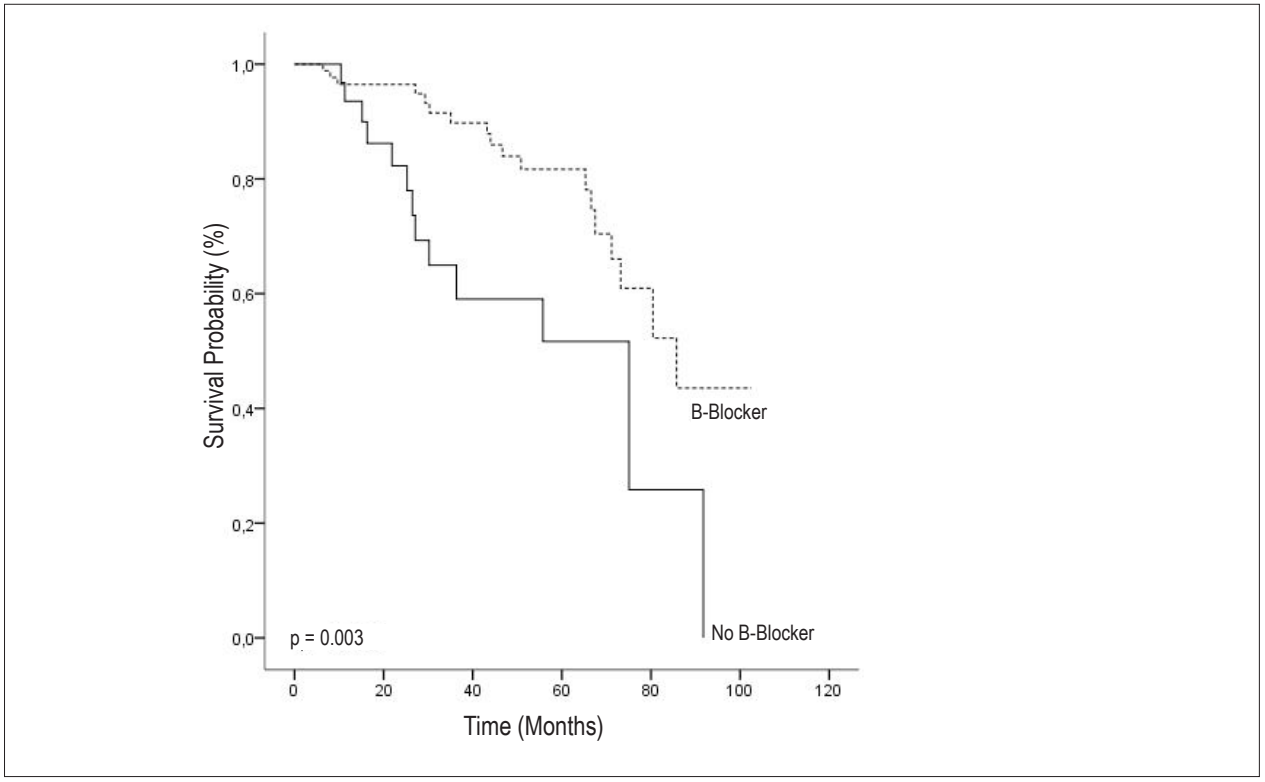

Figure 4 - *Probability of survival according to Beta-Blocker therapy.*

ventricular dilatation, as observed in our investigation, may predispose patients to both sudden cardiac death (perhaps due to inadequate activation of the Bezold-Jarisch reflex), as well as irreversible myocardial pump failure secondary to increased oxygen consumption rate leading to ischemia and cell death[19].

Another interesting finding of this work was the recognition of underuse of Beta-Blocker therapy as an independent predictor of mortality. Observational studies are not adequate for establishing association of drugs with mortality, such as randomized trials, due to the inherent appearance of selection and detection biases and risk overestimation. However, the results reported here are in accordance with those reported by Herlitz et al[15], who specifically studied a subgroup of patients with chronic systolic heart failure secondary to systemic arterial hypertension enrolled in a randomized, double-blinded, placebo-controlled clinical trial (MERIT trial).

It is necessary to point out that the independent predictors of mortality detected in our study are different from those reported by others. Sanchez et al[11] observed that only poor control of blood pressure was an independent predictor of death or hospitalization for heart failure. Our study is different from that of Sanchez et al[11] in terms of end-point and the fact that our patients had normal pressure values on average at admission, which may explain the differences observed in both studies. Carvalho Frimm et al[14] observed that left ventricular ejection fraction was an independent predictor of mortality. However, it must be remembered that left ventricular ejection fraction correlates inversely with left ventricular diastolic dimension. In practice, therefore, both abnormalities have the same prognostic significance.

A key point in this investigation is the low mortality rate of patients with chronic systolic heart failure secondary to systemic arterial hypertension. Sanchez et al[11] followed 49 consecutive patients with chronic systolic heart failure secondary to systemic arterial hypertension with a median follow-up of 45 months. Five (10%) patients died. Survival probability at 4-year follow-up was 84%. Survival probability in our investigation was similar to that reported by Sanches et al[11]. It is conceivable that the similarity of the proper medical treatment has determined the good prognosis observed in both studies.

Szygufa-Jurkiewicz et al[12] studied 132 hypertensive patients with chronic systolic heart failure during a 3-year follow-up. All patients received modern therapy for chronic systolic heart failure. Twenty four (18%) patients died during the study period. Survival probability was about 50% at a 3-year follow-up. Compared with that study, our patients' survival probability at 3-year follow-up was much higher (82%). We suggest that the high proportion of patients with depressive symptoms observed in the study by Szygufa-Jurkiewicz et al[12] may explain this disparity.

Felker et al[13] reported the results of 49 patients with chronic systolic heart failure due to hypertensive cardiomyopathy among 1230 patients with different types of cardiomyopathy over a follow-up of 15 years. Survival probability at 5-year follow-up was about 75%, similar to that found in our study. The reasons for the similarity observed in the results of two studies are uncertain.

Carvalho Frimm et al[14] enrolled 90 consecutive patients in a mean follow up of 4.3±1.6 years. Twenty four patients (27%) died during the study period. Compared to our study, Carvalho Frimm et al[14] patients had a higher mortality rate. It is conceivable that the determinant of worse prognosis observed in the study by Carvalho Frimm et al[14] was the lack of B-blocker therapy in any patient in that study.

It is interesting to note that diabetes mellitus had no impact on outcome of patients with chronic systolic heart failure secondary to systemic arterial hypertension. Diabetes mellitus has been found to be a risk factor for chronic heart failure in patients with systemic arterial hypertension. In fact, Levy et al[17] studied a cohort of 5143 patients in a population-based setting during a mean follow-up of 14 years and showed that the presence of diabetes mellitus increased the risk of heart failure appearance in men (hazard ratio=1.78, 95% confidence interval 1.23 to 2.59) and women (hazard ratio=3.57, 95% confidence 2.59 to 4.94) with systemic arterial hypertension. Our study suggests that, following the appearance of chronic systolic heart failure, diabetes mellitus has no impact on outcome of patients with this condition.

Several mechanisms have been proposed to explain the transition of hypertrophy, a hallmark morphological sign of systemic arterial hypertension, to chronic hypertensive systolic dysfunction. Microangiopathy[20], imbalanced mass to volume ratio and stress[21], impairment in the coronary vasodilator reserve[22] and oxidative stress[23] have all been implicated. In our study, however, the underlying mechanism leading to chronic systolic dysfunction associated with chronic heart failure in our patients remains unclear because neither endomyocardial biopsies nor post-mortem examination have routinely been performed.

The data obtained in this investigation should be received with caution because it is a prospective longitudinal cohort study improper to evaluate the impact of treatment on outcome. However, it must be pointed out that data were obtained from a cohort of hypertensives with chronic heart failure with no obstructive coronary artery disease as large as the largest previously reported.

In conclusion, age, left ventricular diastolic dimension and underuse of Beta-Blocker therapy are independent predictors of mortality for patients with chronic systolic heart failure secondary to systemic arterial hypertension. -

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Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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