Role of BNP Levels on the Prognosis of Decompensated Advanced Heart Failure

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Abstract

Background: Heart failure (HF) is a condition with poor outcome, especially in advanced cases. Determination of B-type natriuretic peptide (BNP) levels is useful in the diagnosis of cardiac decompensation and has also been proving useful in the prognostic evaluation.

Objectives: To verify whether BNP levels are able to identify patients with a poorer outcome and whether it is an independent prognostic factor considering age, gender, cardiac and renal functions, as well as the cause of heart disease.

Methods: 189 patients in functional class III/IV advanced HF were studied. All had systolic dysfunction and had their BNP levels determined during hospitalization. Variables related to mortality were studied using univariate and multivariate analyses.

Results: BNP levels were higher in patients who died in the first year of follow-up (1,861.9 versus 1,408.1 pg/dL; p = 0.044) and in chagasic patients (1,985 versus 1,452 pg/mL; p = 0.001); the latter had a higher mortality rate in the first year of follow-up (56% versus 35%; p = 0.010). The ROC curve analysis showed that the BNP level of 1,400 pg/mL was the best predictor of events; high levels were associated with lower LVEF (0.23 versus 0.28; p = 0.002) and more severe degree of renal dysfunction (mean urea 92 versus 74.5 mg/dL; p = 0.002).

Conclusion: In advanced HF, high BNP levels identified patients at higher risk of a poorer outcome. Chagasic patients showed higher BNP levels than those with heart diseases of other causes, and have poorer prognosis (Arq Bras Cardiol. 2013;100(3):281-287).

Keywords: Heart Failure; Natriuretic Peptides; Prognosis; Survivorship (Public Health).

Introduction

HF is a condition known to have a poor prognosis, with significant reduction in the quality of life, increased hospitalization rates, and reduced life expectancy, especially in advanced cases[1].

Innumerable clinical and laboratorial data help identify patients with a potentially poorer outcome[2]. BNP determination is useful in the diagnosis of cardiac decompensation and has also been proven useful in the prognostic evaluation; in addition, it is a non-subjective variable[3-6]. The higher the peptide levels, the worse the patient's outcome, the longer the length of hospital stay, and the higher the mortality rate[2,3]. However, BNP levels are under the influence not only of the patient's functional status, but also of factors such as age, gender, associated comorbidities, and obesity. There are no studies available on the relationship between the cause of HF and BNP levels.

In this study, we sought to verify whether BNP levels can identify a poorer prognosis among patients with advanced HF, and whether BNP is an independent prognostic factor considering age, gender, cardiac function, renal function, and cause of heart disease.

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Methods

A total of 189 patients admitted to a tertiary care hospital in Sao Paulo, all with advanced HF, systolic dysfunction with ejection fraction < 40%, and in functional class III/IV were prospectively studied. These patients came from the InCor emergency department and were transferred when they could not be compensated after the first measures taken in the emergency department, or when they required inotropic support for compensation. Selection criteria for hospitalization were severe cases with important clinical manifestations.

All patients underwent clinical and laboratory evaluation, including complete blood count and determination of urea, creatinine, BNP, sodium and potassium levels.

Plasma concentration of B-type natriuretic peptide (BNP) was obtained by two-site sandwich immunoassay using direct chemiluminescent technology which uses constant amounts of two monoclonal antibodies. The kit and automated equipment used were ADVIA Centaur® (Siemens Medical Solutions Diagnostic, Los Angeles, CA, USA). Results are expressed as pg/mL.

As regards the cause of heart disease, the patients were divided into three groups: chagasic, ischemic and non-ischemic heart disease. The diagnosis of chagasic heart disease was confirmed by the presence of positive serologic tests; ischemic heart disease was confirmed by a history of infarction, angina or by coronary cineangiography. In the absence of these characteristics, the patient was considered as having a non-ischemic heart disease.

The patients were followed-up after admission as regards mortality during hospitalization and for one year after discharge. To date, they are still being followed up.

For analysis purposes, we compared the variables of patients who died in-hospital with those of who did not; of patients who died within the first year of follow-up with those patients who did not; and of chagasic with those of non-chagasic patients.

The ROC curve identified the BNP value which best predicted events in patients; the clinical characteristics of patients with values above or below that level were compared.

In the statistical analysis, continuous variables were expressed as mean ± standard deviation, and categorical variables as frequencies and percentages. Patients' characteristics were compared in relation to mortality at the end of the follow-up period. Continuous variables were analyzed using the Mann-Whitney U test, and categorical variables, using the chi-square test or Fisher's exact test. Predictors of mortality were determined by univariate and multivariate analyses, using the Cox proportional hazards method. Based on the follow-up data, the survival curve was constructed using the Kaplan-Meier method. The p values reported are two-tailed, and the significance level was set at < 0.05.

Results

Table 1 shows the main characteristics of the study population; the mean age was 58.8 years, most were males (57.7%), with a mean LVEF of 0.26, and mean BNP level of 1,591.6 pg/mL; 26.5% of patients were chagasic, 25.9% had ischemic heart disease and 47.6% had non-ischemic heart disease. Throughout the study, 30 (15.9%) patients died in hospitalization and 98 (51.9%) within the first year of follow-up.

No significant differences were observed in the clinical and laboratory variables studied among patients who died or not in hospital.

Patients who died in hospital more frequently required vasoactive drugs (80.0% versus 57.2%; p = 0.026), which characterizes them as a group of more severely ill patients.

Table 1 – Population characteristics

Characteristics	n = 189 patients	Variation (min-max)
Age (years)	58.83 ± 14.37	17–94
Gender: male/fem. - n (%)	109 (57.7)/80 (42.3)	
Cause of HF - n (%):		
Chagasic	50 (26.5)	
Ischemic	49 (25.9)	
Non-ischemic (non-chagasic)	90 (47.6)	
Vasoactive drugs - n (%)	115 (73.7)	
LVEF (%)	26.3 ± 9.6	
Baseline urea (mg/dL)	82.2 ± 43.6	
Baseline creatinine (mg/dL)	1.6 ± 0.7	
BNP (pg/dL)	1,591.6 ± 1,186.0	
In-hospital death - n (%)	30 (15.9)	
Follow-up death - 1 year - n (%)	77 (40.7)	
1-year follow-up (days)	213.2 ± 143.9	4.0–365.0

HF: Heart failure; LVEF: Left ventricular ejection fraction; BNP: B-type natriuretic peptide.

Patients who died within the first year of follow-up were older, had higher BNP levels (1,861.9 versus 1,408.1 pg/dL; p = 0.044), and higher urea levels (94.4 versus 74.0 mg/dL; p = 0.001). Mortality was higher among chagasic patients and lower among non-ischemic patients (Table 2).

When data from chagasic patients were compared with those of non-chagasic patients, we observed that a higher percentage of chagasic patients required vasoactive drugs to compensate; and that ejection fraction was lower (26.6% versus 27.3%, p = 0.019), and BNP levels were higher (1,985.0 versus 1,452.9 pg/mL; p = 0.001) among chagasic patients. These patients had a worse outcome in the first year of follow-up (mortality of 56% versus 35.3%; p = 0.010); however, in-hospital mortality was not different among chagasic and non-chagasic patients (Table 3).

According to the ROC curve, the BNP level of 1,400 pg / mL was the best predictor of events; high BNP levels were associated with lower LVEF (0.23 versus 0.28; p = 0.002) and with a more severe degree of renal dysfunction (mean urea of 92 versus 74.5 mg/dL; p = 0.002) (Table 4).

Table 2 – Comparison of the characteristics in relation to 1-year death

	Death in 1-year follow-up		
Characteristics	Yes (n = 77)	No (n = 112)	p
Age (years)	61.9± 13.8	56.7 ± 14.4	0.015
Male gender - n (%)	40 (51.9)	69 (61.6)	0.187
Cause of HF - n (%):			
Chagasic	28 (36.4)	22 (19.6)	0.010
Ischemic	20 (26.0)	29 (25.9)	0.990
Non-ischemic (non-chagasic)	29 (37.7)	61 (54.5)	0.023
Vasoactive drugs - n (%)	52 (67.5)	63 (56.3)	0.075
LVEF (%)	26.0 ± 7.7	26.6 ± 10.7	0.792
Baseline urea (mg/dL)	94.4 ± 48.5	74.0 ± 38.0	0.001
Baseline creatinine (mg/dL)	1.7 ± 0.8	1.6 ± 0.7	0.062
BNP (pg/dL)	1,861.9 ± 1,265.6	1,408.1 ± 1,012.7	0.044

HF: Heart failure; LVEF: left ventricular ejection fraction; BNP: B-type natriuretic peptide.

Table 3 – Comparison between the characteristics of chagasic and non-chagasic patients

	Chagasic cause		
Characteristics	Yes (n = 50)	No (n = 139)	p
Age (years)	55.4 ± 12.9	60.1 ± 14.7	0.056
Male gender -n (%)	30 (60.0)	79 (56.8)	0.698
Vasoactive drugs - n (%)	40 (80.0)	75 (54.0)	0.002
LVEF (%)	26.6 ± 7.2	27.3 ± 10.1	0.019
Baseline urea (mg/dL)	81.4 ± 43.1	82.5 ± 43.9	0.945
Baseline creatinine (mg/dL)	1.6 ± 0.7	1.6 ± 0.7	0.709
BNP (pg/dL)	1,985.0 ± 1,149.5	1,452.9 ± 1,171.3	0.001
In-hospital death	10 (20.0)	20 (14.4)	0.352
1-year death	28 (56.0)	49 (35.3)	0.010

LVEF: left ventricular ejection fraction; BNP: type-B natriuretic peptide.

Gender and age did not influence BNP levels.

BNP levels ≥ 1,400 pg/mL were also associated with a higher probability of dying in hospital and during follow-up, and were more common among chagasic patients (Table 4).

In the multivariate analysis (Table 5), chagasic heart disease, BNP levels ≥1,400 pg/dL, and age ≥ 65 years were independent predictors of increased death risk in one-year follow-up in patients hospitalized for decompensated HF.

Figure 1 shows the ROC curve with the identification of the best BNP value to predict events.

Figure 2 shows the survival curves using the Kaplan-Meier method in the first year of follow-up; we can observe that chagasic patients had a poorer outcome than those with heart diseases of other causes. Patients with non-ischemic heart diseases had the best outcome.

Figure 3 shows Kaplan-Meier survival curves in the first year of follow-up for patients with BNP values above or below 1,400 pg/mL; those with higher levels had a poorer outcome than those with lower levels.

Table 4 – Comparison between the patients' characteristics in relation to BNP values ≥ 1,400 and <1,400 pg/dL

	BNP		
Characteristics	≥1,400 pg/dL (n = 78)	<1,400 pg/dL (n = 110)	p
Age (years)	58.7 ± 15.0	58.9 ± 14.0	0.901
Male gender - n (%)	44 (56.4)	65 (59.1)	0.714
Cause of HF - n (%):			
Chagasic	29 (37.2)	20 (18.2)	0.003
Ischemic	15 (19.2)	34 (30.9)	0.072
Non-ischemic (non-chagasic)	34 (43.6)	56 (50.9)	0.322
Vasoactive drugs - n (%)	57 (73.1)	57 (51.8)	0.005
LVEF (%)	23.5 ± 6.6	28.3 ± 10.8	0.002
Baseline urea (mg/dL)	92.0 ± 45.4	74.5 ± 40.6	0.002
Baseline creatinine (mg/dL)	1.7 ± 0.7	1.6 ± 0.7	0.102
BNP (pg/dL)	2,734.0 ± 995.4	781.5 ± 341.8	<0.001
In-hospital death	17 (21.8)	12 (10.9)	0.042
1-year death	40 (51.3)	36 (32.7)	0.011

HF: Heart failure; LVEF: left ventricular ejection fraction; BNP: type-B natriuretic peptide.

Table 5 – Univariate and multivariate regression analyses of 1-year death predictors using the Cox proportional hazards method

Univariate analysis	**Hazard rate**	**95% CI**	**p**
Age ≥ 65 years	2.27	1.45–3.56	<0.001
Male gender	0.71	0.45–1.11	0.128
Cause of HF:			
Chagasic	1.87	1.78–2.98	0.008
Ischemic	1.05	0.63–1.74	0.862
Non-ischemic (non-chagasic)	0.57	0.36–0.90	0.017
Use of vasoactive drugs	1.64	0.88–3.08	0.122
LVEF ≤ 25%	1.06	0.68–1.66	0.803
Creatinine ≥ 1.5 mg/dL	1.47	0.92–2.35	0.108
BNP ≥1400 pg/dL	1.91	1.22–3.00	0.005
Multivariate analysis			
Chagasic cause	1.87	1.15–3.03	0.012
BNP ≥1400 pg/dL	1.89	1.19–3.00	0.007
Age ≥ 65 years	2.71	1.70–4.30	<0.001

HF: Heart failure; LVEF: left ventricular ejection fraction; BNP: type-B natriuretic peptide.

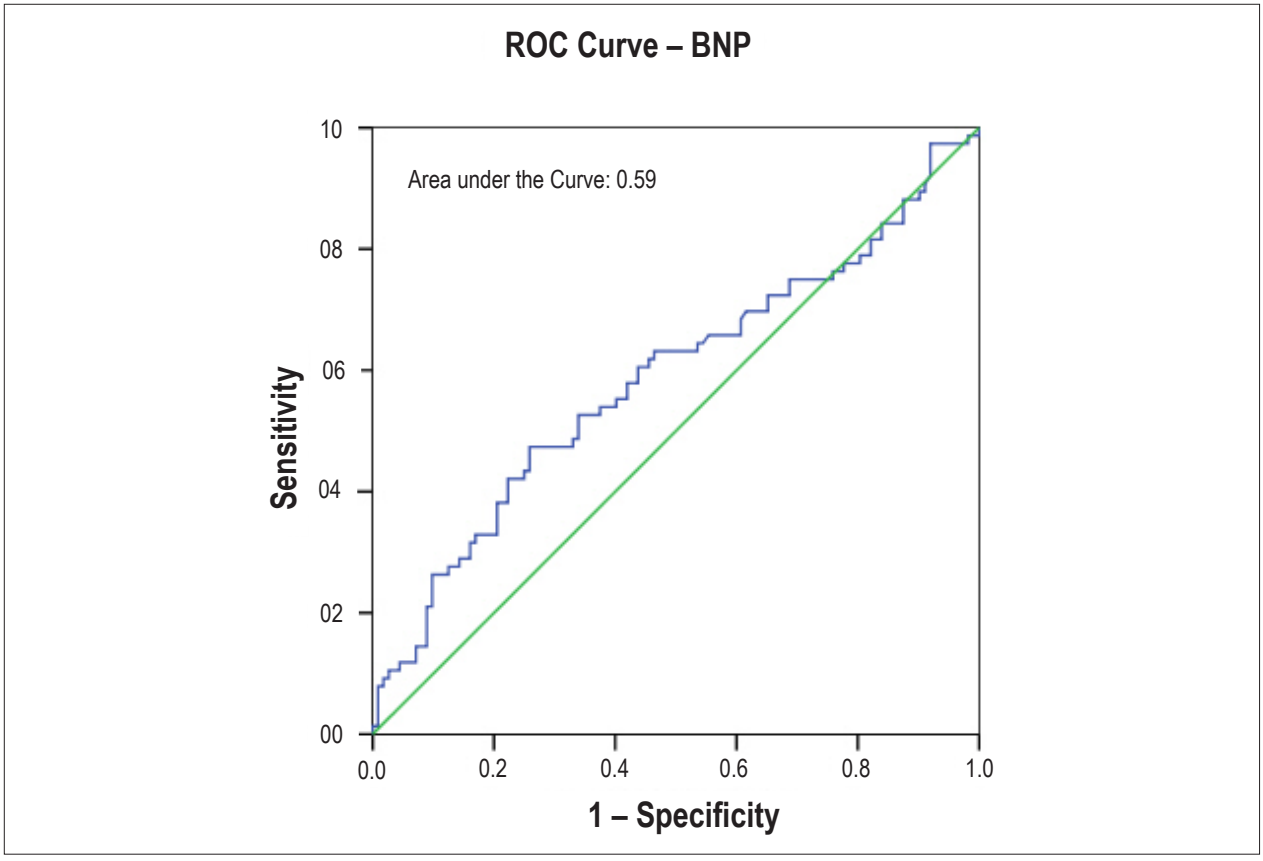

Figure 1 – *ROC curve according to BNP values for 1-year death prediction. The area under the curve was 0.59. The cut-off point for BNP for 1-year death prediction was estimated at 1,400 pg/dL with 53% sensitivity and 69% specificity.*

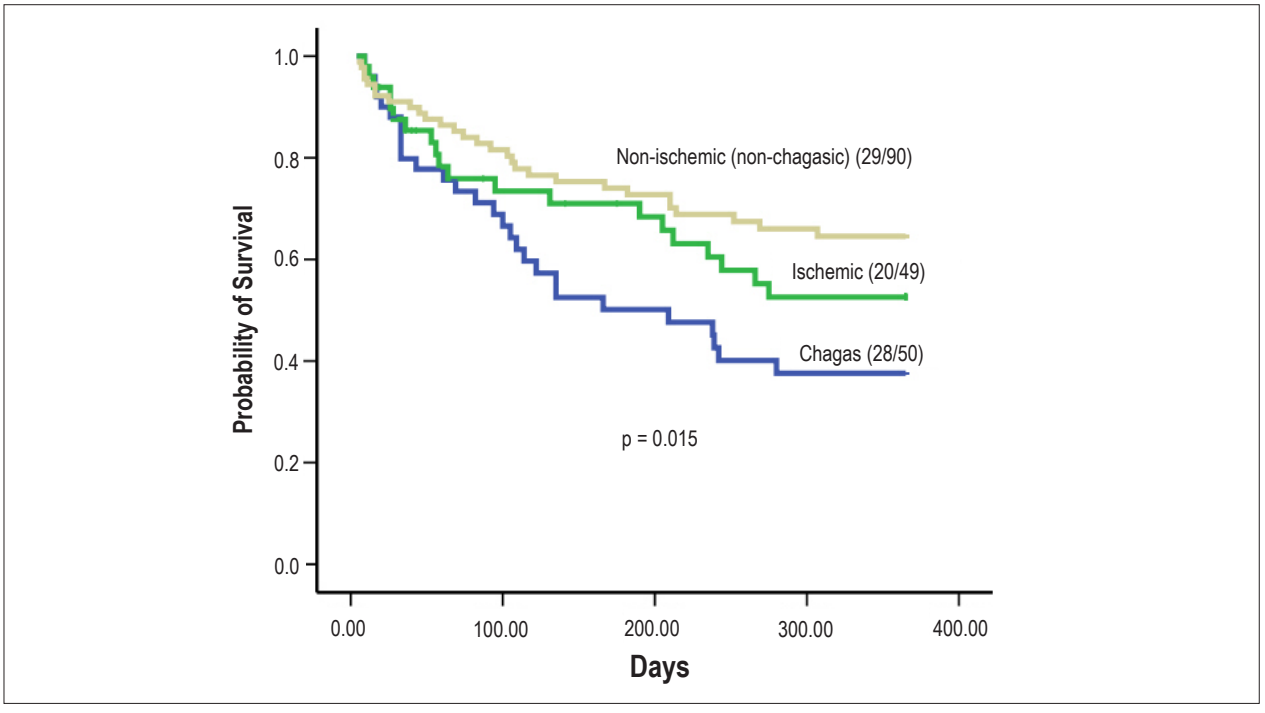

Figure 2 – *Survival curve using the stratified Kaplan-Meier method according to the cause of heart failure. Chagasic patients had poorer survival in the 1-year follow-up (37.6%), followed by ischemic (52.6%) and non-ischemic patients (64.5%).*

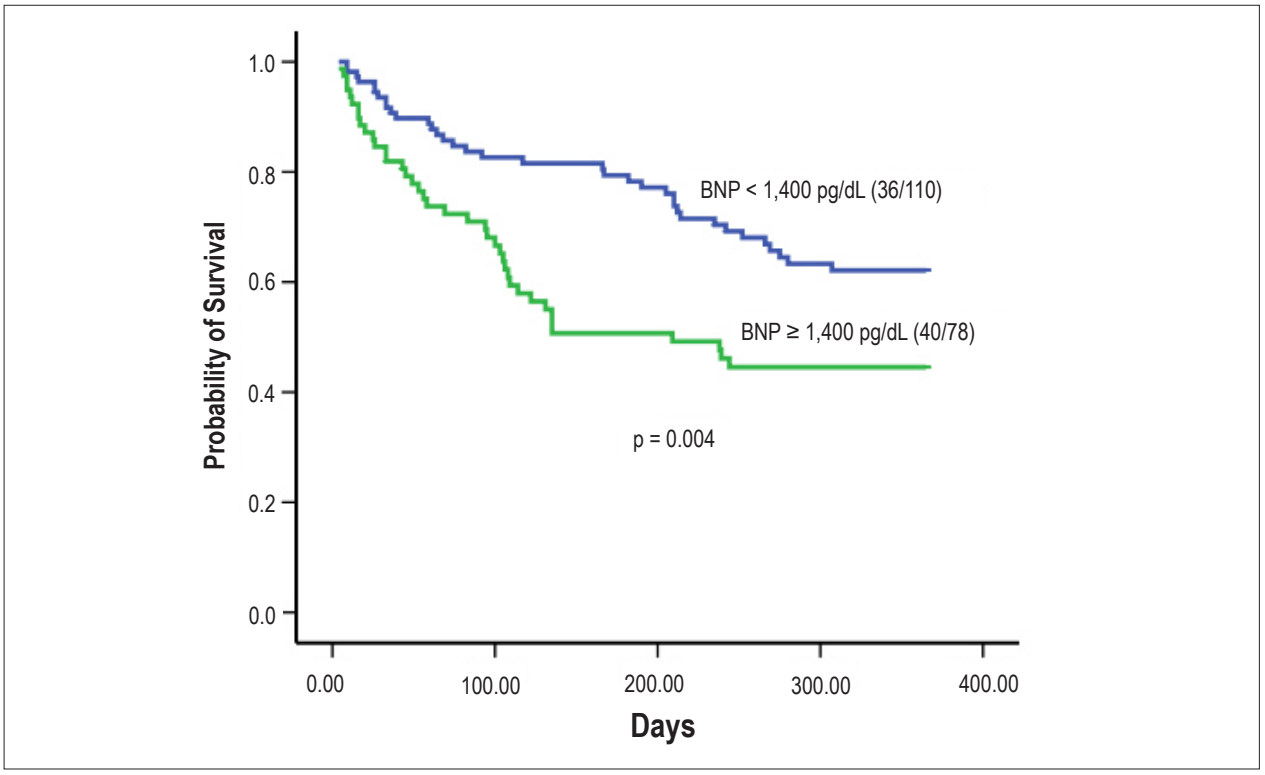

Figure 3 – *Survival curve using the Kaplan-Meier method in relation to the BNP level: patients with BNP ≥ 1,400 pg/dL showed worse survival in relation to patients with BNP <1,400 pg/dL (44.5% versus 62.1%, p = 0.004).*

Comments

Data show that BNP values help in the prognostic stratification of patients with decompensated advanced HF. Patients with BNP levels ≥1,400 pg/mL during hospitalization had higher mortality rates either in hospital or within the first year of follow-up. Among the variables studied, BNP level was the best predictor of events. High BNP levels were associated with the need for treatment with inotropic drugs, worse ejection fraction and poorer renal function.

Chagasic patients had higher BNP levels, a poorer outcome, and higher mortality than non-chagasic patients.

The outcome of patients with decompensated HF depends on innumerable clinical variables such as the form of presentation, patient's characteristics, severity of disease, and the treatment the patient had been receiving and will receive during and after cardiac decompensation[1,7-9]. Patients with cardiogenic shock, renal failure, Chagas disease, severe myocardial impairment, and those who had been poorly advised comprise the group with a worse outcome; these characteristics are common in the population admitted to our hospital[1,2]. More severe cardiac impairment is a possible reason for the relatively high mortality observed among our study population[1].

Together with clinical markers, BNP levels have proven an important non-subjective tool in the identification of more severely ill patients[4,5]. BNP levels increase when the patient decompensates, due to ventricular distension; the higher the levels the higher the ventricular distension and, therefore, the more significant the clinical manifestation and severity of decompensation[3]. Several studies have shown that high BNP levels are able to identify patients with a worse prognosis[3-6]. Our study corroborates these findings. This study differs from most studies published because it analyses a population with extremely advanced HF comprised mostly of patients who required vasoactive drugs to compensate and who also presented with renal dysfunction, which is another important prognostic marker in decompensated HF.

High BNP levels are one more finding that permits the characterization of this population as with having extremely advanced HF, because the levels found are much higher than those described in studies with BNP determination in general. We found mean values of 1,500 pg/mL. In the pioneering Maisel et al's study[3], the mean BNP value among those diagnosed with HF was 675 pg/mL. In the stratification according to the NYHA functional class III or IV, the mean value described was 900 pg/mL, a value much lower than those found in our study population. In the Val-HeFT study on more than 4,300 patients with chronic HF, the mean BNP values were 97 pg/mL; in patients in functional class III/IV, it was 244 pg/mL[10]. In the ADHERE registry, the mean BNP value in the 48,629 patients hospitalized for decompensated HF in the USA was 840 pg/mL[11]; similar to our findings, higher BNP levels were associated with a higher mortality rate[11].

Patients with high BNP levels had more compromised ejection fraction, thus showing the relationship between these higher values and more severe cardiac impairment. Urea levels were also higher, which is usually associated with more

severe cardiac involvement and cardiac decompensation, thus identifying patients with a poorer prognosis[1,2]. Undoubtedly, more severe impairment of the renal function is one of the factors that may contribute to higher BNP levels because the renal function is frequently associated with more congestion and, therefore, with more ventricular wall stretching and higher release of the peptide[12].

Regardless of the pathophysiology, high BNP levels were important prognostic markers in this population with advanced HF, and were the best predictor of events among the variables studied. Our study found a correlation between BNP values above 1,400 pg/mL and patients who will require a more careful management, so that it is fundamental to optimize treatment in an attempt to modify the natural history of the disease[1,7-9].

This study proves one more time that chagasic patients have a poorer outcome, with a 1.87-times higher death risk than non-chagasic patients[13,14] (Figure 2). The worse outcome of chagasic individuals probably results from more severe cardiac and systemic involvement, findings that are common in this disease[14]. In the group studied, we could observe that, despite being younger, chagasic patients more frequently required vasoactive drugs to compensate and had lower ejection fraction, thus characterizing that chagasic individuals show more severe cardiac involvement and a worse clinical status and, consequently, showed more difficulty to respond to the usual treatment without the combination of vasoactive drugs; these findings are related to a poorer prognosis. Given its temporal profile, Chagas disease begins many years prior to the cardiac decompensation and the cardiac involvement progresses slowly, thus permitting the heart and body as a whole to optimize all the compensatory mechanisms, which keeps the patients asymptomatic for years. However, when the patients decompensate, they usually are clinically more refractory to treatment because all their mechanisms are already optimized and no longer able to keep them compensated. In agreement with the greater severity of disease and worse outcome of the population of chagasic patients in this study, their BNP levels were higher than those of non-chagasic patients.

In advanced HF, higher BNP levels identify patients who will potentially have a poorer outcome. Patients hospitalized with BNP values above 1,400 pg/mL comprise a group of very severely ill individuals who have a two-fold higher chance of in-hospital death, and a 1.56-times higher chance of dying within the first year of follow-up in comparison to those with lower BNP levels. BNP level was an excellent predictor of prognosis, with the advantage of not being based on subjective data, in addition to being easily determined. When values ≥1,400 pg/mL are found, the possibility of optimizing treatment more intensively should be considered, since these patients are those with a higher potential for a poor outcome, and only a well-planned treatment may modify this natural history.

Author contributions

Conception and design of the research: Pereira-Barretto AC, Ramires JAF; Acquisition of data: Pereira-Barretto AC, Cardoso JN, Ochiai ME, Lima MV, Curiati MC, Scipioni AR; Analysis and interpretation of the data: Pereira-Barretto AC, Del Carlo CH, Cardoso JN, Ochiai ME, Curiati MC; Statistical analysis: Del Carlo CH; Writing of the manuscript: Pereira-Barretto AC; Critical revision of the manuscript for intellectual content: Pereira-Barretto AC, Del Carlo CH, Cardoso JN, Ochiai ME, Lima MV, Curiati MC, Ramires JAF.

Potential Conflict of Interest

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

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Study Association

This study is not associated with any post-graduation program.

References

1. Pereira-Barretto AC, Del Carlo CH, Cardoso JN, Morgado PC, Munhoz RT, Eid MO, et al. Re-hospitalizações e morte por insuficiência cardíaca: índices ainda alarmantes. Arq Bras Cardiol. 2008;91(5):335-41.
2. Pocock SJ, Wang D, Pfeffer MA, Yusuf S, McMurray JJ, Swedberg KB, et al; CHARM investigators. Predictors of mortality and morbidity in patients with chronic heart failure. Eur Heart J. 2006;27(1):65-75.
3. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, et al; Breathing Not Properly Multinational Study Investigators. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med. 2002;347(3):161-7.
4. Mueller C, Scholer H, Laile-Kilian K, Martina B, Schindler C, Buser P, et al. Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. N Engl J Med. 2004;350(7):647-54.
5. Verdiani V, Nozzoli C, Bacci F, Cecchin A, Rutili MS, Palodini S, et al. Pre-discharge B-type natriuretic peptide predicts early recurrence of decompensated heart failure in patients admitted to a general medical unit. Eur J Heart Fail. 2005;7(4):566-71.
6. Bettencourt P, Ferreira S, Azevedo A, Ferreira A. Preliminary data on the potential usefulness of B-type natriuretic peptide outcome after hospital discharge in patients with heart failure. Am J Med. 2002;113(3):215-9.
7. Bocchi EA, Marcondes-Braga FG, Ayub-Ferreira SM, Rohde LE, Oliveira WA, Almeida DR, et al.; Sociedade Brasileira de Cardiologia. III Diretriz brasileira de insuficiência cardíaca crônica. Arq Bras Cardiol. 2009;93(1 supl.1):1-71.
8. Krum H, Teerlink JR. Medical therapy for chronic heart failure. Lancet. 2011;378(9792):713-21.
9. Gislason GH, Rasmussen JN, Abuldstrom SZ, Schramm TK, Hansen ML, Bush P, et al. Persistent use of evidence based pharmacotherapy in heart failure is associated with improve outcomes. Circulation. 2007;116(7):737-44.
10. Anand IS, Fisher LD, Chiang YT, Latini R, Masson S, Maggioni AP, et al; Val-HeFT investigators. Changes in brain natriuretic peptide and norepinephrine

overtime and mortality and morbidity in the Valsartan Heart Failure Trial(Val-HeFT). Circulation. 2003;107(9):1278-83.

11. Fonarow GC, Pocock WF, Korwich TB, Phillips CO, Givertz MM, Lapatin M, et al; ADHERE Scientific Advisory Committee and Investigators. Usefulness of B-type natriuretic peptide and cardiac troponin levels to predict in hospital mortality from ADHERE. Am J Cardiol. 2008;101(2):231-7.

12. Lanfear DE, Peterson EL, Campbell J, Phatak H, Wu D, Wells K, et al. Relation of worsened renal function during hospitalization for heart failure to long-term outcomes and re-hospitalization. Am J Cardiol. 2011;107(1):74-8.

13. Freitas HF, Chizzola PR, Paes AT, Lima AC, Mansur AJ. Risk stratification in a Brazilian hospital based cohort of 1220 outpatients with heart failure: role of Chagas' disease. Int J Cardiol. 2005;102(2):239-47.

14. Silva CP, Del Carlo CH, Oliveira Junior MT, Scipioni A, Strunz-Cassaro C, Ramires JA, et al. Porque os portadores de cardiomiopatia chagásica têm pior evolução que os não chagásicos? Arq Bras Cardiol. 2008;91(6):358-62.