

Serum NT pro-BNP: Relation to Systolic and Diastolic Function in Cardiomyopathies and Pericardiopathies

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Summary

Background: NT pro-BNP is a marker of systolic and diastolic dysfunction.

Objective: To determine NT pro-BNP levels in patients with chagasic, hypertrophic, and restrictive heart diseases, as well as with pericardial diseases, and their relation to echocardiographic measurements of systolic and diastolic dysfunction.

Methods: A total of 145 patients were divided into the following groups: 1) Chagas' heart disease (CHD) – 14 patients; 2) hypertrophic cardiomyopathy (HCM) – 71 patients; 3) endomyocardial fibrosis (EMF) – 26 patients; 4) pericardial effusion (PE) – 18 patients; and 5) constrictive pericarditis (CP) – 16 patients. The control group was comprised of 40 individuals with no heart disease. The degree of myocardial impairment and pericardial effusion were assessed by two-dimensional echocardiography and the degree of restriction by pulsed Doppler transmitral flow. The diagnosis of CP was confirmed through magnetic resonance imaging. NT pro-BNP levels were determined through electrochemiluminescence immunoassay.

Results: NT pro-BNP was increased ($p < 0.001$) in CHD (median = 513.8 pg/ml), HCM (median = 848 pg/ml), EMF (median = 633 pg/ml), CP (median = 568 pg/ml), and PE (median = 124 pg/ml), when compared with the control group (median = 28 pg/ml). No statistically significant differences were found between CP and EMF ($p = 0.14$). In the hypertrophic group, NT pro-BNP was correlated with left atrial size ($r = 0.40$; $p < 0.001$) and with E/Ea ratio ($p < 0.01$). In the restrictive group, there was a trend of correlation with E-wave peak velocity ($r = 0.439$; $p = 0.06$).

Conclusion: NT pro-BNP is increased in the different cardiomyopathies and pericardial diseases and is correlated with the degree of systolic and diastolic dysfunction. (Arq Bras Cardiol 2008;91(1):46-50)

Key words: Cardiomyopathies; pericardial effusion; pericarditis, constrictive.

Introduction

The World Health Organization defines cardiomyopathies as diseases of the myocardium associated with cardiac dysfunction, and classifies them as dilated, hypertrophic, restrictive and right ventricular arrhythmogenic cardiomyopathies¹.

In our midst, Chagas' heart disease (CHD) is one the most frequent forms of myocardial aggression that progress with dilation^{2,3}.

Hypertrophic cardiomyopathy (HCM) is a primary disease characterized by myocardial hypertrophy, which determines increased wall thickness without ventricular dilation in the absence of hypertension, heart valve diseases, congenital or systemic diseases that can lead to increased wall thickness. It is usually asymmetric with significant diastolic dysfunction,

whereas the systolic function at rest is normal⁴.

The restrictive form is the most uncommon among the cardiomyopathies. It results from local or systemic conditions. Cardiac amyloidosis is the most prevalent form in non tropical countries. In regions such as India, Africa, South and Central America, in turn, endomyocardial fibrosis (EMF) is the most frequent⁵. It is characterized by fibrosis of the endocardium and adjacent myocardium, thus leading to atrioventricular dysfunctions⁶.

Pericardial diseases that lead to diastolic dysfunction are pericardial effusions and constrictive pericarditis, however with different hemodynamic features⁷.

The high prevalence of cardiomyopathies and pericardial diseases has a strong impact on morbidity and mortality, with direct and indirect medical social costs, repeated hospitalizations and loss of productivity. Hence the importance of using ancillary diagnostic methods with the purpose of evaluating and selecting patients at higher risk. These methods also enable the identification of individuals at initial phases of the disease before the onset of the clinical manifestations

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resulting from ventricular dysfunction.

NT pro-BNP is described as a marker of systolic and diastolic dysfunction and is used as an ancillary method in the assessment and follow-up of heart failure patients^{8,9}.

The objective of this study was to determine serum NT pro-BNP levels in the different cardiomyopathies and pericardial diseases, and to evaluate their relation to measurements of systolic and diastolic function as obtained with resting echocardiogram.

Methods

A total of 145 patients were prospectively evaluated in the period between 2003 and 2005. Patients were divided into five groups: with Chagas' heart disease (CHD), hypertrophic cardiomyopathy (HCM), endomyocardial fibrosis (EMF), pericardial effusion (PE), and constrictive pericarditis (CP).

Patients with CHD (n = 14) had a mean age of 48±9 years and were characterized by myocardial dysfunction and heart failure (CHF), as well as < 40% ejection fraction, as assessed by echocardiogram.

A total of 71 HCM patients with mean age of 35±12 years were studied. Diagnosis was based on a >15-mm septal hypertrophy.

A total of 26 EMF patients with mean age of 49±7 years were evaluated. Diagnosis was based on apical obliteration of one or both ventricles.

After clinical evaluation, the type of impairment in the patients with pericardial diseases was characterized by echocardiogram and, when necessary, by magnetic resonance imaging in the cases with pericardial thickening. The patients were divided into the following groups: pericardial effusion (PE), 18 patients, mean age of 53±17 years; and constrictive pericarditis (CP), 16 patients, mean age of 32±16 years.

For comparison of results, a control group (CG) was formed with 40 patients with no structural heart disease, and mean age of 36±10 years (Table 1).

The echocardiographic study was performed with the patients in the supine and left lateral position using an Acuson equipment (Sequoia 512, Mountain View, CA) equipped with a 2.5-4.0 MHz multifrequency transducer. Complete echocardiographic studies were performed and at least three

measurements of each variable were taken; then, the mean values of each of them were calculated.

The M-mode measurements were taken according to the recommendations of the American Society of Echocardiography¹⁰. Left ventricular mass was calculated using the modified Devereux formula corrected for body surface area and also expressed as mass index¹¹. Left ventricular ejection fraction was determined using the Teichholz method¹². Large pericardial effusion was defined by the presence of >20 mm posterior and anterior effusion, and moderate pericardial effusion between 10 and 20 mm¹³. All patients with pericardial effusion were symptomatic, therefore with restriction.

Mitral and tricuspid flows were obtained using pulsed Doppler in the four-chamber apical view, with the volume sample positioned on the edge of the valve leaflets, and the least possible gain and lowest possible filter in order to obtain the best definition. To characterize a restrictive pattern, the E and A wave peak velocities were measured, and the E/A ratio was calculated¹⁴.

The diagnosis of constrictive pericarditis was confirmed by the magnetic resonance imaging findings and the presence of a > 4 mm pericardial thickness.

Restriction in patients with pericardial effusion was defined by the presence of significant effusion accompanied by clinical symptoms and alterations of the mitral flow pattern. In constrictive pericarditis, in addition to indirect signs of alterations of diastolic relaxation on cinemagnetic resonance and inferior vena cava dilation, measurements of the mitral flow were also considered (E and A wave velocities, and E/A ratio), with the presence of a greater than 25% reduction in the mitral flow during inspiration. Endomyocardial fibrosis was defined by the presence of apical obliteration of one or both ventricles with alterations suggestive of fibrosis, in addition to alterations in the mitral inflow filling.

NT pro-BNP was determined in peripheral blood drawn from a forearm vein, in a dry tube kept in ice and centrifuged under refrigeration for 10 minutes at 3,000 rpm. Serum was separated for NT pro-BNP determination using electrochemiluminescence immunoassay. The blood samples for NT pro-BNP determination were collected during the performance of the echocardiogram.

Table 1 - Clinical and epidemiological characteristics in the control group and in the different cardiomyopathies and pericardial diseases

Variables	CHD	HCM	EMF	PE	CP	Control
Age (years)	48 ± 9	35 ± 12	49 ± 7	53 ± 17	32 ± 16	36 ± 10
Male gender	7	36	3	15	9	19
Female gender	7	35	23	3	7	21
Functional class I/II	-	59	19	-	-	-
Functional class III/IV	14	12	4	18	16	-
EF	0.44 ± 0.12	0.72 ± 0.07	0.60 ± 0.04	0.72 ± 0.02	0.63 ± 0.7	0.71 ± 0.03
NT pro-BNP	513	848	633	124	568	28

CHD - Chagas' heart disease; HCM - hypertrophic cardiomyopathy; EMF - endomyocardial fibrosis; PE - pericardial effusion; CP - constrictive pericarditis; EF - ejection fraction; median NT pro-BNP.

Statistical analysis

Descriptive statistical analysis of NT pro-BNP was made using medians and standard errors for each disease group.

Next the following statistical tests were performed:

- Analysis of variance to compare NT pro-BNP values between the disease groups. In order to use the parametric analysis of variance for independent samples or the unpaired Student's t test, the variables have to meet the assumption of normality and homogeneity. When one of these conditions was not met, the Kruskal-Wallis and the Mann-Whitney tests were used.

- The Spearman test was used to analyze the association between NT pro-BNP and the echocardiographic parameters (E and A wave velocities, and E/A ratio).

Results

NT pro-BNP values were increased ($p < 0.001$) in patients with CHD, HCM, EMF, CP, and PE when compared with the control group (Table 1 and Figure 1).

In patients with HCM, NT pro-BNP was correlated with NYHA functional class III/IV (median of 3.357 pg/ml), when compared with those in functional class I/II (median of 669 pg/ml; $p < 0.001$). NT pro-BNP also correlated with the left atrial size ($r = 0.40$; $p < 0.001$) (Figure 2), septal thickness ($r = 0.35$, $p = 0.02$), presence of obstruction ($r = 0.23$, $p = 0.05$) and with the E/Ea ratio ($p < 0.01$).

All patients with PE presented with significant effusions and were symptomatic. All patients with CP underwent surgery, except for one who died before the operation. This patient had the highest NT pro-BNP levels.

No differences were observed between CP and EMF patients ($p = 0.14$).

In the restrictive group, there was a trend of correlation

between NT pro-BNP and E-wave peak velocity ($r = 0.439$; $p = 0.06$) (Table 2).

Discussion

In this study, we observed that NT pro-BNP is increased in chagasic and hypertrophic cardiomyopathy, as well as in endomyocardial fibrosis and pericardial diseases.

Natriuretic peptides are synthesized in the heart ventricles and their levels are increased specifically for elevated filling pressures in patients with ventricular dysfunction, and may provide important diagnostic and prognostic information. High NT pro-BNP levels (usually above 400-500 pg/ml) are related to a worse prognosis⁹. In our study, the mean NT pro-BNP level in patients with Chagas heart disease and heart failure was 800 pg/ml, thus suggesting a worse prognosis.

Like the results we found in patients with Chagas disease, other authors^{15;16} demonstrated that brain natriuretic peptides may be considered markers of ventricular dysfunction. Ribeiro et al¹⁷ observed that BNP determination is more accurate than the conventional methods (ECG and chest radiography) in the detection of patients with ventricular dysfunction.

We observed high NT pro-BNP levels in patients with hypertrophic cardiomyopathy when compared with the control group.

In HCM, hypertrophy is usually asymmetrical and the left ventricular cavity is normal or reduced, with significant diastolic dysfunction, whereas the systolic function at rest is normal. A good correlation of the measurements of diastolic dysfunction and hypertrophy with NT pro-BNP levels was observed. Increased NT pro-BNP values were also observed in the cases of outflow tract obstruction. Similar to our findings, Nishigaki et al¹⁸ observed plasma BNP levels higher in patients with the obstructive form than in those without obstruction.

Increased NT pro-BNP levels were observed in EMF

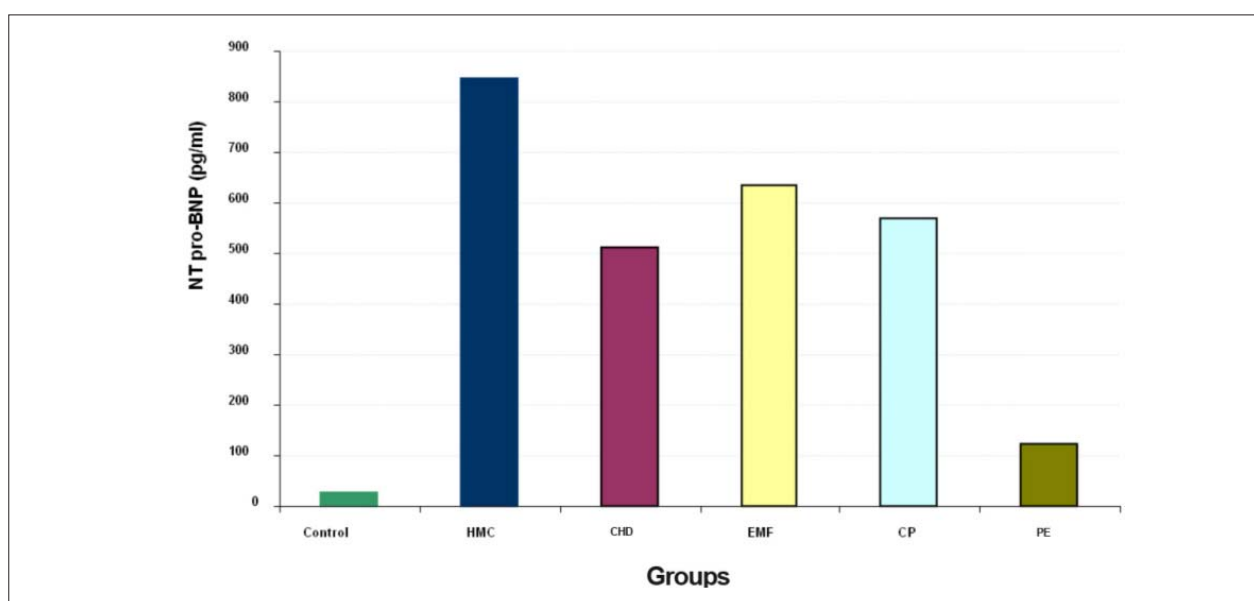


Figure 1 - Median values of NT pro-BNP in the control group and in the different cardiomyopathies and pericardial diseases; HCM - hypertrophic cardiomyopathy; CHD - Chagas' heart disease; EMF - endomyocardial fibrosis; CP - constrictive pericarditis; PE - pericardial effusion.

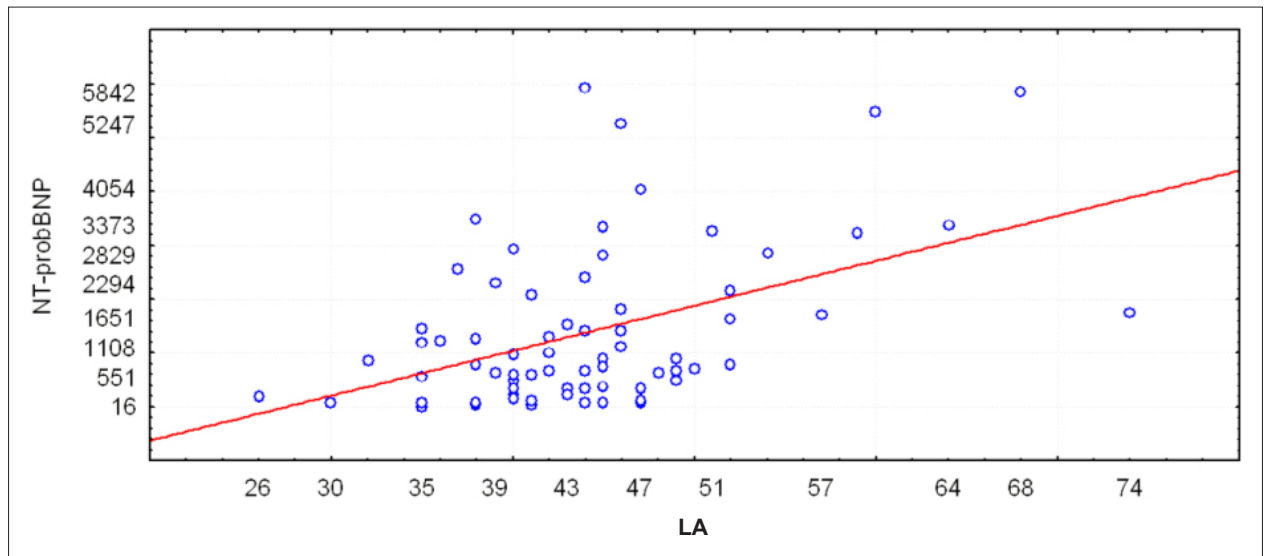


Figure 2 - Association between NT pro-BNP and echocardiographic parameters in patients with restrictive syndrome. LA - left atrium.

Table 2 - Association between NT pro-BNP and echocardiographic parameters in patients with restrictive syndrome

Measurements	Spearman correlation	p
E wave	0.439	0.060
A wave	-0.399	0.112
DT	-0.144	0.554
IVRT	0.1165	0.392

DT - Deceleration Time; IVRT - Isovolumic Relaxation Time.

patients when compared to the CG. Patients with PE and CP and preserved ventricular systolic function at rest were also observed to present high NT pro-BNP levels.

One of the possible explanations for the elevation of NT pro-BNP in pericardial diseases is the diastolic dysfunction. Regional collapse is associated with reduction in cardiac output, and this echocardiographic finding occurs before the development of hypotension and pulsus paradoxus¹⁹. Kaszaki et al²⁰, in turn, demonstrated that by reducing cardiac output in experimental pericardial tamponade, vasoactive substances were released. Among the vasoconstrictor mediators, the greatest rise occurred in vasopressin, epinephrine, norepinephrine and renin concentrations. Additionally, to attenuate and counter-regulate the excessive release of vasoconstrictor substances, histamine, which is a vasodilator substance, was also released. This may perhaps be another explanation for the increased levels of natriuretic hormones which are known to be vasodilator substances.

Our study demonstrated that NT pro-BNP levels increase in symptomatic patients with pericardial constriction. The subclinical forms of constriction include patients who develop pericardial thickening after one or several episodes of pericardial inflammation. Some of these patients are asymptomatic and present echocardiographic changes and normal systolic function at rest. The fact that they are

asymptomatic makes the diagnosis difficult and consequently the problem is underestimated. Since part of these patients progress to constriction with all its consequences, a deep knowledge of this phase of the disease is important. If we can follow up these individuals with serial determinations of dysfunction markers, then the survival curves can be modified by means of the early indication of pericardiectomy. NT pro-BNP could be an additional ancillary method in the follow-up of initial cases of pericardial thickening.

CP may be difficult to differentiate from restrictive cardiomyopathy, since these conditions share the same clinical and pathophysiological manifestations²¹.

Few studies used natriuretic factors to differentiate CP from restrictive cardiomyopathy. Leya et al²² determined BNP levels in six patients with constrictive pericarditis and in five patients with restrictive cardiomyopathy, and concluded that BNP was higher in restrictive cardiomyopathy when compared to CP, and therefore that it could be used as an ancillary diagnostic method to differentiate these two conditions. Our findings, unlike those of Leya et al's²², did not show differences between CP and EMF; however, the EMF patients were in NYHA functional class II.

Natriuretic peptides (BNP and NT pro-BNP) play a role in the diagnosis of diastolic dysfunction, especially in patients with a restrictive pattern⁸. In this study, there was a trend of correlation between mitral flow velocity and early ventricular filling in the restrictive syndromes. Perhaps with a greater number of patients these findings could be confirmed. In HCM, there was a good correlation with direct measurements of diastolic dysfunction and with indirect measurements such as left atrial size. In HCM, diastolic function is a marker of more severe heart failure, as indicated by the association with high NT pro-BNP levels. NT pro-BNP may be one more useful ancillary diagnostic method in the assessment and quantification of dysfunction in HCM patients.

We believe that serial measurements of this marker could help clinicians in the follow-up, diagnosis and prognosis of the

different myocardial and pericardial diseases.

Potential Conflict of Interest

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

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There were no external funding sources for this study.

Study Association

This study is not associated with any graduation program.

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