

Measurement of Human Brain Natriuretic Peptide in Patients with Chagas' Disease

Railton Bezerra de Melo, Giordano Bruno de Oliveira Parente, Edgar Guimarães Victor
Recife, PE - Brazil

Objective

To measure the serum levels of brain natriuretic peptide (BNP) in patients with chronic chagasic heart disease and in individuals with positive serology for Chagas' disease and no heart impairment, and to correlate the serum BNP levels with the degree of cardiac impairment, cardiac dimensions, presence of a pacemaker, and ejection fraction.

Methods

Serum BNP concentrations were determined by use of the Triage - BNP Test produced by BIOSITE. Serum BNP was assessed in 25 patients from the Chagas' disease outpatient clinic of the Hospital Universitário Oswaldo Cruz, who were divided into 2 groups as follows: 1) G1 - comprising 13 asymptomatic patients with positive serology for Chagas' disease and no heart disease detectable on electrocardiography, chest X-ray, and echocardiography; and 2) G2 - comprising 12 patients with Chagas' disease and heart impairment.

Results

Significantly more elevated BNP levels were detected in the chagasic patients with cardiac impairment: (G1=4.4 ±4.4 pg/ml, G2=293.0±460.2 pg/ml); ($P<0.01$). In the 2 groups, the serum levels of BNP correlated neither with age nor with sex. The levels were directly proportional to functional class and cardiac area on chest X-ray. Although a trend towards an increment in systolic function impairment was observed, no linear correlation with the ejection fraction on echocardiography occurred. The presence of definitive pacemaker and electrocardiographic alterations did not change the serum BNP levels.

Conclusion

Asymptomatic individuals with a positive serology for Chagas' disease and no evidence of ventricular dysfunction have serum BNP levels similar to those of the general population.

Key words

Chagas' disease, natriuretic peptides, cerebral natriuretic peptide, congestive heart failure

Chagas' disease is the fourth major cause of impairment among transmissible diseases in Latin America, where 16 to 18 million people are estimated to be infected¹. In Brazil, 6 to 8 million infected people exist². Chagas' heart disease may manifest in several forms, and the individual may either be asymptomatic with no evidence of cardiac impairment, or have cardiomyopathy with heart failure and several cardiac arrhythmias.

Patients with congestive heart failure have been demonstrated to have high serum levels of ANP and brain natriuretic peptide (BNP), and those levels correlate with the extension of ventricular dysfunction, being increased by 30 times in patients with advanced heart disease. High concentrations also predict short survival and correlate more closely with prognosis³⁻⁵.

Due to the importance of BNP as a marker of severity and mortality in several diseases, mainly in heart diseases, measurement of its serum levels in Chagas' disease is justified. Alterations in BNP levels may be involved in the different clinical phases of the disease. This technique may support the formulation of more adequate therapeutic strategies according to the patient's biochemical profile.

Methods

The participants in the study originated from the Chagas' disease outpatient clinic of the Hospital Universitário Oswaldo Cruz of the Universidade de Pernambuco. They were recruited through a letter.

The population studied comprised 25 individuals divided into 2 groups as follows: 1) group 1 (G1) - comprising 13 individuals referred by a hemotherapy institution due to positive serology for Chagas' disease. The individuals had no cardiac impairment, verified through the lack of clinical symptomatology and no alteration suggestive of heart disease on electrocardiography, chest X-ray, and Doppler echocardiography; 2) group 2 (G2) - comprising 12 patients with the chronic cardiac form of Chagas' disease who were followed up at that outpatient clinic, seropositive for Chagas' disease, and who had cardiac impairment identified by the presence of symptomatology and alterations compatible with chagasic heart disease on electrocardiography, chest X-ray or Doppler echocardiography, or both.

For serologic confirmation of Chagas' disease, indirect hemagglutination and indirect immunofluorescence were used in both groups.

The exclusion criteria were as follows: presence of any other heart or systemic disease; use of noncardiologic medication that could significantly alter BNP levels; physiological states that could significantly change BNP levels, such as pregnancy, being less than 18 years old, and mental disability.

After collecting the blood sample, transferring micropipettes available with the BNP kit were used, and their content was added to the Triage BNP Test Device at room temperature.

The following variables were studied: age, sex, NYHA functional class of heart failure, medication use, presence of pacemaker, and electrocardiographic, echocardiographic and radiographic alterations.

The echocardiographic parameters analyzed were as follows: the dimensions, thickness and volumes of the cardiac cavities; the characteristics of left ventricular regional and overall contractility; and the flow waves on Doppler, from which the left ventricular diastolic function derived. If the systolic function (measured by Simpson method) was decreased, the impairment was classified as mild, moderate or severe. Structural alterations, mobility of the cardiac valves, and presence of intracavitary thrombi were assessed.

As the samples studied had a markedly asymmetric distribution, the groups were compared by using the Kruskal-Wallis nonparametric test.

The present study was approved by the Committee on Ethics of the HUOC-UPE, which follows the guidelines of the resolution 196/96 of the National Health Council. After being more carefully instructed about the research, all patients signed the written informed consent.

Results

The total population of the study comprised 25 patients divided into the 2 following groups: 1) G1 - comprising 13 individuals, 7 men (69.2%) and 6 women (30.8 %); and 2) G2 - comprising 12 individuals, half of them women, with a mean age greater than that in G1 (62.7 ± 7.7 anos vs 42.2 ± 11.7 anos).

The G1 participants had no heart disease, and, on echocardiography, the mean end-diastolic and end-systolic diameters were 49.6 mm and 30.8 mm, respectively. The ejection fraction of the participants was normal, its mean being 67.2%. The participants used neither a pacemaker nor medication.

The distribution of G2 patients according to NYHA functional classes was as follows: functional class I, 8.3%; functional class II, 50%; functional class III, 8.3%; and functional class IV, 33.3%.

The most used medications by G2 patients were as follows: ACE inhibitors, 91.7%; diuretics, in general, 66.7%; spironolactone, 50.0%; carvedilol, 50.0%; digoxin, 33.3%; and amiodarone, 33.3%. The patients usually were on more than one medication.

Seven (58.3%) patients had a definitive pacemaker. The major electrocardiographic alterations found in the 5 patients who had no pacemaker were as follows: right bundle-branch block, 40%; left anterior hemiblock, 60%; ESV, 40%; and left bundle-branch block, 40%.

Of the 12 G2 patients, only 2 had a normal echocardiogram. Table I shows the distribution of the alterations found.

The alterations in segmentary contractility always correlated with the defects of intraventricular conduction observed. No thrombi were observed.

The mean BNP level was more elevated in G2 ($G2=293.0 \pm 460.2$ pg/ml vs $G1=4.4 \pm 4.4$ pg/ml). This difference was statistically significant ($P < 0.001$).

No statistically significant difference was observed in BNP levels in regard to sex and age in both groups.

Table II correlates the serum levels of BNP and NYHA functional

class classification, showing a trend towards an increase in BNP levels as symptomatology worsens.

No statistically significant difference was observed in BNP levels between the individuals with a definitive pacemaker (PM, $n=217$) and those who had no PM ($n=49.8$; $P=0.062$).

Although not statistically significant, a correlation between BNP levels and heart size on chest X-ray was observed.

No significant differences were observed between the individuals with electrocardiographic alterations (right bundle-branch block, left anterior hemiblock, ESV, and left bundle-branch block) and the serum BNP levels.

In G2, the patients with enlarged cardiac chambers on the echocardiogram had the following BNP values: minimum, 3.6 pg/mL; maximum, 1,300.0 pg/mL; and mean, 344.9 pg/mL. In the 2 patients whose hearts were of normal dimensions, those values ranged from 4.9 to 63.20 pg/mL, with a mean of 34.05; the difference, however, was not statistically significant ($P=0.41$).

Left ventricular systolic function was also directly related to BNP levels. A trend towards an increase in BNP levels was observed, with a greater impairment in ventricular function, although the finding was marginally significant ($P=0.06$).

In regard to diastolic function impairment, no difference in the respective BNP levels was observed in the sample studied ($P=0.43$). Table III shows the correlation of BNP values and left ventricular

Discussion

Natriuretic peptides have been increasingly used as markers of morbidity and mortality in heart diseases. In regard to Chagas' disease, prevalent in economically less favored populations, so far no study has been reported using the Triage BNP Test, commercially available for serum BNP measurement. The existing studies used other techniques for BNP measurement and assessed the congestive form of the disease, in which cardiac impairment is evident. In the intermediate or undetermined phase, which has only positive serology and no clinical, electrocardiographic, radiological, or echocardiographic alteration, no investigation exists about BNP measurement using any technique.

Table I - Distribution of the echocardiographic alterations found in group 2

Echocardiographic alterations	Echocardiographic variables (n=12)
Enlargement in left ventricular dimensions	10 (83.3 %)
Diastolic dysfunction	8 (66.7 %)
Systolic function impairment	
Mild	2 (16.7 %)
Moderate	1 (8.3 %)
Significant	4 (33.3 %)
Normal systolic function	5 (41.7 %)

Table II - BNP values and functional class

Functional class	Number of patients	BNP values		
		Minimum	Maximum	Mean
I	1	3.6	3.6	3.6
II	6	4.9	217.0	70.6
III	1	49.8	49.8	49.8
IV	4	132.0	1,300.0	760.0
Kruskal-Wallis H3=7.763		P= 0.05		



Table III - BNP values and ventricular function in G2

Ventricular function	Number of patients	BNP values		
		Minimum	Maximum	Mean
Normal systolic function	5	3.6	70.5	30.4
Systolic function impairment	7	49.8	1,300.0	480.7
Mild	2	49.8	58.0	53.9
Moderate	1	217.0	217.0	217.0
Severe	4	132.0	1,300.0	760.0
Normal diastolic function	4	10.1	418.0	137.1
Impaired diastolic function	8	3.6	1,300.0	371.0

The technology of the Triage BNP Test (Biosite, San Diego, CA) has already been approved, due to its efficacy and accuracy for determining the serum levels of BNP⁶, and the North American FDA has licensed its use.

In the present study, the 2 groups investigated had statistically significant differences in BNP levels ($P < 0.01$). The chagasic patients with no cardiac impairment had BNP levels recommended as normal according to the method; however, the chagasic patients with cardiac impairment had different serum levels that increased according to functional class and cardiac dimensions.

Group 2 comprised 12 patients with different degrees of cardiac impairment. Most patients were in functional classes I or II, because 58.4% had few symptoms, and, supposedly, had lower indices of heart chamber dilation and, probably, lower BNP levels. It is worth noting that distension of the cardiac cavities stimulates the release of that peptide. If the study had comprised only patients with the congestive form of chronic chagasic heart disease, greater differences might have been observed between the 2 groups. On the other hand, the fact that the study comprised patients with different degrees of cardiac involvement and in different stages of the disease allowed the inference of the importance of BNP not only in patients with congestive heart failure, but also in individuals without signs or symptoms, or both, of left ventricular dysfunction.

The NYHA functional class was directly related to serum BNP levels, which is in accordance with the literature, except for functional class III, which did not show values greater than those in functional class II. It is worth noting that only one individual was in functional class III, which represents a bias in the sample. However, if functional classes III and IV are combined, the BNP levels are statistically different from those in functional classes I and II.

Pacemaker implantation, even indicating a greater severity of

the disease, regardless of the cardiac area and ventricular volumes, did not significantly increase BNP levels.

Alterations in segmentary contractility, and presence of apical aneurysm or intracavitary thrombus are elements frequently found on echocardiograms of chronic chagasic patients. The fact that they were not observed in the present study may be attributed to the small size of the sample: 12 patients with cardiac impairment, 7 of whom had pacemakers, a condition that hinders the observation of the alterations in contractility.

In group 2, the mean ejection fraction was 50.9% (SD=14.2), indicating that that group was mostly formed of individuals with a mild impairment in their left systolic ventricular function.

Ejection fraction did not directly correlate with BNP levels. However, although no linear relation existed, the individuals with impairment in their systolic function had increased BNP levels. In the present sample, no correlation could be established between BNP levels and diastolic dysfunction.

Considering the cost/benefit ratio, the use of this technology cannot be recommended for national programs of public health, because other less expensive diagnostic techniques remain useful.

It is worth noting that in chronic patients with cardiac impairment, even without dilation in the cardiac chambers, a statistically significant difference in the serum levels of BNP was observed in comparison with patients who had only positive serology. This makes us believe that BNP may be useful for assessing the severity of Chagas' disease not only in congestive individuals but also in those with the incipient forms of the disease.

New studies with larger population samples are required for more safely assessing the usefulness of BNP in risk stratification in patients with chronic chagasic heart disease, who have different degrees of impairment⁷. Serum measurement of BNP may help in establishing the most adequate therapeutic strategy, similarly to that which occurs in heart failure of other causes. Measurement of that peptide in chronic chagasic patients may also serve for the differential diagnosis of heart decompensation, as other causes may have an identical symptomatology without a significant change in BNP levels, such as chronic obstructive pulmonary disease and other respiratory syndromes. Complications or associated diseases, such as anemias and infections, mainly respiratory, which may affect the chronic chagasic patient, may have its participation in cardiac decompensation stratified by the determination of BNP levels. A larger understanding of the pathophysiology of those peptides in Chagas' disease may propitiate their therapeutic application.

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