N-terminal proBNP levels in patients with Chagas disease: A marker of systolic and diastolic dysfunction of the left ventricle

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KEYWORDS
Chagas disease; NT-proBNP; Heart failure; Doppler echocardiography

Abstract Aims: NT-proBNP levels are known to be elevated in systolic and diastolic dysfunction. Doppler indices of diastolic dysfunction (DD) have been shown to have prognostic value in patients with Chagas’ cardiomyopathy (CC). However, the additional value of NT-proBNP levels in further stratifying these patients according to DD has not been established. This study analyzed the correlation of N-terminal proBNP (NT-proBNP) levels with systolic and diastolic function in patients with CC. Methods and results: NT-proBNP levels were measured in 59 patients with dilated cardiomyopathy due to Chagas disease without other systemic illness that were studied by Doppler echocardiography, including left atrial volume (LAV) calculation and tissue Doppler evaluation of LV longitudinal function.

Univariate analysis showed a strong correlation of NT-proBNP values with LVEF (r = −0.733, p < 0.001) and a weak correlation with most Doppler echocardiographic parameters of diastolic function. On a multivariate analysis, LVEF and LAV volume emerged as correlating with elevated levels of the NT-proBNP. Patients with restrictive filling pattern (n = 10), when compared to other patterns of DD, (n = 49), showed a lower LVEF (25.4 ± 6.4% vs. 39.8 ± 9.4, p < 0.001), a larger LAV (50.1 ± 17.2 vs. 37.7 ± 15.6 ml/m², p = 0.004) and higher NT-proBNP levels (median ± IQR: 3488 ± 3056 vs. 492 ± 700 pg/dl, p < 0.001). A marked elevated concentration of
NT-proBNP (≥800 pg/ml) had a sensitivity of 90.0%, specificity of 70.5%, positive predictive value of 40.9% and negative predictive value of 96.9% for detecting a restrictive filling pattern.

Conclusion: In patients with CC, NT-proBNP augmentation is a marker of LV dysfunction, with higher levels correlating with the more severe forms of both systolic and diastolic dysfunction.

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Introduction

For many years, diagnosis of heart failure has relied mainly on clinical symptoms and echocardiographic evaluation of left ventricular systolic function. More recently, biochemical markers have been suggested as an alternative indicator of the disease. BNP and its amino-terminal portion pro BNP (NT-proBNP), which may be advantageous because of its greater stability, has proven to be specially promising.1 B-type natriuretic peptide (BNP) is a cardiac neurohormone specifically secreted from the cardiac ventricles as a response to ventricular volume expansion, pressure overload and resultant increased wall tension.2,3 The source of plasma BNP is the cardiac ventricle, which suggests that BNP and NT-proBNP may be more sensitive and specific indicators of ventricular disorders than other natriuretic peptides.2,4

BNP levels are known to be elevated in patients with symptomatic left ventricular dysfunction and correlate to NYHA class and prognosis. It may also reflect isolated diastolic dysfunction,5,6 with higher levels being reported in systolic heart failure than in patients with heart failure and preserved systolic function.7 Associated diastolic dysfunction of the left ventricle8–10 has been shown to indicate a worse prognosis in patients with dilated cardiomyopathy. Although high levels of BNP have already been reported in patients with Chagas dilated cardiomyopathy and systolic dysfunction,11–13 the contribution of diastolic dysfunction to the increased level of natriuretic peptides in Chagas disease has not been established. Since Chagas dilated cardiomyopathy presents with some peculiar aspects that may differ from other forms of dilated cardiomyopathies, the purpose of this study was to investigate if NT-proBNP levels could predict the degree of diastolic dysfunction in patients with Chagas dilated cardiomyopathy.

Methods

The study was conducted at the Chagas Disease Outpatient Clinic of the University Hospital, a referring center for this disease, and at Eco-center, in Hospital Socor, both in Belo Horizonte, Minas Gerais, Brazil. This is a prospective study and its protocol was approved by the Ethics Committee of the Federal University of Minas Gerais.

Study group

The study population consisted of 59 patients with the established diagnosis of dilated cardiomyopathy (enlarged left ventricle and/or systolic dysfunction) due to Chagas disease studied from March 2003 to May 2004. The diagnosis of Chagas disease was based on the presence of at least two positive serological examinations using distinct techniques (ELISA, indirect hemagglutination or indirect immunofluorescence) and all patients signed an informed consent form. Clinical examination, NT-pro BNP levels and a comprehensive Doppler echocardiogram were obtained from all patients. Patients were excluded if they had associated valvular or other significant cardiac or systemic diseases, were not in sinus rhythm, had a pacemaker or in case of alcoholism or pregnancy.

BNP levels

Venous blood samples were obtained by direct venous puncture on the same day of the echocardiogram. After centrifugation, serum was frozen at −20 °C in aliquots and the laboratory analysis was performed in the next 24 hours. Serum NT-proBNP was determined with a sandwich immunoassay on an Elecsys 2010 (Roche diagnostics). The NT-proBNP method is considered precise (CV < 6.1%), has a wide dynamic measuring range (30–35,000 ng/l), is free from common interferences, and does not cross-react with BNP.14

Doppler echocardiogram

A comprehensive transthoracic Doppler echocardiogram with color flow mapping was performed in standard views, using a Phillips system 5500 (Phillips Medical Systems N.A., Bothell, WA). All exams
were performed by two experienced echocardiologists, blinded to all clinical and NT-proBNP data. Measurements according to ASE recommendations were obtained and averaged over three cycles. Left ventricular ejection fraction (LVEF) was calculated by the area-length method in the 4-chamber view.

Left atrial volume was obtained by tracing the area of the left atrium from the 4- and 2-chamber views at end ventricular systole, before opening of the mitral valve. The perpendicular lengths from these views were measured from the middle of the plane of the mitral annulus to the superior aspect of the left atrium. Left atrial volume was calculated by the formula, $0.85 \times 4$-chamber area $\times$ 2-chamber area/common length, and indexed for body surface area.

In the apical four-chamber view, mitral inflow was obtained with pulsed-wave Doppler at the tips of the mitral valve. E and A peak velocities, A wave duration and a deceleration time (DT) of the E wave were measured from the mitral inflow. Systolic (S), diastolic (D) and atrial reversal (AR) peak velocities, as well as the duration of the AR, were obtained from the pulmonary venous flow at the right upper pulmonary vein. The isovolumic relaxation time was also measured.

Tissue Doppler was obtained with the sample volume placed at the lateral mitral annulus and the peak systolic ($S'$), early ($E'$) and late diastolic ($A'$) velocities were measured. An $E'$ value of $\geq 10$ cm/s was used as a cut-off value to distinguish normal filling pressures. The velocity of propagation (Vp) of early filling from the mitral annulus to the left ventricle was measured using color M-mode, as previously described.

Among all the data obtained, the following parameters were used to classify the different diastolic filling patterns described below, as previously validated.

**Normal filling pattern**

Standard Doppler indices of LV filling and pulmonary venous flow were characterized by: high E, E/A ratio $> 1$, IVRT $< 100$ ms and early deceleration time (DT) $< 220$ ms; pulmonary venous peak atrial contraction reversed (AR) velocity $< 35$ cm/s and a venous systolic/diastolic (S/D) velocity ratio $> 1$; tissue Doppler $E'$ velocity $> 10$ cm/s.

**Stage I**

This pattern was characterized by: E/A ratio $< 1$, prolonged DT ($> 220$ ms), an IVRT $> 100$ ms; pulmonary venous flows with S/D $> 1$, RA $< 35$ cm/s and E' $< 8$ cm/s.

**Stage II**

This pattern refers to the normal appearance of ventricular inflow (E/A between 1 and 2, DT between 150 and 220 ms, IVRT between 60 and 100 ms) with abnormal pulmonary venous flow (S/D $< 1$ and AR $\geq 35$ cm/s). $E' < 8$ cm/s.

**Stage III**

This pattern was characterized by: E/A $> 2$, a short DT ($< 150$ ms), short IVRT ($< 60$ ms); pulmonary venous flow with blunted S (S/D $< 1$) and AR ($\geq 35$ cm/s). Tissue Doppler was the lowest ($E' < 8$ cm/s).

Systolic pulmonary artery pressure was calculated using the peak velocity of the tricuspid regurgitation to calculate the gradient between right ventricle and right atrium using the simplified Bernoulli equation and adding 10 mmHg to the obtained gradient. Using color flow mapping, mitral valve regurgitation was subjectively semiquantified from absent to mild, moderate or severe, according to the visual aspect of the length and width of the jet in the left atrium.

**Statistical analysis**

Data were expressed as mean $\pm$ standard deviation, median (interquartile range) or proportions and were compared among groups using Student t-test, ANOVA with Fisher multiple comparisons procedure, Kruskal–Wallis test or the Chi square test for $2 \times k$ contingency tables, with Bonferroni correction. Logarithm transformation of non-normal or heteroscedastic data (for example, NT-proBNP levels) was performed to allow subsequent analysis. Pearson or Spearman coefficients were used to measure correlations between variables and linear regression analysis was performed to further describe the relationship between variables. Multiple linear regression analysis was constructed with NT-proBNP as the dependent variable and the ejection fraction and Doppler-echocardiographic parameters of diastolic function to obtain the best regression model. The diagnostic performance of the NT-proBNP values in the diagnosis of diastolic restrictive pattern was evaluated using the receiver-operator-characteristic (ROC) curve.

**Results**

**Study group**

The mean age was 48 $\pm$ 11 years, ranging from 24 to 71. Thirty-nine patients (61%) were males. Fifty
patients (85%) were receiving angiotensin-converting enzyme inhibitors, 18 (31%) diuretics and 11 (19%) digoxin. Since bradycardia is frequent in patients with Chagas dilated cardiomyopathy, no patients were on β-blockers.

Doppler echocardiogram

Most patients (76%) had an ejection fraction lower than 45%. Thus, 24% of the patients still had preserved systolic function but in the presence of an enlarged left ventricle. Overall diastolic function by Doppler echocardiographic parameters was normal in six patients (10%), 37 (63%) had stage I of diastolic dysfunction (abnormal relaxation pattern), six (10%) stage II (pseudonormal) and ten (17%) stage III (restrictive pattern). Patients with normal diastolic function and patients in stages I and II were grouped together as a less compromised group (non-restrictive) and compared to patients in stage III, who presented with more severe forms of diastolic filling patterns (restrictive). These latter patients were in a higher NYHA class, had higher heart rates and lower blood pressure levels, lower ejection fraction and a larger LAV (Table 1).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Non-restrictive</th>
<th>Restrictive</th>
<th>p</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>47.9 ± 11.1</td>
<td>49.0 ± 11.9</td>
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</tr>
<tr>
<td>NYHA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I and II</td>
<td>48</td>
<td>6</td>
<td>0.049</td>
<td></td>
</tr>
<tr>
<td>Class III and IV</td>
<td>1</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>60.1 ± 9.5</td>
<td>82.1 ± 20.3</td>
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<td>SBP (mmHg)</td>
<td>117.8 ± 12.0</td>
<td>105.0 ± 12.7</td>
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<td>DBP (mmHg)</td>
<td>74.1 ± 8.9</td>
<td>67.0 ± 8.2</td>
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</tr>
<tr>
<td>LVD (mm)</td>
<td>61.7 ± 5.9</td>
<td>67.4 ± 6.8</td>
<td>0.03</td>
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<tr>
<td>LVs (mm)</td>
<td>48.9 ± 6.8</td>
<td>58.3 ± 6.7</td>
<td>0.001</td>
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<tr>
<td>LVEF (%)</td>
<td>39.8 ± 9.4</td>
<td>25.4 ± 6.4</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>E/E ratio</td>
<td>5.9 ± 2.2</td>
<td>9.9 ± 4.3</td>
<td>0.016</td>
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<tr>
<td>LAV (ml/m²)</td>
<td>37.7 ± 15.6</td>
<td>50.1 ± 17.2</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>NT-proBNP (pg/ml)*</td>
<td>492 (700)</td>
<td>3488 (3056)</td>
<td>0.008</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as number of cases (proportion), means ± standard deviation or *median (IQR = interquartile range). NYHA, New York Heart Association; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVD, left ventricular diastolic diameter; LVS, left ventricular systolic diameter; E/E’, E wave of the mitral annulus. Mitral regurgitation was absent in five patients (9%), mild in 42 (71%), moderate in ten (17%) and severe in two (3%). In 31 patients, pulmonary pressure could be obtained from the tricuspid regurgitation and its mean value was 33.6 ± 12.1. Assuming an estimated right atrial pressure of 10 mmHg, 20% of the patients had some degree of pulmonary hypertension (systolic pulmonary artery pressure > 35 mmHg).

Plasma NT-proBNP levels

The median plasma NT-proBNP levels for the study group was 691 pg/ml (IQR = 1033 pg/dl), ranging from 56.1 to 9302 pg/ml. Plasma NT-proBNP levels were significantly elevated in patients with NYHA classes III and IV (n = 5, median = 3354 pg/ml, IQR = 6424 pg/ml) when compared to those in classes I or II (n = 49, median = 593 pg/ml, IQR = 933 pg/ml, p = 0.04). NT-pro BNP levels showed a strong correlation with left ventricular ejection fraction (r = −0.733, p < 0.001) and a weak correlation with many Doppler echocardiographic parameters of diastolic function (see Table 2). Moreover, some Doppler parameters, such as peak E velocity, E/E’ ratio, and E/Vp rate, significantly correlated with LVEF (Fig. 1). NT-proBNP levels increased with the deterioration of the diastolic function, with significantly higher levels in patients with a restrictive filling pattern (p < 0.001, Fig. 2). The presence of pulmonary hypertension and the degree of mitral regurgitation also correlated to the levels of NT-proBNP (r = 0.662, p < 0.001 and r = 0.638, p < 0.001) in univariate analysis. In this sample, NT-proBNP levels were not correlated with age (r = −0.221, p = 0.109) or sex (male: median = 575, IQR = 899 pg/ml, female: median = 799, IQR = 2665 pg/ml, p = 0.119).

In multivariate analysis, logₐ NT-proBNP levels correlated significantly with LVEF (partial r = −0.695, p < 0.001) and left atrial volume index (partial r = 0.410, p = 0.004), but not with other diastolic indexes. The final regression equation (r = 0.770, p < 0.001) was: logₐ NT-proBNP = 8.546 + (−0.082 * LVEF) + (0.022 * left atrial volume).

Plasma NT-proBNP levels and diastolic restrictive pattern

NT-proBNP levels were markedly increased in those patients with restrictive diastolic pattern (median = 3488 pg/ml, IQR = 3056 pg/dl) when compared to other patterns of diastolic function (median = 492 pg/ml, IQR = 700 pg/dl, p < 0.001).
Table 2  Pearson’s correlation coefficient between NT-proBNP levels and left ventricular ejection fraction (LVEF) and Doppler echocardiographic data in 59 patients with Chagas cardiomyopathy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NT-proBNP</th>
<th>LVEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
<td>r</td>
<td>p value</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>-0.733</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LAV (ml/m²)</td>
<td>0.460</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak E velocity (cm/s)</td>
<td>0.409</td>
<td>0.002</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.370</td>
<td>0.006</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>-0.385</td>
<td>0.004</td>
</tr>
<tr>
<td>Pulmonary vein diastolic velocity (cm/s)</td>
<td>0.340</td>
<td>0.013</td>
</tr>
<tr>
<td>Pulmonary vein atrial reversal velocity (cm/s)</td>
<td>0.295</td>
<td>0.034</td>
</tr>
<tr>
<td>Peak E’ velocity (cm/s)</td>
<td>-0.074</td>
<td>0.595</td>
</tr>
<tr>
<td>E/E’ ratio</td>
<td>0.289</td>
<td>0.034</td>
</tr>
<tr>
<td>Vp Color M mode (cm/s)</td>
<td>0.045</td>
<td>0.749</td>
</tr>
<tr>
<td>E/Vp ratio</td>
<td>0.337</td>
<td>0.014</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>-0.138</td>
<td>0.329</td>
</tr>
<tr>
<td>PASP (mmHg)</td>
<td>0.662</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

After Bonferroni correction, p < 0.01 was considered significant (in bold). LVEF, left ventricular ejection fraction; LAV, left atrial volume, E/A ratio, E to A wave ratio of the mitral valve; DT, deceleration time of the E wave of the mitral valve; E/E’, E wave of the mitral valve to tissue Doppler E’ wave at the lateral wall of the mitral annulus ratio; E/Vp ratio, E wave of the mitral valve to velocity of propagation (Vp) of early filling from the mitral annulus to the left ventricle ratio; IVRT, isovolumic relaxation time of the left ventricle; PASP, pulmonary artery systolic pressure.

Figure 1  Correlation of NT-proBNP levels in Chagas disease patients with left ventricular ejection fraction (A), left atrial volume (B), E/E’ ratio (C) and E/Vp ratio (D).
A marked elevated concentration of NT-proBNP, defined as concentrations of 800 pg/ml or more, had a sensitivity of 90%, specificity of 70.5%, positive predictive value of 40.9% and negative predictive value of 96.9% for detecting a restrictive filling pattern. A ROC curve on the diagnostic performance of NT-proBNP values in the diagnosis of high filling pressures illustrates these findings (Fig. 3).

Discussion

BNP levels and systolic function

NT-proBNP levels were elevated in patients in NYHA classes III or IV, and there was a significant inverse correlation between NT-proBNP levels and LVEF. This is in agreement with most studies in the literature, which have shown excellent negative correlation between these natriuretic peptides and LVEF. The concentrations are correlated to the extent of ventricular dysfunction, reaching very high levels in patients with advanced disease.

BNP levels and diastolic function

Several studies have shown a high correlation between clinical status and Doppler echocardiographic indices reflecting diastolic dysfunction. Recently, diastolic dysfunction has been shown to be associated with elevated levels of BNP. Lubien et al., studying patients shown by echocardiography to have normal systolic function, demonstrated that normal diastolic function was associated with lower levels of BNP than diastolic dysfunction. Similar to our findings, in their study BNP levels were not able to differentiate the various diastolic filling patterns, although patients with a restrictive pattern by Doppler echocardiography also had the highest levels of NT-proBNP.

A poorer performance of BNP in diagnosing heart failure with preserved systolic function in comparison to systolic dysfunction has also been described. Data from the Breathing Not Properly Multinational Study showed that BNP levels were accurate in separating all patients with congestive heart failure from those without heart failure. However, BNP levels were not very accurate separating systolic from diastolic heart failure, and the marked overlap in BNP values clearly limits its usefulness in separating the two groups in the clinical setting. A possible explanation for this lower performance may be the fact that symptoms in both conditions relate to elevated filling pressures, the mechanism responsible for rising BNP levels. In fact, in a recent study comparing the accuracy of both BNP and Doppler mitral E/E' index in predicting a pulmonary capillary wedge pressure (PCWP) greater than 15 mmHg, BNP correlated poorly with PCWP (r = 0.32), while E/E' showed a better correlation (r = 0.69). In our study, there was a weak but significant correlation between BNP and E/E' (r = 0.289, p = 0.034). Since EF was highly correlated with levels of BNP, in a multivariate analysis, BNP correlation with E/E' lost power
and only the correlation of BNP with LA volume remained. LA volume was more independent of the EF and suffered less influence of the correlation between BNP and EF (see Table 2).

The trend to higher levels of BNP in systolic heart failure is probably related to a greater duration and severity of systolic dysfunction. In our study, most patients had moderate systolic dysfunction (mean EF = 37.3 ± 10.4%) and all patients with a restrictive pattern of diastolic function also had a low EF. BNP seems to relate more strongly to systolic than to diastolic function. That may be the reason why high levels of BNP had a low positive predictive value (40.9%) to detect a restrictive pattern. Because NT-proBNP level is greatly elevated by reduced EF alone, its utility in such patients for further identifying diastolic dysfunction may be limited and restricted to cases where diastolic function is severely impaired, with high filling pressures. Some reports that show correlation of BNP levels with diastolic dysfunction studied patients with isolated diastolic or systolic dysfunction. This is a quite different scenario from the one in the present study, where patients with isolated diastolic dysfunction were not included. In the present study, the high correlation of NT-proBNP with EF in our group of patients with significant systolic dysfunction may have prevented the separation of different degrees of diastolic dysfunction by NT-proBNP levels in the multivariate analysis, allowing only for the discrimination of the more severe forms of diastolic dysfunction.

In our study, multivariate analysis showed that only EF and left atrial volume correlated with NT-proBNP levels. The reason why left atrial volume, but not other Doppler parameters of diastolic function, correlated with NT-proBNP levels may be explained by the fact that left atrial volume reflects the duration and severity of increased left atrial pressure. In contrast, Doppler parameters express instantaneous Doppler pressures. Significant mitral regurgitation was not frequent in this group (valvar diseases had been excluded). Thus, left atrial volume appears to be a useful index of cardiovascular disease burden and risk. During ventricular diastole, left atrium is directly exposed to left ventricular pressures through the open mitral valve. Therefore, its size is greatly determined by the same factors that influence diastolic filling of the left ventricle, representing, however, a more stable indicator of diastolic dysfunction. Left atrial pressure rises, increasing left atrial wall tension and stretching the atrial myocardium. Since both left atrial stretch and left ventricular pressure are the main stimuli for secretion of cardiac peptides, BNP levels are expected to be high in the setting of large left atria, and the correlation of BNP levels and left atrial volume is not surprising.

A restrictive filling pattern has been shown to be related to high filling pressures and to a poorer prognosis in dilated cardiomyopathy. Higher filling pressures are probably the reason why NT-proBNP levels were able to separate only patients presenting a restrictive pattern (stage III), among all patients with different stages of left ventricular filling pressures. This is clinically important, since these are the patients who seem to have a worse prognosis, not only in dilated cardiomyopathies but also in Chagas disease. However, further studies are necessary to define the role of BNP and/or NT-pro-BNP measurements in managing patients with Chagas disease, and especially in establishing its role in detecting the prognostic value of associated restrictive pattern and elevated BNP levels in these patients.

Limitations of the study

Blood samples were not taken at the same time of the day, although they were always collected on the same day of the Doppler echocardiographic study. Although it is known to vary with age and renal function, NT-proBNP values were not corrected for age or for the creatinine level. However, NT-proBNP values were not correlated with age in this sample and none of the patients were in established renal failure or had had abnormal creatinine levels.

BNP levels are highly sensitive to drugs used in the treatment of heart failure and, as expected, all patients with systolic dysfunction were included, independent of the medications they were taking or their clinical status. The study group included several individuals with severe left-ventricular systolic function on treatment for congestive heart failure, which may have influenced NT-proBNP concentrations.

Indices of filling pressures were derived from Doppler echocardiogram and no invasive measurements were performed. However, Doppler parameters have been extensively validated to correlate with diastolic filling pressures in the presence of systolic dysfunction.

Conclusions

In patients with Chagas dilated cardiomyopathy, NT-proBNP levels showed a strong correlation with
left ventricular ejection fraction, with indices of the duration of diastolic dysfunction (left atrial volume), as well as with the more severe forms of the disease. It could not separate all the patterns of diastolic dysfunction, but it could separate milder from severe forms of the disease. It may be that, in patients with Chagas disease, NT-proBNP levels represent an additional method to detect the most severe forms of the disease.

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