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N-terminal prohormone brain natriuretic peptide (NT-proBNP) as a noninvasive marker for restrictive syndromes

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Constrictive pericarditis (CP) and restrictive cardiomyopathy share many similarities in both their clinical and hemodynamic characteristics and N-terminal prohormone brain natriuretic peptide (NT-proBNP) is a sensitive marker of cardiac diastolic dysfunction. The objectives of the present study were to determine whether serum NT-proBNP was high in patients with endomyocardial fibrosis (EMF) and CP, and to investigate how this relates to diastolic dysfunction. Thirty-three patients were divided into two groups: CP (16 patients) and EMF (17 patients). The control group consisted of 30 healthy individuals. Patients were evaluated by bidimensional echocardiography, with restriction syndrome evaluated by pulsed Doppler of the mitral flow and serum NT-proBNP measured by immunoassay and detected by electrochemiluminescence. Spearman correlation coefficient was used to analyze the association between log NT-proBNP and echocardiographic parameters. Log NT-proBNP was significantly higher ($P < 0.05$) in CP patients (log mean: 2.67 pg/mL; 95%CI: 2.43-2.92 log pg/mL) and in EMF patients (log mean: 2.91 pg/mL; 95%CI: 2.70-3.12 log pg/mL) compared with the control group (log mean: 1.45; 95%CI: 1.32-1.60 log pg/mL). There were no statistical differences between EMF and CP patients ($P = 0.689$) in terms of NT-proBNP. The NT-proBNP log tended to correlate with peak velocity of the E wave ($r = 0.439$; $P = 0.060$, but not with A wave ($r = -0.399$; $P = 0.112$). Serum NT-proBNP concentration can be used as a marker to detect the presence of diastolic dysfunction in patients with restrictive syndrome; however, serum NT-proBNP levels cannot be used to differentiate restrictive cardiomyopathy from CP.

Key words: Constrictive pericarditis; Endomyocardial fibrosis; NT-proBNP; Restrictive cardiomyopathy

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Introduction

Restrictive heart disease may be caused by disorders of any of the 3 layers of the heart. Constrictive pericarditis (CP) and restrictive cardiomyopathy share many similarities in both their clinical and hemodynamic characteristics. In patients with any of these anomalies, the main physiologic characteristic is a disturbance in the filling and the relaxation of the heart (1).

Pericardial disorders leading to diastolic heart failure are usually in the form of constrictive physiology (2). Myocardial disorders include a broad range of pathologies leading to restrictive physiology. Endomyocardial fibrosis (EMF) is a prototype of restrictive cardiomyopathy leading to diastolic dysfunction and preserved systolic function (3).

It is difficult to diagnose diastolic heart failure accurately in restrictive syndromes. Doppler echocardiography is the most readily available and useful noninvasive method for assessing diastolic dysfunction in these patients (4). Measuring serum N-terminal prohormone brain natriuretic peptide (NT-proBNP) and brain natriuretic peptide (BNP) are useful methods for diagnosing heart failure (5). These

peptides are sensitive markers of cardiac diastolic dysfunction and measuring them may be useful as an early diagnostic tool in restrictive syndromes (4).

The purpose of this study was to determine whether serum NT-proBNP levels are elevated in patients reporting restrictive syndromes, as well as to investigate how this relates to echocardiographic indices of diastolic dysfunction.

Subjects and Methods

Thirty-three patients underwent prospective, consecutive evaluations from 2003 to 2005 in the cardiomyopathy group of Heart Institute of the University of São Paulo. Patients were divided into two groups: CP (16 patients, 7 females, age range 16-71 years old, mean 32 ± 16 years); EMF (17 patients, 14 females, age range 28-63 years old, mean 49 ± 9 years). A control group consisted of 30 healthy individuals who did not report any heart disease (15 females, age range 36-56 years old, mean 44 ± 5).

After initial clinical evaluation, echocardiography and magnetic resonance imaging (MRI) were used to characterize disease in patients reporting pericardial thickening. The following exclusion criteria were followed: serum creatinine >1.4 mg/dL, left ventricular systolic dysfunction (ejection fraction <55%, assessed by echocardiography, Teichholz method), atrial fibrillation, pregnancy, and obesity (BMI >30 kg/m^2).

The echocardiographic study was carried out with patients in the left lateral and dorsal decubitus position using Acuson (Sequoia 512, USA), equipped with a 2.5-4.0-MHz multifrequency transducer. Full echocardiographic studies were carried out with at least 3 measures for each variable, and means were calculated for each value. M-mode indices were obtained in compliance with the American Society of Echocardiography (6).

Mitral flow was measured with an apical 4-chamber view using pulsed-wave Doppler, with sample volume placed on the edge of the valvular leaflets with a decrease in the gain and filter for better definition of the flow. E and A waves peak velocity as well as the E/A ratio were measured. For the analysis of respiratory variation of mitral flow velocity, the E wave mean was obtained from 3 heart cycles in inspiration and 3 cycles in expiration. The percentile variation was calculated based on these mean values. The reference variation value was 25%. CP diagnosis was confirmed by MRI findings of pericardial thickening of more than 4 mm (7).

The diagnosis of EMF was established on the basis of the following echocardiographic findings present in all patients: obliteration of the ventricular apex, atrial dilation, an increase in endocardial echo reflectivity, and atrioventricular regurgitation (8). Patients with atrial fibrillation were excluded.

NT-proBNP was determined by collecting peripheral blood from the forearm into a dry tube kept in ice and centrifuged at 10 to 3000 rpm while refrigerated. After the serum was separated, NT-proBNP levels were measured by immunoassay and detected by electrochemiluminescence (Roche Diagnostics, Brazil) using 20 µL serum and polyclonal antibodies that detect epitopes in the N-terminal region (amino acids 1-76) of the proBNP (108 amino acids). The assay is fully automated using the Elecsys 2010 automated analyzer (Roche Diagnostics).

The coefficient of variation for the NT-proBNP assay was 7.0% (mean concentration 57 pg/mL) and the inter- and intra-assay variations were 4.0 and 2.6%, respectively; concentration ranged from 5 up to 35,000 pg/mL (data from the manufacturer). The threshold (lower limit of detection) was 5 pg/mL

Cross-reactivity with other natriuretic peptides (BNP, proANP1, CNP2) as well as the angiotensins was <0.001% (data from the manufacturer).

ANOVA and the Bonferroni test were used to analyze log differences of NT-proBNP between groups. Spearman correlation coefficient was used to analyze the association between log NT-proBNP and echocardiographic parameters (E and A waves velocity peaks, and the E/A ratio). A P value <0.05 was considered to be statistically significant.

All patients signed a written consent form to participate in the study after being instructed about the objectives and methods of the study. The procedures were performed according to the recommendations of the Institutional Ethics Review board, which approved the protocol based on the principles defined by the Helsinki Declaration.

Results

For CP, diagnosis was secondary to tuberculosis in 2 patients; in all others, it was idiopathic. Symptoms reported included dyspnea on effort (9 patients), increased abdominal volume with ascites (5 patients), and edema in the lower limbs (6 patients). All CP patients underwent surgery, except one, whose death occurred while the patient awaited clinical compensation before surgery.

The distribution of functional class in endomyocardial fibrosis patients according to the New York Heart Association (NYHA) criteria was as follows: class I for 10 patients and class II for 7 patients.

NT-proBNP

Log serum NT-proBNP was statistically increased (P <

0.05) in CP, with a log mean of 2.67 pg/mL (95%CI: 2.43-2.92 log pg/mL), and EMF with a log mean of 2.91 (95%CI: 2.70-3.12 log pg/mL) compared with the control group, log mean of 1.45 pg/mL (95%CI: 1.32-1.60 log pg/mL). No statistically significant difference was detected in log serum NT-proBNP values between EMF and CP patients (P = 0.689). Log serum NT-proBNP tended to correlate with echocardiographic parameter E wave peak velocity (r = 0.439; P = 0.060; Table 1).

Discussion

The data reported here showed that patients with restrictive physiology (CP and EMF) had higher serum NT-proBNP levels compared with controls.

Few studies have been published investigating an association of natriuretic factor levels and pericardial diseases and most of them have focused on atrial natriuretic factor. These studies report increases in serum atrial natriuretic factor after surgical correction of tamponade and CP. This increase could be explained by the fact that pericardial diseases may cause atrial distensibility restriction, thus limiting atrial natriuretic factor secretion and reducing its diuretic and natriuretic effects (9,10).

Lubien et al. (11) reported that, in the absence of left ventricular (LV) systolic dysfunction, plasma BNP levels were significantly higher in patients with LV diastolic dysfunction assessed with echocardiography than in subjects without LV diastolic dysfunction. Plasma BNP levels were markedly higher in the subgroup of patients with impaired relaxation than in controls (202 *vs* 33 pg/mL).

The encasement of the heart by rigid, nonpliable pericardium results in characteristic pathophysiologic effects, including impaired diastolic filling of the ventricles, exaggerated ventricular interdependence and dissociation of intracardiac and intrathoracic pressures during respiration. CP typically presents chronic insidious signs and symptoms of predominantly systemic venous congestion (12). We believe that diastolic dysfunction secondary to pericardial effusion and pericardial constriction might be associated with an increase in NT-proBNP serum levels.

Computed tomography and MRI have been used to measure pericardial thickness. However, these methods provide only anatomic information without hemodynamic physiology. The finding of a thickened pericardium does not necessarily indicate CP (13). In pericardial constriction, classic surgery is indicated for cases involving clinical heart failure. For such a condition, intervention must not be postponed, because patients in advanced functional class (IV in NYHA criteria) have higher mortality rates (30-40% *vs* 6-19%) and lower benefits. Improvement in symptoms and normalization of cardiac pressures may occur within a few months after pericardiectomy (14). As for patients in functional class I with no clinical signs of heart failure, pericardiectomy is not to be recommended (9).

The present study demonstrates that patients with pericardial constriction who are symptomatic have increased serum NT-proBNP levels and patients with EMF who have mild symptoms also have an increase in NT-proBNP levels. The determination of serum NT-proBNP might be one more complementary method useful for the follow-up of early cases of pericardial thickening when patients do not yet have signs or symptoms of heart failure. We did not observe differences in the causes of CP, although only analysis of a greater number of patients can elucidate this fact.

EMF is characterized by a fairly normal appearance of the myocardium, but the stiffness of the ventricle is markedly increased due to thickening and scarring of the endocardium leading to slow relaxation of the underlying myocardium. The LV fibrotic involvement may decrease diastolic suction and restrict the increase of end-diastolic volume, which reduces ventricular filling and hinders the Frank-Starling mechanism (3,8). The fibrous involvement of the endocardium and myocardium adjacent to the apex and inflow of both ventricles causes a restrictive syndrome characteristic of the disease. Usually, the fibrotic tissue involves the papillary muscles, leading to additional atrioventricular valvular dysfunctions that, combined with restriction of ventricular filling, cause the clinical manifestations of the disease. The overall systolic function of the left ventricle is usually preserved, except in advanced forms.

The occurrence of EMF is supposedly restricted to tropical zones. Recent studies, however, have reported a universal distribution of this disease, contrary to the preceding statement (3,8).

CP and restrictive cardiomyopathy create a diagnostic problem primarily because of the many similarities in both their clinical and hemodynamic presentations (15)

Table 1. Association between log NT-proBNP and echocardiographic parameters.

Measures	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

The Spearman correlation coefficients are presented in the Table. E wave = peak wave of early mitral inflow; A wave = peak wave of late mitral inflow; DT = deceleration time; IVRT = isovolumic relaxation time.

requiring careful attention to hemodynamic and Doppler echocardiographic features (2). In recent years, new diagnostic techniques have become available to differentiate the causes of diastolic dysfunction from each other (16).

Few studies have determined the efficacy of BNP measurements to differentiate CP from restrictive cardiomyopathy. Leya et al. (17) measured BNP levels in 6 patients with CP and 5 patients with restrictive cardiomyopathy (172.2 ± 825.8 *vs* 128.0 ± 52.7 pg/mL, respectively) and concluded that BNP levels were significantly elevated in restrictive cardiomyopathy compared with those in CP and might be a useful non-invasive marker for the differentiation of the two conditions. On the other hand, we did not observe differences in NT-proBNP levels between CP and restrictive cardiomyopathy. However, all patients with EMF were mildly symptomatic.

Echocardiography is the imaging modality most often used for the initial evaluation of pericardial disease, especially in patients suspected of effusion and tamponade (1). Doppler echocardiography is the most non-invasive measurement used to assess diastolic dysfunction in these patients. The natriuretic peptides (BNP or NT-proBNP) may be useful for detecting patients with diastolic dysfunction especially in those patients with a restrictive filling pattern (4).

This study confirms that the restrictive filling pattern of transmitral flow velocity is a marker of more severe heart failure, as indicated by its association with higher NT-proBNP levels in restrictive syndromes. Serum NT-proBNP may be useful for identifying those patients with more severe diastolic heart failure (4,18).

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