NT Pro-BNP Levels in Pericardial Diseases and How They are Used as Complementary Evaluation Method of Diastolic Restriction. Inititial Experience: 25 Cases

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Objective

To determine whether NT pro-BNP levels are high in patients reporting pericardial diseases, as well as to investigate how they relate to diastolic dysfunction echocardiographic measures.

Methods

Twenty-five patients were split into two groups: 1) pericardial effusion (PE): 15 patients; 2) constrictive pericaditis (CP): 10 patients. A control group was made up with 30 individuals reporting no heart disease. Pericadial effusion was evaluated by bidimensional echocardiogram, with restriction evaluated by pulsed Doppler of mitral flow. CP diagnosis was confirmed by MRI. NT pro-BNP levels were measured by immunoassay and detected by electrochemiluminescence.

Results

From the 15 PD patients, 14 reported relevant PD, and only 1, moderate PD. Log NT pro-BNP was shown to be higher in PD ($p < 0.05$), with log mean of 2.31 pg/ml and CP ($p < 0.05$), with log mean of 2.67 pg/ml, when compared to control group, log mean of 1.32 pg/ml. No difference was reported between PD and CP ($p = 0.149$). The NT pro-BNP log showed to be correlated to peak velocity of the E wave ($r = 0.845$; $p = 0.001$) and with E/A ($r=0.717$; $p= 0.003$).

Conclusion

NT pro-BNP is shown to have increased in pericardial diseases, and is associated to diastolic dysfunction. It may serve as an additional method in quantifying restriction.

Key words

Pericardial effusion, constrictive pericaditis, NT pro-BNP.

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Pericardial diseases are presented through different etiologies, leading to different morphologic conditions. Physical examination and non-invasive complementary methods are useful in diagnosing pericardial effusion and constriction. However, difficulties are still being faced for restriction quantification in those patients.

The decision to adopt an invasive technique is affected by patient's condition. When the condition is obvious, with records of hypotension, dyspnea, and paradoxal pulse, no controversy is posed regarding procedures. However, if findings include significant pericardial effusion and no symptoms, the need for intervention is questioned[1].

NT pro-BNP is described as a systolic and diastolic dysfunction marker. It is used as a complementary method for the evaluation and the monitoring of heart failure patients[2].

The purpose of the present study was to determine NT pro-BNP serum level in patients reporting pericardial effusion and constrictive pericarditis, as well as evaluating their association with echocardiographic diastolic function measures.

Methods

Twenty-five patients were submitted to prospective and consecutive evaluation between 2003-2004. Patients were split into the pericardial effusion (PE) group - 15 patients, 10 females, being 3 Black women, age range 21-76 years old (mean 54±15); and 10 patients reporting constrictive pericarditis (CP), 3 females, being 2 Black women, age range 16-71 years old (mean 32±17). A control group was made up with 30 individuals reporting no heart diseases: 15 females, being 2 Black women, age range 37-68 years old (mean 47±12).

After initial clinical evaluation, condition was characterized by echocardiogram and MRI for those cases reporting pericardial thickening.

The following exclusion criteria were used: serum creatinine > 1.4 mg/dl; left ventricular dysfunction (ejection fraction < 55%, as assessed by echocardiogram, Teichholz method); atrial fibrillation; pregnancy; and lactation.

The echocardiographic study was carried out with patients in left lateral and dorsal decubitus, using *Acuson* (Sequoia 512, Montain View, CA), equipped with a 2.5 – 4.0 MHz multifrequency probe. Full echocardiographic studies were carried out, with at least three measures for each variable, after which means were calculated for each value obtained.

M-mode measures were taken in compliance with the American Society of Echocardiography[3]. Left ventricular mass was calculated by Devereux-modified formula, corrected by body surface area, and also expressed as mass index[4]. Left ventricle ejection fraction was obtained through Teichholz[5] method. Significant previous pericardial effusion was defined as larger than 20 mm posterior pericardial effusion; moderate was considered to be between 10 and 20 mm[6].

Mitral flow was obtained by apical 4-chamber view pulsed Doppler, with volume sample placed on valvar leaflets ridges, with gain reduction and filter for better definition of flow. E and A waves velocity peak as well as E/A ratio were measured[7].

For the analysis of respiratory variation of mitral flow velocity, E wave mean was obtained from 3 heart cycles in inspiration and 3 cycles in expiration. Then, based on those means, percentual variation was calculated. Reference variation value: ≥ 25%[8,9].

Constrictive pericarditis dignosis was confirmed by MRI findings: pericardial thickening above 4 mm.

NT pro-BNP was determined by the collection of peripheral blood from the forearm into a dry tube, kept in ice and centrifuged at 10 minutes to 3,000 rpm under refrigeration. After serum used to determine NT pro-BNP was separated, levels were measured through immunoassay and detected by electrochemiluminescence.

For the purpose of statistical analysis, ANOVA and Tukey HSD tests were used to investigate log NT pro-BNP differences between groups. Spearman correlation coeficient was used for the analysis of the association between log NT pro-BNP and echocardiographic parameters (E and A waves velocity peak, and E/A ratio).

Results

Fourteen patients reported significant pericardial effusion; only one of them reported moderate effusion. Three patients presented echocardiographic signs of cardiac tamponade. Etiologic diagnosis was: tuberculosis (2), pulmonary adenocarcinoma (1), hypothyrodism (1), rheumatologic condition (3), rheumatoid arthritis (2), sclerodermy - CREST syndrome (1) and idiopathy (10). Pericardiocentesis was not carried out in four patients only. Specific treatment was introduced for base disease (thyroid and anti-inflamatory hormones).

For constrictive pericarditis, diagnosis was secondary to tuberculosis in 2 patients; in all others, it was idiopathic. Symptoms reported included: dyspnea under effort (8 patients); increased abdominal volume with ascites (5 patients); edema in lower limbs (6 patients). All CP patients underwent surgery, except for one, whose death occurred while awaiting clinical compensation before surgery - the very patient who reported the highest NT pro-BNP levels in the study.

Echocardiographic results of patients with pericardial effusion and constrictive pericarditis are described in Table 1.

Log NT pro-BNP was shown to be statistically increased ($p < 0.05$) in PE, with log mean of 2.31 pg/ml (95% CI): 2.00-2.61 log pg/ml), and CP ($p < 0.05$), with log mean of 2.67 pg/ml (CI 95%: 2.29-3.05 log pg/ml),

Table 1 – Echocardiographic measures of patients with pericardial effusion (PE) and constrictive pericarditis (CP)

Variables	PE	CP
Septum (cm)	0.8 ± 0.2	0.9 ± 0.1
PW (cm)	0.8 ± 0.2	0.9 ± 0.1
LVDD (cm)	4.6 ± 0.6	4.6 ± 0.7
LVSD (cm)	2.9 ± 0.5	3.1 ± 0.7
LA cm	3.4 ± 0.5	4.5 ± 0.8
EF (%)	72 ± 3	68 ± 2

LVDD- diastolic diameter of left ventricle; LVSD- systolic diameter of left ventricle; LA – left atrium size; EF- ejection fraction of left ventricle; PW - posterior wall

when compared to control group, log mean of 1.32 pg/ml (CI 95%: 1.18-1.47 log pg/ml). No statistically significant difference was reported between PE and CP (p=0.149) (Figs. 1 and 2). Log NT pro-BNP showed to be correlated to echocardiographic parameters E/A (r = 0.717; p = 0,003) an E wave peak velocity (r = 0.845; p= 0.001). (Figs. 3 and 4).

Discussion

The study showed that patients reporting pericardial impairment and preserved ventricular function presented high levels of NT pro-BNP. Such finding opens the perspective for the use of the method as complementary exam for the diagnosis of restriction in patients with pericardial effusions and constrictions.

The echocardiographic finding of significant pericardial effusion in patients who present no signs or clinical symptoms of restriction makes pericardiocentesis, or any other surgical procedure, questionable.

The indication for pericardial intervention is controversial. Some authors suggest routine pericardiocentesis should be carried out for diagnosis purposes, despite tamponade[10]. To such purpose, pericardial biopsy by Marfan reports low sensitivity – approximately 10.5%. Decision is to be made on case by case basis[11]. On the other hand, not always can one find correlation between clinical findings and echocardiographic findings when diagnosing tamponade pericardial effusion in patients reporting moderate to significant pericardial effusion. Mercé and collaborators[6] found left chamber collapses in 53% of patients reporting significant effusion. Approximately 89% of patients presenting tamponade clinical symptoms reported collapse in at least one chamber. However, 33% of patients that did not present tamponade symptoms reported collapse in at least one chamber.

Level of volemia, intracardiac pressures, thickening, and cardiac walls stiffness are echocardiographic factors that partially influence the presence of a collapse in the chambers[12]. Sagristà-Sauleda and collaborators[13], while on long-term evaluation of patients with pericardial effusion, concluded that effusion is well tolerated by most patients; however, tamponade occurred unexpectedly.

In the present study, the investigation of LV diastolic function was carried out by pulsed Doppler of mitral flow. That flow oscilates, though, in a U shape or a parabola shape. So, normal individuals present E/A ratio between 1 and 2. As diastolic dysfunction occurs, it is shown to be < 1 (pattern change for relaxation), when only relaxation is changed. When, in addition to slow relaxation, ventricular compliance or distensibility is compromised, a pseudonormal pattern can be observed, characterized by E/A between 1 and 2. Under slow relaxation, reduced compliance and significant increase of left atrial pressure, ventricular filling flow becomes restrictive, and is characterized by E/A >2. The limitation posed to the analysis of diastolic function by pulsed Doppler of mitral flow only is that the method does not allow normal ventricular filling to be differentiated from pseudonormal filling, and other methods have to be put to use, such as pulmonary veins flow or tissue pulsed Doppler. Therefore, the excellent correlation between

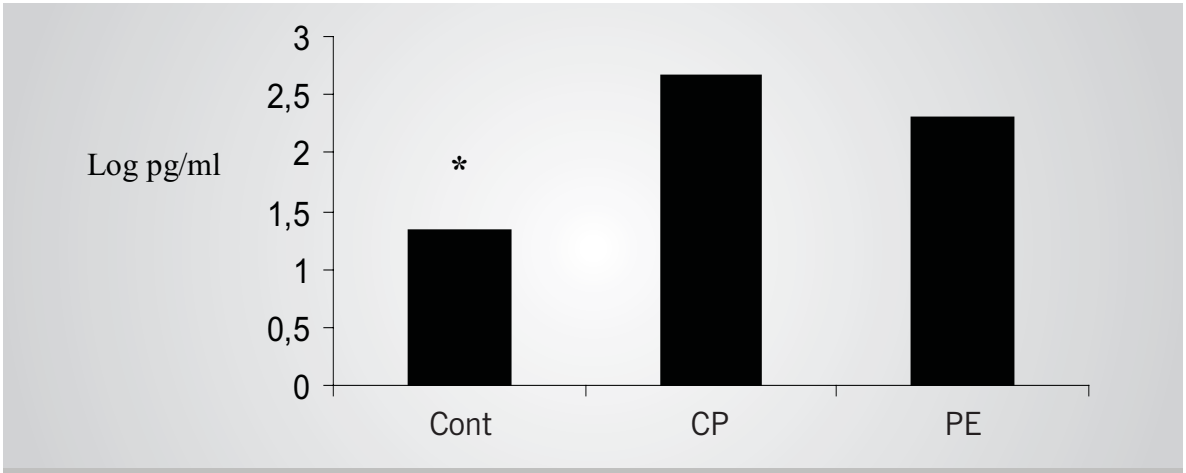

***Fig. 1** – Levels of log NT pro-BNP in control group (Cont), pericardial effusion (PE) and constrictive pericarditis (CP). *p<0.05*

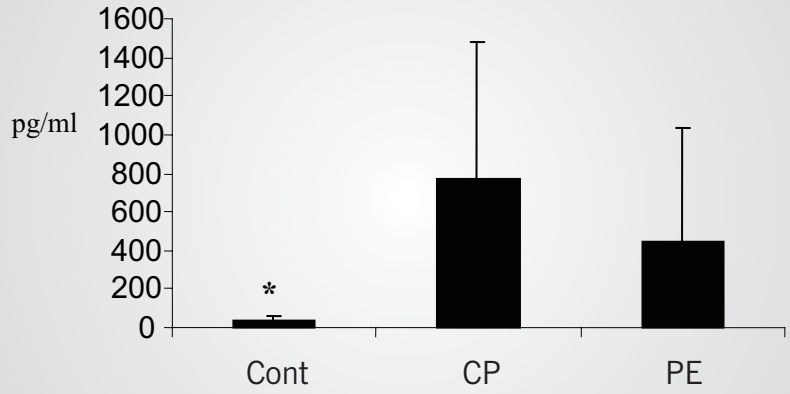

Fig. 2 *– Absolute measures of NT pro-BNP in pericardial effusion (PE) group, in constrictive pericarditis (CP) group, and in control group (Cont) *p<0.05*

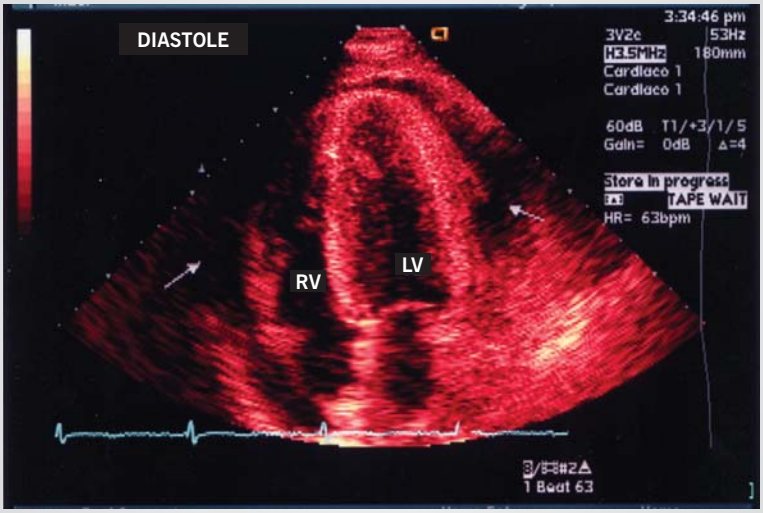

Fig. 3 *– 4 Chamber apical view – significant pericardial in diastole (arrows); LV - left ventricle; RV - right ventricle*

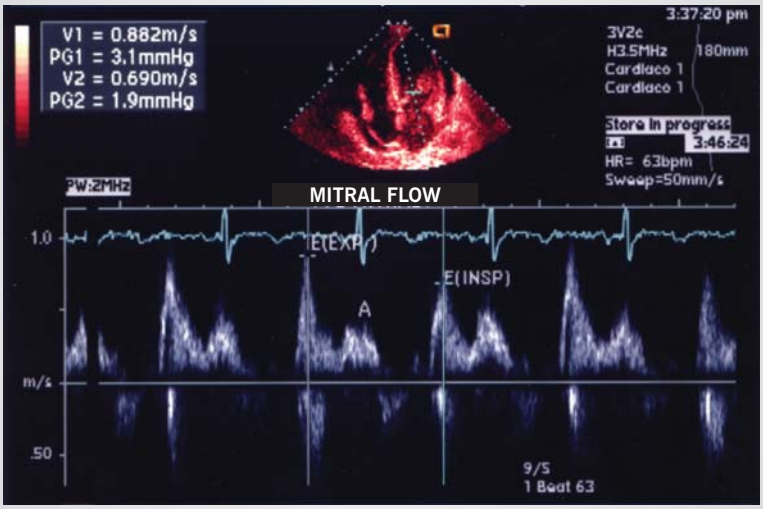

Fig. 4 *– Pulsed Doppler with sample positioned at the ridges of mitral valve leaflets – restrictive pattern of diastolic mitral flow can be observed. Variation of mitral E wave velocity can also be observed with respiration at 28%. That patient presented NT pro-BNP at 1,996 pg/ml*

diastolic function ratio (E and E/A) and NT pro-BNP, as observed in the present study, resulted from the extremely improbable scenario of our counting on a patient reporting normal ventricular filling pattern. Therefore, considering relaxation, pseudonormal, and restrictive changes only, which oscilate linearly, excellent correlation with NT pro-BNP could be found.

Mérce and collaborators [6] have decribed sensitivity and specificity at 75% and 91%, respectively, for the venous flow in patients with tamponade clinical symptoms. Therefore, resorting to other complementary methods for diagnosis – such as NT pro-BNP – could help in choosing the best moment for intervention.

Literature makes available few studies investigating the presence of natriuretic factors in pericardial diseases; most of them focus atrial natriuretic factor. Those studies report increase in atrial natriuretic factor after surgical correction of tamponade and of constrictive pericarditis. That could be explained by the fact that pericardial diseases supposedly cause atrial distensibility restriction, thus limiting atrial natriuretic factor secretion and reducing its diuretic and natriuretic effects[14,15]. In regard to BNP, only one study investigated those levels in patients with tamponade prior to and 30 minutes after pericardiocentesis. Results show that BNP was significantly increased as compared to control group. No differences were reported after therapeutic procedure[16].

The authors believe that diastolic dysfunction secondary to effusion and to pericardial constriction might be associated to NT pro-BNP serum level increase. Experimental studies have shown that even regional collapses are associated to cardiac debit, and that such echocardiographic finding usually occurs before the development of hypotension and paradoxical pulse[17].

Kaszaki and collaborators[18] have demonstrated that cardiac debit reduction in experimental pericardial tamponade was associated to the release of vasoactive substances. Among the vasoconstrictive substances, vasopresine, epinephrine, and renin stand out. Additionally, to atennuate and counter-regulate excessive release of vasoconstricting substances, the release of a vasodilating substance – histamine – also occurred. That might also explain the increase of natriuretic hormone levels – substances known to be vasodilating.

In pericardial constriction, classic surgery is indicated for cases involving clinical heart failure. For such condition, intervention must not be postponed, since patients under advanced functional class (IV in NYHA) report higher mortality rate (30 - 40% x 6 - 19%) and lower benefits. Improvement of symptoms and normalization of cardiac pressures may occur within a few months after pericardiectomy[19]. As for patients in functional class I with no clinical signs of heart failure, pericardiectomy is not to be carried out[12].

Subclinical forms of constriction include patients that develop pericardial thickening after one or many outbreaks of pericardial inflammation. That group has deserved little attention up to this point in time; and this is the least studied aspect of the condition. Patients are asymptomatic, report echocardiographic alterations, and systolic function at normal rest position. By being asymptomatic, patients' diagnosis is made more difficult, which results in underestimating the condition. As some patients develop into constriction, with all its consequences, it is important for physicians to be deeply aware of such stage in the course of the condition. If those individuals can be monitored with serial doses of diastolic dysfunction markers, survival curves will be changed, with early indication for pericardiectomy. Our study has demonstrated that pericardial constriction patients who are symptomatic report increase in NT pro-BNP levels. NT pro-BNP might be one more complementary method for the follow-up of early cases of pericardial thickening when patients do not yet present signs or symptoms of heart failure.

On the other hand, NT pro-BNP might also be used as a prognostic factor. The patient in the constrictive pericarditis group whose condition developed into death was the same who reported the highest levels of NT pro-BNP.

The present study demonstrates initial experiences with the use of NT pro-BNP as complementary diagnosis for pericardial diseases. However, the authors believe that only a study including a wider number of patients could answer some of the questions posed to the method regarding sensitivity, specificity, positive and negative predictive values, as well as prognostic markers for pericardial restrictions.

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