Original Research

Significance of Brain Natriuretic Peptide in the Evaluation of Symptoms and the Degree of Left Ventricular Diastolic Dysfunction in Patients with Hypertrophic Cardiomyopathy

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Introduction: Brain natriuretic peptide (BNP) correlates well with left ventricular wall hypertrophy and the severity of left ventricular outflow tract (LVOT) obstruction in patients with hypertrophic cardiomyopathy (HCM). The purpose of this study was to investigate the correlation of BNP levels with clinical status and left ventricular function in HCM patients.

Methods: In 32 patients with HCM (age 58 ± 14 years) we evaluated: a) the severity of dyspnea and angina; b) BNP plasma levels; c) left ventricular wall thickness, sphericity index and mitral regurgitation; d) LVOT obstruction; e) ejection fraction; f) left ventricular diastolic function, global and regional, by tissue Doppler imaging.

Results: BNP plasma levels correlated positively with dyspnea ($r=0.460$, $p<0.001$), angina ($r=0.460$, $p=0.008$), mitral regurgitation ($r=0.600$, $p<0.001$), thickness of interventricular septum ($r=0.526$, $p=0.002$), and LVOT obstruction ($r=0.551$, $p=0.001$ and $r=0.603$, $p<0.001$ for latent obstruction), while they were negatively correlated with left ventricular sphericity index ($r=-0.368$, $p=0.038$). BNP plasma levels were strongly correlated with E/Vp and E/Eal (Vp: flow propagation velocity, Eal: E on the lateral side of the mitral annulus), representing the left ventricular filling pressures, and with some other parameters of regional diastolic function: Ams (A at the mid-segment of the interventricular septum) $r=-0.518$, $p=0.002$; Aas (A on the septal side of the mitral annulus) $r=-0.454$, $p=0.009$; Aal (A on the lateral side of the mitral annulus) $r=-0.467$, $p=0.007$. From multiple regression analysis, angina and the ratio E/Eal were the strongest predictors of BNP plasma levels.

Conclusions: BNP plasma levels in HCM patients can be used as an adjunctive objective method of evaluating cardiac dysfunction through their correlation with angina and left ventricular filling pressures.

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Measurement of brain natriuretic peptide (BNP) plasma levels helps us to estimate the severity of patient disability in cardiac dysfunction.[1-3] Production of BNP is also activated in hypertrophic cardiomyopathy (HCM), while there are reports in the medical literature that BNP plasma levels in patients with HCM are correlated with clinical status, left ventricular diastolic dysfunction, or the severity of left ventricular outflow tract (LVOT) obstruction.[4-7] In a recent study of patients with hypertrophic cardiomyopathy,[8] despite its potential clinical role for a more objective evaluation of dyspnea in hypertrophic car-

diomyopathy, BNP was found to be limited by a considerable overlap in values between categories of heart failure severity and confounding variables, left ventricular wall thickness and age. The group consisted of patients with a wide range of ages, systolic and pure diastolic dysfunction, in sinus rhythm as well as in atrial fibrillation.

The present study was designed to reassess the relationship between BNP and clinical symptoms and to clarify the possible connection of BNP to a great variety of echocardiographic variables reflecting the severity of the disease in a more homogeneous group of patients. That connection could be a solution to finding an objective way of assessing clinical status in patients with hypertrophic cardiomyopathy.

Methods

Study population

Thirty-two patients with HCM (25 men and 7 women), aged 58 ± 14 years (range 27-78 years), were recruited for this study. Diagnosis of HCM was based on two-dimensional echocardiographic evidence of a hypertrophied, non dilated left ventricle, in the absence of any obvious cause of secondary hypertrophy.[9,10]

All patients had asymmetrical hypertrophy of the interventricular septum and preserved systolic function. They were in sinus rhythm and none of them had bundle branch block or a permanent pacemaker. Other exclusion criteria were coronary artery disease or valvular disease, hypertension, liver or renal dysfunction, and pulmonary disease. Medication was withdrawn two days before the study and blood sampling.

This study was undertaken in accordance with the Helsinki Declaration 1975. The patients gave informed consent to the procedures in this study as well as to the interruption of their medical treatment for two days. They underwent a careful and detailed examination for the presence and grade of exertional dyspnea, angina and syncope.

Blood sampling-measurement of BNP plasma levels

Blood was sampled from each patient after 30 minutes of quiet bed rest at the time that the echocardiographic examination was being performed. Blood samples were collected in tubes containing EDTA and aprotinin. The plasma was separated from mixed blood samples by centrifugation at 3000 rpm (4^{o} C). Plasma samples that were not assayed during stability time were stored in plastic tubes and frozen at -70^{o} C as previously described,[11] until later assay.

For the assessment of BNP plasma levels we used the "ShionoRIA BNP" immunoradiometric assay (Schering - CIS bio international). It is a solid-phase "sandwich" immunoradiometric assay. This method has the following advantages: 1) No extraction is required; 2) It is a one-step method; and 3) the method evaluates a wide measuring range (0-2000 pg/ml), with normal values <18.4 pg/ml and cross-reactivities to atrial natriuretic peptide and C-natriuretic peptide <10^{-5})

Echocardiography

Echocardiographic and Doppler ultrasound examinations were performed using a Toshiba 7000 imaging phased array system with a 2.5 MHz transducer and equipped with tissue Doppler imaging technology.

Two-dimensional echocardiography was used to measure left ventricular diameters, thickness of the interventricular septum and posterior wall, and left ventricular ejection fraction (by Simpson's method).

Left ventricular diastolic function was estimated by the following echocardiographic methods:

a) From transmitral flow, by assessing peak flow velocity in early diastole (E), peak flow velocity in late diastole (A), their ratio E/A, deceleration time of early diastolic flow velocity, and isovolumic relaxation time.

b) By using color Doppler echocardiography, combined with M-mode, to obtain early flow propagation velocity (Vp), as previously reported.[12-14]

c) By calculating the E/Eal ratio (where Eal was the early diastolic velocity on the lateral side of the mitral annulus, obtained by tissue Doppler imaging).[15,16]

The tissue Doppler imaging program was set to pulsed wave mode with gain adjusted to minimize background noise from the 4-chamber apical view. A 5 mm sample volume was placed as follows:

1) At the lateral border of the mitral annulus, where two major velocities were recorded, one during early diastole (Eal) and the other during late diastole (Aal).

2) On the septal side of the mitral annulus, where two velocities were recorded, during early and late diastole (Eas and Aas).

3) In the mid-segment of the thick interventricular septum, where two velocities were measured, one in early diastole (Ems) and the other during late diastole (Ams).

A Doppler velocity range of -20 to +20 cm/s was selected and the velocities were recorded on line at a sweep speed of 50 mm/s.

The presence and severity of LVOT obstruction were evaluated with continuous wave Doppler using the simplified Bernoulli equation ($\Delta P=4v^2$, where P is pressure and v is velocity). Care was taken to differentiate ejection velocity from the mitral regurgitation wave.[17]

The severity of mitral regurgitation was also estimated according to the recommendations of the American Society of Echocardiography.[18]

A mean of 5 consecutive cycles was used for the calculation of all echocardiographic parameters. Measurement of echocardiographic parameters, of left ventricular function and BNP plasma levels, as well as clinical examination, were performed separately and by observers who were blinded to the other study results.

Statistical analysis

Data are expressed as mean ± standard deviation (range) for continuous variables, and where necessary as median (interquartile range). For discrete variables (categorical data), frequencies n and the respective percentages (%) are given.

Given the sample size (n=32), the distribution of some variables (for example non-normal distribution of BNP values), and the type of some other variables (variables in ordinal scale), we chose to use Spearman's correlation coefficient to examine correlations between BNP and other clinical or echocardiographic characteristics of the study. The sign of the coefficient indicates the direction of the relationship, which is not necessarily linear, and its absolute value indicates the strength, with larger absolute values indicating stronger relationships. We also tested the hypothesis that the two variables in question were correlated statistically significantly (at a=0.05 or a=5%). For strong relationships between variables, the corresponding scatter plots were collocated.

We used the Kruskal-Wallis test (a non-parametric test equivalent to one way ANOVA) to test whether several independent samples were from the same population.

The Shapiro-Wilk and Kolmogorov-Smirnov tests showed that BNP values were not normally distributed. To determine which clinical and echocardiographic parameters best described BNP, the values were transformed into natural logarithms to overcome the problem of non-normal distribution; then stepwise multiple linear regression analysis was used with ln(BNP) as dependent variable. A p-value of less than 0.05 was considered significant for all statistical tests. All statistical calculations were performed using SPSS 11.0 for Windows.

Results

All baseline clinical and echocardiographic characteristics are shown in table 1. Baseline demographic and clinical data are given in table 2.

Symptoms and BNP plasma levels

Dyspnea was graded according to the New York Heart Association classification. Angina was graded according to the Canadian Cardiovascular Society classification. Concerning syncope, grade 1 was the presence of presyncope, while grade 2 was true syncope (complete loss of consciousness).

All patients had normal or supernormal values of left ventricular ejection fraction. From our results we observed a positive correlation of dyspnea ($r=0.875$, $p<0.001$) and angina ($r=0.460$, $p=0.008$) with BNP plasma values (Figures 1 and 2).

No association was found between BNP plasma levels and syncope.

Morphological parameters and BNP plasma levels

Maximal thickness of the interventricular septum was strongly related to BNP plasma levels ($r=0.526$, $p=0.002$).

Left ventricular diastolic function and BNP plasma levels

We found that BNP was correlated with peak early diastolic wave velocity from transmitral flow (E) ($r=0.704$, $p<0.001$), but not with peak late diastolic velocity (A) or the E/A ratio, a conventional index of left ventricular global diastolic function that has not proved its usefulness in HCM.

Concerning left ventricular regional diastolic function, as evaluated by tissue Doppler imaging, BNP was found to be inversely correlated with velocities in late diastole at the basal (Aas) and the midsegment of the interventricular septum (Ams), as well as the basal (annular) segment of the lateral wall

Table 1. Baseline clinical and echocardiographic characteristics.

Variables	Values	Range
Dyspnea (NYHA)		
I	15 (46.9%)	
II	4 (12.5%)	
III	8 (25.0%)	
IV	5 (15.6%)	
Angina (CCS)		
I	20 (62.5%)	
II	10 (31.3%)	
III	2 (6.3%)	
Syncope		
0	26 (81.3%)	
1	3 (9.4%)	
2	3 (9.4%)	
Ejection fraction (%)	70.8 ± 5.7 %	
Mitral regurgitation		
0	6 (18.8%)	
I	15 (46.9%)	
II	8 (25.0%)	
III	3 (9.4%)	
Gradient-rest (mmHg)		
≤30	24 (75.0%)	
>30	8 (25.0%)	
Gradient-Valsalva (mmHg)		
≤30	18(56.25%)	
>30	14(43.75%)	
E/Eal		
≤10	20 (62.5%)	
>10	12 (37.5%)	
BNP (pg/ml)	41.1 (10.45 - 74.35)	
E/Eal	8.54 ± 3.25	(4.69 - 14.67)
E/Vp	1.64 ± 0.53	(1.068 - 3.12)
E (m/s)	0.68 ± 0.145	(0.4 - 0.96)
Eal (m/s)	0.0867 ± 0.0238	(0.06 - 0.13)
Vp (m/s)	0.43156 ± 0.088	(0.282 - 0.566)
IVS-D (cm)	1.89 ± 0.385	(1.26 - 2.97)
A ms (m/s)	0.092 ± 0.028	(0.04 - 0.138)
Aas (m/s)	0.0957 ± 0.03	(0.053 - 0.2)
Aal (m/s)	0.1075 ± 0.029	(0.06 - 0.17)

Values are expressed as number (percent), or mean ± SD (range), or median (interquartile range).
Aal – late diastolic velocity at the lateral border of the mitral annulus, by TDI; Aas – late diastolic velocity on the septal side of the mitral annulus, by TDI; Ams – late diastolic velocity in the mid segment of the thick interventricular septum, by TDI; BNP – brain natriuretic peptide; CCS – Canadian Cardiovascular society; E – peak flow velocity in early diastole (transmitral flow); Eal – early diastolic velocity on the lateral side of the mitral annulus, by TDI; IVS-D – thickness of interventricular septum; NYHA – New York Heart Association; PW – thickness of posterior wall; TDI – tissue Doppler imaging. Vp – propagation velocity.
Mitral regurgitation categories as mentioned in text: 0 = no mitral regurgitation, I = mild, II = moderate, III = severe mitral regurgitation.

(Aal) (r=-0.454, p=0.009; r=-0.518, p=0.002; r=-0.467, p=0.007, respectively). It was also found to be strongly inversely correlated with the early peak diastolic velocity of the annular segment of the lateral wall (Eal) (r=-0.802, p<0.001).

BNP was inversely related to flow propagation velocity (Vp) from color M-mode echocardiography (r=-0.613, p<0.001).

Left ventricular filling pressures were estimated by measuring E/Vp and E/Eal ratios. Both ratios were well correlated with BNP plasma levels (E/Vp r=0.851, p<0.001 and E/Eal r=0.862, p<0.001).

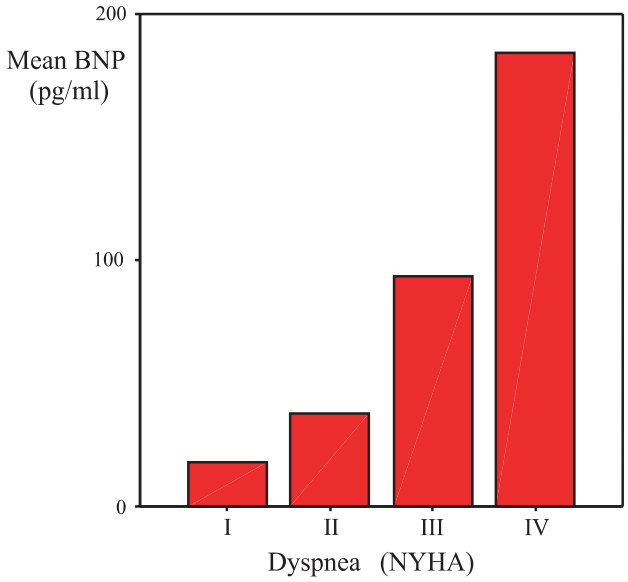

Figure 1. Relationship of mean plasma levels of brain natriuretic peptide (BNP, pg/ml) to dyspnea according to the New York Heart Association (NYHA) classification.

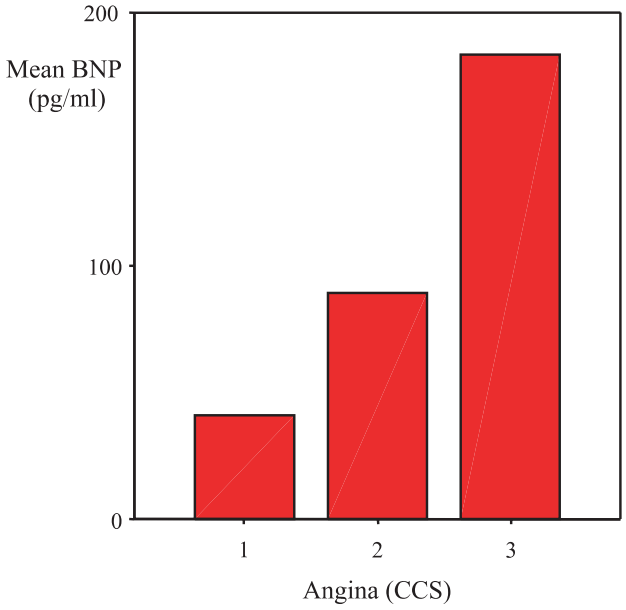

Figure 2. Relationship of mean plasma levels of brain natriuretic peptide (BNP, pg/ml) to angina according to the Canadian Cardiovascular Society (CCS) classification.

LVOT obstruction, mitral regurgitation and BNP plasma levels

Eight of 32 patients had a resting LVOT gradient >30 mmHg, while six patients exhibited a dynamic increase of LVOT gradient to >30 mmHg during the Valsalva maneuver. Obstruction at rest, as well as after the Valsalva maneuver, proved to be closely associated with BNP plasma levels ($r=0.551$, $p=0.001$, $n=8$, and $r=0.603$, $p<0.001$, $n=14$, respectively).

Mitral regurgitation was detected as mild (in 15 patients), moderate (in 8 patients), and severe (in 3 patients). Six patients did not exhibit mitral regurgitation. The severity of mitral regurgitation was found to be associated with BNP plasma levels ($r=0.600$, $p<0.001$).

All the above results are summarized in table 3.

BNP was not related to age, body surface area, blood pressure, heart rate or ejection fraction.

Table 2. Baseline demographic and clinical data.

Gender		
Male	25 (78.1%)	
Female	7 (21.9%)	
Age (yrs)	58.09 ± 14.13	(27-78)
Height (cm)	171.53 ± 7.32	(158-184)
Weight (Kg)	80.72 ± 10.93	(65-105)
BSA (m^2)	1.92 ± 0.15	(1.69-2.24)
SBP (mmHg)	135.31 ± 15.4	(100-160)
DBP (mmHg)	80 ± 9.2	(60-100)
HR (bpm)	66.94 ± 11.85	(51-108)

Values expressed as mean ± SD (range).
BSA – body surface area; DBP – diastolic blood pressure; HR – heart rate; SBP – systolic blood pressure.

Table 3. Correlation coefficients between clinical and echocardiographic indexes and BNP levels.

Variable	r	p
Dyspnea (NYHA)	0.875	<0.001
Angina (CCS)	0.460	0.008
Mitral regurgitation	0.600	<0.001
E/Eal	0.862	<0.001
E/Vp	0.851	<0.001
Eal (m/s)	-0.802	<0.001
Vp (m/s)	-0.613	<0.001
IVS-D (cm)	0.526	0.002
Ams (m/s)	-0.518	0.002
Aas (m/s)	-0.454	0.009
Gradient-Valsalva (mmHg)	0.603	<0.001
Aal (m/s)	-0.467	0.007

Abbreviations as in table 1.

Interrelations between clinical and echocardiographic parameters

Dyspnea was associated with: 1) left ventricular filling pressures (E/Eal, r=0.908, p<0.001 and E/Vp, r=0.885, p<0.001); 2) LVOT obstruction with gradient ≥30 mmHg (n=14, r=0.621, p<0.001); 3) mitral regurgitation (n=26, r=0.554, p=0.001); 4) Interventricular septum thickness (r=0.456, p=0.009). Angina was only associated with left ventricle outflow tract obstruction (r=0.355, p=0.046).

Mitral regurgitation was related to left ventricular filling pressures (E/Eal r=0.472, p=0.006, E/Vp r=0.513, p=0.003, interventricular septum thickness (r=0.471, p=0.007) and LVOT gradient (r=0.627, p<0.001).

Main predictors of BNP plasma levels

Multiple regression analysis was used to investigate more about the relationship between several independent (predictor) variables and the dependent (criterion) variable ln(BNP) and to determine which of the variables strongly correlated with BNP best describe ln(BNP) levels.

Because of the strong statistical relation between a considerable number of the independent variables, to avoid the problem of multicollinearity, we had to choose some of them to include in our regression model. Based on a recent report by Maron et al,[16] in which BNP was limited by a considerable overlap in values between heart failure classes, we chose to include E/Eal in the regression model instead of dyspnea class. We also included angina, LVOT gradient and mitral regurgitation.

By stepwise multiple linear regression analysis, using ln(BNP) as an independent variable, E/Eal and angina were the best predictors of ln(BNP) levels (Table 4). Specifically, this analysis resulted in a regression equation of the form:

ln(BNP)=0.601 + 0.315 E/Eal + 0.569 ANGINA

Table 4. Predictors of ln(BNP) levels.

Variable	RC	SE	95% C.I.	p
Constant	0.601	0.351	-0.116 – 1.318	0.097
E/Eal	0.315	0.040	0.233 – 0.397	<0.001
Angina	0.569	0.266	0.025 – 1.114	0.041

BNP – brain natriuretic peptide; CI – confidence interval; E – peak flow velocity in early diastole (transmitral flow); Eal – early diastolic velocity on the lateral side of the mitral annulus, by TDI; RC – regression coefficient; SE – standard error.

E/Eal is a continuous variable which includes the values of E/Eal for each patient and angina is an indicator variable (pseudovariable) that took the value 1 if the patient had the symptom and 0 if not.

Discussion

BNP plasma levels and clinical status

In the present study, severity of dyspnea and angina, two of the most common symptoms in patients with HCM, were found to be well correlated with BNP plasma levels. This finding is of clinical significance regarding the reliable evaluation of HCM patients, since it enables us to make a quantitative assessment of not only dyspnea but also angina, a symptom with a complicated pathophysiology and a yet unexplored relationship to objective clinical markers in this disease. Exertional dyspnea and angina occur in the presence of pure diastolic dysfunction, as a result of impaired relaxation and increased chamber stiffness, interwoven with myocardial ischemia, LVOT and mitral regurgitation.[10] The final common result is limited exercise capacity. The complexity and variety of mechanisms could possibly explain the interrelation between clinical and echocardiographic parameters observed in this study.

It is of note that while dyspnea was related to a considerable number of echocardiographic parameters, angina was only associated with LVOT obstruction. Neither filling pressures nor septal thickness were related to angina in this study. Perhaps a combination of pathophysiological mechanisms, apart from those linked to dyspnea individually or a group, lead to the provocation of angina and elevation of BNP plasma levels in patients with hypertrophic cardiomyopathy.

BNP plasma levels and morphological parameters of the left ventricle

The influence of left ventricular hypertrophy on BNP plasma levels has been reported previously. Nigishaki et al[4] pointed out the role of interventricular septal thickness in the control of BNP. Hasegawa et al[6] mentioned that in hypertrophic cardiomyopathy the immunohistochemical expression of BNP has a significant relation to myocardial hypertrophy, apart from disarray and fibrosis. Interventricular septal thickness was found to be positively correlated with BNP plasma levels in our study, in agreement with the results of other investigators.

BNP plasma levels and left ventricular diastolic function

In a study by Briguori et al,[7] there was no association of BNP plasma levels with left ventricular filling parameters from transmitral flow by pulsed wave Doppler. This finding was probably due to the fact that conventional methods of evaluation of left ventricular diastolic function are unreliable in patients with HCM.[19] To overcome this problem, we used two relaxation indices that appear less preload-dependent: early Vp, by color M-mode, and early diastolic annular velocity (Eal), by tissue Doppler imaging. Nagueh et al[15] reported that left ventricular filling pressures can be estimated with reasonable accuracy in HCM patients by measuring E/Vp and E/Eal ratios.

As for the evaluation of regional left ventricular diastolic function by pulsed wave tissue Doppler imaging, we found that BNP plasma levels increase as local diastolic function acquires a "restrictive" pattern (with low values of A velocity), at the level of the mitral annulus and at the mid segment of the thick interventricular septum.

BNP plasma levels and LVOT obstruction

Some patients are more disabled by elevated left ventricular filling pressures due to LVOT and concomitant mitral regurgitation than by left ventricular diastolic function. This ventricular overload results in elevation of BNP plasma levels.

The present study confirms the results of Nigishaki et al[4] and Briguori et al,[7] showing high BNP plasma levels especially in patients with HCM. The most evident explanation for this finding is that left ventricle outflow obstruction is connected with a systolic overload of the left ventricle. However, taking into consideration the correlation of BNP plasma levels and the extent of left ventricular hypertrophy, it is possible that the rise in BNP levels could be an "epiphenomenon" of hypertrophy-induced re-expression of the fetal gene program, and not necessarily a marker of systolic overload, according to WJ Paulus' editorial comment.[20]

Principal determinants of BNP plasma levels

Considering the aforementioned data, it is clear that BNP plasma levels were well correlated with symptoms and a variety of echocardiographic parameters that determine both left ventricular structure and performance. LVOT obstruction (through systolic overload), left ventricular hypertrophy and left ventricular diastolic dysfunction (via elevation of end-diastolic pressures, which further increase end-diastolic stress), are factors that closely interact with and impact on BNP plasma levels.

Finally, after stepwise multiple linear regression analysis, we found that angina and left ventricular filling pressures, as reflected by the E/Eal ratio, seem to be the main determinants of BNP plasma levels.

According to this study, left ventricular diastolic dysfunction seems to be the fundamental stimulus for BNP secretion in hypertrophic cardiomyopathy. Possibly because of the homogeneity of the patient group, BNP was independent of such patient characteristics as age, heart rate, blood pressure, and body surface area.

There has been a growing awareness of the complicated pathophysiology and clinical heterogeneity of HCM. We believe that measurement of BNP plasma levels can help us substantially in our understanding of the sophisticated substrate and clinical course of this disorder. Echocardiography, on the other hand, can serve as a tool for objectively and independently assessing the severity of heart failure to aid in clinical decision and patient management.

The association of angina and left ventricular filling pressures with BNP plasma levels gives us the opportunity to combine two important symptoms in HCM: dyspnea, through filling pressures, and angina.

Study limitations

The two major limitations of this study were as follows: 1) patients did not undergo a cardiopulmonary exercise test (in order to determine maximal oxygen consumption), and 2) coronary angiography was not performed for elimination of the possible presence of underlying coronary artery disease.

Conclusions

In this study, not only dyspnea but also angina, another common symptom in HCM with various explanations, were found to be closely related to BNP plasma levels. On the other hand, left ventricular filling pressures obtained by echocardiography, which represent dyspnea in a more objective way than the NYHA classification, are closely related to BNP in HCM.

That means that, according to this study, the two most common symptoms in HCM, as well as left ventricular filling pressures, are correlated with BNP,

which can thus be used as an adjunctive, reliable and objective way of estimation of cardiac dysfunction in HCM.

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