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Original article

# N-terminal pro-brain natriuretic peptide is related with coronary flow velocity reserve and diastolic dysfunction in patients with asymmetric hypertrophic cardiomyopathy

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ABSTRACT

*Background:* The relations of elevated N-terminal pro-brain natriuretic peptide (NT-pro-BNP) and cardiac ischemia in hypertrophic cardiomyopathy (HCM) patients is uncertain. Therefore we designed the study with the following aims: (1) to analyze plasma concentrations of NT-pro-BNP in various subsets of HCM patients; (2) to reveal the correlations of NT-pro-BNP, myocardial ischemia, and diastolic dysfunction; (3) to assess predictors of the elevated plasma levels of NT-pro-BNP.

*Methods and results:* In 61 patients (mean age 48.9 ± 16.3 years; 26 male) with asymmetric HCM plasma levels of NT-pro-BNP were obtained. Standard transthoracic examination, tissue Doppler echocardiography with measurement of transthoracic coronary flow velocity reserve (CFVR) in left anterior descending artery (LAD) was done. Mean natural logarithm value of NT-pro-BNP was 7.11 ± 0.95 pg/ml [median value 1133 (interquartile range 561–2442) pg/ml]. NT-pro-BNP was significantly higher in patients with higher NYHA class, in obstructive HCM, more severe mitral regurgitation, increased left atrial volume index (LAVI), presence of calcified mitral annulus, elevated left ventricular (LV) filling pressure and in decreased CFVR. Levels of NT-pro-BNP significantly correlated with the ratio of E/e′ ($r = 0.534$, $p < 0.001$), LV outflow tract gradient ($r = 0.503$, $p = 0.024$), LAVI ($r = 0.443$, $p < 0.001$), while inversely correlated with CFVR LAD ($r = -0.569$, $p < 0.001$). When multivariate analysis was done only CFVR LAD and E/e′ emerged as independent predictors of NT-pro-BNP.

*Conclusion:* Plasma levels of NT-pro-BNP were significantly higher in HCM patients with more advanced disease. Elevated NT-pro-BNP not only reflects the diastolic impairment of the LV, but it might also be the result of cardiac ischemia in patients with HCM.



## Introduction

Brain natriuretic peptide (BNP) is an active hormone released from the cardiac ventricles as a prohormone in response to ventricular overloading and wall stress [1–3]. Both BNP and

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N-terminal fragment of prohormone (NT-pro-BNP) are accurate markers of abnormal left ventricular (LV) wall stress, indicating LV systolic and diastolic dysfunction [3]. NT-pro-BNP is known to be elevated in patients with hypertrophic cardiomyopathy (HCM) which correlates with echocardiographic and clinical variables [4]. However, it has been suggested that elevated levels of NT-pro-BNP might also result from cardiac ischemia [1,3,5–7]. In patients with HCM ischemia is a common finding, due to microvascular dysfunction, and is reflected by decreased coronary flow velocity reserve (CFVR) [8,9]. The relations of elevated NT-pro-BNP and cardiac ischemia in HCM patients is uncertain. Therefore we designed the study with the following aims: (1) to analyze plasma concentrations of NT-pro-BNP in various subsets of HCM patients; (2) to reveal the correlations of NT-pro-BNP, myocardial ischemia, and diastolic dysfunction; (3) to assess predictors of the elevated plasma levels of NT-pro-BNP.

## Methods

### *Study population*

The study group consisted of 61 patients (mean age 48.9 ± 16.3 years; 26 male), with asymmetric HCM [20 patients with significant LV outflow tract gradient (LVOTG), and 41 patients without obstruction] prospectively included. The investigation was carried out from October 2009 to June 2013 at the Clinic for Cardiology, Clinical Center of Serbia, Belgrade.

The patients were recruited according to the following inclusion criteria: echocardiographic evidence of asymmetric myocardial hypertrophy, defined as a LV myocardial wall thickness ≥15 mm and septum/posterior wall ratio >1.3, in the absence of another cardiac or systemic cause of LV hypertrophy [10]. Hypertrophic obstructive cardiomyopathy was diagnosed if systolic gradient at rest was ≥30 mmHg in the LV outflow tract [10]. All patients had preserved ejection fraction (>50%). Coronary angiography was performed in 35 patients, and did not reveal significant coronary stenosis or epicardial coronary "bridging". The rest of the patients had either less than 5% probability of having coronary artery disease [11] or negative stress echocardiography test [12].

Exclusion criteria were: New York Heart Association (NYHA) class III or IV, severe mitral regurgitation, poor echocardiographic window, diabetes, chronic obstructive pulmonary disease, chronic renal impairment, and atrioventricular block.

Plasma levels of NT-pro-BNP were obtained immediately before echocardiographic and CFVR examinations in all patients and were analyzed by electrochemiluminescence immunoassay technique (ECLIA, Roche Diagnostics, Basel, Switzerland).

Patients' clinical characteristics, NYHA class, and arrhythmias on 24-hour Holter monitoring, and medical therapy were recorded in each patient.

Informed consent was obtained for all participants and the Medical Ethical Committee of the Clinical Center of Serbia approved the study protocol.

### *Echocardiographic examination*

Echocardiographic studies were performed with digital ultrasound system (Acuson Sequoia C256; Siemens Medical Solutions USA, Inc., Mountain View, CA, USA) with a 3V2C multifrequency transducer using second-harmonic technology. Standard two-dimensional, M-Mode, pulsed Doppler measures were done according to the current guidelines [13]. The average of three cardiac cycles was used for measurements of cardiac dimensions. The following data were collected in M-mode in parasternal long-axis view: LV end-diastolic diameter, LV end-systolic diameter, end-diastolic left atrial diameter, end-diastolic LV interventricular septum (IVS), and left posterior wall (PW) thickness. In addition, we also calculated IVS/PW ratio, as LV morphological parameter. LV and atrial volumes and ejection fraction were assessed using the modified Simpson biplane method [13]. Left atrial volume was indexed for body surface area (LAVI) and LAVI enlargement was considered as >34 ml/m$^2$ [13]. LVOTG was examined by combined use of color Doppler, pulsed-wave Doppler, and continuous-wave Doppler echocardiography at rest.

Early and late diastolic peak filling velocities E and A wave were measured at the mitral leaflet tips. The early (e′) and late (a′) diastolic velocities at lateral corner of mitral annulus were assessed with pulse-wave tissue Doppler from a standard apical 4-chamber view. Filters were set to exclude high-frequency signals, while direction of annulus motion was aligned with the scan line direction. Signals were obtained in end-expiratory cycle. Ratio of early transmitral flow velocity to early diastolic lateral mitral annulus velocity (E/e′) has been shown to be a reasonably accurate noninvasive predictor of elevated LV filling pressure [14,15]. In addition, the cut-off value of 10 for lateral E/e′ ratio was used to predict elevated LV filling pressure as previously reported in HCM patients [14,15].

### *Coronary flow velocity reserve*

CFVR was measured by transthoracic Doppler echocardiography. Distal part of left anterior descending coronary artery (LAD) was evaluated using a 4-MHz transducer. For color Doppler flow mapping the velocity range was set in the range of 16–24 cm/s. Visualization of distal segment of LAD artery was done in a modified three-chamber view. Blood flow velocity was measured by pulsed wave Doppler echocardiography using a sample volume of 3–5 mm wide. Alignment of ultrasound beam direction with distal LAD flow was as parallel as possible, with the stable transducer position at rest and during maximal hyperemia. Peak diastolic coronary flow velocity was measured in basal conditions and during maximal hyperemia, which was induced with adenosine (0.14 mg/kg/min intravenously, during 2 min). Three optimal diastolic flow profiles at rest and during hyperemia were measured, and results averaged. CFVR was calculated as the ratio of hyperemic to basal peak diastolic flow velocities, and preserved CFVR values were considered to be above 2 [9,16,17]. All studies were stored on magneto-optical discs for offline analysis. Blood flow velocity measurements were done offline, using the integrated softer package of the ultrasound system, by two experienced investigators. We have previously reported interobserver agreement for CFVR evaluation of 90% [15].

### *Statistical analysis*

All data were entered into a database, and then processed in the statistical program SPSS (version 15; Chicago, IL, USA). All numeric data were expressed as mean ± standard deviation (SD), and attributed as frequency, or percentages. Differences in continuous variables were assessed with the Student's *t* test. Chi-square test was used for categorical variables. Statistical correlation between echocardiographic variables was examined with Pearson's linear correlation coefficient. Multivariable linear regression was done, allowing all continuous variables (for greater statistical power) with $p < 0.05$ from univariable linear regression analysis to enter the model. Results are expressed as partial linear regression coefficients ($B$) and their 95% confidence intervals (CIs) for a 1 SD change in the variable. Backward stepwise method of variable entry in multivariable linear regression analysis was used to detect independent predictors of natural logarithm value of NT-pro-BNP for patients with HCM. Statistical significance was defined as $p < 0.05$.

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