ORIGINAL ARTICLE

Evaluation of NT-proBNP concentrations during exercise in asymptomatic patients with severe high-gradient aortic stenosis

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KEY WORDS

asymptomatic severe aortic stenosis, echocardiography, NT-proBNP, stress echocardiography

ABSTRACT

INTRODUCTION The effect of asymptomatic severe aortic stenosis (ASAS) on N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels ar rest and during exercise, as well as their relevance for clinical practice remain controversial.

OBJECTIVES The aim of this study was to test the hypothesis of whether the evaluation of NT-proBNP concentrations during exercise provides additional information about the severity of aortic stenosis and left ventricular remodeling in patients with ASAS.

PATIENTS AND METHODS A total of 50 patients with ASAS (mean age, 38.4 ±18.1 years) and 21 healthy subjects (mean age, 43.4 ±10.6 years) were enrolled. Rest and exercise echocardiography was performed to evaluate maximum velocity (V_{max}), mean aortic gradient (AG), and aortic valve area (AVA). The left ventricular mass index (LVMI) was calculated. NT-proBNP concentrations at rest and during exercise were assessed, and the difference between the 2 values was calculated (ΔNT-proBNP).

RESULTS NT-proBNP and ΔNT-proBNP levels at rest and during exercise were significantly higher in the ASAS group compared with the control group. In the ASAS group, NT-proBNP levels at rest significantly correlated with LVMI ($r = 0.432$; $P < 0.0001$), AVA ($r = -0.408$; $P < 0.0001$), V_{max} ($r = 0.375$; $P = 0.002$), and mean AG ($r = 0.257$; $P = 0.03$). NT-proBNP levels during exercise significantly correlated with LVMI ($r = 0.432$; $P < 0.0001$), mean AG ($r = 0.401$; $P = 0.001$), and AVA ($r = -0.375$; $P = 0.001$). In the multivariate logistic regression model, the factors independently associated with NT-proBNP both at rest and during exercise were age, AVA, and LVMI.

CONCLUSIONS NT-proBNP levels at rest provide valuable information for identifying patients with more advanced left ventricular hypertrophy secondary to severe aortic stenosis. NT-proBNP levels during exercise do not provide new information on the severity of AS.

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INTRODUCTION Aortic stenosis (AS) is the most common acquired valvular heart disease in Western countries. The diagnosis is usually made by auscultation and confirmed by echocardiography before clinical symptoms develop.[1] Both the American College of Cardiology/American Heart Association and European Society of Cardiology (ESC) guidelines recommend aortic valve replacement for patients with severe AS, who present with clinical symptoms or left ventricular (LV) systolic dysfunction (LV ejection fraction [LVEF] <50%).[2,3] However, the management of asymptomatic patients with severe AS remains a subject of debate.

Severe AS results in increased plasma levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP). Several studies have shown a correlation between plasma NT-proBNP levels and parameters describing the severity of AS.[4-6] On the basis of the currently available evidence, the need for better risk stratification of asymptomatic patients with severe AS is widely recognized, and biomarkers may play an important role here.[7,8] Recent ESC guidelines have suggested the usefulness of measuring NT-proBNP levels in asymptomatic patients with severe AS in order to better stratify the disease.[3]

Previous studies reported that exercise echocardiography improves risk stratification of patients with asymptomatic AS.[9-11] Additionally, NT-proBNP concentrations at rest and during exercise are associated with increased risk of cardiovascular events.[5,12] NT-proBNP is often used as a surrogate marker for the biologically active hormone (brain natriuretic peptide [BNP]), as it is more stable in vivo. The release of BNP is primarily caused by myocyte stretch and its half-life is about 20 minutes, whereas the half-life of NT-proBNP is 2 hours. Longer half-life is favorable in the evaluation of exercise echocardiography.

There are no data on whether an increase in NT-proBNP levels during exercise (ΔNT-proBNP) in patients with asymptomatic severe AS (ASAS) is of any value for a more precise prognostication. Therefore, the aim of this study was to evaluate plasma NT-proBNP levels both at rest and during exercise in patients with high-gradient ASAS with preserved LVEF, as well as to test the hypothesis of whether the evaluation of NT-proBNP levels during exercise and ΔNT-proBNP may add information about the severity of AS and of left ventricular remodeling.

PATIENTS AND METHODS

Study population From January 2011 to October 2013, 50 consecutive patients with high-gradient ASAS (the ASAS group) determined on transthoracic echocardiography were included in the study. All patients were diagnosed with high-gradient valvular ASAS (aortic valve area [AVA] <1 cm^2 or AVA index <0.6 cm^2/m^2) with preserved LVEF. All patients were fit to undergo stress echocardiography. An asymptomatic patient was defined as an individual without any of the classic triad of symptoms, namely, dyspnea, angina, or syncope. The exclusion criteria were as follows: technically inadequate echocardiogram, more than trivial aortic regurgitation, coexistence of other valvular diseases, arrhythmias (including atrial fibrillation or flutter), uncontrolled arterial hypertension, coronary artery disease (diagnosed by clinical, electrocardiographic, and echocardiographic evaluation at rest or by exercise echocardiography) or myocardial infraction in the past, and muscular or lung disease. The control group consisted of 21 healthy subjects. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. The local ethics committee approved the study protocol, and written informed consent was obtained from each patient.

Measurement of NT-proBNP levels A venous blood sample was collected before and during peak exercise. Blood was collected into tubes containing EDTA. NT-proBNP levels were determined using an immunoradiometric assay (Cobas e 601 analyzer, Roche Diagnostics, Germany). The normal range for NT-proBNP levels was determined as 5 to 125 pmol/l.

Echocardiography All patients underwent a complete transthoracic echocardiographic study with a GE Medical System Vivid 9 (GE Vingmed Ultrasound, Horten, Norway) with a 2.5-MHz transducer. M-mode, 2-dimensional, and Doppler techniques were used. The values of all echocardiographic parameters were obtained as the average of 3 consecutive cardiac cycles. Doppler echocardiographic data were obtained at rest and at peak exercise.

LV end-systolic and end-diastolic diameters, interventricular septal diastolic diameter, and posterior wall diastolic diameter were measured using the M-mode technique according to the American Society of Echocardiography recommendations.[13] The left ventricular mass was calculated using the modified cube formula proposed by Devereux et al[14] and was indexed to the body surface area to obtain the LV mass index (LVMI). LV hypertrophy (LVH) was defined as an LVMI of 95g/m^2 or higher for women and 115 g/m^2 or higher for men.[15] LVEF was measured by the biplane Simpson disk method. AVA was calculated using the continuity equation, while the maximum velocity (V_{max}) and mean aortic gradient (AG) were obtained with continuous-wave Doppler ultrasound.

Exercise echocardiography Stress echocardiography was performed on a cycloergometer, in the supine position, according to the World Health Organization protocol, beginning at a load of 25 Watt with an increase of 25 Watt every 2 minutes at each stage. The electrocardiogram monitoring and blood pressure control were performed continuously throughout the stress test. The criteria for stress test interruption were as follows: reaching the heart rate limit appropriate for the age, the occurrence of symptoms (shortness of breath, chest pain), a decrease in systolic blood pressure (SBP) by more than 10 mmHg despite an increase in the load, an excessive increase in blood pressure (SBP ≥220 mmHg), complex ventricular arrhythmia, fatigue, and the patient's request.

The echocardiography and stress echocardiography study protocols were identical for the ASAS and control groups.

Statistical analysis Continuous variables were expressed as mean ± SD. The *t* test was used to assess differences between mean values, and categorical variables were compared with the χ^2 test and Fisher exact test, as appropriate. Pearson's correlation was used to investigate the correlations of variable factors with echocardiographic parameters. The receiver operating characteristic (ROC) analysis was used to assess the predictive accuracy of NT-proBNP at rest and during exercise for detecting LVH. The areas under the ROC curve were calculated for NT-proBNP concentrations at rest and during exercise for their performance to LVH. The parameters identified as statistically significant based on a univariate analysis (P <0.05) were included in multivariate linear regression models to determine the combined effect of several variables on the NT-proBNP concentration. A P value of less than 0.05 was

TABLE 1 Clinical and echocardiographic variables in the study and control groups

Variables	ASAS group (n = 50)	Control group (n = 21)	*P* value
age, y	38.4 ±18.1	43.4 ±10.6	0.2
sex, female/male	26/24	10/11	0.7
BSA, m^2	1.84 ±0.24	1.84 ±0.23	0.1
SBP at rest, mmHg	116.5 ±22.1	123.4 ±18.4	0.2
DBP at rest, mmHg	79.0 ±10.7	79.7 ±9.6	0.8
SBP on exercise, mmHg	162.0 ±27.2	194.9 ±29.3	<0.0001
DBP on exercise, mmHg	90.8 ±12.8	95.0 ±14.9	0.3
maximum load exercise test, PW	132.7 ±36.9	150.0 ±41.1	0.1
LVMI, g/m^2	117.0 ±27.7	88.2 ±20.6	<0.0001
SVI at rest, ml/m^2	46.4 ±7.1	42.9 ±13.4	0.1
SVI on exercise, ml/m^2	47.3 ±9.1	45.4 ±10.1	0.3
LVEF at rest, %	72.3 ±3.91	65.4 ±3.97	<0.0001
LVEDV, ml	89.6 ±23.1	90.5 ±33.4	0.9
LVESV, ml	25.0 ±7.3	31.7 ±13.9	0.01
V_{max} at rest, m/s	4.6 ±0.4	1.3 ±0.2	<0.0001
V_{max} on exercise, m/s	5.6 ±0.6	1.9 ±0.3	<0.0001
mean AG at rest, mmHg	52.3 ±10.6	4.1 ±1.4	<0.0001
mean AG on exercise, mmHg	82.3 ±18.2	9.0 ±2.9	<0.0001
AVA at rest, cm^2	0.8 ±0.1	2.8 ±0.7	<0.0001
AVA on exercise, cm^2	0.8 ±0.2	2.7 ±0.6	<0.0001

Data are presented as mean ± SD except for sex (number of patients).

A *P* value of less than 0.05 was considered statistically significant.

Abbreviations: AG, aortic gradient; ASAS, asymptomatic severe aortic stenosis; AVA, aortic valve area; BSA, body surface area; DBP, diastolic blood pressure; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVMI, left ventricular mass index; SBP, systolic blood pressure; PW, peak watts; SVI, stroke volume index; V_{max}, maximum velocity

TABLE 2 N-terminal pro-B-type natriuretic peptide concentrations at rest and during exercise in patients with asymptomatic severe aortic stenosis

Variables	ASAS group (n = 50)	Control group (n = 21)	*P* value
NT-proBNP at rest, pmol/l	167.6 ±147.2	50.9 ±41.0	<0.0001
NT-proBNP on exercise, pmol/l	180.3 ±152.0	56.4 ±44.9	<0.0001
ΔNT-proBNP, pmol/l	12.8 ±19.1	5.5 ±6.7	0.02

Data are presented as mean ± SD.

A *P* value of less than 0.05 was considered statistically significant.

Abbreviations: NT-proBNP, N-terminal pro-B-type natriuretic peptide; others, see **TABLE 1**

considered statistically significant. All statistical analyses were performed with commercially available computer software: PASW Statistics 18 (SPSS Inc., Chicago, Illinois, United States).

RESULTS The study included 50 patients with high-gradient ASAS (mean age, 38.4 ±18.1 years) and 21 healthy subjects (control group; mean age, 43.4 ±10.6 years). Clinical and echocardiographic data are shown in **TABLE 1**. There were no significant differences in age, body surface area, or systolic and diastolic blood pressures between the analyzed groups. Well-controlled arterial hypertension was observed in 20% of the patients in the ASAS group and in 19% of controls. Bicuspid aortic valve was found in 31 patients (62%) in the ASAS group. There were no differences in the maximum load in stress echocardiography. LVH was found in 72% of the patients in the ASAS group.

Data on NT-proBNP at rest and peak exercise as well as on ΔNT-proBNP in the ASAS and control groups are shown in **TABLE 2**. In the ASAS group, ΔNT-proBNP was significantly higher in patients with concentric hypertrophy compared with those with concentric remodeling (16.8 ±17.7 and 7.1 ±5.0, respectively, $P = 0.007$). In the ASAS group, NT-proBNP levels at rest were significantly correlated with LVMI ($r = 0.432$; $P < 0.0001$), AVA ($r = -0.408$; $P < 0.0001$), V_{max} ($r = 0.375$; $P = 0.002$), and mean AG ($r = 0.257$; $P = 0.03$) at rest.

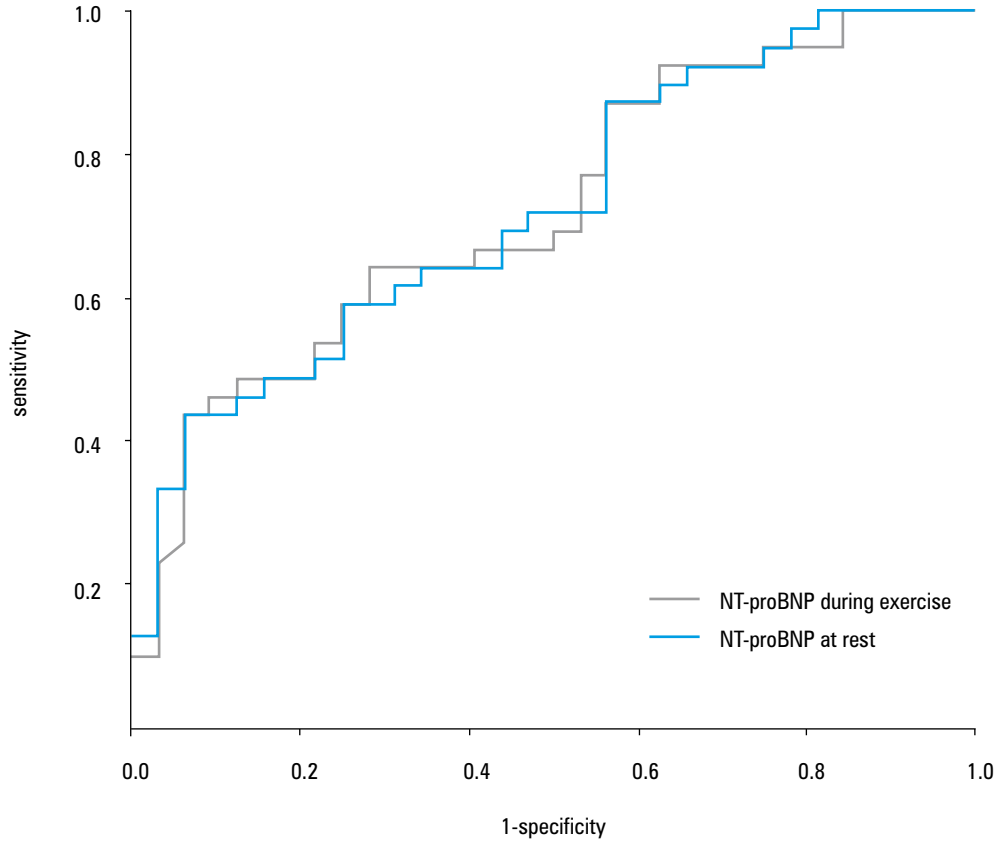

FIGURE 1 Receiver operating characteristic (ROC) curve for identification of left ventricular hypertrophy; for N-terminal pro-B-type natriuretic peptide (NT-proBNP) at rest: area under the ROC curve (AUC), 0.723; for NT-proBNP during exercise: AUC, 0.724

Exercise NT-proBNP levels significantly correlated with LVMI (r = 0.432; P <0.0001), mean AG (r = 0.401; P = 0.001), and AVA (r = –0.375; P = 0.001). There were no significant correlations between NT-proBNP levels at rest and during exercise and LVEF, stroke volume index, LV end-diastolic volume, and LV end-systolic volume. In addition, there was no significant correlation between ΔNT-proBNP and AVA (r = –0.172; P = 0.16), mean AG (r = 0.160; P = 0.18), and V_{max} (r = –0.220; P = 0.07) at rest. Finally, there were no significant correlations with parameters describing the severity of AS during exercise.

NT-proBNP levels at rest and during exercise were characterized by similar performance, with the areas under the ROC curve of 0.723 and 0.724, respectively, for performance to LVH (FIGURE 1).

To evaluate independent factors related to NT-proBNP levels at rest and during exercise, logistic regression models were performed. In the multivariate logistic regression model including age, sex, LVMI, mean AG, and AVA, the factors independently associated with NT-proBNP levels at rest and during exercise were age, AVA, and LVMI (TABLE 3).

DISCUSSION The management of asymptomatic patients with aortic valve stenosis remains a challenge for cardiologists and surgeons. According to the ESC guidelines concerning the management of valvular heart disease, aortic valve replacement may be considered (Class IIb) in asymptomatic patients with severe AS, normal EF, and excessive LVH in the absence of hypertension and significantly elevated levels of biomarkers.[3] Still there is no cut-off point established for myocardial thickness, LVMI, or biomarker levels in relation to timing of aortic valve replacement. This is also related to other causes of LVH, such as arterial hypertension. Antonini-Canterin et al[16] found that in patients with symptomatic AS with coexisting arterial hypertension, symptoms of AS develop at an earlier stage of the disease, with larger valve areas as compared with patients with isolated severe AS.

Biomarkers are used to assess the severity and prognosis in a particular disease or to monitor the response to treatment of a disease.[17] In evaluating the severity of valvular heart disease, a sensitive biomarker would be very useful, potentially providing support to clinical management in asymptomatic patients with AS.[8,12,18] A previous study found that AS is strongly associated with increased NT-proBNP levels.[7] Several studies showed a correlation between plasma NT-proBNP levels and the severity of AS.[4,5] Talwar et al[6] found higher NT-proBNP concentrations in patients with AS compared with the control group. Additionally, these authors proved that NT-proBNP levels correlated with the value of mean transvalvular gradient across the aortic valve. Similar data were provided by Prasada et al.[7] Qi et al[19] discovered that resting NT-proBNP levels negatively correlated with AVA (r = –0.60; P ≤0.001). Moreover, as stated by other authors, NT-proBNP levels at rest seem to be useful for better risk stratification in this group of patients.[20,21] In the present study, a similar correlation was found for NT-proBNP concentrations at rest and parameters describing the severity of AS (AVA, V_{max}, and

TABLE 3 Univariate and multivariate linear regression models for factors associated with N-terminal pro-B-type natriuretic peptide levels at rest and during exercise

Variables	NT-proBNP at rest				NT-proBNP during exercise			
	univariate model		multivariate model		univariate model		multivariate model	
	ß	*P*	ß	*P*	ß	*P*	ß	*P*
age, y	0.413	<0.0001	0.458	<0.0001	0.414	<0.0001	0.458	<0.0001
sex	0.147	0.22	–	–	0.167	0.16	–	–
LVMI, g/m^2	0.462	<0.0001	0.341	0.001	0.477	<0.0001	0.290	0.004
mean AG[a], mmHg	0.397	0.001	–	–	0.358	0.68	–	–
AVA[a], cm^2	–0.368	<0.002	– 0.333	0.001	– 0.839	<0.0001	–0.372	<0.0001

A *P* value of less than 0.05 was considered statistically significant.

a In the univariate and multivariate models for NT-proBNP at peak exercise, mean AG and AVA were measured at rest and during exercise.

Abbreviations: see TABLES 1 and 2

mean AG). However, the strongest correlation of NT-proBNP concentrations was found for LVMI.

Patients with asymptomatic AS and abnormal response to exercise testing are at increased risk for cardiovascular events, and they should be considered as candidates for surgery (Class IIa). There are plenty of available data on an increase in exercise NT-proBNP levels in patients with AS. According to the ESC guidelines concerning the management of valvular heart disease, stress echocardiography is not recommended in patients with ASAS. In the present study, the test has been used to evaluate the relation between the concentrations of NT-proBNP during exercise and parameters of AS severity. Henri et al[22] studied 61 patients with at least moderate AS and preserved LVEF. They concluded that diastolic function assessed by E/e' was independently associated with the BNP concentration assessed during exercise. Capoulade et al[12] analyzed an inhomogeneous group of 211 asymptomatic patients with AS, of whom 157 patients had severe AS. They reported that BNP levels at peak exercise were significantly associated with the higher risk of cardiovascular events during follow-up (1.5 ±1.2 years).

Elevated levels of biomarkers at rest or during exercise are not specific to AS severity alone but rather reflect the total burden of disease on the left ventricle. Therefore, they should be interpreted in the context of other parameters reflecting AS severity. In our study, the factors independently associated with NT-proBNP levels at rest and during exercise were similar: LVMI, AVA, and age. Moreover, based on the ROC curves, we confirmed a similar sensitivity of NT-proBNP concentrations at rest and during exercise for prediction of LVH. It indicates that NT-proBNP levels during exercise did not provide any additional information about the consequence of AS on LV remodeling. It was reported that higher LVMI is a risk factor providing independent prognostic information, in addition to the clinical evaluation.[23] Cioffi et al[24] showed that excessive LVH strongly correlated with death, congestive heart failure, and nonfatal myocardial infarction in 218 patients with ASAS. These correlations were independent of the patient's age, extent of aortic valve calcification, renal dysfunction, or the presence of concomitant diabetes mellitus, the factors that have been associated with worse prognosis in patients with ASAS in previous studies.

One of the aims of this study was to answer the question of whether ΔNT-proBNP provided additional data on the severity of AS. We showed that the parameter was significantly increased in patients with severe AS compared with the control group. However, we did not find any correlation between the degrees of the increase in ΔNT-proBNP and parameters describing the severity of AS.

Data presented in this paper emphasize the role of a detailed assessment of LVH by echocardiography and the role of elevated concentrations of NT-proBNP at rest in studying patients with ASAS. In conclusion, our study showed that plasma NT-proBNP concentrations at rest provide valuable additional information for selecting patients with more advanced LVH secondary to severe AS and selecting patients with more advanced disease. The study revealed no additional information regarding the severity of AS related to an increase in NT-proBNP levels during exercise.

Limitations Although our findings are encouraging, the study has several limitations. The sample size was relatively small. Further longitudinal studies with the assessment of clinical outcomes during follow-up are essential to confirm the applicability of our findings for clinical practice and for the management of asymptomatic patients with severe AS.

Contribution statement PD, AL, AK, and PH conceived the idea of the study. All authors were involved in data collection. AL performed the echocardiographic studies. PD, AL, AK, and PH analyzed the data. All authors edited and approved the final version of the manuscript. AK and PH contributed equally and may be both considered as equal "senior" authors.

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Ocena stężenia NT-proBNP w czasie wysiłku u chorych z ciężką bezobjawową stenozą aortalną

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SŁOWA KLUCZOWE

ciężka bezobjawowa stenoza aortalna, echokardiografia, echokardiograficzny test wysiłkowy, NT-proBNP

STRESZCZENIE

WPROWADZENIE Wpływ ciężkiej bezobjawowej stenozy aortalnej (*asymptomatic severe aortic stenosis* – ASAS) na spoczynkowe i wysiłkowe stężenia N-końcowego propeptydu natriuretycznego typu B (*N-terminal pro-B-type natriuretic peptide* – NT-proBNP) oraz ich znaczenie kliniczne jest niejednoznaczne.

CELE Celem badania było sprawdzenie hipotezy, czy ocena stężenia NT-proBNP w czasie wysiłku dostarcza dodatkowych informacji dotyczących ciężkości stenozy aortalnej i zmian geometrii lewej komory serca u chorych z ASAS.

PACJENCI I METODY Do badania włączono 50 pacjentów z ASAS (średni wiek: 38,4 ±18,1 roku) i 21 zdrowych osób (średni wiek: 43,4 ±10,6 roku). W badaniu echokardiograficznym w spoczynku i wysiłku oceniono maksymalną prędkość (V_{max}), średni gradient aortalny (GA) i pole powierzchni zastawki (*aortic valve area* – AVA). Obliczono indeks masy lewej komory (*left ventricular mass index* – LVMI). Oznaczono stężenie NT-proBNP w spoczynku i wysiłku oraz obliczono różnicę między obiema wartościami NTpro-BNP (ΔNT-proBNP).

WYNIKI Spoczynkowe i wysiłkowe stężenia NT-proBNP i ΔNT-proBNP były istotnie wyższe w grupie ASAS w porównaniu z grupą kontrolną. W grupie ASAS spoczynkowe NT-proBNP istotnie korelowało z: LVMI ($r = 0,432$; $p < 0,0001$), AVA ($r = -0,408$; $p < 0,0001$), V_{max} ($r = 0,375$; $p = 0,002$) oraz średnim GA ($r = 0,257$; $p = 0,03$). Wysiłkowe NT-proBNP istotnie korelowało z: LVMI ($r = 0,432$; $p < 0,0001$), średnim GA ($r = 0,401$; $p = 0,001$) i AVA w wysiłku ($r = -0,375$; $p = 0,001$). W modelu regresji wieloczynnikowej czynnikami niezależnie związanymi ze spoczynkowymi i wysiłkowymi stężeniami NT-proBNP były wiek, AVA i LVMI.

WNIOSKI Spoczynkowe stężenie NT-proBNP pozwala wyodrębnić chorych o bardziej zaawansowanym przeroście mięśnia lewej komory, związanym z ciężką stenozą aortalną. Wysiłkowe stężenie NT-proBNP nie dostarcza nowych danych dotyczących zaawansowania stenozy aortalnej.

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