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NT-proBNP increase during stress echocardiography predicts significant changes in ischemic mitral regurgitation severity in patients qualified for surgical revascularization

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NT-proBNP increase during stress echocardiography predicts significant changes in ischemic mitral regurgitation severity in patients qualified for surgical revascularization

Running Title: NT-proBNP increase with exercise in patients with ischemic mitral regurgitation

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Abstract

Background: In many patients, significant changes in ischemic mitral regurgitation (IMR) severity during exercise can be observed independent of the degree of IMR at rest. This study aimed to investigate the correlations between N-terminal fragment B-type natriuretic peptide (NT-proBNP) and echocardiography measurements at rest and at peak exercise in patients with moderate IMR who qualified for surgical revascularization.

Methods: A total of 100 patients eligible for coronary artery bypass grafting, were included in this prospective study. All patients underwent exercise echocardiography. Additionally, the levels of NT-proBNP were measured at rest and after peak exercise.

Results: A positive correlation of absolute NT-proBNP levels with effective regurgitant orifice area (EROA) were observed and with tricuspid regurgitant peak gradient (TRPG) at peak exercise. Absolute ΔNT-proBNP during exercise and the tenting area at rest were independent predictors of severe IMR at peak exercise. The level of absolute ΔNT-proBNP during exercise and coaptation height at rest were the most important predictors of significant increases in TRPG. The best cutoff value for ΔNT-proBNP as a predictor for increases in EROA at peak exercise was 68.9 pg/mL and to predict an increase in TRPG ≥ 50 mmHg at peak exercise was 68 pg/mL.

Conclusions: The level of ΔNT-proBNP during exercise was the most important

parameter in predicting significant changes in IMR severity and pulmonary pressure. Based on the present data, it can be speculated that integration of the assessment of NT-proBNP at rest and at exercise might improve patient selection for valve surgery.

Key words: natriuretic peptides, ischemic mitral regurgitation, exercise echocardiography

Introduction

Secondary ischemic mitral regurgitation (IMR) has a dynamic nature. In many patients, significant changes in IMR severity during exercise can be observed independent of the degree of IMR at rest [1–3]. An exercise-induced increase in IMR severity is related to left ventricle (LV) remodeling and mitral valve deformation indices, namely, tenting area (TA) and coaptation height (CH), as well as LV synchronicity [4–6].

Natriuretic peptides such as B-type natriuretic peptide (BNP) and its N-terminal fragment (NT-proBNP) are released from ventricular and atrial myocardium in response to increased wall stress (left and right ventricle) and left atrial pressures due to increasing severity of mitral regurgitation [7–11]. Previous studies have suggested that BNP or NT-proBNP levels increase with exercise in patients with coronary artery disease [12], heart failure [13], organic mitral regurgitation [14], and mitral stenosis [15]. However, NT-proBNP levels during exercise do not provide new information on the severity of aortic stenosis [16]. The value of serial measurements of NT-proBNP at rest and during exercise in patients with IMR has not yet been evaluated.

Optimal management of moderate IMR in patients qualified for coronary artery bypass grafting (CABG) is still controversial [17, 18]. Hypothesized herein, that the absolute increase in NT-proBNP with exercise is a reliable parameter in predicting a significant increase in IMR severity and pulmonary systolic artery pressure and may help in the identification of high-risk patients with moderate IMR qualified for CABG. This would help improve risk stratification and identification of the subgroups of patients who could benefit from various surgical strategies (CABG or CABG with mitral repair).

The main purpose of the present study was to assess the correlation between NT-proBNP levels and echocardiography measurements at rest and at peak exercise in patients with moderate IMR, qualified for surgical revascularization.

Methods

Study population

A total of 100 patients (mean age 64.4 ± 7.9 years) with a history of myocardial infarction (MI) and were eligible for CABG were included in a prospective study. The time frame for enrollment of patients into the study was 24 months. All patients had moderate IMR caused by restrictive systolic leaflet motion (Carpentier's type IIIb), with or without annular dilatation, which occurred in ≥ 16 days from MI, with no evidence of primary leaflet, chordal, or papillary muscle pathology, excluding mechanical complications of MI.

The study inclusion criterion was the presence of a significant area of viable myocardium, as seen in the improvement in wall motion of at least four dysfunctional segments during dobutamine stress echocardiography (DSE). Exclusion criteria included left bundle branch block, unstable angina, prosthetic heart valve, other valvular or congenital heart diseases, renal failure (creatinine > 2 mg/dL), history of CABG, severe heart failure symptoms (New York Heart Association [NYHA] IV), clinical limitations to exercise testing, and atrial fibrillation before exercise testing.

Echocardiographic and clinical assessment were performed before surgery.

Each patient signed an informed consent form, and the study was approved by the institutional review board of the Medical University of Warsaw. The study had been conducted according to the principles stated in the Declaration of Helsinki.

Clinical data

Clinical assessment was comprised of a careful exploration of patient history and physical examination and was performed at the time of enrollment. Experienced cardiologists blinded to the results of NT-proBNP measurements and echocardiographic findings assessed the functional status. Clinical status was determined according to the criteria of the NYHA classification system and the Canadian Cardiovascular Society (CCS) functional class for heart failure and angina symptoms, respectively.

Echocardiographic measurements and calculations

Transthoracic echocardiograms (TTE) were performed within 2 days before surgery. All patients underwent TTE in the left lateral decubitus position at rest and during DSE. For accuracy purposes, the images obtained at rest and during stress tests were independently analyzed with a blinded method by two experienced echocardiographers.

All examinations were carried out using the iE33 system manufactured by Philips, a broadband transducer for TTE of 2.5 to 3.5 MHz frequencies. Echocardiographic measurements were averaged over three cardiac cycles.

Ischemic mitral regurgitation severity was assessed by measuring the effective regurgitant orifice area (EROA), with EROA > 10 mm^2 and < 20 mm^2 considered moderate and EROA $\geq$ 20 mm^3 considered severe, as well as mitral regurgitation volume (MRvol) with MR vol $\geq$ 30 mL considered severe [18–20]. EROA and MRvol was calculated using flow convergence (proximal isovelocity surface area-proximal isovelocity surface area [PISA] method). The radius of the PISA (r) is measured from the vena contracta level to the point of color Doppler aliasing. EROA is calculated as: $6.28 \times r^2 \times$ Va/Peak V RegJet where Va is aliasing velocity and VRegJet is the peak velocity of the regurgitant jet by Continuous Wave Doppler. The MRvol is calculated as EROA $\times$ VTI RegJet where VTI RegJet is the VTI of the regurgitant jet. Wall motion abnormalities were evaluated in accordance with the recommendations of the American Society of Cardiology. The wall motion score index was calculated according to a 17-segment model [21]. The left ventricular volumes and ejection fraction (EF) were assessed by the biapical Simpson disk method [22]. Sphericity indices (SI) were obtained at end-diastole (SId) and end-systole (SIs) in the apical view. Pulmonary systolic arterial pressure can be estimated from the maximal tricuspid regurgitant peak gradient (TRPG) using the simplified Bernoulli equation ($\Delta P = 4V^2$, where V = maximal tricuspid regurgitant velocity [TRV] in m/s), adding an assumed right atrial pressure (RAP) which can be estimated by echocardiography based on the diameter and respiratory variation in diameter of the inferior vena cava. However, TRV > 3.4 m/s indicates a high probability of pulmonary hypertension. In the present analysis it was assumed that TRPG $\geq$ 50 mmHg means significant pulmonary hypertension [23]. Mitral valve deformation was evaluated by measuring TA, i.e., the area enclosed between mitral leaflets and the line of annular plane, and

CH, i.e., the distance between leaflet coaptation and mitral annular plane from the parasternal long-axis view at mid-systole [24].

Low-dose DSE was used in IMR patients to distinguish akinetic viable segments from nonviable myocardial regions of the LV [25]. DSE was performed in accordance with current guidelines [26]. A graded dobutamine infusion started at 5 mcg/kg/min and was increased at 3-min intervals to 10, 20 mcg/kg/min.

Exercise echocardiography

All subjects underwent a symptom-limited graded exercise echocardiography (ExE) test to assess the dynamics of IMR changes and TRPG, the latter as the exponent of right ventricle overload. The symptom-limited grade ExE was performed according to the following protocol: the initial workload of 25 watts was maintained for 3 min, and then the workload was increased every 2 min by 25 W. Blood pressure and a 12-lead electrocardiogram was recorded every 2 min. Two-dimensional and Doppler echocardiographic recordings were available throughout the test. Exercise was interrupted when ischemic electrocardiographic signs, fatigue, or intolerable dyspnea appeared [24].

NT-proBNP measurements

Venous blood samples were collected from an antecubital vein and placed into chilled EDTA tubes before and immediately after exercise. The specimens were centrifuged within half an hour at $-4^{\circ}C$ and then plasma was frozen at $-80^{\circ}C$ until analysis. NT-proBNP was measured by an electrochemiluminescence immunoassay (ProBNP Elecsys®, Roche Diagnostics GmbH). The absolute increase in NT-proBNP during exercise (absolute ΔNT-proBNP) was calculated as the difference between NT-proBNP at peak exercise and NT-proBNP at rest. An NT-proBNP value of 125 pg/mL was used to differentiate between normal and abnormal NT-proBNP levels.

Statistical analysis

All data were prospectively recorded using the institution's database. Continuous variables are presented as mean ± standard deviation (SD), and categorical variables are presented as either absolute numbers or percentages. The Spearman correlation coefficient was used to assess the relation between NT-proBNP changes and exercise echo parameters. Multiple linear regression analysis was used to

identify important predictors of significant increase of IMR severity (ERO exe ≥ 20 mm^2) and probability of pulmonary hypertension (TRPG ≥ 50 mmHg) at peak exercise echocardiography examination. Stepwise logistic regression analysis included age, NT-proBNP at rest and at peak exercise, and ΔNT-proBNP, as well as some echocardiography parameters at rest and at peak exercise, namely, EROA, MRvol, TRPG, TA, CH, left ventricular end-systolic volume (ESV), EF, and SIs. A receiver-operating characteristic (ROC) curve analysis was performed to identify the optimal cutoff point of NT-proBNP levels (at which sensitivity and specificity were maximal) to predict the increase in IMR severity and pulmonary systolic arterial pressure at peak exercise. Optimal cutoff values were determined as the rounding cutoff that gives the maximum sum of sensitivity and specificity. This value should be the shoulder at the top left of the ROC curve. The area under the curve (AUC) value was calculated as a measure of accuracy of the test. ROC analysis was performed for NT-proBNP at rest, NT-proBNP at peak exercise (NT-proBNP exe), and absolute ΔNT-proBNP as predictors of reaching the above-mentioned echo endpoints (EROA exe ≥ 20 mm^2 and TRPG ≥ 50 mmHg at peak exercise). The AUCs of the ROC curve for NT-proBNP at rest, NT-proBNP exe, and ΔNT-proBNP are given together with their 95% confidence intervals (95% CI) and are compared by the nonparametric test proposed by DeLong et al. [27]. A p value of < 0.05 was considered significant. Statistical analyses were performed with SAS software version 8.02 (SAS Institute Inc., Cary, NC).

Results

The mean age of the patients was 64.4 ± 7.9 years. Of the 100 patients analyzed, 56 were men and 44 were women. The mean logistic EuroSCORE was 7.1 ± 5.1%. All the patients were given optimal pharmacological treatment. Table 1 shows the clinical characteristics and NT-proBNP levels, and Table 2 the echocardiographic variables at rest and at peak exercise of the IMR patients. Table 3 presents correlation coefficients for associations between NT-proBNP (rest, exercise, and delta) and echocardiographic measures at rest and at peak exercise. Significant negative correlations were found between the plasma level of NT-proBNP and EF both at rest and after exercise (p < 0.0001), whereas positive moderate correlations were found between NT-proBNP and ESV (p < 0.0001) and TA (p < 0.0001) both at rest and after exercise. The correlation coefficients were similar for NT-proBNP at rest and NT-

proBNP exe. There were also weak, but significant, correlations between NT-proBNP and other resting or post exercise measurements of LV dimensions (LV end-diastolic dimension, LV end-systolic dimension), right ventricle function assessed using tricuspid annular plane systolic excursion (TAPSE), severity of IMR (EROA, MRvol), and probability of pulmonary hypertension assessed using TRPG. The correlation coefficients for the above-mentioned parameters were similar for NT-proBNP at rest and NT-proBNP exe, and no statistically significant correlation existed between NT-proBNP and patient age. Furthermore, significant changes in IMR severity and maximal TRPG during an exercise test were strongly associated with the level of absolute ΔNT-proBNP after exercise. A significant positive correlation was found between the level of absolute ΔNT-proBNP and EROA, MRvol, and TRPG at peak exercise (p < 0.001 for each). There was also a positive moderate correlation between ΔNT-proBNP and TA at rest (p < 0.0001). Multivariate stepwise logistic regression analysis showed that the levels of absolute ΔNT-proBNP and TA at rest were the only independent predictors of the development of severe IMR at peak exercise (p = 0.033 and p < 0.0001, respectively). Absolute ΔNT-proBNP and CH were independent predictors of a significant increase in TRPG at peak exercise (p = 0.033 and p = 0.0006, respectively) (Table 4).

The AUC for ΔNT-proBNP predicting an increased EROA of ≥ 20 mm^2 was 0.812 (95% CI 0.721–0.884; p = 0.0001; Fig. 1). The absolute increase in NT-proBNP level of > 68.9 pg/mL was the optimal cutoff, with a sensitivity of 67% and a specificity of 90%. For NT-proBNP exe, the AUC was 0.702 (95% CI 0.602–0.790; p = 0.0003), with an optimal cutoff of 924 pg/mL, sensitivity of 67%, and specificity of 74%. For NT-proBNP at rest, the AUC was 0.685 (95% CI 0.583–0.774; p = 0.0012); the optimal cutoff was 596 pg/mL, with sensitivity of 83% and specificity of 55%. The AUC that predicted an increased TRPG of ≥ 50 mmHg at peak exercise for ΔNT-proBNP was 0.842 (95% CI 0.756–0.908; p = 0.0001; Fig. 2). The absolute increase of NT-proBNP level of > 68 pg/mL was the optimal cutoff, with a sensitivity of 80% and specificity of 76%. For NT-proBNP exe, the AUC was 0.768 (95% CI 0.672–0.847; p = 0.004), with an optimal cutoff of 1015 pg/mL, sensitivity of 87%, and specificity of 74%. For NT-proBNP at rest, the AUC was 0.756 (95% CI 0.659–0.837; p = 0.0008), with an optimal cutoff of 926 pg/mL, sensitivity of 87%, and specificity of 73%. The ROC analysis confirmed the high predictive value of ΔNT-proBNP at peak exercise for reaching the analyzed endpoints (increased EROA of ≥ 20 mm^2 and

TRPG $\geq$ 50 mmHg at peak exercise). Table 5 presents the sensitivity, specificity, and AUC of the ΔNT-proBNP level for predicting abnormal peak-exercise pulmonary pressure thresholds and a significant increase in IMR severity (EROA $\geq$ 20 mm^2) at peak exercise.

Analyses of the ROC curves for EROA $\geq$ 20 mm^2 also indicated differences in the AUCs for NT-proBNP at rest, NT-proBNP exe, and ΔNT-proBNP. Pairwise comparisons of the ROC curves showed significant differences between ΔNT-proBNP and NT-proBNP at rest (p = 0.006), as well as between ΔNT-proBNP and NT-proBNP exe (p = 0.011). Similar results were not observed in the analysis of the ROC curves for TVP $\geq$ 50 mmHg (Figs. 1, 2).

Discussion

Secondary IMR considerably worsens the prognosis of patients after acute MI, both in the short- and long-term follow-up [1, 5]. It is difficult to elaborate on uniform treatment standards in this group of patients because of the complex mechanism and dynamic nature of IMR. In many patients, significant changes in IMR severity during exercise can be observed independent of the degree of IMR at rest [1–3]. Surgical correction should be considered in patients with severe secondary IMR undergoing CABG, but optimal management of moderate IMR in patients qualified for CABG remains controversial [17–18, 28–29].

When the complex and dynamic nature of IMR is taken into consideration, it seems that a more precise qualification of a patient to a proper surgical procedure should be broadened by the evaluation of the IMR variability in the exercise test as well as myocardial viability during DSE. The most important element of the analysis was the assessment of the relationships of the NT-proBNP levels, LV function, IMR severity, and maximal tricuspid regurgitant peak gradient changes at rest and during exercise, observed through echocardiography.

It was hypothesized that the NT-proBNP level with exercise could be a reliable parameter in predicting a significant increase in IMR severity and pulmonary systolic artery pressure and may help in the identification of high-risk patients with moderate IMR qualified for surgical revascularization. The presumption was that this would help in identifying subgroups of patients who could benefit from better qualification to different surgical strategies (CABG alone or CABG with mitral repair).

In the present study, observations revealed a significant correlation of NT-

proBNP levels at rest and at peak exercise with LV volumes and function. Yusoff et al. [11] reported statistically significant associations between the plasma level of N-terminal-BNP and LV end systolic volumes in patients with severe non-ischemic mitral regurgitation. Detaint et al. [30] found LV end-systolic volume index as the major determinant of the plasma level of BNP. Herein, it was shown that in patients with moderate IMR, an absolute increase in the NT-proBNP level at peak exercise was significantly correlated with changes in IMR severity and maximal tricuspid regurgitant peak gradient at peak exercise. It has been shown that BNP concentrations are strictly associated with hemodynamic status in patients with heart failure [31]. It was known that in some patients with moderate IMR at rest, an increase in mitral regurgitation severity and TRPG is associated with an increase in NT-proBNP levels during exercise. Natriuretic peptides are usually produced by ventricular and atrial myocytes in response to increases in LV stress, and by atrial myocytes in response to increased atrial wall stress [8, 9, 32]. In patients with IMR, the predominant pressure load in mitral regurgitation is on the left atrium; in some patients it is on the right ventricle if there is an increase in pulmonary pressure [10–11]. The strong association between an exercise-induced absolute increase in NT-proBNP levels and pulmonary artery pressure also raises the possibility of increased NT-proBNP secretion from the right ventricle. The present data supports those obtained by Kerr et al. [14], who demonstrated that in patients with moderate to severe or severe MR and preserved resting LV EF, an increase in BNP level is associated with pulmonary artery hypertension on exercise and left atrial enlargement. The results of the current study suggest that in the analyzed models, only ΔNT-proBNP and TA at rest as well as ΔNT-proBNP and CH value at rest were good predictors of an increase in TRPG of ≥ 50 mmHg and in EROA of ≥ 20 mm^2 at peak exercise, respectively. An absolute increase in the NT-proBNP level was a more important predictor of the analyzed endpoint than were the levels of NT-proBNP at rest and at peak exercise.

According to available research, this is the first prospective study to investigate the relation between changes in NT-proBNP with exercise and IMR severity, as well as the pulmonary pressure at rest and at peak exercise in patients with moderate IMR qualified for CABG. At this time combined surgery is more likely to be considered if myocardial viability as well as exercise-induced symptoms and increase in IMR severity are present.

Based on the present data, it can be speculated that integration of the

assessment of NT-proBNP at rest and at exercise might improve patient selection for valve surgery

Limitations of the study

A limitation of this study is that it does not include follow-up for clinical outcome or reassessment of NT-proBNP level after surgery.

The study was a part of a grant from the Ministry of Science and Higher Education and not every routine echo parameter was analyzed.

Although the relationships between NT-proBNP and both pulmonary pressures and IMR severity are statistically significant, the predictive value of NT-proBNP for individual patients requires further study using a larger cohort. Therefore, larger prospective studies should be conducted and the use of NT-proBNP in the diagnostic workup of patients with moderate IMR should be considered.

The present study used EROA and MRvol as reference parameters to estimate the degree of mitral regurgitation. Unfortunately, the regurgitant orifice is often non-spherical shaped in ischemic MR. In such cases, using two-dimensional PISA method may result in underestimation of IMR. Moreover, when IMR is not holosystolic, the degree of IMR may be overestimated [33]. However, EROA and MR vol are the most repeatable parameters of mitral regurgitation and using of three-dimensional echocardiography is very difficult in exercise echocardiography. Moreover, previous studies suggest that absolute measurements of EROA and MRvol provide the strongest predictors of outcome.

Conclusions

The level of absolute ΔNT-proBNP during exercise has been found to be the most important parameter in predicting significant changes in IMR severity and pulmonary pressure following exercise. Thus, data herein suggests that NT-proBNP measurement during exercise might be of diagnostic value with therapeutic implications. This hypothesis must be confirmed in larger multicenter studies.

Conflict of interest: None declared
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Table 1. Baseline clinical characteristics — all groups (n = 100).

Age [years]	64.4 ± 7.9
BMI [kg/m^2]	27.1 ± 4.0
Sex, male	56 (56%)
NT-proBNP at rest, median [pg/mL]	769.5 (395.5–1334)
NT-proBNP exe, median [pg/mL]	789.9 (429.9–1478)
ΔNT-proBNP, median [pg/mL]	30.1 (14.7–89)
NYHA:	
Mean ± SD	2.0 ± 0.8
I	28 (28%)
II	47 (47%)
III	25 (25%)

Euroscore Logistic [%]	7.1 ± 5.1
Smoking (actual)	15 (15%)
Hypertension	67 (67%)
Diabetes mellitus	32 (32%)
Hyperlipidemia	67 (67%)
Atrial fibrillation	17 (17%)
Two-vessel disease	27 (27%)
Three-vessel disease	70 (70%)
ACEI	94 (94%)
Beta-adrenolytics	96 (96%)
Statins	96 (96%)
acetylsalicylic acid	91 (91%)

Data are presented as mean ± standard deviation or number (percentage) as shown; exe — at peak exercise; NT-proBNP — N-terminal fragment B-type natriuretic peptide; ΔNT-proBNP — difference between NT-proBNP level at peak exercise and NT-proBNP level at rest; BMI — body mass index; NYHA — New York Heart Association; ACEI — angiotensin converting enzyme inhibitors

Table 2. Baseline echocardiographic characteristics — all groups (n = 100).

ECHO rest	
LVDD [mm]	54.0 ± 6.0
LVDS [mm]	40.5 ± 7.4
LVEDV [mL]	125.8 ± 46.9
LVESV [mL]	73.9 ± 38.6
EF rest [%]	44.0 ± 9.3
WMSI rest	1.57 ± 0.3
TRPG rest [mmHg]	23.7 ± 8.5
EROA rest [mm^2]	15.0 ± 2.0
MRvol rest [mL]	22.5 ± 5.5
CH rest [cm]	0.8 ± 0.2
TA rest [cm^2]	2.0 ± 0.6
TAPSE [mm]	15.0 ± 4.1
SIs	0.38 [0.3–0.45]
ECHO exercise	
EF exe [%]	44.8 ± 9.8
TRPG exe [mmHg]	33.6 ± 14.7
EROA exe [mm^2]	18.0 ± 8.0
MR vol exe [mL]	26.8 ± 11.7

Data are presented as mean ± standard deviation. TAPSE — tricuspid annular plane systolic excursion; rest — echo examination at rest; exe — exercise; WMSI — wall motion score index; EROA — effective regurgitant orifice area; MRvol — mitral regurgitation volume; TA — tenting area; CH — coaptation height; EF — ejection fraction; LVDD — left ventricular end-diastolic dimension; LVDS — left ventricular end-systolic dimension; SIs — sphericity index at end-systole; LVEDV — left ventricular end-diastolic volumes; LVESV — left ventricular end-systolic volume; TRPG — maximal tricuspid regurgitant peak gradient

Table 3. Correlation between the plasma level of NT-proBNP and clinical and echocardiographic measures at rest and at peak exercise.

	NT-proBNP at rest, r value	P value	NT-proBNP exe, r value	P value	ΔBNP, r value	P value
Age	0.11389	0.2617	0.11966	0.2381	0.00469	0.9633
WAT	−0.29797	0.0027	−0.28685	0.0040	0.00170	0.9867
LVDD	0.25969	0.0094	0.25200	0.0119	0.19841	0.0490
LVDS	0.34539	0.0005	0.33043	0.0008	0.19839	0.0490
SIs	0.33863	0.0006	0.33315	0.0008	0.19755	0.05
ESV	0.43340	< 0.0001	0.42522	< 0.0001	0.26054	0.0092
EF rest	−0.51588	< 0.0001	−0.50414	< 0.0001	−0.28304	0.0045
EF exe	−0.57531	< 0.0001	−0.57102	< 0.0001	−0.37037	0.0002
TAPSE	−0.21553	0.0322	−0.21390	0.0335	−0.06326	0.5339
TRPG rest	0.2	0.0471	0.20376	0.0431	0.21811	0.0301
TRPG exe	0.34616	0.0004	0.36661	0.0002	0.44151	< 0.0001
EROA rest	0.27049	0.0068	0.26598	0.0078	0.24631	0.0140
EROA exe	0.29030	0.0036	0.31848	0.0013	0.49240	< 0.0001
MRvol rest	0.17308	0.0867	0.17990	0.0748	0.32621	0.001
MRvol exe	0.31338	0.0016	0.33844	0.0006	0.47944	<0.0001
CH rest	0.3487	0.0004	0.35787	0.0003	0.44185	< 0.0001
TA rest	0.43884	< 0.0001	0.44	< 0.0001	0.42485	< 0.0001

WAT — workload in watts; rest abbreviations — see Tables 2 and 3

Table 4. Multivariate stepwise logistic regression analysis for the prediction of a significant increase in mitral regurgitation severity and pulmonary arterial pressure during exercise.

	F value	P value
EROA ≥ 20 mm²		
TA rest	28.48	0.0001
ΔNT-proBNP	4.66	0.03
TRPG ≥ 50 mmHg		
CH rest	12.76	0.0006
ΔNT-proBNP	4.65	0.03

Abbreviations — see Tables 2 and 3

Table 5. Sensitivity, specificity, and area under the curve (AUC) of N-terminal fragment B-type natriuretic peptide (NT-proBNP) at rest, NT-proBNP exe, and ΔNT-proBNP for prediction of exercise-induced pulmonary hypertension and severe mitral regurgitation.

	Cutoff [pg/mL]	Sensitivity [%]	Specificity [%]	AUC
EROA ≥ 20 mm²				
NT-proBNP at rest	596	83	55	0.685
NT-proBNP exe	924	67	74	0.702
ΔNT-proBNP	68.9	67	90	0.812
TRPG ≥ 50 mmHg				
NT-proBNP at rest	926	87	73	0.756
NT-proBNP exe	1015	87	74	0.768
ΔNT-proBNP	68	80	76	0.842

Abbreviations — see Table 2 and 3

Figure 1. Receiver-operating characteristic (ROC) curve analysis for N-terminal fragment B-type natriuretic peptide NT-proBNP) at rest, NT-proBNP exe, and ΔNT-proBNP as predictors of reaching exercise-induced severe mitral regurgitation (EROA ≥ 20 mm^2).

Figure 2. Receiver-operating characteristic (ROC) curve analysis for N-terminal fragment B-type natriuretic peptide (NT-proBNP) at rest, NT-proBNP exe, and ΔNT-proBNP as predictors of reaching exercise-induced significant pulmonary hypertension (TRPG ≥ 50 mmHg).