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The Effect of Maximal and Submaximal Exercise Testing on NT-proBNP Levels in Patients with Systolic Heart Failure

Efectul testelor de efort maximale si submaximale asupra nivelelor serice ale NT-proBNP la pacienţii cu insuficienţă cardiacă sistolică

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Abstract

***Background**: The submaximal exercise testing, four hundred meters walking test (400mWT), respectively six minutes walking test (6MWT) were proposed as an alternative to classical exercise stress testing on cycloergometer in heart failure patients. **Purpose**: to compare 400mWT and 6 MWT between them, but also with classical exercise stress testing on cycloergometer, by using amino-terminal pro-B-type natriuretic peptide values (NT-proBNP) before and after exercise. **Method**: 20 patients were studied with systolic heart failure (LVEF<40%), 16 males and 4 females aged 37-70 years. After the relief of congestive syndrome, each patient was submitted, on three consecutive days, to a classical cycloergometer exercise stress testing, 6 MWT and 400mWT. Plasma NT- proBNP levels were measured at rest and also immediately after exercise by using ELISA method. **Results**: NT-proBNP values on three consecutive days were already increased at rest. During exercise, NT-proBNP increased for cycloergometer from 688±72 fmol/ml to 1868±91 fmol/ml (p<0.05), for 6MWT from 843±90 fmol/ml to 977±93 fmol/ml (15%, p<0.05) and for 400mWT from 676±63 fmol/ml to 927±95 fmol/ml (37%, p<0.05). The correlation of the peak values of NT-proBNP on cycloergometer /6 MWT and for cycloergometer/ 400mWT was r=0.71; for 400mWT/6MWT r=0.81, p<0.01 . **Conclusion**: NT-proBNP concentrations increase significantly and similarly in patients with chronic heart failure, both during maximal and submaximal exercise. The two submaximal tests from the current study have a sufficient intensity in order to stimulate the release of the natriuretic cardiac peptides and may be used as alternative approaches to maximal exercise testing.*

Keyword: *NT-proBNP, heart failure, maximal and submaximal exercise*

Rezumat

***Premise**. La pacienţii cu insuficienţă cardiacă, testele de efort submaximale (testul de mers 400 metri şi testul de efort 6 minute) reprezintă o alternativă a testului de efort clasic pe cicloergometru. **Scopul studiului** este de*

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a compara creşterea la efort a peptidului natriuretic-NT-proBNP după testul de mers 400 m, respectiv testul de efort 6 minute faţă de testul clasic de efort pe cicloergometru. ***Material şi metodă****. Au fost studiaţi 20 de pacienţi cu insuficienţă cardiacă (fracţie de ejecţie <40%) , cu vârste între 37 şi 70 de ani, 16 bărbaţi şi 4 femei. După retrocedarea fenomenelor congestive, toţii pacienţii au efectuat în trei zile consecutive, cele trei tipuri de teste: testul de efort clasic pe cicloergometru, testul de mers 400 de metri, respectiv testul de efort de 6 minute. Valorile NT-pro BNP au fost determinate utilizând metoda ELISA înainte şi după cele trei teste de efort.* ***Rezultate****. Valorile medii ale NT-proBNP au fost crescute în repaus în toate cele trei zile, crescând apoi semnificativ, indiferent de tipul de test de efort efectuat: de la 688±72 fmol/ml la 1869±91 fmol/ml (p<0.05) în cazul testului de efort clasic, de la 843±90 fmol/ml la 977±93 fmol/ml (15%, p<0.05) în cazul testului de efort 6 minute şi de la 676±63 fmol/ml la 927±95 fmol/ml (37%, p<0.05) pentru tesul de mers 400 de metri. Totodată au existat corelaţii semnificative între valorile maxime ale NT-proBNP din cursul efortului pe cicloergometru /test de efort 6 minute (r=0.71), cicloergometeru/ test de mers 400 metri, (r=0.71), respectiv test de mers 400 metri/test de efort 6 minute (r=0.81), p<0.01. În* ***concluzie*** *concentraţia NT-proBNP creşte semnificativ şi similar la bolnavii cu insuficienţă cardiacă, atât în cursul efortului maximal cât şi în cursul efortului submaximal. Atât testul de efort 6 minute cât şi la testul de mers 400 metri, sunt suficiente ca intensitate pentru eliberarea de hormoni natriuretici cardiaci, putând fi folosite ca variante ale testului de efort maximal clasic.*

Cuvinte cheie: *NT-proBNP, insuficienţă cardiacă, teste de efort maximale şi submaximale.*

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Introduction

The natriuretic peptide family has three members: atrial (ANP) and brain (BNP) natriuretic peptides, both secreted by the cardiomyocytes, and also C-type natriuretic peptide (CNP), with endothelial origin. They have common structures and degradation pathways, but are genetically distinct (1). Both ANP and BNP are generated endogenously and activated in response to increased atrial and ventricular pressure and volume. Both peptides are synthesized as precursors.

BNP is secreted as a preprohormone (protein precursor) composed of 134 amino acids. It is subsequently cleaved into a BNP precursor molecule with 108 amino acids and a signal peptide of 26 aa, which is removed during the protein synthesis in the rough sarcoplasmic reticulum, prior to the completion of the C-terminal part of the prohormone sequence synthesis (2). 108 amino acid proBNP is cleaved by furin enzyme into two molecules released simultaneously: 32 amino acid BNP - the biologically active part of proBNP and NT-proBNP, the inactive part, which includes the amino acids 1 to76 (2).

There are three mechanisms involved in the BNP clearance: glomerular filtration, natriuretic peptide receptors- mediated degradation and degradation by the neutral endopeptidase. The plasma half-life for BNP ranges from 13 to 20 min, as opposed to 25-70 minutes for NT-proBNP. Plasma NT-proBNP values are about 6 to 10 times higher than the BNP levels due to the prolonged NT-proBNP half-life (3).

BNP is secreted immediately after its synthesis. Only small amounts of BNP can be stored in the atrial secretory granules together with the ANP. Thus, BNP seems to use the constitutive secretory pathways (4). An increased BNP synthesis, secretion and release requires prolonged stimulation. Neurohormonal activation occurs early in patients with left ventricular dysfunction, even in those who are asymptomatic (4). Physical exercise increases cardiac pressure, which represents the main stimulus for the natriuretic peptides secretion. Also, it stimulates the sympathetic nervous system. Therefore, physical effort increases both cardiac peptides and norepinephrine plasma levels (5-7).

Exercise testing on cycle ergometer and treadmill exercise testing are the most commonly used methods in patients with ischemic heart disease, but also in patients with chronic heart failure (8).

Unfortunately, for many chronic heart failure patients, exercise intolerance is one of the important markers of the disease severity (8). Therefore, exercise or cardiopulmonary testing cannot be performed. Moreover, the large number of clinical cases limits the use of exercise testing in all heart failure patients. In the current medical practice, the main applications of the submaximal exercise tests in heart failure patients are focused therefore on exercise capacity assessment and on evolution of the disease (8).

The most widely used submaximal test is the 6 minutes walk test (6MWT), which showed its efficiency in large studies on heart failure patients (8). Also, an alternative submaximal test for heart failure patients could be the 400mWT (8, 9). It has advantages over other protocols because of the fixed distance, which motivates the patients and the similar involvement of the peripheral musculature in all patients with heart failure, which plays an essential role in effort capacity limitation.

There are no previous reports regarding the correlation between either of the submaximal tests mentioned above and the NT-proBNP levels. Therefore, we aimed to determine whether the measurement of the NT-proBNP plasma levels could replace the classic symptom- limited maximal effort test in heart failure patients.

Materials and methods

We studied 20 patients, 16 men and 4 women, all diagnosed with dilated cardiomyopathy and systolic heart failure. They were aged between 37 to 70 years with a mean age of 55 ± 10.27 years. The etiology of heart failure was ischemic in 14 patients and idiopathic dilated cardiomyopathy was found in 6 patients. The diagnosis of dilated cardiomyopathy was carried out based on the clinical and echocardiographic examinations. An ejection fraction less than 40% was a mandatory inclusion criterion. All patients were under treatment with diuretics, ACE inhibitors and low- medium doses of beta- blockers.

Venous blood samples were taken into 5-mL potassium EDTA tubes. Plasma NT-proBNP levels were measured at rest and immediately after exercise (before and 1 minutes after exercise) by using a high specificity competitive immunoassay test provided by Biomedica, based on purified sheep antibody specific for NT-proBNP immobilized to the surface of microtiter plate wells. The ELISA test was performed on an automated system. Normal NT-proBNP levels ranged up to 250 fmol/ml or 600 pg/ml (1 fmol=2.4pg). The test has two limit values: 125 pg / mL in patients under 75 years and 450 pg/mL in those over 75 years, with a specificity of 89% CI.

After the relief of congestive syndrome, all patients performed three effort tests in consecutive days, at the same hour in the morning and without prior administration of any medication: a symptom- limited maximal exercise testing on cycle ergometer, a 6 min walk test (6MWT) and also a 400mWT. The cycle ergometer test consisted of workloads of 1 minute and 10 WATTs, using the standard ramp protocol. Exercise testing was discontinued when the theoretical maximum heart rate was achieved, which is 220-age in years or for limiting symptoms (dyspnea, chest pain, etc). Heart rate, blood pressure and 12-lead ECGs were recorded throughout the entire duration of the test.

6MWT and 400mWT were performed using a similar standard protocol. Patients were advised to go as fast as possible on a 30 meters long corridor, free of obstacles. Stops were allowed during testing in case of limiting symptoms. Patients were supervised, but not helped in walking, in order not to influence their speed. Systolic and diastolic blood pressure and heart rate were monitored during the test. The 6MWT provided the walking distance in meters during 6 minutes. The 400mWT results consist of the time (seconds) necessary in order to complete the 400 meters distance.

Statistical analysis was carried out using the SPSS for Windows (v 16.0, IBM Corporation, Armonk, NY, USA) and MedCalc (v 10.3.0.0, MedCalc Software, Ostend, Belgium) software programs. The analysis of the differences between qualitative variables was performed using the $\chi 2$ test. The Kolmogorov–Smirnov test was used to assess the normal distribution of continuous numerical variables. Mean differences among continuous qualitative variables were evaluated with the Student's t-test (unpaired and paired), while nonparametric tests (Mann–Whitney U) were used to assess distribution variables that did not comply with normal conditions. A value of $p < 0.05$ was considered statistically significant.

The selected patients were informed about the study protocol and gave their signed informed consent.

Results

The main parameters registered during the symptom- limited maximal exercise testing on cycle ergometer, 6MWT and 400mWT and also the echocardiographic data are presented in *Table I*.

Patients presented a depressed left ventricle ejection fraction (LVEF) and most of them were included in NYHA class II, performing 5 to 7 MWTs. LVDD (left ventricle diastolic diameter) was markedly increased in all patients as well as the anteroposterior diameter of the LA. Patients performed between 7.4 and 3.1 METs, with an average of 5.8 METs during the symptom-limited maximal exercise testing on cycloergometer. We determined also the double product (systolic blood pressure multiplied by the heart frequency), which recorded moderately low values, similar to those of the effort capacity. The low effort capacity was almost entirely secondary to the reduced cardiac performance.

Table I. Exercise testing and echocardiographic data.

Variables	Mean value
LVEF (%)	35.4 ± 30.40
METs ($kcal \cdot kg^{-1} \cdot h^{-1}$)	5.8 ± 0.6
6MWT (meters)	411.4 ± 394
400mWT (seconds)	360.5 ± 329
LVDD (mm)	71.1 ± 69.58
LA diameter (mm)	48 ± 37
DT mitral (ms)	192 ± 180

LVEF – left ventricle ejection fraction
METs – Metabolic Equivalents of Task (the energy cost of physical activity)
LVDD – left ventricle diastolic diameter
LA – left atrial
DT – deceleration time

The mean distance completed during the 6MWT was of 411.4 ± 394 meters. There were no values under 250 m, which is the severity limit or higher than 500 m, which shows a good effort capacity.

The 400mWT recorded mean walking distances of 360 ± 329 seconds. There were no values less than 300 seconds, meaning a good effort capacity, but none of them exceeded 500 seconds, which would have meant a strongly depressed exercise capacity.

The exercise tests data include the majority of the patients in a moderate class of severity, NYHA II.

The increase in the NT-proBNP levels was highly significant ($p < 0.01$) for all of the three effort tests. The increase was similar both in absolute and percentage values (*Figure 1*).

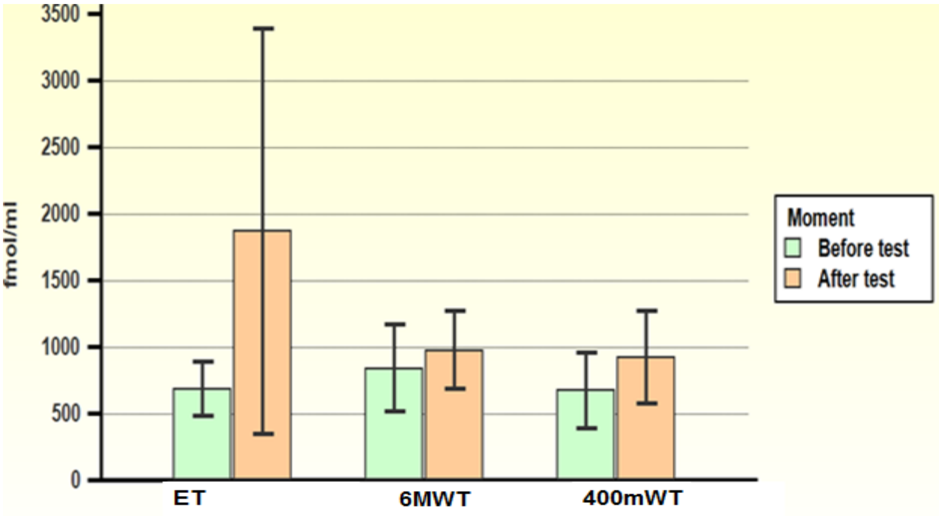

Figure 1. Comparison of the NT-proBNP values during the three types of exercise testing.

The maximal exersice testing on cycle ergometer results are similar to those of the submaximal effort tests (6MWT and 400mWT). Also, there is a good correlation in every patients between cyclergomter exercise testing and submaximal test and also between 6MWT and 400mWT (*Figure 2, 3, 4*). Therefore, the diagnostic and prognostic significance of the three exercise tests should be similar. The results of the submaximal tests (6MWT and 400mWT) were strongly correlated.

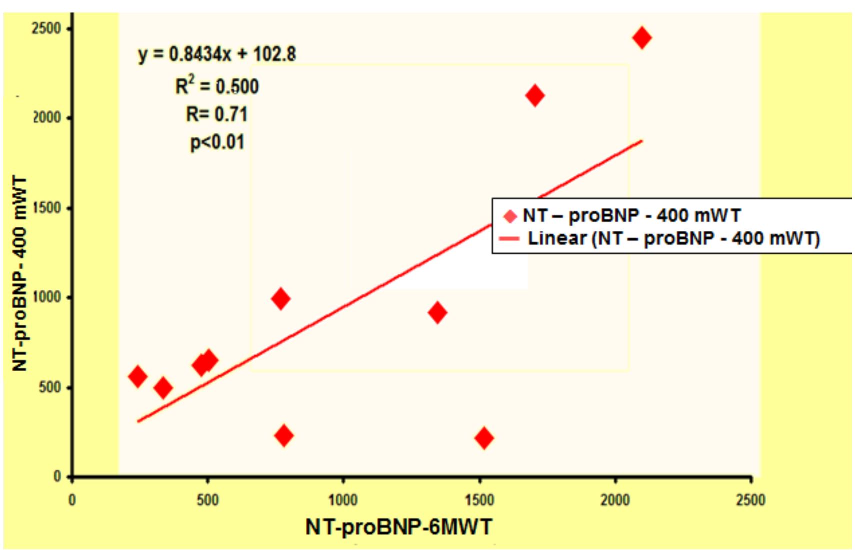

Figure 2. Correlation between NT-proBNP-400mWT and NT-proBNP-6mWT.

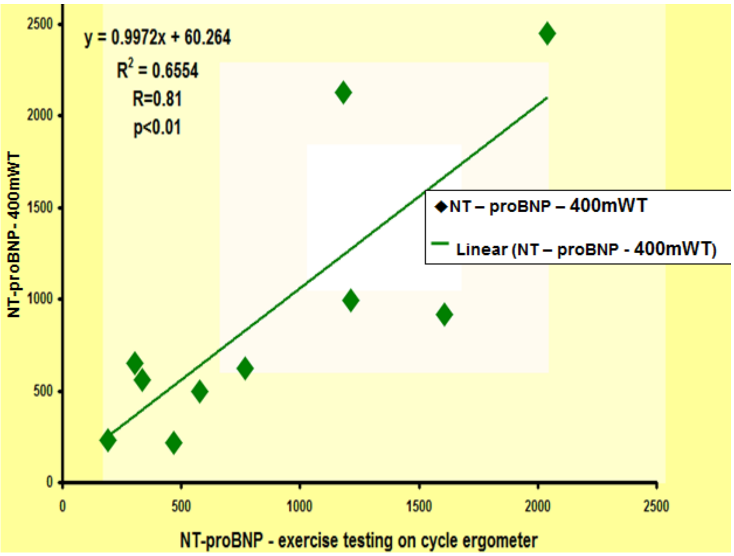

Figure 3. Correlation between NT-proBNP-400mWT and NT-proBNP-exercise testing.

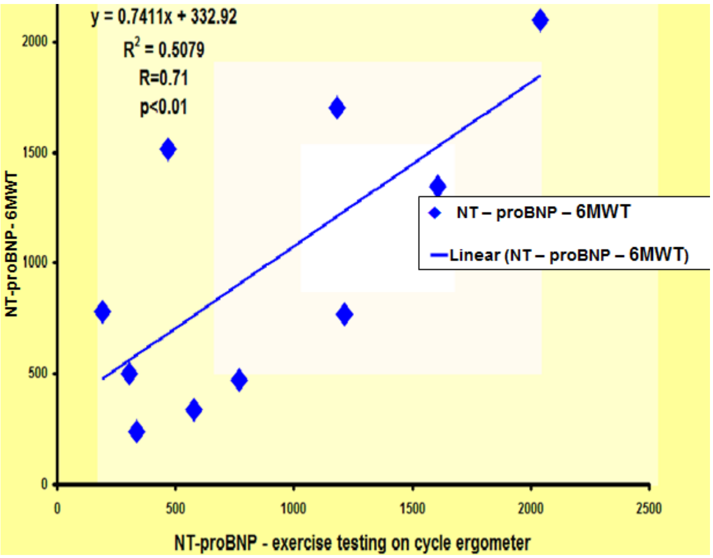

Figure 4. Correlation between NT-proBNP-6MWT and NT-proBNP-exercise testing.

Discussion

Current European Society of Cardiology (ESC) guidelines recommend one of the three types of natriuretic hormones to be performed for an accurate diagnosis of chronic heart failure: B-type natriuretic peptide, N-terminal pro B-type natriuretic peptide or mid-regional atrial (or A-type) natriuretic peptide (MR-proANP) (8).

The interpretation of the results should take into account the multiple variables that may influence the levels of natriuretic peptides, such as: the circadian variation, age or sex. BNP concentration is 36% higher in women than in men under the age of 50 years (10). Premenopausal women present higher levels of cardiac hormones due to the physiological stimulation of the sex steroid hormones (10). The growth of the cardiac peptides with age may be in response to the decrease of their myocardial function, changes in their physiologically effects on the kidneys, which is typical for senescence or to the decrease of platelet C-peptide receptors clearance rate (10).

The progressive increase of the natriuretic peptide levels reflects the heart failure severity up to a certain point, after which there are other factors which strongly affect the BNP plasma levels. Extremely high BNP levels (over 4000 pg/mL) do not bring additional data regarding the heart failure severity or the morphological changes of the heart (11). Renal dysfunction, which may be quantified by determining the serum creatinine levels, is the major determinant of the BNP values increase (11).

Plasma natriuretic peptides levels in our study grow both with the maximal exercise testing and with the two types of submaximal effort tests (6MWT, 400mWT). This may suggest that submaximal effort tests are sufficiently intense in order to increase the intraventricular pressure and the secretion of NT- proBNP in heart failure patients.

Our study showed a significant correlation between the maximal exercise testing and the two types of submaximal exercise tests (6MWT, 400mWT). In addition to our findings, we can assert that all three-exercise tests bring similar data regarding the NT-proBNP secretion. The correlation between the two submaximal exercise tests shows that both of them may be used when the symptom- limited maximal exercise testing cannot be performed. The specialized literature brings data which confirms our results (12, 13).

A recent study performed by Ingle et al. aimed to assess the 6MWT prognostic value in relation to plasma levels of NT-proBNP at rest in patients diagnosed with systolic heart failure (14). They reported that both, 6MWT and NT-proBNP levels are strong predictors of mortality over a period of one or two years. However, other studies suggest a moderate negative correlation between BNP levels at rest and the distance completed during the 6MWT (15). These results are unconfirmed by other authors. We consider that these results are dependent on the different levels of physical training.

NT-proBNP values increase during exercise also in healthy subjects in relation to the venous return and preload (16-18). NT-proBNP values grow in patients with known or newly diagnosed myocardial ischemia (19, 20).

NT-proBNP values significantly increase during exercise in heart failure patients. We found a better correlation between NT-proBNP levels during effort, systolic dysfunction and LV dimensions in comparison with NT-proBNP levels at rest. Asymptomatic patients with degenerative mitral regurgitation (16) present no relation between BNP levels and the mitral regurgitation grade or left ventricle ejection fraction. However, BNP levels correlate with echocardiographic longitudinal systolic function parameters. Therefore, BNP is considered a marker of early detection of LV systolic dysfunction. There is sufficient data (21) showing a significant correlation between effort BNP values and tissue Doppler diastolic dysfunction. Also, recent studies have demonstrated that BNP levels during effort are an accurate surrogate marker of systolic and diastolic dysfunction and low exercise capacity in patients with mitral regurgitation (16).

The relation between cardiac peptides during effort, diastolic function and diastolic heart failure was also supported by the significant increase of NT-proBNP values in patients with pseudonormalization or restrictive diastolic dysfunction (22). Conversely, NT-proBNP values do not significantly increase during isometric exercise (handgrip), suggesting that isolated isometric exercise does not have marked effects on the intraventricular pressure in patients with diastolic heart failure (23). However, NT-proBNP values have not been extensively modified during isotonic exercise.

There is compelling evidence that NT-proBNP increases during exercise in coronary patients (24). However, another study showed higher values in those with non ischemic dilatative cardiomyopathy than in those with an ischemic etiology (7). Those patients presented a lower ejection fraction and a more severe systolic dysfunction (7).

Kallistratos reported in a recent study that NT-proBNP levels at rest or during exercise are similar prognostic tools in patients with systolic dysfunction (12).

It is well-known that NT-proBNP values at rest decrease after long term exercise training, but the effects of physical exercise on the NT-pro BNP plasma levels have not been yet studied (25).

There is no data regarding the NT-proBNP responses to submaximal effort in patients with heart failure. However, studies showed that both NT-proBNP at rest and submaximal effort (6MWT) have similar prognostic accuracy for preoperative risk assessment (26, 27). Also, it seems that NT-proBNP correlates with the 6MWT in patients with chronic pulmonary thromboembolism treated with treprostinil (28, 29).

In conclusion, NT-proBNP concentrations increase significantly and similarly in patients with chronic heart failure, both during maximal and submaximal exercise. The two submaximal tests from the current study have a sufficient intensity in order to stimulate the release of the natriuretic cardiac hormones and may be used as alternative approaches to maximal exercise testing.

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