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APPLICATION OF DETERMINED NT-proBNP IN PHYSICAL STANDARDIZED EXERCISE

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Natriuretic peptides can be used as markers of heart failure, its severity and also in the differential diagnosis of dyspnea. Moreover, the dynamics of natriuretic peptides in physical standardized exercise may be used in the assessment of latent heart failure.

Aim of the study: Can determination of NT-proBNP be used in the diagnosis of exercise-induced ischemia or latent heart failure?

18 probands (10 men, 8 women) under study were risk persons with unspecified ECG, without signs of manifest heart failure. They were subjected to ergometric bike exercises up to the subjective maximum, SPECT myocardium with estimated ejection fraction of the left ventricle at peak ergometric exercise. The following parameters were followed-up: a) before ergometric exercise: NT-proBNP, CRP, TNF-α, Hb, Htc, lactate b) at subjective maximum: NT-proBNP, Hb, Htc, lactate c) 30 min after stopping the exercise: NT-proBNP d) 60 min after stopping the exercise: NT-proBNP. The volume blood changes were taken into account (estimation from the dynamics of Htc, Hb with calculation of metabolic changes of NT-proBNP). To evaluate the dynamics of NT-proBNP, the group was divided into subgroups according to the results obtained in ergometric exercises.

Results: initial values of NT-proBNP within normal limits (< 59 pmol/l, 500 ng/l) in 94%, the submaximal pulse rate was reached in 94%, ischemic changes in ECG were observed in 59%, typical clinical signs of heart ischemia were recorded in 35%. Signs of heart dysfunction according to SPECT were found in 47% and ischemic symptoms were observed in 43%. In general, the plasmatic volume decreased by 24% at maximal exercise. Lactate concentration in the plasma increased in all cases. Conversion of NT-proBNP into volume blood changes revealed that increased NT-proBNP occurred only in 22%. Differences between NT-proBNP before exercises and at maximal exercise prior and after correction into volume blood changes were statistically insignificant. 30 and 60 min after the exercise, no significant differences were found in NT-proBNP concentrations. Dividing into subgroups according to the results of ergometric exercises, showed no significant differences in NT-proBNP concentrations.

Dynamics of NT-proBNP changes during and after ergometric exercises cannot be used for the diagnosis of exercise-induced heart failure. The high stability of NT-proBNP related to physical activity was confirmed.

INTRODUCTION

At present, many reports and recommendations appear dealing with diagnostic use of natriuretic peptides for estimation of heart dysfunction. Several papers dealt with the determination of dynamics of values of natriuretic peptides and its use in diagnosis of latent heart failure[1, 8].

However, in diagnosis of latent heart failure, mostly BNP was examined (natriuretic peptide of type B), whose analysis is not still available in automatized systems that meet the short time of laboratory response (TAT). These conditions appeared to be necessary.

Since 2002, determination of NT-proBNP is available and meets these requirements (short TAT, automatization, satisfying analytical characteristics)[9], and we were interested if the determination of NT-proBNP could be used in diagnosis of exercise-induced ischemia or latent heart failure. No studies reporting on the use of evaluation of NT-proBNP in similar indication are available.

METHODS

We examined the group of 18 probands (10 men, 8 women). They were risk persons with nonspecific ECG (sinus rhythm, no transfer disorders, without typical ischemic changes), without signs of manifested heart failure (anamnesis, clinical examination, X-ray of heart and lungs).

These persons were treated either for ischaemic heart disease (CCS I-II) or had several risk factors (diabetes mellitus, hypertension, obesity, dyslipidemia, smoking).

All probands were subjected to ergometric bike exercise up to subjective maximum (50 W of initial exercise for 1 minute, then exercise increased each minute by 10 W, in the absence of clinical problems the exercise was stopped at subjective feeling of fatigue a.

SPECT myocardium (exercise perfusion of the myocardium) referring to the estimation of ejection fraction of the left ventricle (LVEF) at maximal exercise.

In all probands, the following laboratory examination was performed in collections:

BNP1 before ergometric exercise: NT-proBNP (Elecsys 2010, kit ROCHE), CRP (ILAB 600, kit Biovendor, immunoturbidimetry), TNF-α (Immulite, Biovendor), Hb, Htc (Excell 22), lactate (enzyme, Ilab600, kit Biovendor)
BNP2 at reaching subjective maximum: NT-proBNP, Hb, Htc, lactate
BNP3 30 min after stopping the exercise: NT-proBNP
BNP4 60 min after stopping the exercise: NT-proBNP

In all probands the volume blood changes were taken into account (estimation from the dynamics of Htc, Hb with calculation of metabolic changes of NT-proBNP)[10].

The change of plasmatic volume after exercise is calculated as follows[10]:

$$dPV = \frac{Hb_b \times (1 - Htc_a)}{Hb_a \times (1 - Htc_b)} - 1$$

$_b$...value before
$_a$...value after

The expected concentration of the substance after exercise is calculated as follows[10]:

$$c_e = c_b \times \frac{Hb_a \times (1 - Htc_b)}{Hb_b \times (1 - Htc_a)}$$

c_e... expected concentration
c_b... concentration before

c) "Metabolic difference" of the concentration of the studied substance after changed volume is calculated as follows[10]:

$$dC = \frac{C_a}{Ce} - 1$$

C_e... expected concentration
C_a... real concentration after
dC... "metabolic difference"

To evaluate the dynamics of NT-proBNP, the whole group was divided into subgroups according to results of ergometric exercises (persons with ECG ischemic symptoms, persons with positive SPECT myocardium with respect to ischemic changes, persons with symptoms of latent heart failure according to SPECT, persons with clinically positive ergometry with regard to ischemic disease).

In these subgroups we compared the values of the markers under study (ANOVA, Kruskal-Wallis). For statistic processing we used the software MedCalc.

RESULTS

We examined 18 probands (mean age was 58 years, 10 men, 8 women).

Laboratory examination before the test: 17 probands (94%) had the initial values of NT-proBNP within normal limits (< 59 pmol/l, 500 ng/l). No one proband had any higher value of TNF-α.

Bike ergometry: 94% probands reached at the test the submaximal pulse rate, 59% probands had at the test ischemic ECG changes, 35% probands showed at the test the typical clinical signs of heart ischemia (Table 2).

SPECT: 47% of the group had signs of heart dysfunction (transient postexercise dilatation of heart sections) and 43% showed signs of ischemia (Table 2).

Laboratory examination after the test: on average, the examined probands at maximal exercise had a decreased plasmatic volume by 24%. All probands had a significantly increased lactate concentration in the plasma.

Conversion of NT-proBNP values into volume blood changes revealed that increased NT-proBNP occurred only in 4 probands (22%), the changes remained insignificant.

In general, the whole group showed even an insignificant decrease of NT-proBNP.

Difference between NT-proBNP before the test and at maximal exercises prior to and after correction into volume blood changes was statistically insignificant (Table 1).

Laboratory examination 30 and 60 min after stopping the test: No significant differences were found in NT-proBNP concentrations after stopping the test (Table 1, Fig. 1)

Significant differences in values of the measured parameters in the defined subgroups: no significant difference were found.

When studying correlation, statistically significant negative correlations were recorded between LVEF (%) found at maximal exercise (SPECT) and NT-proBNP concentration in all 4 collection intervals.

We also observed significant negative correlations between NT-proBNP and volume blood change (the higher NT-proBNP, the lower reduction of plasmatic volume) and negative correlations between NT-proBNP and lactate concentration and the maximal activity (W/kg) reached. Lactate concentration correlated positively with LVEF (Table 3).

Table 1. Basic statistic. Significance of differences of individual parameters between initial examination and performed test.

Parameter	Mean	Median	SD	Difference
Age (years)	60.0	58.0	9.3	
BNP1 (pmol/l)	35.5	10.1	86.0	
BNP2 (pmol/l)	42.0	10.7	103.0	ns
Exp. BNP2 (pmol/l)	44.4	11.1	107.1	ns
Met. difference BNP2-1 (%)	-12.0	-8.0	3.0	
BNP3 (pmol/l)	57.0	11.4	88.5	ns
BNP4 (pmol/l)	55.0	10.9	83.9	ns
Hb1 (g/l)	148.1	146.5	16.2	
Hb2 (g/l)	161.6	162.0	15.4	VA
Htc1 (j)	0.5	0.5	0.1	
Htc2 (j)	0.5	0.5	0.1	VA
Change of plasm.volume (%)	-24	-25	10	
Lactate (mmol/l)	6.0	6.1	2.6	
LVEF (%)	64.0	68.0	10.7	
Reached load (W/kg)	1.4	1.4	0.3	
TNF-α (ng/l)	7.1	6.0	4.4	

SD standard deviation
Difference significance of differences between initial examination and performed test
VA $p < 0.01$
ns $p > 0.05$

Table 2. Presence of individual features in 18 probands.

	Yes (%)
CAD in anamnesis	35
Ischaemia at load ECG	59
Clinic of CAD ergometry	35
Men/women	60
SPECT positive – ischaemia	47
Submaximal excercise	92
Heart dysfunction at exercise	43

Table 3. Significant correlations between NT-proBNP and other parameters, $p < 0.5$.

BNP1	LVEF (–0.71) BNP2 (0.99) Hb1 (–0.63) Change of plasm. volume (–0.63) Lactate (–0.41) W/kg (–0.53)
BNP2	LVEF (–0.73) W/kg (–0.1)
Lactate	LVEF (0.87) BNP1 (–0.44)

LVEF left ventricle ejection fraction at maximum exercise (%)
Correlation coefficient is given in parentheses

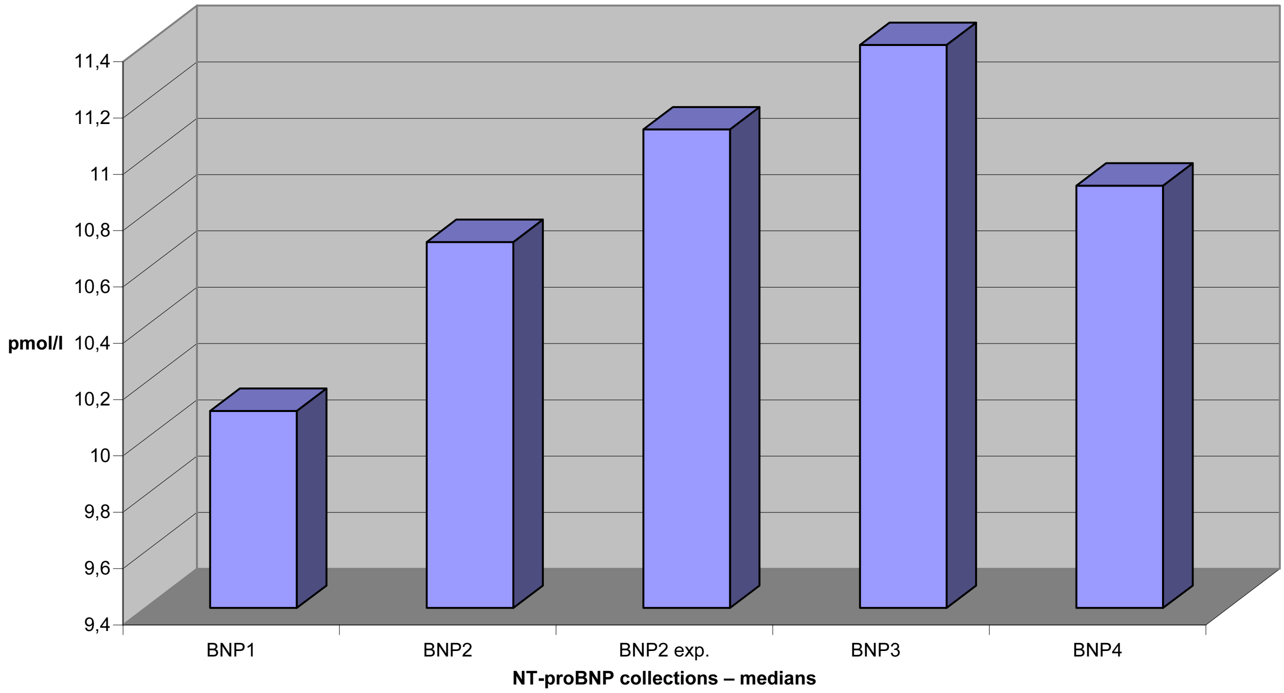

Fig. 1. NT-pro BNP concentrations before and after exercise.

BNP1	immediately before the test
BNP2	at peak exercise
BNP3	0 min after exercise
BNP4	60 min after exercise
BNP2 exp.	expected value according to changed plasma volume (0 min after exercise)

DISCUSSION

Natriuretic peptides display a strong vasorelaxation, natriuretic and diuretic effects, exhibit anti-mitogenetic effect and inhibit renine activity. It can be summarized that natriuretic peptides act as a defence against the extra load of the organism by fluids and prevent hypertension reactions.

Many papers confirmed that the value of BNP (natriuretic peptide B) correlates in patients suffering from heart failure with clinical severity of the disease (classification NYHA) and is in a direct relation with filling pressure, function and load of the left ventricle[1, 8].

No differences were found between BNP in patients with ischemic/another type of heart disease. On the basis of these results, determination of BNP seems to be a first-line examination for differential diagnosis of dyspnea and for identification of patients with various abnormalities of the cardiovascular system[1].

Determination of BNP is mostly appreciated for its high negative predictive value for diagnosis of heart failure (up to 100%) as well as the fact that BNP provides information independently of radiological and other laboratory examinations.

Moreover, BNP in patients with heart failures has an important prognostic value for assessment of long-term mortality[1, 10].

Recently, numerous reports have appeared on the use of determination of natriuretic peptides in the diagnosis of latent heart failure, when BNP (or ANP) was determined before and after submaximal up to maximal exercise. These authors suggest that BNP in particular can be considered as a predictor of the risk of heart failure during excess physical activity (concentration of BNP correlated closely with pressure in pulmonary artery and impaction). The study proved that BNP increases during physical exercise; patients with hypertrophy of the left ventricle have higher values than patients without hypertrophy[2–5, 7, 8].

The values of BNP also seem to correlate negatively at ergometric exercises with the date of maximal oxygen consumption; thus, determination of BNP could predict patients with a low exercise capacity (a high value indicates a low exrcise capacity)[6, 7, 8].

Since 2002, there is available in the Czech Republic determination of NT-pro BNP (Roche), which displays, compared to other available methods for determination of natriuretic peptides, many advantages, namely: automated measurement (Elecsys 2010) with a high laboratory response (determination within 20 min) and satisfying analytical characteristics[9].

The next advantage covers minimal preanalytical conditions, insignificant circadian rhythms and marker good stability in the serum at room temperature.

The producer reports that the product is not influenced by excessive physical activity (in contrast to BNP)[11].

As the method of assessment of latent heart failure induced by physical activity by means of the natriuretic peptides dynamics was described only for BNP (ANP) and the determination of NT-proBNP displays many advantages, compared to other natriuretic peptides and propeptides (see above), we decided to test whether the dynamics of values of NT-proBNP could indicate the presence of exercise-induced latent heart failure.

Calculation of "metabolic differences" was based on the fact that just as after physical exercises, acute stress stimulus results in changed volume of plasma and erythrocytes. We assume that a mean volume erythrocytes is reflected in changed mean concentration of Hb and plasma volume in values of Htc. Thus, suitable parameters for evaluation of volume blood changes are hematocrit and hemoglobin. We used mathematical formulas after Costillo and Sparks[10] that we consider most suitable.

Changed concentrations of plasmatic proteins are an unsuitable parameter, because their increase in the plasma does not reflect the water loss from the plasma, but also intake of extravascular proteins into the blood.

At calculation, only loss of water is expected from the plasma (or its intake); thus we assume that a given amount of the substance remains the same before and after volume change. When we thus calculate the expected concentration of the substance after volume change and then measure a real concentration after volume change, a mutual difference of these quantities can be evaluated, i.e. "metabolic difference".

Our findings confirmed the fact that the values of NT-proBNP in the serum are stable and not significantly affected by the submaximal or maximal physical activity.

Negative correlation between lactate and NT-proBNP corresponds to the fact that probands with a good exercise tolerance, i.e. with a good cardiovascular compensation, who are able to work up to subjective maximum, have a higher lactate concentration due to higher anaerobic involvement.

Similarly, a negative correlation between NT-proBNP and the achieved maximal performance (W/kg) could support the literary fact that probands with heart dysfunction are able to reach lower performances than probands without hear dysfunction[6, 7, 8].

As no significant changes of NT-proBNP concentration were recorded 60 min after the exercise, we assume that evaluation of the dynamics of NT-proBNP can be used neither for diagnosis of latent heart failure nor ischemic disorder induced by physical exercise (with respect to usual time possibilities in hospital practice).

CONCLUSIONS

Evaluation of the dynamics of changes of NT-proBNP during ergometric exercise and immediately after stopping it cannot be used in:

a) clinical diagnosis of exercise-induced heart failure;
b) clinical diagnosis of exercise-induced myocardial ischemia.

Our findings confirmed the data on the high stability of NT-proBNP related to_submaximal up to maximal physical activity. With respect to preanalytical conditions and possible interpretation problems in the evaluation of single collections, this conclusion is considered highly positive.

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