Association of NT-proBNP levels and physical fitness in long-term heart transplant recipients

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Background: The diagnostic value of N-terminal pro-brain natriuretic peptide (NT-proBNP) after heart transplantation is still a matter of debate. As cardiac graft dysfunction affects both, functional performance and synthesis of BNP, we hypothesized a relationship between exercise variables and NT-proBNP levels after heart transplantation .

Patients and Methods: 105 asymptomatic heart transplantation recipients (92 men, 13 women) aged 59 ± 10 years, 88 ± 52 months after heart transplantation, were studied. In these patients 120 graded symptom-limited bicycle exercise tests and NT-proBNP assays (by Roche Diagnostics) were performed.

Results: Maximum exercise tolerance was 74 ± 17% predicted normal (0 – 49% n = 10; 50 – 69% n = 37; 70 – 84% n = 38; 85 – 115% n = 35). Peak systolic blood pressure and heart rate were 184 ± 27 mmHg and 140 ± 19 bpm, respectively. Median resting NT-roBNP level was 282 pg/ml (25th – 75th percentile 132 – 584; range 29 – 4143 pg/ml). Log-transformed NT-proBNP levels correlated inversely with peak systolic blood pressure (r = -0.38, p = 0.0001), peak heart rate (r = -0.25; p = 0.004) and exercise tolerance (r = - 0.23; p = 0.011) and directly with glomerular function rate (r = 0.50; p = 0.00001) and time after heart transplantation (r = 0.30; p = 0.001)

Conclusion: Our data demonstrate that limited exercise tolerance and corresponding exercise variables in heart transplantation recipients are associated with increased secretory activity of the transplanted heart. NT-proBNP – in analogy to BNP – may serve as a useful screening test for the presence of cardiac graft dysfunction, independent of the underlying structural abnormality.

Key words: NT-proBNP – Heart transplantation – Systolic blood pressure – Heart rate

STANEK B, BERGER R, ALIABADI A, GRIMM M, ZUCKERMANN A, RÖDLER S. **Asociácia hladín NT-proBNP a fyzickej kapacity u pacientov po transplantácii srdca v dlhodobom horizonte.** Cardiol 2007;16(6):272–276

Cieľ: Diagnostická hodnota N-terminálneho fragmentu natriuretického peptidu typu B (NT-proBNP) po transplantácii srdca je stále predmetom diskusie. Keďže dysfunkcia štepu srdca ovplyvňuje funkčnú kapacitu aj syntézu BNP, skúmali sme vzťah medzi ukazovateľmi telesnej záťaže a hladinami NT-proBNP po transplantácii srdca.

Pacienti a metódy: Sledovali sme 105 asymptomatických pacientov (92 mužov, 13 žien) vo veku 59 ± 10 rokov s časovým odstupom 88 ± 52 mesiacov po transplantácii srdca. U týchto pacientov sme vykonali 120 bicyklových záťažových testov limitovaných symptómami a vyšetrení NT-proBNP (podľa Roche Diagnostics).

Výsledky: Maximálna záťažová tolerancia bola 74 ± 17 % normálnych prediktívnych hodnôt (0 –49 % n = 10; 50 – 69 % n = 37; 70 – 84 % n = 38; 85 – 115 % n = 35). Systolický tlak krvi a srdcová frekvencia na vrchole záťaže boli 184 ± 27 mmHg, respektíve 140 ± 19/min. Medián hladiny NT-proBNP v pokoji bol 282 pg/ml (25. – 75. percentil 132 – 584; rozsah 29 – 4 143 pg/ml). Prispôsobené (log-transformed) hladiny NT-proBNP korelovali inverzne so systolickým tlakom (r = - 0,38, p = 0,0001) a srdcovou frekvenciou (r = - 0,25; p = 0,004) na vrchole zaťaženia a záťažovou toleranciou (r = - 0,23; p = 0,011) a priamo s glomerulárnou funkciou (r = 0,50; p = 0,00001) a odstupom od transplantácii srdca (r = 0,30; p = 0,001).

Záver: Naše výsledky ukázali, že limitovaná záťažová tolerancia a s ňou súvisiace ukazovatele u pacientov po transplantácii srdca sa spájajú so zvýšenou sekretorickou aktivitou tranpslantovaného srdca. NT-proBNP – analogicky ako BNP – môže slúžiť ako užitočný skríningový test na prítomnosť dysfunkcie srdcového štepu, nezávisle od základného štrukturálneho postihnutia.

Kľúčové slová: NT-proBNP – transplantácia srdca – systolický tlak krvi – srdcová frekvencia

Introduction

It was in the 1980s when scientists found that the heart does not only react to neurohumoral stimuli (such as adrenaline and noradrenaline) but that the cardiac muscle is an endocrine organ itself releasing natriuretic and vasodilating peptides into the circulation (1, 2). This secretory function is preserved after heart transplantation (HTx) and appears to have clinical importance (3 – 7). Also in HTx patients, BNP levels were demonstrated to reflect the degree of pressure and/or volume overload in the transplanted ventricles and are currently used as a surrogate marker for the assessment of cardiac graft function and hemodynamics in many centers (8 – 13). As frequent in cardiovascular humoral regulation, also the biosynthesis of BNP implies a propeptide called N-terminal pro-brain natriuretic peptide (NT-proBNP), which is co-released from the cardiomyocyte and circulates in detectable amounts together with the mature active hormone. The advantage of measuring this propeptide is a greater stability in blood and a higher blood level compared to the final compound. In fact, both, circulating BNP and NT-proBNP are

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reliable markers of left ventricular overload in (nontransplanted) patients with heart failure (14 – 17).

We used NT-proBNP measurements in our center to investigate the issue of physical fitness and cardiac hormone production. To quantify physical fitness, which is known to be impaired after HTx to approximately 70%, peak exercise capacity was assessed on the bicycle (18).

Patients and Methods

The population consisted of 105 patients (92 men, 13 women, mean age 59 years) who had received a cardiac transplant 7 years ago on average. Half of the patients had an ischemic etiology of endstage heart failure leading to HTx. Mean donor age at time of surgery was 33 years. All patients were asymptomatic and ambulatory at time of study with no signs of rejection in their biopsy samples. All patients were free of cardiovascular symptoms at the time of exercise testing. Clinical characteristics of the patients are given in **Table 1**.

Table1 Clinical characteristics of patients

N	105
Male/Female	92/13
Etiology	
Ischem. (%)	44
not-ischem. (%)	56
Time after HTx (months)	88 ± 52
Donor age (years)	33 ± 11
Body mass index (kg/m^2)	27 ± 4
Blood pressure (mmHg)	
Systolic	126 ± 18
Diastolic	86 ± 2
Heart rate (bpm)	92 ± 13
Creatinine (mg/ml)	1.4 ± 0.2
GFR (ml/min)	48 ± 13

An overview of the medication is illustrated in **Figure 1**. From 2004 April to 2005 June 120 graded symptom-limited exercise tests were performed in this population. Maximum workload was evaluated on a bicycle using a stepwise protocol with increases in workload by 25 watts every two minutes up to severe dyspnea and/or leg fatigue. Peak exercise capacity is given as a percentage predicted by an age and sex-matched scale which also considers height and weight of the patients. Patients were subgrouped according to the individual maximum workload. A level of up to 50% predicted comprise exercise level I, up to 70% level II , 70 to 85 % level III and more than 85% level IV.

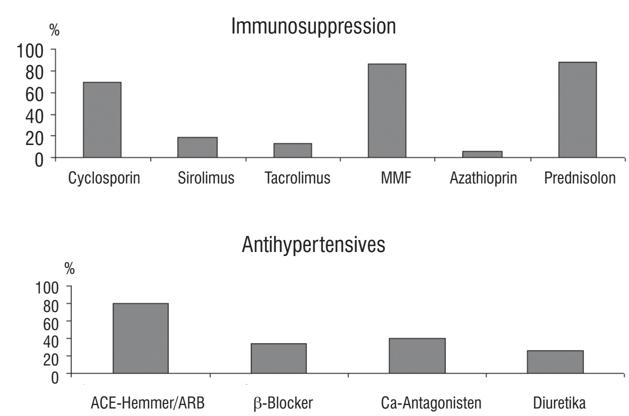

Figure 1 An overview of the medication

Laboratory

Figure 2 illustrates the biosynthesis of BNP, which is produced in a proform, named prepro BNP. On release this molecule is split into two parts, the active hormone BNP and the N-terminal 76 aminoacid proBNP, which is more stable and has a longer half-life than BNP. NT-proBNP was measured in EDTA plasma using the sandwich immunoassay technique provided by Roche Diagnostics.

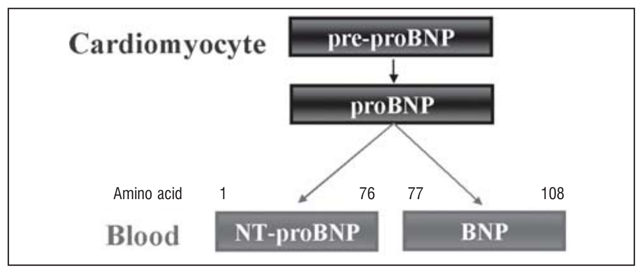

Figure 2 Biosynthesis brain natriuretic peptide

As with BNP, also the normal values of NT-proBNP increase with age and differ in men and women with higher values in females. So, for instance, in healthy men younger than 50 years, NT-proBNP levels do not exceed 100 pg/ml, while in females of the same age group these values average up to 150 pg/ml. In older women, values up to 200 pg/ml are still considered normal (**Figure 3**). Since NT-proBNP levels in HTx patients are not normally distributed, they are expressed as median values and quartiles. For regression analysis these values were transformed into a logarithmic scale.

Results

The mean maximum workload of the group as a whole was 74% predicted (**Figure 4**). Patients were then subgrouped according to workload groups (level I through IV). Only 10 tests of 9 patients (one patient performing

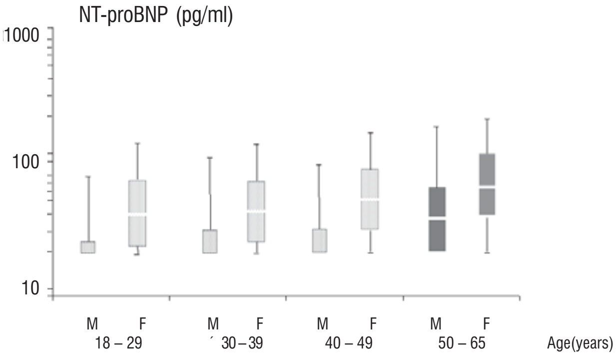

Figure 3 Normal values of NT-proBNP
M – Male, F – Female

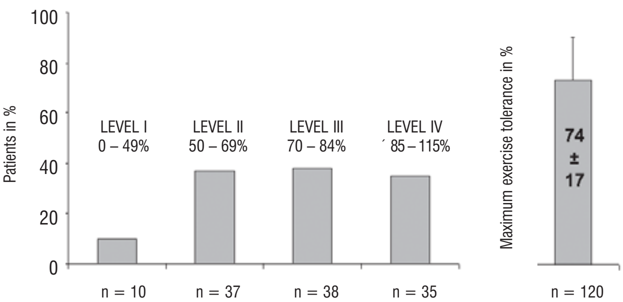

Figure 4 Exercise tolerance

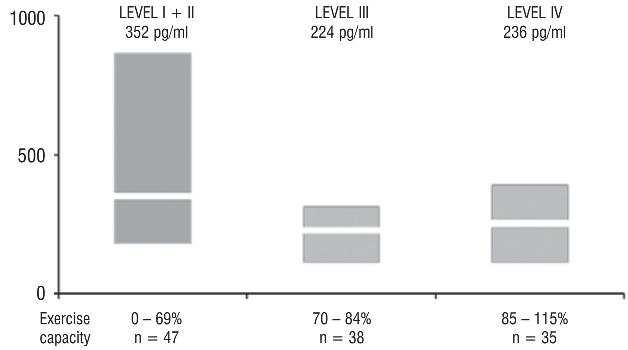

Figure 5 NT-proBNP values by workload groups

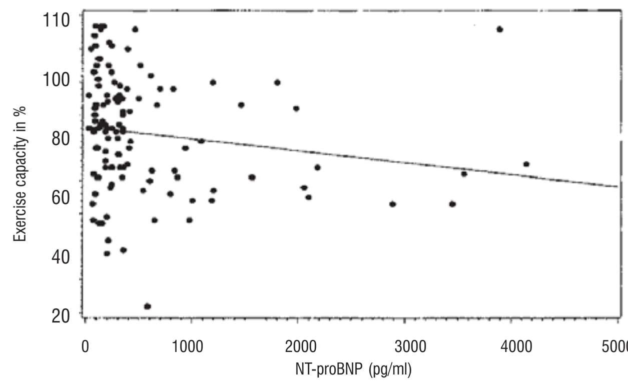

Figure 6 Exercise tolerance versus NT-proBNP

twice) comprised level I, while in the exercise levels II – IV the remaining 96 patients were equally distributed (14 patients performing twice).

The median NT-proBNP level for the whole population was 282 pg/ml (25% percentile 132/75% percentile 584 pg/ml). **Figure 5** shows the NT-proBNP values by workload groups (level I plus II, level III and level IV), **Figure 6** provides an overview of individual data of NT- proBNP in absolute values plotted against percentage workload predicted.

In **Table 2** results of regression analysis of log NT-proBNP and clinical variables are listed. A close inverse relationship was found between NT-proBNP levels and systolic blood pressure (p = 0.00001) and heart rate (p = 004) at peak exercise. The percentage predicted maximum exercise level also correlated inversely with NT-proBNP (p = 0.011). A direct relationship of NT-proBNP levels was found with glomerular filtration rates (p = 0.00001), time (months) after transplant operation (p = 0.001), and donor age at time of surgery (p = 0.04). Other recipient variables, such as age, body mass index, resting systolic blood pressure or resting heart rate were not significantly associated with NT-proBNP levels.

Table 2 Regression analysis log NT-proBNP

	ß-coeff	p
GFR	+0.50	0.0001
Maximal SBP	-0.38	0.0001
Time after HTx	+0.30	0.001
Maximal HR	-0.25	0.004
Exercise capacity	-0.23	0.011
Donor age	+0.18	0.04
Recipient age		NS
SBP (rest)		NS
HR (rest)		NS
BMI		NS

Discussion

Most ambulatory HTx patients report unlimited daily activities during routine control interviews, but formal graded testing on a bicycle often reveals considerable limitations to exercise tolerance despite a preserved left ventricular ejection fraction (18, 19). In the early days, reduced maximum heart rate during exercise and increased peripheral resistance have usually been blamed for causing these limitations (20). However, the delay of heart rate to increase properly may be partly compensated by a more pronounced increase in stroke volume during exercise. In certain patients, this may not suffice to reach peak exercise levels, since transplanted hearts must fill against a restrictive physiology which must be overcome to sustain blood flow (21, 22). Moreover, correlation studies suggest that reduced muscle strength and area contribute to the impaired exercise capacity after HTx (23). In the present evaluation of 105 asymptomatic patients exercise capacity was restricted to 74% predicted and corresponding peripheral NT-proBNP levels were moderately raised over values in matched nontransplanted controls. Abnormally elevated NT-proBNP levels, however, were detected in patients with poor fitness (less than 50% predicted) whose systolic blood pressure and heart rate remained rather low during exercise. Thus, fitness level and cardiac secretory function in the transplanted heart are inversely correlated. This result suggests that the restricted exercise capacity in some longterm HTx recipients may be attributable to abnormal pressure and/or volume in the graft in addition to a number of noncardiac factors. Vice versa, adequate NT-proBNP levels would reflect normal cardiac pressure and/or volume and these patients seem to reach a higher exercise level more easily. The closest relationship on statistical terms, was detected between high peripheral NT-proBNP levels and poor kidney function. To interprete this finding properly, the nephrotoxic in addition to the vasoconstrictive and fluid retention properties of calcineurin inhibitors and probably also of prednisolone, must be taken into account (24). Thus, in some patients not only the increased release of NT-proBNP but also the decline in renal clearance rate of the propeptide might lead to abnormally high circulating NT-proBNP levels. A rather close direct relationship of NT-proBNP was also found with time elapsed after transplant surgery, and, to a lesser degree with the respective age of the donor. These findings correspond well with the hypothesis that structural changes within the transplanted ventricles develop gradually and result in steadily increasing BNP production. Any persistence of structural abnormalities in the cardiac graft certainly is of clinical importance. This is strongly suggested by the result that the fitness level of the patients corresponded with the level of endocrine activity, a surrogate for structural abnormalities in the ventricles.

Studies of cardiac natriuretic peptides after HTx

In transplant cardiology it was an important finding that the graft expresses natriuretic peptides in considerable amounts. (3, 4, 7). Ationu and coworkers (7) were the first to demonstrate in a pediatric population that, as soon as the sick heart (as a source of high natriuretic levels before HTx) is removed, these hormone levels decline for a short period until the secretory function of the donor heart sets in, stimulates its dual hormone system and releases ANP and BNP into the circulation. Both plasma levels re-rise and plateau at an enhanced level.

Of note, this procedure does not require cardiac innervation! Normally, BNP synthesis results from increased intraventricular pressure or volume. After heart transplantation, however, plasma and ventricular tissue levels of BNP seem to increase due to ischemic tissue healing injury, but they appear to plateau after 45 days (11). Further studies of natriuretic peptides in adult HTx recipients confirmed higher natriuretic peptide levels in this population (6, 17). One study prospectively evaluated the association of peripheral BNP levels with clinical symptoms and central hemodynamics in 87 stable HTx recipients. Patients with BNP values higher than 150 pg/ml also had self reported symptoms of dyspnea, fatigue and edema, increased right atrial pressures, higher pulmonary artery systolic pressures, and lower cardiac index, as well as right ventricular dysfunction (9). BNP levels can thus predict cardiopulmonary hemodynamic aberrations despite preserved left ventricular systolic function in HTx recipients. Some investigators have also reported increases in BNP levels associated with acute rejection episodes (8, 11). In all, BNP appears to be an important noninvasive marker of cardiac graft performance. The background for higher BNP production in the transplanted ventricles is very complex including the operation technique, the known restrictive filling pattern and perturbations in right ventricular function (9, 17). Nevertheless the side effects of immunosuppression also have to be considered. Calcineurin inhibitors (Cyclosporin and Tacrolimus) by vasoconstriction, salt retention and nephrotoxic effects may result in chronic volume and pressure overload, both potent stimuli of BNP production. These cardiovascular abnormalities most probably account for a great part of the limited exercise capacity post-transplantation.

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