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Exercise Dependence of N-Terminal Pro-Brain Natriuretic Peptide in Patients with Precapillary Pulmonary Hypertension

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Key Words
Pulmonary hypertension · N-terminal pro-brain natriuretic peptide · Cardiopulmonary exercise test · Biomarker

Abstract
Background: N-terminal pro-brain natriuretic peptide (NT-proBNP) is secreted by cardiac ventricular myocytes upon pressure and volume overload and is a prognostic marker to monitor the severity of precapillary pulmonary hypertension and the extent of right heart failure. ***Objectives:*** The impact of physical exercise on NT-proBNP levels in patients with left heart disease was demonstrated previously. No data regarding patients with isolated right heart failure and the influence of acute exercise on NT-proBNP serum levels exist. ***Methods:*** Twenty patients with precapillary pulmonary hypertension were examined. Hemodynamic parameters were measured during right heart catheterization. Serum NT-proBNP of patients was measured at rest, after a 6-min walking test, during ergospirometry and during recovery, all within 7 h. Significant differences in sequential NT-proBNP values, relative changes compared to values at rest and the correlation between NT-proBNP and obtained parameters were assessed. ***Results:*** At rest, the mean serum level of NT-proBNP was 1,278 ± 998 pg/ml. The mean level of NT-proBNP at maximal exercise was increased (1,592 ± 1,219 pg/ml), whereas serum levels decreased slightly during recovery (1,518 ± 1,170 pg/ml). The relative increase of serum NT-proBNP during exercise correlated with pulmonary vascular resistance ($r = 0.45$; $p = 0.026$) and cardiac output ($r = -0.5$; $p = 0.015$). ***Conclusions:*** In this study, we demonstrated acute changes in NT-proBNP levels due to physical exercise in a small group of patients with precapillary pulmonary hypertension. Our results also confirm the predominant usefulness of NT-proBNP as an intraindividual parameter of right heart load.

Introduction

Precapillary pulmonary hypertension is a rare disease characterized by an elevated pulmonary artery pressure exceeding 25 mm Hg at rest [1]. Persistent elevation of pulmonary vascular resistance of different causes induces right ventricular dysfunction resulting in a decrease in

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cardiac output and progressive right heart failure, eventually leading to death. Echocardiography and right heart catheterization are used to assess the extent of right ventricular dysfunction and the severity of pulmonary hypertension in patients [2]. Biomarkers correlating with the extent of heart failure, such as the N-terminal probrain natriuretic peptide (NT-proBNP), have been used to avoid frequent invasive procedures in patients with pulmonary hypertension [3, 4].

NT-proBNP is a cleavage product of the neurohormone B-type natriuretic peptide (BNP) synthesized in the cardiac ventricles and released upon ventricular myocyte stretch [5]. The half-life of NT-proBNP is 120 min before it is degraded by neutral endopeptidase and excreted renally [6]. NT-proBNP levels are age and gender dependent and most likely related to the age-related decline in the glomerular filtration rate [7].

NT-proBNP has been described as a marker for ventricular dysfunction and hypertrophy [8]. Serum levels of natriuretic peptides correlate with elevated end-diastolic pressure and left ventricular wall tension as well as the New York Heart Association classification [9–11].

In patients with precapillary pulmonary hypertension, serum NT-proBNP correlates with mean pulmonary artery pressure and pulmonary vascular resistance [12], functional parameters of exercise tests (peak oxygen uptake, 6-min walking distance) [13] and echocardiographic indices of right ventricular dysfunction [4]. NT-proBNP has become a useful marker for the assessment of disease severity and therapeutic efficacy [14]. In the treatment of patients with pulmonary hypertension, serum levels of natriuretic peptides are often used to monitor the course of the disease and adjust specific therapy [15, 16].

Beside the interindividual influences of age, gender and renal function on serum levels, intraindividual differences exist in the extent of secretion of natriuretic peptides during a given cardiac load. Hermann et al. [17] showed a significant elevation of serum NT-proBNP levels immediately following a marathon in healthy runners in comparison with levels at rest. The influence of physical exercise on NT-proBNP serum levels was demonstrated in several studies in patients with chronic left heart failure, hypertensive cardiac disease and atrial fibrillation [18–21]. In addition, in patients with left heart failure, a greater elevation of NT-proBNP serum levels than in healthy subjects was found after exercise, which correlated with a decreased left ventricular ejection fraction as an indicator of cardiovascular mortality [22].

There is a lack of data regarding the influence of physical exercise on serum levels of natriuretic peptides in patients with precapillary pulmonary hypertension and right ventricular dysfunction.

In this cross-sectional study, we examined the influence of physical exercise on NT-proBNP serum levels and the time course of this interaction.

Patients and Methods

Patients

In this study, 20 hospitalized patients (nonsmokers; 9 male, 11 female; mean age 55.3 years; table 1) with mild to severe precapillary pulmonary hypertension of different causes (idiopathic, n = 13; chronic thromboembolic, n = 5; tissue associated, n = 2) were examined. Inclusion criteria included cardiac recompensation, sinus rhythm and normal serum creatinine and urea. Exclusion criteria were atrial fibrillation and left heart failure. No patient had an implantable device. Liver function and hemoglobin values were normal. Patients were in New York Heart Association functional classes II (n = 6), III (n = 13) and IV (n = 1). In 9 patients, a specific therapy had been started before the study. All other patients had received only diuretics, and specific therapy was started after the diagnosis of pulmonary hypertension. All examinations included in this study were performed within 2 days.

Hemodynamic and Exertional Parameters

A right heart catheter was inserted via the internal jugular vein (7.5-Fr Baxter®, Baxter Healthcare Corp., Irvine, Calif., USA). The following hemodynamic parameters were obtained: mean pulmonary artery pressure, pulmonary capillary wedge pressure, pulmonary vascular resistance, right atrial pressure, mean systemic pressure, central venous oxygen saturation, cardiac output and cardiac index. In all patients, the Tei index (the Doppler-measured sum of isovolumetric contraction and relaxation time divided by the ejection time of the right ventricle [23]) was calculated by echocardiography of the right heart.

On the second day, a 6-min walking distance test and cardiopulmonary exercise test were performed using a predefined schedule including time spans for rest (table 2). Exertion at the anaerobic threshold, peak oxygen uptake, peak oxygen pulse (oxygen uptake/heart frequency) and maximum systemic systolic pressure (peak RR) were measured.

Measurement of NT-proBNP

Blood was drawn for measurements of serum NT-proBNP on day 2 at 5 defined time points at rest, at maximum exercise and during recovery (table 2). Patients were asked to stay at relative rest in between. Light physical activity (standing up, slow walking up to 50 m) was allowed. Blood samples were kept at 4°C and centrifuged at 3,300 rpm at 4°C for 10 min, and serum was stored at –70°C until being analyzed. Measurements of serum NT-proBNP concentrations were performed using a radioimmunoassay (Elecsys proBNP immunoassay, Roche Diagnostics, Basel, Switzerland) with a sensitivity of 88% and a specificity of 92%. The normal range is below 125 pg/ml.

Table 1. Patients' characteristics

Patient No. (gender)	Age years	Type of pulmonary hypertension	NYHA class	BMI	Specific therapy	mPAP mm Hg	VO_2max ml/min/kg	Tei index
1 (F)	27	CTEPH	II	26.2	bosentan	41	12.2	0.24
2 (F)	41	IPAH	II	24.4	bosentan	65	12.6	0.26
3 (M)	46	CTEPH	III		–	40	13.6	0.28
4 (F)	44	CTEPH	III	23.18	–	44	15	0.24
5 (M)	66	IPAH	III	23.14	–	44	9.6	0.28
6 (F)	70	tissue associated	III	24.17	bosentan	47	10.2	0.25
7 (M)	68	IPAH	II	22.6	–	51	13.4	0.23
8 (F)	58	CTEPH	II	30.4	calcium channel antagonist	51	14.7	0.27
9 (M)	50	IPAH	III	23.55	–	53	7.5	0.29
10 (M)	63	tissue associated	III	25.3	–	45	7.1	0.23
11 (F)	63	IPAH	III	30.7	sitaxsentan, calcium channel antagonist	68	9	0.23
12 (F)	42	IPAH	III	38.6	sildenafil	77	10.3	0.27
13 (F)	65	IPAH	II	28.4	bosentan, calcium channel antagonist	31	16	0.22
14 (M)	57	IPAH	III	30.1	–	48	19.3	0.22
15 (F)	42	IPAH	IV	35.4	sildenafil, bosentan	82	6.7	0.34
16 (M)	84	IPAH	III	24.5	bosentan	40	11	0.29
17 (F)	71	CTEPH	III	25.3	–	51	11.6	0.24
18 (M)	43	IPAH	III	37.9	–	56	15.9	0.25
19 (M)	52	IPAH	II	36.5	bosentan	60	10.5	0.25
20 (F)	54	IPAH	III	29.4	–	57	13.4	0.27

NYHA = New York Heart Association; mPAP = mean pulmonary artery pressure; VO_2max = peak oxygen uptake; CTEPH = chronic thromboembolic pulmonary hypertension; IPAH = idiopathic pulmonary arterial hypertension; – = no specific therapy.

Data Analysis

All data obtained were tested for normal distribution (Kolmogorov-Smirnov test), and means ± SD were calculated. Significant differences between two sequential NT-proBNP values were examined using the t test for paired samples. Relative changes according to the base value at T1 (Δ) were standardized with the following formula:

$$\Delta_n\text{NT-proBNP} = \frac{\text{NT} - \text{proBNP}_n}{\text{NT} - \text{proBNP}_1} - \text{NT} - \text{proBNP}_1.$$

The interactions of exercise and right heart catheterization with serum values were examined using the Pearson correlation test. Statistical significance was accepted at $p < 0.05$.

Written informed consent was received from all patients for intravenous catheterization and obtaining blood samples. Both procedures were reviewed and accepted by the institutional review board of the University of Leipzig, Faculty of Medicine.

Table 2. Time points of NT-proBNP measurements within the exercise schedule

T1	at 6 a.m., at rest in bed
T2	at 10.30 a.m. (30 min after 6-min walking distance test)
T3	at maximum exercise (ergospirometry), 11 a.m.
T4	30 min after ergospirometry, at rest (recreation)
T5	120 min after ergospirometry, at rest

Results

The parameters of all patients are listed in table 3. Data are presented as mean values and SD. All parameters were found to be normally distributed ($p < 0.05$).

Mean serum levels of NT-proBNP at the 5 time points (T1–T5) are shown in table 4. The NT-proBNP values of patient 10 differed widely from those of the remaining patients. In this patient, NT-proBNP increased from 1,500 pg/ml at T1 to >10,000 pg/ml at T3 after light to severe physical exercise. According to the Dean-Dixon test for normally distributed samples, these values were identified as outliers ($p < 0.001$) and were therefore eliminated from the test group. A significant elevation of NT-proBNP from rest to maximal physical exercise is apparent (T1 to T3; $p = 0.0002$). Thirty minutes later (at T4), serum levels were decreasing ($p = 0.0073$). Values at T5 (after 2 h of recovery following physical exercise) were not different from T4 ($p = 0.3391$).

Table 3. Parameters of the 20 patients from echocardiography, ergospirometry and right heart catheterization

Parameters	Mean ± SD
Tei index	0.26 ± 0.03
Maximum exercise, W	69.8 ± 26.8
VO_2max, ml/min/kg	12 ± 3.28
O_2 pulse, ml/min/heart frequency	7.09 ± 2.36
$EqCO_2$ at anaerobic threshold, mm Hg	50.16 ± 16.8
PaO_2 at maximum exertion, kPa	8.2 ± 1.5
mPAP, mm Hg	52.55 ± 12.82
PVR, dyn·s/cm^5	999.2 ± 424.5
PC, mm Hg	9.5 ± 3.1
CO, l/min	3.75 ± 1.02
CI	2 ± 0.6
SvO_2, %	64.4 ± 9

VO_2max = Peak oxygen uptake; $EqCO_2$ = ventilatory equivalent for carbon dioxide; PaO_2 = partial pressure of oxygen in arterial blood; mPAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance; PC = pulmonary capillary wedge pressure; CO = cardiac output; CI = cardiac index; SvO_2 = central venous oxygen saturation.

Table 4. NT-proBNP serum levels of 19 patients (excluding patient 10) at the 5 measurement times (table 2)

Measurement time	NT-proBNP, pg/ml
T1	1,278 ± 998
T2	1,426 ± 1,110
T3	1,592 ± 1,219
T4	1,518 ± 1,170
T5	1,597 ± 1,266

Values are shown as means ± SD.

All absolute NT-proBNP values at rest (T1) and at maximum exercise (T3) are shown in figure 1 (except patient 10). In all patients, except patient 8, an increase in serum levels from T1 to T3 was observed. Compared to values at rest (T1), a mean elevation of 24% (range 3–54%; Δ_3NT-proBNP) was found. In the patients of this study, serum levels at rest showed a mean 9-fold elevation (1.7- to 19-fold) compared to the given cutoff [6], while at the point of maximum exertion, a mean elevation of 11-fold was measured. In patient 13, the serum level at rest was within the normal range (77.7 pg/ml). Also in this patient, there was a significant elevation of the value presented at maximum exertion (103.2 pg/ml). Resting, i.e. baseline, serum levels were correlated with the hemodynamic parameters cardiac output and cardiac index as well as the exercise test parameters (table 5). There was also a correlation with the Tei index ($p = 0.03$). Resting NT-proBNP levels were not correlated with levels at maximum exercise ($p = 0.4393$). However, a correlation between the individual relative changes and pulmonary vascular resistance ($p = 0.025$), cardiac output ($p = 0.015$) and cardiac index ($p = 0.003$) was calculated.

Discussion

The present study demonstrates elevation of serum NT-proBNP following physical exercise in patients with precapillary pulmonary hypertension. A significant increase in NT-proBNP was seen in all but one patient (patient 8) at maximum exertion.

After a 30-min period of relaxation (T4), a significant decrease in serum levels was measured in comparison to those at maximum exercise. The relative increase in NT-proBNP from rest to exercise correlated with cardiac output and pulmonary vascular resistance.

All patients exhibited chronic right heart failure with right heart enlargement. We therefore expected elevated serum NT-proBNP levels in all patients [11]. A mean 9-fold increase in this marker was measured at rest compared to the cutoff of the normal value for healthy subjects.

In one patient (patient 13), a normal resting serum level may be explained by the mild idiopathic pulmonary hypertension with only slightly increased pulmonary vascular resistance and a cardiac output of 4.9 liters/min. Nevertheless, a significant rise in NT-proBNP was also observed in this patient following exercise. The observation of right ventricular dysfunction without significant elevation of serum NT-proBNP was previously described in a retrospective study in 2007 [24]. Normal serum NT-proBNP levels were found in 22 of 86 patients with mild to moderate precapillary pulmonary hypertension and a pathologic Tei index.

As shown in figure 1 in this study, a wide range of serum levels at rest was observed, which most likely demonstrates the differing extent of right ventricular dysfunction in our patients. However, the parameter of right ventricular function (Tei index) did not correlate well with NT-proBNP. In future investigations, right ventricular mass will have to be focused or the measured values be referenced to body surface. Since we did not find elevated creatinine values in these patients, reduced glomer-

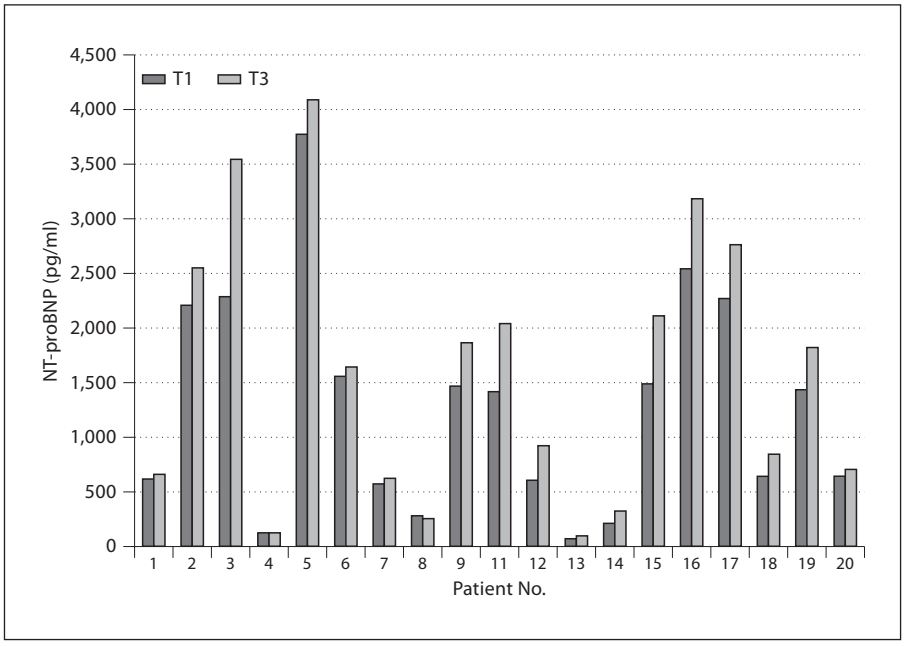

Fig. 1. Absolute NT-proBNP levels in 19 patients (excluding patient 10) at T1 and T3.

Table 5. Pearson correlations (p value/R value)

	Tei index	Maximum exertion	VO_2max	O_2 pulse	$EqCO_2$	PaO_2	mPAP	PVR	CO	CI	SvO_2
NT-proBNP$_1$	S (0.03/0.44)	S (0.006/–0.56)	S (0.009/–0.54)	S (0.034/–0.43)	S (0.003/0.6)	S (0.02/–0.47)	NS (0.48/–0.009)	NS (0.103/0.3)	S (0.002/–0.62)	S (0.02/–0.49)	S (0.03/–0.45)
Δ_3NT-proBNP	NS (0.35/0.1)	NS (0.31/0.12)	NS (0.04/–0.44)	NS (0.37/0.08)	NS (0.15/–0.25)	NS (0.22/0.19)	NS (0.1/0.31)	S (0.025/0.45)	S (0.0145/–0.5)	S (0.0027/–0.61)	NS (0.09/–0.32)
Tei index	–	S (0.021/–0.47)	S (0.002/–0.62)	NS (0.12/–0.28)	NS (0.08/0.33)	NS (0.17/–0.23)	S (0.04/0.41)	S (0.04/0.41)	NS (0.06/–0.37)	NS (0.09/–0.33)	NS (0.06/–0.37)

NT-proBNP$_1$ = NT-proBNP at T1; Δ_3NT-proBNP = relative change between T1 and T3; VO_2max = peak oxygen uptake; $EqCO_2$ = ventilatory equivalent for carbon dioxide; PaO_2 = partial pressure of oxygen in arterial blood; mPAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance; CO = cardiac output; CI = cardiac index; SvO_2 = central venous oxygen saturation; S = significant; NS = not significant.

ular filtration rates should be considered as a possible source of variation.

In this study we observed a clear dependence of NT-proBNP serum levels on physical exercise. At maximum exercise, NT-proBNP levels were elevated by 24 ± 18% compared to resting levels, which were already increased up to 23-fold over values of healthy controls. Statistical analyses demonstrated a significant correlation of the exercise-induced increase with cardiac output and pulmonary vascular resistance.

We tried to eliminate additional sources of variation. Blood samples were taken under standardized conditions. The best interindividual comparability was observed at time points T1–T3. At these time points, patients followed a well-defined schedule controlling the level of physical exercise. The level of control was not the same for subsequent time points. Despite hospitalization, 3 patients did not get to rest in between T3 and T4, and about half of the patients did not strictly follow the schedule between T4 and T5, which may have prevented a further decrease in serum NT-proBNP at T5. However, taking into consideration the fact that the half-life of NT-proBNP is approximately 120 min [6], elevation at T3 could still have been caused by the slight exertion in the hours before and not only by the maximal exercise. The combined exercise tests performed within 1 h could have

been the reason for the lack of a significant drop in serum levels at T5.

A correlation of mean pulmonary artery pressure with the levels of NT-proBNP at rest was not observed in this study. Similarly, the individual increase in NT-proBNP levels following maximum exercise did not correlate with mean pulmonary artery pressure. However, resting serum levels of NT-proBNP correlated with the Tei index and cardiac output and thus with the extent of right heart failure. This might support the consideration that the extent of right heart failure as indicated by NT-proBNP does not correlate with the level of pulmonary arterial pressure but is characterized by the cardiac output. Interestingly, the Tei index did correlate slightly better with NT-proBNP at rest than with mean pulmonary artery pressure and pulmonary vascular resistance, but not with cardiac output. Since a relationship between body mass index (BMI) and NT-proBNP has been discussed [25], BMI was calculated in our patients (table 1). It was normally distributed and did not show a significant correlation with NT-proBNP in our patients (BMI vs. NT-proBNP at rest: $p = 0.055$, $r = -0.38$; BMI vs. Δ_3NT-proBNP: $p = 0.067$; $r = 0.35$). These findings are probably due to the small number of patients in this study.

We observed a correlation of central venous oxygen saturation, peak oxygen uptake and peak oxygen pulse with NT-proBNP at rest. The change in NT-proBNP between T1 and T3 was not directly correlated with these parameters. Since NT-proBNP indicates the extent of right heart failure, lack of a relationship of the change in NT-proBNP with O_2 parameters only suggests that NT-proBNP elevation is caused by multiple factors.

In spite of the small number of patients in this study, we demonstrated acute effects of physical exercise on NT-proBNP serum levels in patients with right heart failure. One patient, in our series labeled patient number 10, had to be excluded from further statistical evaluation. In this patient, very high serum levels were detected, suggesting considerable right heart failure during exercise. However, even in this patient a significant increase in the NT-proBNP serum level at T3 and a decrease following recovery was observed, emphasizing the results of our study.

For patients with pulmonary hypertension, even mild physical exercise such as standing tall, walking at normal speed and climbing stairs may represent great physical challenges involving increased load on the right ventricular muscle leading to increased cellular distension, which is the stimulus for the release of NT-proBNP into the serum, as is demonstrated here at T2 compared to resting conditions. A half-life of 120 min, renal elimination and bursts of secretion characterize the release of NT-proBNP following even mild physical exercise. Serum NT-proBNP is therefore considered to be a useful diagnostic parameter for the evaluation of heart failure [13–16]. Values measured after mild physical exercise do not appear to be very useful for the accurate long-term follow-up of patients with pulmonary hypertension. In order to be able to compare intraindividual and interindividual values of patients, measurements should take into account that even mild physical exercise, as is involved in the patients coming into the physician's office, may significantly alter NT-proBNP levels. Based on the half-life of NT-proBNP, one might opt for a 2-hour period more or less devoid of physical activity, but our T5 value suggests that even this might not be enough. We are well aware that these conditions are not easily applicable in the real world. Therefore, wider variation limits of serum levels allow only an approximation of the extent of chronic (right) heart failure and should be used with caution and in addition to a distinct clinical examination, exercise tests and echocardiography. Given the costs of the examination, extensive application of this diagnostic instrument should be avoided. Furthermore, studies involving hemodynamics at exercise with distinction of right and left heart failure are needed for a better understanding of the pathophysiologic basis of NT-proBNP elevation.

Financial Disclosure and Conflicts of Interest

No conflict of interest declared.

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