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Original Scientific Paper

Short-term residential cardiac rehabilitation reduces B-type natriuretic peptide

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Background **The inactive *N*-terminal pro-BNP (NT-proBNP) serves as a marker of heart failure. We evaluated the effects of moderate exercise on NT-proBNP and other cardiovascular disease risk factors in 359 consecutive patients admitted for residential cardiovascular rehabilitation.**

Methods and results **Patients underwent cycle ergometry, blood sampling, and fasting glucose tests at the beginning and end of 25 ± 4 days of the exercise program. Maximal oxygen uptake (VO_{2max}) was estimated from the maximal watts achieved. The program consisted of cycling for 17 ± 4 min, 6 times/week, and daily walking for 45 min at intensity of 60–70% of the individual maximal heart rate (HR). Patients underwent echocardiographic examination and were categorized according to left ventricular ejection fraction. NT-proBNP decreased to 29% ($P=0.001$) for entire group after training. Maximal performance and VO_{2max} improved significantly ($P=0.001$). NT-proBNP was inversely related to pulse pressure at maximal exercise (−0.39), HR range (−0.35), and HR recovery in 1 min (−0.28).**

Conclusion **Four weeks of exercise reduced NT-proBNP, independent of left ventricular ejection fraction, and improved physical fitness and blood lipid profiles. NT-proBNP as a prognostic biomarker of heart failure patients was reduced and was inversely related to maximal performance and VO_{2max}. *Eur J Cardiovasc Prev Rehabil* 16:603–608 © 2009 The European Society of Cardiology**

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Keywords: echocardiography, exercise, heart failure, natriuretic peptides

Introduction

An increase in wall tension and release of *N*-terminal pro-BNP (NT-proBNP) reflects hemodynamic myocardial stress independent of the underlying pathology. NT-proBNP and B-type natriuretic peptide (BNP) are not specific for a distinct pathology, such as heart failure (HF), but more so for cardiovascular disease (CVD) in general. Both forms are elevated in patients with HF and serve as an established marker for the diagnosis and the associated severity of congestive HF [1,2]. An increase in the circulating NT-proBNP signifies both left ventricular systolic and diastolic dysfunction and provides a diagnostic tool to confirm or rule out HF [3,4].

NT-proBNP is reduced when hemodynamic equilibrium of the heart is reestablished, and serial measurements of NT-proBNP may become clinically important in the management of patients with HF [5]. In addition, NT-proBNP provides strong and independent prognostic information in patients with HF, stable coronary artery disease, acute coronary syndromes, and valvular heart disease, and is a predictor of cardiac mortality [6–9].

Exercise therapy has become an integral part of secondary prevention programs for CVD. Exercise training in cardiac

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rehabilitation, and especially in the treatment of HF patients, results in an improvement in symptoms, exercise tolerance, quality of life, and may aid in the determination of clinical outcome [10,11].

The primary purpose of this study was to determine whether short-term moderate exercise training as part of a comprehensive residential cardiac rehabilitation program will reduce NT-proBNP and improve overall cardiac risk. The secondary purpose was to determine the relationships between NT-proBNP, hemodynamic variables, and exercise capacity.

Methods

Patients

Participants in our study were 359 consecutive patients (63 women, 296 men) with mean age of 63 ± 11 years referred to the Center for Cardiovascular Rehabilitation at Bad Schallerbach, Austria.

Disease diagnoses and medications of the participants are depicted in Table 1. The study was approved by the local ethics committee, and a signed written informed consent was obtained from all patients prior to data collection.

Biochemical analysis

Blood samples of 5 ml were collected from each patient in the morning after an overnight fast at the beginning and again at the end of their 25-day cardiac rehabilitation residency. NT-proBNP was measured using immunoassay sandwich principle based on electrochemiluminescence technology (analytical range 5–35 000 pg/ml) (Elecsys 2010; Roche Diagnostics, Mannheim, Germany). Standard measurements of lipids, lipoproteins, and fasting glucose were determined by Hitachi 717 instrument (Roche Diagnostics).

Table 1 Disease diagnosis (%) at entry and medications (%) at entry and discharge

Variable	Pre-rehabilitation	Post-rehabilitation
Diseases		
CVD	81	
MI	41	
PCI + stent	42	
Coronary bypass surgery	34	
Valve surgery	12	
Hypertension	68	
Diabetes	23	
Atrial fibrillation	6	
Medications		
Beta-blocker	81	83
ACE inhibitor	57	60
AT II RA	19	21
Statins	73	83
Diuretics	48	54
Amiodarone	5	6

ACE, angiotensin-converting enzyme; AT II RA, angiotensin II receptor antagonist; CVD, cardiovascular disease; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Echocardiography

Transthoracic echocardiography was performed by Toshiba Aplio CV instrument (Toshiba Medical Systems, Japan) for determination of ejection fraction (EF) according to the modified Simpson's rule [12]. EF was classified as normal if the EF was ≥ 55%; mildly reduced, if 45–54%; moderately reduced, if 30–44%; and severely reduced, if < 30%.

Physiologic testing and training

Patients underwent cycle ergometry tests. The tests began with a workload of 25 Watts (W) followed by 25-W increments every 2 min until individual maximal performance was achieved. Heart rate (HR), systolic blood pressure, and diastolic blood pressure (DBP), were determined every 2 min, and maximal oxygen uptake (VO_{2max}) was estimated from the maximal workload measured in Watts according to the guidelines of the American College of Sports Medicine [13]. In recovery, we assessed hemodynamic variables during 1, 3, and 5 min.

All 359 patients completed the prescribed exercise program. It consisted of daily cycle ergometry for 17 ± 4 min, 6 times/week, and daily walking for 45 min at intensity of 60–70% of the individual maximal HR [14]. The exercise HR intensity was determined in the beginning according to the Karvonen formula [resting HR + (maximal HR – resting HR)] × 0.6 and monitored by Polar (Polar, Kempele, Finland) chest strip and watch telemetry apparatus [15]. The mean residency time for our patients was 25 ± 4 days. All patients completed prescribed exercise cardiac rehabilitation program; however, 93 of the initial 359 patients did not complete post-exercise tests because of medical, personal reasons, or personal choice.

Statistical analysis

Statistical analysis was conducted using paired and unpaired *t*-tests (SAS version 9.1.3; SAS Institute Inc., Cary, North Carolina, USA). Pearson's product moment correlations were calculated for selected dependent variables. To control for an inflated type I statistical error that can occur when multiple *t*-tests are used to analyze intercorrelated dependent variables, we selected a conservative $\alpha = 0.01$ for all statistical tests of significance.

Results

NT-proBNP was significantly reduced by 29% in patients completing the exercise rehabilitation program (Table 2). Furthermore, quintile distribution of NT-proBNP showed significant reductions (Table 3). When comparing patients with different diseases, each group of patients exhibited a highly significant reduction ($P \leq 0.0001$) in NT-proBNP after rehabilitation (Fig. 1).

For our analytical procedure, normal NT-proBNP values were defined as less than 125 pg/ml. Rehabilitation training did not significantly change the number of patients with normal values, 17% at entry and 16% at the end.

Patients with normal systolic EF, who were older than 50 years of age, had NT-proBNP values of greater than 900 pg/ml at entry comprised 27%, compared with 18% at the end of the program ($P = 0.0001$), representing a 41% reduction in NT-proBNP (Fig. 2). When classifying the patients based on their left ventricular EF at entry according to the combined guidelines of the American and European Society of Echocardiography, all groups showed a significant decrease in NT-proBNP after rehabilitation (Fig. 3).

Patients that had blood NT-proBNP values greater than 450 pg/ml after rehabilitation program comprised 47%, compared with 54% at entry. When age and EF were considered, 23% of our patients aged 50 years or younger with normal systolic EF on admission had NT-proBNP values greater than 450 pg/ml; this was reduced to only 8% after rehabilitation ($P > 0.05$), a change that corresponds to a 51% reduction in NT-proBNP (Fig. 2).

In our patients, NT-proBNP concentrations showed an inverse and significant relationship with maximal exercise HR, systolic blood pressure, and DBP, pulse pressure at maximal exercise, maximal workload, and VO_{2max} (Table 4).

Rehabilitation training resulted in significant improvements in several measures of physical fitness and cardiovascular performance (Table 5).

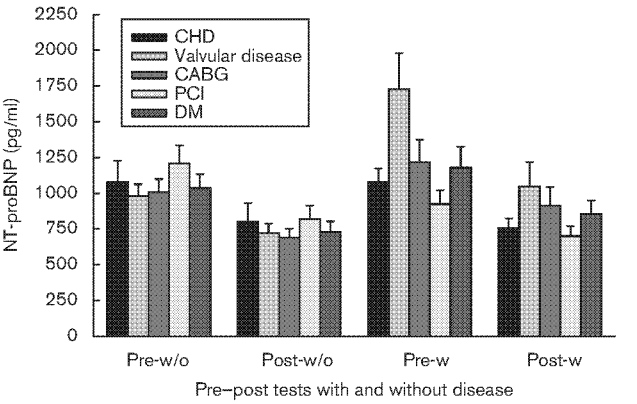
Table 2 NT-proBNP and selected blood laboratory data before and after rehabilitation

Variable	Pre-rehabilitation	Post-rehabilitation	*P* value
NT-proBNP (pg/ml)	1079±1412 (*n*=359)	765±955 (*n*=359)	0.001
Fasting glucose (mg/dl)	108±26 (*n*=349)	104±25 (*n*=223)	0.064
Cholesterol (mg/dl)	176±44 (*n*=342)	147±37 (*n*=314)	0.001
HDL-cholesterol (mg/dl)	49±13 (*n*=342)	47±11 (*n*=314)	NS
LDL-cholesterol (mg/dl)	111±37 (*n*=342)	84±31 (*n*=314)	0.001
Triglyceride (mg/dl)	150±98 (*n*=342)	123±64 (*n*=312)	0.001

Values are expressed as mean±SD. HDL, high-density lipoprotein; LDL, low-density lipoprotein; NT-proBNP, *N*-terminal pro-BNP.

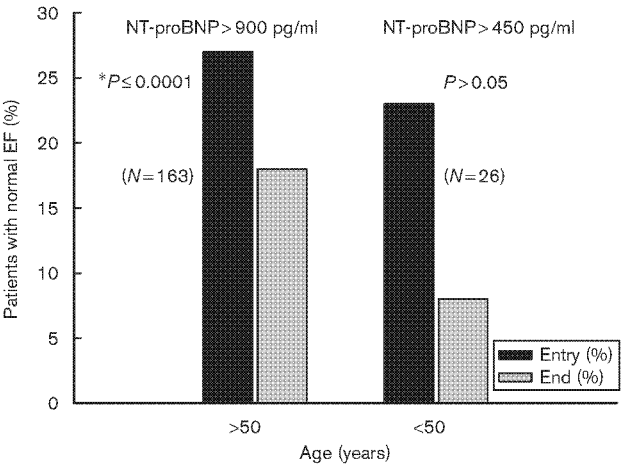
The average maximal cycle ergometry power (+18%), VO_{2max} (+14%), and HR recovery 1 min after maximal exercise (+14%) increased in response to training.

Fig. 1



Reduction in *N*-terminal pro-BNP (NT-proBNP) measured after cardiac rehabilitation in patients with (w) and without (w/o) documented disease. All pretest to post-test changes were significantly different (all $P \leq 0.0001$). Values are means±SEM. CABG, coronary artery bypass graft; CHD, coronary heart disease; DM, diabetes mellitus; PCI, percutaneous coronary intervention.

Fig. 2



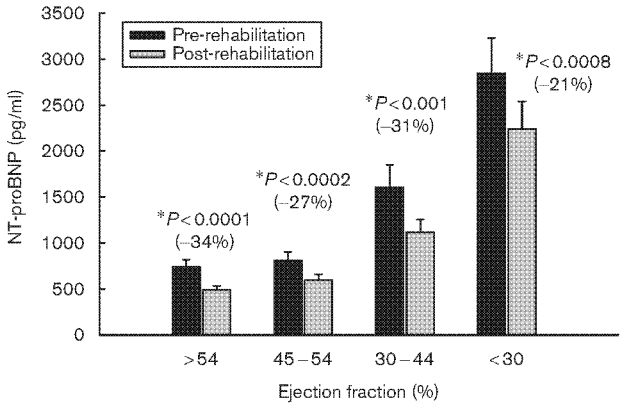
Reduction in *N*-terminal pro-BNP (NT-proBNP) as a function of age and age-adjusted cut-off values in patients with normal ejection fraction (EF). *$P < 0.0001$, significantly different between pretest and post-test for NT-proBNP value of greater than 900 pg/ml.

Table 3 Quintile distribution and reduction of NT-proBNP during rehabilitation

Quintiles	I	II	III	IV	V
n	287	43	16	6	7
NT-proBNP, pre-rehabilitation (pg/ml)	515±439	2206±453	3897±517	5243±374	7258±511
NT-proBNP post-rehabilitation (pg/ml)	415±354	1603±862	2553±1157	3510±958	3542±1783
P value	0.003	0.001	0.001	0.002	0.001

Values are expressed as mean±SD. NT-proBNP, *N*-terminal pro-BNP.

Fig. 3



N-terminal pro-BNP (NT-proBNP) and ejection fraction (EF) before and after rehabilitation. In our study, the NT-proBNP was inversely related to EF.

Table 4 Correlations between NT-proBNP post-rehabilitation and other variables of interest

NT-proBNP correlates	Pearson's correlation coefficient	*P* value
Age (years)	0.251	<0.0001
Weight (kg)	−0.164	0.0017
BMI (kg/m^2)	−0.167	0.0014
Resting HR (bpm)	0.143	0.0061
HR_{max} (bpm)	−0.267	<0.0001
HR range (bpm)	−0.351	<0.0001
SBP_{max} (mmHg)	−0.402	<0.0001
HR recovery at 1 min (bpm)	−0.281	<0.0001
DBP_{max} (mmHg)	−0.223	<0.0001
PP_{max} (mmHg)	−0.391	<0.0001
P_{max} (W)	−0.408	<0.0001
VO_{2max} (ml/kg/min)	−0.404	<0.0001

DBP_{max}, maximum diastolic blood pressure; HR_{max}, maximum heart rate; NT-proBNP, *N*-terminal pro-BNP; P_{max}, maximal power output expressed in Watts; PP_{max}, pulse pressure at maximal performance; SBP_{max}, maximum systolic blood pressure; VO_{2max}, relative maximal oxygen consumption.

Table 5 BMI, resting, and exercise cardiopulmonary data

Variable	Pre-rehabilitation	Post-rehabilitation	*P* value
BMI (kg/m^2)	28.4±4.5 (*n*=359)	27.9±4.3 (*n*=270)	<0.0001
Resting HR (bpm)	74±14 (*n*=359)	68±13 (*n*=270)	<0.0001
Resting SBP (mmHg)	130±21 (*n*=359)	128±19 (*n*=270)	NS
Resting DBP (mmHg)	80±10 (*n*=359)	78±10 (*n*=270)	0.0067
PP_{max} (mmHg)	97±26 (*n*=364)	102±26 (*n*=269)	0.0276
HR recovery 1 min (bpm)	14±11 (*n*=359)	16±11 (*n*=270)	<0.0001
P_{max} (W)	114±45 (*n*=359)	134±47 (*n*=270)	<0.0001
VO_{2max} (ml/kg per min)	22.0±5.6 (*n*=359)	24.7±5.9 (*n*=270)	<0.0001
VO_{2max} (ml/min)	1840±547 (*n*=359)	2047±563 (*n*=270)	<0.0001

Values are expressed as mean±SD. DBP, diastolic blood pressure; HR, heart rate; P_{max}, maximal power output expressed in Watts; PP_{max}, pulse pressure at maximal performance; SBP, systolic blood pressure VO_{2max}, maximal oxygen consumption (relative: ml/kg per min; absolute: ml/min).

Furthermore, resting HR (−8%), DBP (−2%), and BMI (−2%) were significantly lower at discharge. A 5% increase in pulse pressure at maximal exercise after training was significant ($P = 0.02$). Rehabilitation training resulted in additional benefits of significantly reduced lipids and lipoproteins (Table 2).

Discussion

Our study showed that 25 ± 4 days in cardiac rehabilitation leads to significant increases in maximal exercise performance, improved cardiovascular risk factors, and a significant 34% reduction in NT-proBNP. These findings suggest a relatively powerful effect of short-term exercise training as part of a residential cardiac rehabilitation program to improve myocardial function, to at least partially ameliorate the symptoms of systolic and/or diastolic dysfunction, and to improve cardiac risk profile.

In recent years, biomarkers have emerged as important tools for diagnosis, risk stratification, and therapeutic decision-making in CVDs. The BNP and NT-proBNP are released by the heart in response to myocardial tension and increased intravascular volume. Elevations of BNP and NT-proBNP are found in patients with HF and are associated with disease severity, coincide with functional classification of the New York Heart Association, correlate with the left ventricular systolic EF, and left ventricular diastolic function [16]. Correlations exist between natriuretic peptides and hemodynamic indices, such as left ventricular end-diastolic pressure and pulmonary capillary wedge pressure [17]. Independent of the diagnostic usefulness of this circulating peptide, NT-proBNP concentrations have been shown to be of prognostic value correlated with mortality, cardiovascular death, repeated hospital admissions, and myocardial events in patients with symptomatic HF, and in patients with asymptomatic left ventricular dysfunction as well. In a multivariate statistical analysis, BNP and NT-proBNP were significant prognostic indicators; and in other reports, these were independent prognostic variables of myocardial events [6].

Natriuretic peptides are also linked to coronary heart disease (CHD). Pathologically, myocardial ischemia can induce an increase in myocardial wall tension and invoke systolic or diastolic dysfunction that leads to an increased production of BNP and NT-proBNP. This occurs in acute coronary syndrome and in stable CHD. Thus, NT-proBNP is a marker of long-term mortality in patients with stable CHD and provides prognostic information above and beyond the conventional risk factors. It serves as a predictor of adverse cardiovascular events independent of other prognostic markers using echocardiography, ischemic stress testing, or serum measurement [9,18,19]. These previously published

findings strongly suggest that a reduction in circulating NT-proBNP concentration, as shown in our study, is likely a marker of reduced ventricular wall tension and improved myocardial function. To the extent that the functional status of the myocardium contributes to patient physical capacity and quality of life, a reduced NT-proBNP concentration should signal a valid benefit of residential cardiac rehabilitation.

Research reports indicate an increased risk of mortality and cardiovascular events with small increases in BNP and NT-proBNP [18,20]. In general, blood concentrations of BNP below 100 pg/ml and NT-proBNP below 300 pg/ml have been shown to be optimal for excluding a diagnosis of acute HF, with a negative predictive value of 98% [21]. In patients below 50 years of age, HF is reportedly unlikely at BNP values below 100 pg/ml, but probable at NT-proBNP values greater than 450 pg/ml. In patients aged 50 years and older, NT-proBNP values exceeding 900 pg/ml are predictive of HF [6]. Among all patients older than 70 years, with normal systolic EF, 24% had NT-proBNP greater than 900 pg/ml at entry, and by the end of the program this NT-proBNP category fell to 16%. Using an NT-proBNP greater than 220 pg/ml, the cut-off value recommended in the 2007 consensus document from the European Society of Cardiology, many more patients with normal left ventricular EF would be classified with HF [22]. Corteville *et al.* [23] reported that 11% of 730 patients who had NT-proBNP above 500 pg/ml with normal left ventricular function and stable CHD were likely to have diastolic dysfunction. An NT-proBNP of less than 100 pg/ml was diagnostically associated with a reduced occurrence of a morbidity. In our study, this would apply to 42% of our patients with normal systolic function.

We found a reduction in NT-proBNP after moderate exercise in older and younger patients regardless of the level of NT-proBNP at entry (Fig. 2). In patients with symptomatic HF, a decrease in serial measurements of BNP and NT-proBNP showed clinically significant findings in the management of patients with HF. The decrease in BNP measured during hospitalization yielded an improved outcome compared with no change or an increase in BNP levels [24]. On this basis, we suggest that the reduced NT-proBNP concentrations we report here after 4 weeks of cardiac rehabilitation are important and clinically relevant outcomes indicative of improved cardiac function apart from the severity of the initial cardiac dysfunction.

Medical examinations resulting in the diagnosis of HF are based on systolic dysfunction with reduced left ventricular EF. However, in patients with normal left ventricular systolic function, an elevated NT-proBNP in the absence of pulmonary disease with right ventricular tension may indicate diastolic dysfunction. Although we did not investigate this occurrence in our patients, this matter has been reported earlier in a number of studies [4,23,25–27]. Others have shown that 20–50% of patients with HF retain normal systolic function [22,28]. Most patients with diastolic HF are usually older, often women, are overweight or obese, and frequently have arterial hypertension, diabetes, and CHD [29]. Morbidity and mortality among these patients may be as high as that among patients with preserved systolic HF. Furthermore, there is no difference in rates of rehospitalization or physical work tolerance as a measure of quality of life [30,31].

Compared with placebo, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and their combination were shown to reduce BNP levels in a dose-dependent manner in the acute phase and after long-term therapy in patients with left ventricular dysfunction. Decreased BNP levels were also reported after long-term treatment with β-blockers. Spironolactone administration has also resulted in a significant reduction in BNP levels. Our study suggests that the decrease in NT-proBNP in short-term rehabilitation is comparable with pharmaceutical treatment.

Our findings of improved physical working capacity with training are in themselves not new, but the significant improvements ($>12\%$) in just 25 days of residential cardiovascular rehabilitation are noteworthy. Endurance training is an established basis for rehabilitation therapy in patients suffering from chronic HF [32]. Results of meta-analysis of the available data suggest that exercise training can reduce mortality by approximately 35% in patients with chronic HF owing to left ventricular systolic dysfunction. It is remarkable that on average, one death in 2 years can be prevented in every 17 patients treated with exercise training. Time to death or admission to hospitalization was also significantly extended. The duration of aerobic training in cardiovascular rehabilitation depicted in several studies consisted of 4 weeks to 12 months [33]. It is not clear whether the benefits obtained from exercise training are sustained if exercise is stopped.

An improvement in exercise efficiency and VO_{2max} is typical for cardiac rehabilitation [34,35]. We noted an increase in VO_{2max} by 12%, and an 18% improvement in maximal cycling power. NT-proBNP was significantly and inversely related to VO_{2max} and to maximal exercise cycling power. Our study suggests that an improvement in myocardial performance is at least partly responsible for the increase in VO_{2max}. Our finding that resting HR (-8%) and HR recovery 1 min after exercise ($+14\%$) (Table 5) are improved in our patients adds strong support for the significant cardiovascular benefit that can be achieved in only 4 weeks of exercise training by cardiac patients.

Our study documents that short-term cardiac rehabilitation and exercise training residency program of only 25 days significantly reduces NT-proBNP (29% reduction), with no significant change in prescribed medications. Virtually, all indices of hemodynamics, oxygen utilization, physical working capacity, and established cardiovascular risk factors improved significantly. Serial measurement of NT-proBNP represents a sensible marker for myocardial improvement in patients undergoing cardiovascular rehabilitation, and may be used to document the benefits of recovery.

Acknowledgement

Conflicts of interest: none declared.

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