Aerobic Training Decreases B-Type Natriuretic Peptide Expression and Adrenergic Activation in Patients With Heart Failure

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OBJECTIVES	We sought to evaluate the effect of physical training on neurohormonal activation in patients with heart failure (HF).
BACKGROUND	Patients with HF benefit from physical training. Chronic neurohormonal activation has detrimental effects on ventricular remodeling and prognosis of patients with HF.
METHODS	A total of 95 patients with HF were assigned randomly into two groups: 47 patients (group T) underwent a nine-month training program at 60% of the maximal oxygen uptake ($\dot{V}O_2$), whereas 48 patients did not (group C). The exercise load was adjusted during follow-up to achieve a progressive training effect. Plasma assay of B-type natriuretic peptide (BNP), amino-terminal pro-brain natriuretic peptide (NT-proBNP), norepinephrine, plasma renin activity, and aldosterone; quality-of-life questionnaire; echocardiogram; and cardiopulmonary stress test were performed upon enrollment and at the third and ninth month.
RESULTS	A total of 85 patients completed the protocol (44 in group T, left ventricular ejection fraction [EF] 35 ± 2%, mean ± SEM; and 41 in group C, EF 32 ± 2%, p = NS). At the ninth month, patients who underwent training showed an improvement in workload (+14%, p < 0.001), peak $\dot{V}O_2$ (+13%, p < 0.001), systolic function (EF +9%, p < 0.01), and quality of life. We noted that BNP, NT-proBNP, and norepinephrine values decreased after training (−34%, p < 0.01; −32%, p < 0.05; −26%, p < 0.01, respectively). Increase in peak $\dot{V}O_2$ with training correlated significantly with the decrease in both BNP/NT-proBNP level (p < 0.001 and p < 0.01, respectively). Patients who did not undergo training showed no changes.
CONCLUSIONS	Clinical benefits after physical training in patients with HF are associated with blunting of adrenergic overactivity and of natriuretic peptide overexpression. (J Am Coll Cardiol 2006; 47:1835–9) © 2006 by the American College of Cardiology Foundation

Chronic heart failure (HF) is characterized by fatigue, dyspnea, abnormal peak oxygen uptake (peak $\dot{V}O_2$), and ventilatory efficiency to exercise measured by the slope of increase in ventilation over carbon dioxide output ($\dot{V}E/\dot{V}CO_2$ slope) (1). Despite pharmacologic therapy, the prognosis is poor. Aerobic physical training is known to improve exercise tolerance (2–5), ventilatory efficiency (5), quality of life (QOL) (4), and to counteract sympathetic overactivation (3). Finally, rates of mortality and hospitalization decrease after patients undergo training independently from medical treatment (6).

Neurohormonal activation is a hallmark of HF (7). The production of B-type natriuretic peptide (BNP) by ventricular cardiomyocytes correlates with left ventricular dysfunction (8,9). Thus, the assay of either BNP or amino-terminal pro-brain natriuretic peptide (NT-proBNP) has been proposed as diagnostic and prognostic tool (9). However, studies concerning the influence of training on BNP secretion early after myocardial infarction (10) and in patients with chronic HF (11,12) have given conflicting results. In this study, we evaluated the effect of home-based aerobic physical training, with adjustment of the exercise load during follow-up for achieving a progressive training effect, on neurohormonal activation in patients in HF.

METHODS

Subjects. We screened 158 consecutive patients with HF from 2002 to 2004. Inclusion criteria were impaired left ventricular systolic function (ejection fraction [EF] <45%) and exercise capacity (peak $\dot{V}O_2$ <25 ml/min/kg). Exclusion criteria were New York Heart Association (NYHA) functional class IV, myocardial infarction or unstable angina within six months before the examination, exercise-limiting diseases, and severe pulmonary or renal disease. Of the 158 patients, 35 did not match these criteria, whereas 28 refused to sign the informed consent approved by the institutional ethical committee. Ultimately, 95 patients (80 men and 15 women, mean age 60 ± 1 years) were enrolled. All 95 patients were on stable (i.e., >1 month) optimal pharmacologic treatment (Table 1). A significant change in treat-

Abbreviations and Acronyms

BNP	= B-type natriuretic peptide
CPT	= cardiopulmonary stress test
EF	= ejection fraction
HF	= heart failure
NT-proBNP	= amino-terminal pro-brain natriuretic peptide
NYHA	= New York Heart Association
QOL	= quality of life
V_E/V_{CO_2}	= ventilation/carbon dioxide production ratio
V_{O_2}	= oxygen uptake

ment or hospitalization resulted in withdrawal from the study.

Study design. This was a prospective, randomized, controlled study. Patients were assigned randomly into two groups. The training group (group T) underwent a nine-month training program, whereas control patients (group C) continued their usual lifestyle. The two groups did not differ as to age, gender, NYHA functional class, EF, pharmacologic treatment, or HF etiology (Table 1).

Patients underwent neurohormonal and clinical evaluation and a maximal exercise test with gas exchange (cardiopulmonary stress test [CPT]) within the same morning upon enrollment and at the third and ninth month. An echocardiographic study was performed, and patients rated their QOL on entry and at the end of the study.

Physical training. The training program consisted of cycling on a bike for a minimum of 3 days per week, 30 min per day. Patients were instructed to exercise at 60 rpm, keeping heart rate constantly monitored at 65% of peak V_{O_2} heart rate, by a wearable device. At the enrollment, they

participated to in-hospital training sessions. Their compliance to the program was checked by a physiotherapist and at the first, second, third, sixth, and ninth month. At the third-month visit, workload was adjusted according to a new CPT. Patients in group C underwent follow-up visits at the third and ninth month to exclude changes in their usual lifestyle and physical activity.

Cardiopulmonary exercise test, echocardiographic study, QOL, and plasma assays. A CPT was performed by exercise on a bicycle ergometer using a ramp protocol with increments of 10 W/min. We measured V_{O_2}, CO_2 production, and minute ventilation using breath-to-breath gas analysis (Vmax, Sensormedics, Conshohocken, Pennsylvania). Peak V_{O_2} (the highest value at end-exercise, as a 20-s average) and ventilatory efficiency on exercise (slope of the ventilation vs. V_{CO_2} relation in its linear part) were determined. The same physician performed all the CPTs and was unaware of the results of blood sampling. The echocardiographic studies were all performed by the same physician.

Quality of life was evaluated by means of the Minnesota Living With Heart Failure Questionnaire; BNP, plasma catecholamines, plasma renin activity, and aldosterone were assayed as described elsewhere (9); and NT-proBNP was measured with an automated electrochemiluminescent immunoassay.

Statistics. Because neurohormone values are not distributed normally, natural logarithmic transformation of data was used for parametric statistical analysis, including two-way repeated-measure analysis of variance, Bonferroni post-hoc test, and linear regression analysis. Skewness and Kurtosis tests were used to determine whether data were normally distributed. Chi-square and unpaired t tests were used to evaluate differences between the two groups. Mauchly's test to assess the sphericity assumption was performed. To assess the significance of the interaction between groups, we applied the Greenhouse-Geisser correction factor when Mauchly's test was significant (13). The results are expressed as mean values ± SEM, and p values were considered significant when < 0.05.

Table 1. Baseline Characteristics of the Study Patients Assigned Randomly to Group T or C

	Group T (n = 44)	Group C (n = 41)
Age (yrs)	60 ± 2	61 ± 2
Males/females (n)	39/5	35/6
BMI (kg/m²)	25.8 ± 0.3	25.1 ± 0.8
Idiopathic/postischemic (n)	17/27	18/23
LVEF (%)	35.3 ± 1.6	32.3 ± 2.2
Sinus rhythm/AF (n)	41/3	39/2
NYHA functional class I/II/III (n = mean ± SEM)	6/28/10 (2.1 ± 0.1)	8/23/10 (2.1 ± 0.1)
Treatment (%)		
Furosemide	82	85
Beta-blocker	72	73
ACE inhibitor	78	79
ARB	7	5
Spironolactone	35	38

No significant differences were found for any of the comparisons.
ACE = angiotensinogen-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BMI = body mass index; Group C = control group; Group T = training group; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

RESULTS

Three patients in group T did not complete the program: one required treatment changes, one refused to continue after the first month, and one withdrew a after three weeks because of a stroke. Conversely, seven patients in group C did not complete the program: two were lost at follow-up; two required hospitalization for decompensation; two needed treatment changes; and one withdrew after a diagnosis of lung cancer. A total of 85 patients completed the protocol (44 in group T, 41 in group C); of these, 5 patients (2 in group T and 3 in group C), included in data analysis, required only minimal treatment adjustments (change of furosemide dosage by 25 mg).

Table 2. Echocardiographic, Functional, and Neurohormonal Profile at Baseline and at End of Follow-Up

	Group T		Group C	
	Baseline	**Ninth Month**	**Baseline**	**Ninth Month**
Ejection fraction (%)	35 ± 2	38 ± 2§	32 ± 2	31 ± 2†
LV-EDVi (ml/m²)	111 ± 8	96 ± 6‡	116 ± 7	120 ± 8†
LV-ESVi (ml/m²)	72 ± 6	58 ± 5‡	78 ± 6	80 ± 7†
Peak V$_{O_2}$ (ml/min/kg)	15 ± 1	17 ± 1‖	14 ± 1	13 ± 1†
Workload (W)	99 ± 6	114 ± 6‖	85 ± 6	80 ± 5†
V$_E$/V$_{CO_2}$ slope	34 ± 1	33 ± 1	36 ± 1	37 ± 1*
BNP (ng/l)	187 ± 29	123 ± 23§	188 ± 27	201 ± 32†
NT-proBNP (ng/l)	1,370 ± 234	929 ± 206‡	1,581 ± 251	1,677 ± 291†
Norepinephrine (ng/l)	607 ± 55	447 ± 39§	515 ± 34	609 ± 67†
PRA (ng/ml/h)	3.04 ± 0.66	2.96 ± 0.62	4.26 ± 1.21	2.45 ± 0.56
Aldosterone (ng/l)	198 ± 27	186 ± 24	195 ± 26	216 ± 25

*p < 0.05 vs. group T, †p < 0.001 vs. group T, ‡p < 0.05, §p < 0.01 vs. respective baseline, ‖p < 0.001 vs. respective baseline.
BNP = B-type natriuretic peptide; EDVi = end-diastolic volume normalized by body surface area; ESVi = end-systolic volume normalized by body surface area; LV = left ventricular; NT-proBNP = N-terminal probrain natriuretic peptide; PRA = plasma renin activity; V$_E$ = ventilation; V$_{CO_2}$ = carbon dioxide production; V$_{O_2}$ = oxygen uptake.

Baseline neurohormones and functional capacity. As expected, patients from both group T and C showed neurohormonal activation, depressed functional capacity, and a slightly reduced ventilatory efficiency, with no different baseline values (Tables 1 and 2).

Significant relations were found among exercise variables and neurohormone plasma levels in both groups, for instance, in group T, peak V$_{O_2}$ was inversely correlated with

BNP (R = 0.55, p < 0.001), NT-proBNP (R = 0.55, p < 0.001), and norepinephrine (R = 0.43, p < 0.001), whereas V$_E$/V$_{CO_2}$ slope directly correlated with BNP (R = 0.61, p < 0.001), NT-proBNP (R = 0.54, p < 0.001), and norepinephrine (R = 0.43, p < 0.001).

Effects of physical training on left ventricular volumes and function, functional capacity, and QOL. In group T, EF had increased by the nine-month visit, with a reduction
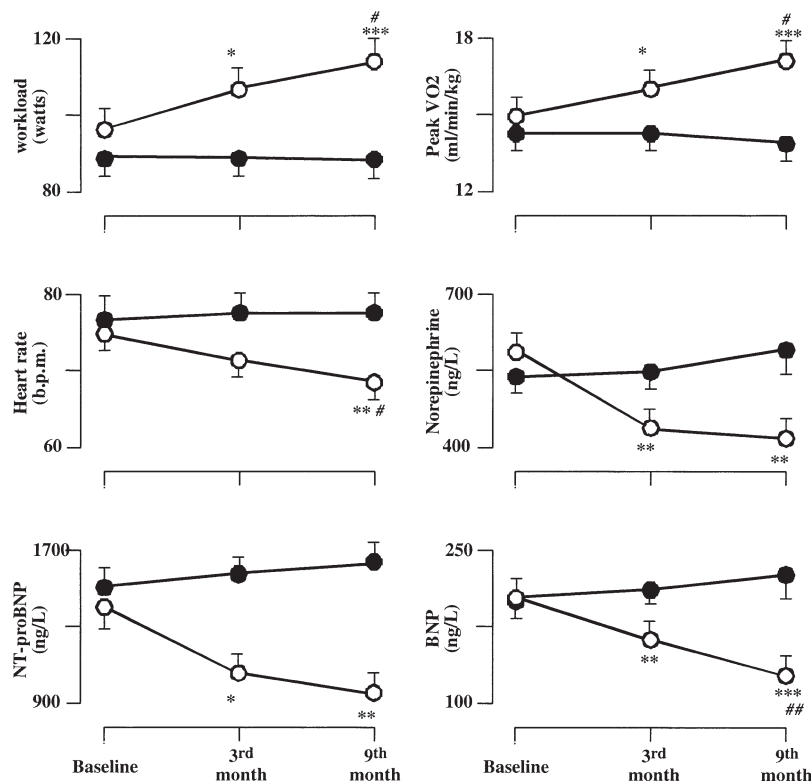

Figure 1. Changes in exercise variables, resting heart rate, and neurohormones for trained **(open circles)** and untrained patients **(closed circles)** at baseline, three, and nine months. *p < 0.05, **p < 0.01, ***p < 0.001 versus baseline (significant values assessed by Bonferroni post-hoc test performed on three groups); #p < 0.05, ##p < 0.01 versus third month. BNP = brain natriuretic peptide; b.p.m. = beats/min; NT-proBNP = amino-terminal pro-brain natriuretic peptide; V$_{O_2}$ = oxygen uptake.
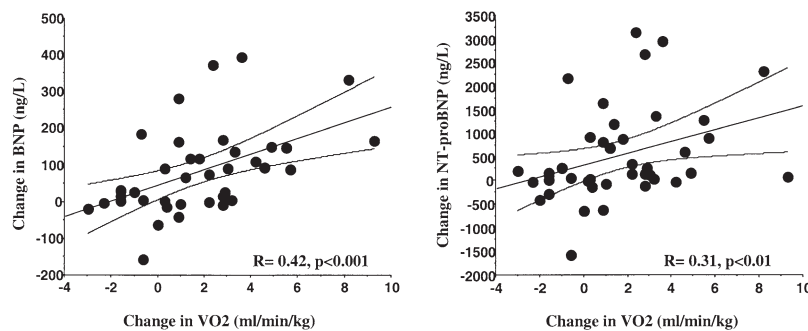
Figure 2. Relation between the changes in peak oxygen uptake (VO2) and in plasma concentration of cardiac natriuretic peptides after training in group T patients. BNP = brain natriuretic peptide.

in end-diastolic and end-systolic left ventricular volumes (Table 2). Conversely, echocardiographic parameters did not change in group C.

Group T progressively increased tolerance to effort from baseline up to the third and the ninth month (peak VO_2 F = 10.35, p < 0.001, and maximum workload F = 13.26, p < 0.001) (Fig. 1). Resting heart rate decreased by the end of the follow-up from 75 ± 2 beats/min to 69 ± 2 beats/min (p = 0.002). No changes were found in these parameters in group C (Fig. 1). By the end of follow-up, VE/VCO_2 slope did not change in either of the two groups, and only patients in group T showed an improvement in their QOL (score from 54 ± 5 to 32 ± 4 in group T, p < 0.01; from 52 ± 6 to 53 ± 5 in group C, p = NS).

Effects of physical training on BNP and neurohormones.
During the follow-up, BNP, NT-proBNP, and norepinephrine progressively decreased in group T (F = 7.49, p < 0.01; F = 4.84, p < 0.01; and F = 9.88, p < 0.001, respectively) but not in group C (Fig. 1). No changes were found in either group with respect to plasma renin activity and aldosterone. At the end of the program, peak VO_2 in group T inversely correlated to BNP (R = 0.52, p < 0.001), NT-proBNP (R = 0.51, p < 0.001), and norepinephrine levels (R = 0.49, p < 0.001) at a similar extent, as compared with baseline. A similar correlation was found between VE/VCO_2 slope and the levels of BNP (R = 0.61, p < 0.001), NT-proBNP (R = 0.60, p < 0.001), and norepinephrine (R = 0.59, p < 0.001). The change in peak VO_2 at the end of the program was correlated with BNP and NT-proBNP changes (R = 0.42, p < 0.001 and R = 0.31, p < 0.01, respectively), but not with norepinephrine changes (Fig. 2). Conversely, no correlation was found between the decrease in BNP, NT-proBNP, and norepinephrine values and the absolute 3% increase in EF in group T. Finally, a relationship was found between the change in either BNP or NT-proBNP level and the norepinephrine change (R= 0.46, p = 0.002 and R= 0.36, p = 0.02, respectively).

DISCUSSION

The present study demonstrates that progressively adjusted aerobic physical training on a nine-month period progres-

sively improves functional capacity, QOL, as well as left ventricular function in patients with HF. These beneficial changes are associated with reduction in plasma levels of BNP/NT-proBNP and norepinephrine. Hence, BNP/NT-proBNP plasma concentration appears to be a valuable marker of positive clinical response to training.

Previous studies have demonstrated that training improves cardiac function, peak oxygen uptake, and QOL (2–6,11,12). However, long-term training programs performed with a constant intensity of exercise do not seem to guarantee a continuous improvement in functional capacity (4). Conversely, a workload adjusted according to the third-month CPT produced a progressive increase in peak VO_2, paralleled by a progressive decrease in neurohormone level in the present study.

The lack of improvement of the VE/VCO_2 slope could be ascribed to the quite-preserved exercise capacity and ventilatory efficiency in our population (Table 2) as compared with a previous study (14). The reduction in plasma BNP/NT-proBNP in group T might be an expression of improved cardiac systolic function (8), sympathetic deactivation (12), and improvement in tissue oxygenation (15). The decrease in plasma norepinephrine level might be explained by the positive modulation of the autonomic balance by physical training (3).

Study limitations. A control group of healthy subjects was not included because it is unlikely that training could affect their BNP/NT-proBNP plasma levels under physiologic conditions (8). Furthermore, women accounted for only 15% of the patients, a figure which reflects the female prevalence of larger HF studies, among which the Extra-MATCH meta-analysis on training in HF (6).

Conclusions. The BNP/NT-proBNP and norepinephrine plasma values progressively decrease after training, paralleling functional and clinical improvement. The present findings suggest the usefulness of the BNP/NT-proBNP assay as an effective tool for the follow-up of patients with HF undergoing physical training.

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