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Neuroendocrine Activation in Heart Failure Is Modified by Endurance Exercise Training

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OBJECTIVES The purpose of this study was to determine whether endurance exercise training could buffer neuroendocrine activity in chronic heart failure patients.

BACKGROUND Neuroendocrine activation is associated with poor long-term prognosis in heart failure. There is growing consensus that exercise may be beneficial by altering the clinical course of heart failure, but the mechanisms responsible for exercise-induced benefits are unclear.

METHODS Nineteen heart failure patients (ischemic disease; New York Heart Association [NYHA] class II or III) were randomly assigned to either a training group or to a control group. Exercise training consisted of supervised walking three times a week for 16 weeks at 40% to 70% of peak oxygen uptake. Medications were unchanged. Neurohormones were measured at study entry and after 16 weeks.

RESULTS The training group (n = 10; age = 61 ± 6 years; EF = 30 ± 6%) and control group (n = 9; age = 62 ± 7 years; EF = 29 ± 7%) did not differ in clinical findings at study entry. Resting levels of angiotensin II, aldosterone, vasopressin and atrial natriuretic peptide in the training and control groups did not differ at study entry (5.6 ± 1.3 pg/ml; 158 ± 38 pg/ml; 6.1 ± 2.0 pg/ml; 37 ± 8 pg/ml training group vs. 4.8 ± 1.2; 146 ± 23; 4.9 ± 1.1; 35 ± 10 control group). Peak exercise levels of angiotensin II, aldosterone, vasopressin and atrial natriuretic peptide in the exercise and control groups did not differ at study entry. After 16 weeks, rest and peak exercise hormone levels were unchanged in control patients. Peak exercise neurohormone levels were unchanged in the training group, but resting levels were significantly ($p < 0.001$) reduced (angiotensin −26%; aldosterone −32%; vasopressin −30%; atrial natriuretic peptide −27%).

CONCLUSIONS Our data indicate that 16 weeks of endurance exercise training modified resting neuroendocrine hyperactivity in heart failure patients. Reduction in circulating neurohormones may have a beneficial impact on long-term prognosis. (J Am Coll Cardiol 1999;34:1170–5) © 1999 by the American College of Cardiology

Neurohormonal mechanisms play a central role in the progression of chronic heart failure (CHF) (1–6). Activation of the sympathetic nervous system and activation of the renin-angiotensin-aldosterone system (RAAS) have adverse hemodynamic consequences in heart failure in part because they enhance vasoconstriction and promote fluid retention. Furthermore, prolonged neurohormonal activation exerts a direct deleterious effect on the heart that is independent of the hemodynamic actions of these systems (7–10). High concentrations of angiotensin II (ANG II) induce necrosis of cardiac myocytes (7,8), adversely influence matrix structure of myocardium (10), increase sympathetic neural drive (9) and impair baroreceptor restraint on sympathetic drive (9). Compelling evidence has been provided that pharmacologic suppression of neurohormonal activation, rather than direct stimulation of the failing myocardium, improves symptoms and survival in CHF (6,9,11–13). These observations support the need for more therapeutic strategies to modulate neurohormonal activation in CHF.

There is growing clinical consensus that exercise training may beneficially alter the clinical course of CHF. However, the specific mechanisms responsible for exercise-induced benefits are unclear. Previous studies in subjects with normal left ventricular function have demonstrated that regular endurance exercise reduces central sympathetic tone (14–16), increases parasympathetic activity (17), decreases plasma renin activity (18) and improves baroreflex sensitivity (19–21). To date, however, no randomized controlled study has investigated the influence of longer-term exercise training on neurohormonal activation in CHF patients.

The purpose of the present study was to determine the effect of intermediate-term endurance exercise training on

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Abbreviations and Acronyms

ALDO = aldosterone
ANG II = angiotensin II
ANP = alpha-atrial natriuretic peptide
AVP = arginine vasopressin
CHF = chronic heart failure
RAAS = renin-angiotensin-aldosterone system
VO_{2peak} = symptom-limited peak oxygen consumption

resting and exercise-induced neurohormonal activation in CHF patients. We hypothesized that exercise could exert a modulating effect upon plasma levels of arginine vasopressin (AVP), alpha-atrial natriuretic peptide (ANP), aldosterone (ALDO) and ANG II. Accordingly, we measured plasma neurohormonal levels at rest and immediately after maximal treadmill exercise in CHF patients before and after either a 16-week exercise training program or control period.

METHODS

Subjects. Nineteen clinically stable coronary artery disease patients with chronic (>4 months) New York Heart Association class II or III symptoms of heart failure were recruited to participate in the study (Table 1). Coronary artery disease was documented by confirmed myocardial infarction (World Health Organization criteria) or coronary angiography (>50% diameter stenosis in a major coronary artery). All had systolic left ventricular (LV) dysfunction documented by an ejection fraction <40%. Pharmacologic therapy with digoxin, angiotensin-converting enzyme (ACE) inhibitors, diuretics, and beta-adrenergic blocking agents had been optimized and maintained for at least one month (Table 1). Pharmacologic therapy was not altered for any subjects after entry into the study.

Contraindications for participation in the study included recent new myocardial infarction (<5 weeks), unstable angina, uncontrolled hypertension or diabetes, significant chronic lung disease, renal failure, cardiac pacemaker or internal defibrillator or musculoskeletal disorder that hindered the ability to exercise. The study protocol was approved by the Institutional Review Board for the protection of human research subjects at the University of Florida, and all subjects provided written informed consent to participate in the study.

Table 1. Descriptive Characteristics of Heart Failure Patients in the Control and Exercise Training Groups Before 16 Weeks of Endurance Exercise or Control Period

	Training Group (n = 10)	Control Group (n = 9)
Age (yr)	61 ± 6	62 ± 7
NYHA (Class)	2.50 ± 0.52	2.52 ± 0.66
EF (%)	30.04 ± 6.59	29.56 ± 6.58
VO_{2peak} (ml/kg/min)	13.00 ± 4.23	12.89 ± 3.56
Digitalis glycosides	8	8
ACE-inhibitors	7	6
Diuretics	8	8
Beta-blockers	2	2

Values are mean ± SD.
NYHA = New York Heart Association classification for heart failure; EF = left ventricular ejection fraction; VO_{2peak} = peak exercise oxygen consumption.

Study design. The study design included a screening and recruitment period, and a randomly assigned treatment period. The treatment period had two parallel arms consisting of a control and exercise training limb with each lasting 16 weeks.

Exercise testing. Before and after application of exercise training, all subjects completed a modified Naughton treadmill protocol for determination of symptom-limited peak oxygen consumption (VO_{2peak}). Treadmill speed remained constant at 2 mph and elevation was increased by 2% grade every 2 min until termination of the test. Expired gasses were collected and analyzed using a metabolic cart (Medical Graphics, St. Paul, Minnesota). Minute ventilatory volume and fractional concentrations of oxygen and carbon dioxide were determined from breath-by-breath expired air samples and used to calculate VO_{2peak}. Heart rate, 12-lead electrocardiogram (ECG), and blood pressure were monitored and recorded throughout the test. Subjective assessment of angina and dyspnea was attained using the 4-point scales recommended by the American College of Sports Medicine (22).

Blood sample collection. Venous blood samples for determination of plasma neurohormone concentrations were collected before and immediately after treadmill tests. A 21-gauge catheter was inserted into a forearm vein 30 min before the treadmill test. At 2 min before the start of the treadmill test, a 20-ml sample of blood was collected, and a second 20-ml sample was drawn immediately on completion of the treadmill test. All blood was collected with subjects in the standing posture.

Blood samples were withdrawn into a plastic syringe containing no additives and were immediately separated into individual aliquots. Blood for AVP, ANG II, ALDO, and ANP assays was added to chilled vacutainers containing EDTA. Plasma was separated by centrifugation at 3,000 *g* at 4°C for 20 min and the samples were frozen at −80°C until the completion of the study so that all samples for each subject could be run in the same assay.

Neurohormone assays. Plasma AVP was measured by radioimmunoassay as previously described (23). Plasma ANG II and ALDO levels were determined by radioimmunoassay as previously described by Braith et al. (24). Also, ANP was extracted from plasma using a modification of a technique described by Braith et al. (25). Plasma (1 ml) was deproteinized by adding 750 μl 0.1 mol/liter acetic acid and 1.25 ml methanol. Samples were placed on a rocking shaker for 10 min followed by centrifugation for 20 min at 6,000 *g* at 4°C. The supernatant was dried by vacuum

centrifugation. Radioimmunoassay was performed with a kit from Peninsula Laboratories (Belmont, California) using ANP antiserum that has 0% cross-reactivity with human brain natriuretic peptide and C-type natriuretic peptide.

Group assignments and exercise training. After conclusion of the screening procedures, the subjects were rank-ordered by VO_{2peak} and randomly stratified to either an exercise group (n = 10) or a control group that would not participate in regular exercise training (n = 9). The control group reported to the laboratory each week during the 16-week study and saw the same physician and health care team, and had the same monitoring of compliance, safety and general physical condition as did the exercise training group. This was part of a program of "usual care" for heart failure patients in the Cardiovascular Medical Division at the University of Florida.

Subjects randomized to the exercise group participated in supervised treadmill walking. The initial exercise intensity was 40% to 50% of VO_{2peak} for a duration of 10 to 20 min, as tolerated. Exercise intensity for all subjects was progressed to 70% to 80% of VO_{2peak} for a duration of 30 to 45 min by approximately the 10th week of the study. All exercise training sessions were monitored according to established guidelines.

Statistical analysis. Descriptive characteristics of the subjects were compared between groups using analysis of variance (ANOVA). The VO_{2peak} values and neurohormone concentrations at rest and peak exercise, at entry and at 16 weeks, were compared between groups using analysis of covariance (ANCOVA). When a significant group-by-time interaction was observed, between-group comparisons were done using ANCOVA with contrast analysis for obtaining appropriate post hoc custom hypothesis tests. All statistical analyses were performed using the SAS statistical program (SAS Institute, Cary, North Carolina). An alpha level of $p \leq 0.05$ was chosen to represent statistical significance.

RESULTS

At study entry, VO_{2peak} did not differ between the two groups (Table 1). The VO_{2peak} did not change in the control group after 16 weeks (12.8 ± 3.5 vs. 12.0 ± 3.3 ml/kg/min) but significantly increased (25%) in the exercise training group (13.00 ± 4.23 vs. 16.3 ± 3.7 ml/kg/min).

At study entry, plasma concentrations of ANG II, ALDO, AVP and ANP at standing rest did not differ ($p \geq 0.05$) between the two groups (Table 2). At termination of the symptom-limited graded exercise test, all neurohormones were significantly elevated above resting levels in both groups, and the magnitude of increase was not significantly different between groups ($p \geq 0.05$).

After 16 weeks the training group had significantly lower resting plasma concentrations of ANG II, ALDO, AVP, and ANP (Table 1). Resting values for all four of the measured neurohormones were diminished by 20% to 30% in the exercise group (Fig. 1). No significant changes in resting neurohormone concentrations were observed in the control group. In contrast, both the absolute and relative increases in neurohormones at peak treadmill exercise were similar ($p \geq 0.05$) to values observed before training in both groups.

Table 2. Plasma Neurohormone Concentrations for Both Groups at Rest and Peak Treadmill Exercise Both Before and After 16 Weeks of Exercise Training or Control Period

Variable	Control Group	Exercise Group
Rest Angiotensin II (pg/ml)†		
Initial	4.8 ± 1.2	5.6 ± 1.3
4 Months	5.0 ± 1.2	4.1 ± 0.9*
Rest Aldosterone (pg/ml)†		
Initial	146 ± 23	158 ± 38
4 Months	151 ± 29	108 ± 31*
Rest Vasopressin (pg/ml)†		
Initial	4.9 ± 1.1	6.1 ± 2.0
4 Months	5.1 ± 1.3	4.2 ± 0.8*
Rest Atrial Natriuretic Peptide (pg/ml)†		
Initial	35 ± 10	37 ± 8
4 Months	37 ± 11	27 ± 6*
Peak Exercise Angiotensin II (pg/ml)		
Initial	16.4 ± 2.2	17.9 ± 1.6
4 Months	17.3 ± 1.9	20.5 ± 1.6
Peak Exercise Aldosterone (pg/ml)		
Initial	202 ± 43	203 ± 51
4 Months	209 ± 39	199 ± 47
Peak Exercise Vasopressin (pg/ml)		
Initial	20.0 ± 3.1	17.9 ± 4.5
4 Months	21.4 ± 2.8	19.2 ± 4.3
Peak Exercise Atrial Natriuretic Peptide (pg/ml)		
Initial	68 ± 13	70 ± 7
4 Months	76 ± 15	67 ± 8

*$p \leq 0.05$ after four months of training vs. initial value. †Measurement taken before symptom-limited graded exercise test with subject standing.
Values are mean ± SD.

DISCUSSION

To our knowledge, this is the first randomized controlled trial of intermediate-term exercise training in CHF patients that examined resting and exercise plasma levels of ANG II, ALDO, AVP, and ANP. Our results indicate that, compared with the untrained control group, the exercise trained group had significant reductions (25% to 30%) in resting levels of each neurohormone measured. In contrast, we did not observe a training-induced reduction in levels of plasma neurohormones at peak exercise. These data support the hypothesis that exercise training buffers resting neuroendo-

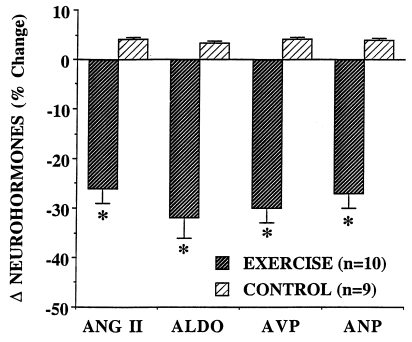

Figure 1. Relative changes in angiotensin II (ANG II), aldosterone (ALDO), arginine vasopressin (AVP), and atrial natriuretic peptide (ANP) after four months of endurance exercise training or control period. Data are mean ± SEM. *$p \leq 0.05$ After training versus before training.

crine hyperactivity associated with CHF, but the neurohormonal activation in response to strenuous exercise stress appears to be unaltered.

Neurohormone concentrations in health and disease. The neurohormone assays used in the present study have been used reliably in our laboratory for numerous experiments with human subjects (24–26). Thus, intralaboratory comparisons are possible that are not limited by the confounding problems associated with interlaboratory comparisons of biochemical data. In an attempt to interpret the physiologic significance of the relative reductions in plasma neurohormone levels in our trained CHF patients, we compared results from the present study with neurohormone levels in two reference groups: 1) age-matched healthy subjects, and 2) age-matched orthotopic heart transplant recipients recently studied in our laboratory (Figs. 2 and 3). The 16-week exercise training period used in our CHF patients was associated with reductions in concentrations of ANG II, ALDO and AVP to levels that are comparable ($p \geq 0.05$) with those observed in age-matched sedentary reference subjects (no medications) and stable heart transplant recipients ("standard transplant care") (Figs. 2 and 3). Plasma ANP in trained CHF patients was also reduced to levels observed in age-matched healthy subjects ($p \geq 0.05$) (Fig. 3).

Mechanism of neuroendocrine activation in CHF. Two principal mechanisms are recognized in neurohormonal activation in CHF patients, and both may be modulated by endurance exercise training. One contends that neuroendocrine hyperactivity in CHF is triggered by baroreflex dysfunction in association with a prolonged exposure to low cardiac output and reduced blood pressure. Sinoaortic and cardiac baroreceptors normally exert a tonic inhibitory influence on resting sympathetic activity, the kidney RAAS, and AVP release (27). In CHF patients, tonic inhibitory baroreflexes are depressed and contribute to sympathetic

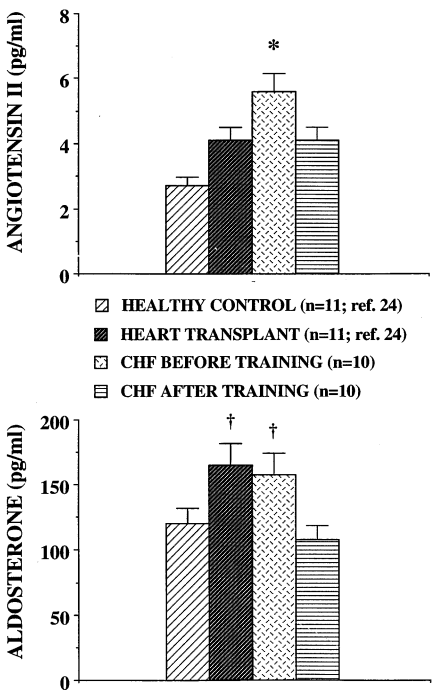

Figure 2. Angiotensin II **(top panel)** and aldosterone **(bottom panel)** concentrations drawn at rest in the standing posture for age-matched healthy control subjects; heart transplant recipients; heart failure patients before four months' exercise training; and heart failure patients after four months' exercise training. Data are mean ± SEM. *$p \leq 0.05$ heart failure before training versus the other three groups. †$p \leq 0.05$ versus heart failure after training and normal control group.

excitation and elevated circulating neurohormone levels (27–33).

An alternative but physiologically related mechanism for neuroendocrine hyperactivity in CHF is associated with the excitatory effects of circulating ANG II. Plasma ANG II levels initially become elevated owing to renal underperfusion, the primary stimulus for ANG II production by the renal RAAS. Elevated ANG II exerts excitatory effects at the level of the brain (34), ganglionic transmission (35) and at adrenergic nerve terminals (36,37).

Exercise and baroreflex sensitivity. The present study was not designed to investigate the possible mechanisms responsible for neuroendocrine modulation in heart failure, but several studies have suggested that strenuous endurance exercise may improve baroreflex sensitivity. Convertino et al. (19,20) have repeatedly observed that a single bout of intense dynamic exercise increased the sensitivity of baroreceptor-cardiac reflexes (i.e., heart rate regulation) and baroreceptor-vascular reflexes (i.e., peripheral vascular resistance regulation), independent of blood volume changes. Pagani et al. (21) used a crossover design to investigate the effects of exercise training (6 months of jogging) and not training (4 months without jogging) on baroreceptor sensitivity in 11 subjects with mild hypertension. The authors

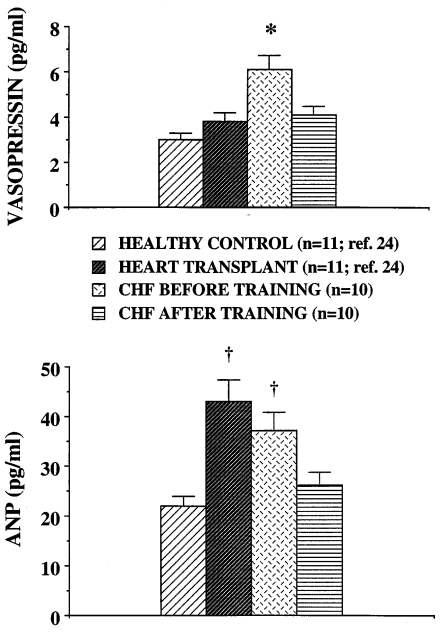

Figure 3. Arginine vasopressin **(top panel)** and atrial natriuretic peptide (ANP) **(bottom panel)** concentrations drawn at rest in the standing posture for age-matched healthy control subjects; heart transplant recipients; heart failure patients before four months' exercise training; and heart failure patients after four months' exercise training. Data are mean ± SEM. *$p \leq 0.05$ heart failure before training versus the other three groups. †$p \leq 0.05$ versus heart failure after training and normal control group.

used IV phenylephrine to study the effects of training on the heart rate–blood pressure relationship and reported a net improvement in the tonic inhibitory activity of the major constituents of the sympathetic-vagal balance. The mechanism responsible for exercise-induced improvements in baroreflex sensitivity is not understood. Investigators have studied all components of the reflex arc, but specific mechanisms have not been identified because of the complexity of the neural circuitry.

Baroreflex sensitivity and exercise capacity and survival rate are also improved in CHF patients by administration of ACE inhibitors (9,11,12,37,38). In aggregate, the angiotensin-converting enzyme (ACE) inhibitor data suggest that ANG II plays an important role in the central integration of baroreflex information. Grassi et al. (9) recently provided the first direct evidence, via muscle microneurography, that chronic ACE inhibitor treatment in CHF patients caused both a reduction in central sympathetic nerve traffic and an improved baroreceptor restraint on sympathetic traffic. Thus, a reduction in circulating ANG II achieved through exercise training may act favorably on baroreflex control of sympathetic activity (9,39).

Cardiac output and renal perfusion. The exercise-induced reduction of plasma neurohormones observed in the present study could possibly be taken as a marker of improved cardiac pump function. Certainly increased cardiac output would augment renal perfusion and thereby diminish the primary stimulus for activation of the kidney RAA system. Although we did not measure cardiac output in the present study, results from previous long-term training studies in CHF patients do not reveal evidence of increased cardiac output. Sullivan et al. (40) reported a 23% increase in VO_{2peak} in patients with CHF (left ventricular ejection fraction [LVEF] 24 ± 10%) after four months of exercise training, but there were no changes in rest or exercise stroke volume, cardiac output or LVEF. Most exercise training studies in CHF patients reporting improvements in VO_{2peak} observe no changes in rest or exercise measurements of left ventricular performance or central hemodynamics. Rather, the beneficial elements of the training response are attributed to peripheral adaptations (41,42).

Study limitations. This study was limited by small sample size, relatively brief duration of exercise training and absence of outcome data. In addition, the study would be strengthened by inclusion of either direct (intraneural recordings) or indirect (plasma norepinephrine or epinephrine data) indexes of efferent sympathetic nerve traffic at study entry and after 16 weeks. Finally, the CHF patients in the present study were carefully selected, and they received very expert heart failure and exercise training care that may not be generalized.

Conclusions. It is generally believed that the neurohormonal activation in heart failure has an adverse prognostic significance and that reduction in circulating neurohormonal levels by treatment represents a favorable therapeutic effect. Thus, demonstration that endurance exercise training is accompanied by a marked reduction (~25% to 30%) in resting levels of plasma ANG II, ALDO, AVP, and ANP has clinical implications. Currently, this demonstration has only been provided in one small cohort of CHF patients who trained for a period of 16 weeks.

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