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Effect of Exercise Training on Autonomic Derangement and Neurohumoral Activation in Chronic Heart Failure

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ABSTRACT

Background: In chronic heart failure (CHF), persistent autonomic derangement and neurohumoral activation cause structural end-organ damage, decrease exercise capacity, and reduce quality of life. Beneficial effects of pharmacotherapy and of exercise training in CHF have been documented at various functional and structural levels. However, pharmacologic treatment can not yet reduce autonomic derangement and neurohumoral activation in CHF to a minimum. Various studies suggest that exercise training is effective in this respect.

Methods and Results: After reviewing the available evidence we conclude that exercise training increases baroreflex sensitivity and heart rate variability, and reduces sympathetic outflow, plasma levels of catecholamines, angiotensin II, vasopressin, and brain natriuretic peptides at rest.

Conclusions: Data on the effect of exercise training on endothelin and aldosterone levels at rest are not conclusive. The mechanism by which exercise training normalizes autonomic derangement and neurohumoral activation is to elucidate for further development of CHF-related training programs aimed at maximizing efficacy while minimizing workload. (*J Cardiac Fail 2007;■:1−10*)

Key Words: Rehabilitation, exercise training, baroreflex sensitivity, heart rate, variability, sympathetic outflow, neurohormones, RAAS, BNP.

Chronic heart failure (CHF) is associated with autonomic derangement, notably, permanent sympathoexcitation and arterial baroreflex sensitivity (BRS) weakening.[1] Autonomic derangement is already present in mild CHF,[2] and is likely to be induced by augmented input from cardiac "sympathetic afferents."[3] The sympathetic nervous system plays a pivotal role in the natural history of chronic heart failure. When the heart begins to fail, a series of neural and hormonal survival adaptations are activated to preserve perfusion pressure and conserve sodium and water. These systems include arterial and cardiopulmonary baroreflexes, natriuretic peptides, nitric oxide, the peripheral chemoreflex, angiotensin II (A-II), endothelin-1, and arginine-vasopressin (AVP) (Fig. 1).[4] There is early activation of cardiac adrenergic drive, which is, with worsening heart failure, followed by an increasing magnitude of generalized sympathetic activation.[5] Eventually, the adverse consequences of this neurohumoral activation will dominate over the short-term compensatory effects (compensation of a diminished heart function by increase of cardiac rate and contractility, vascular tone, venous return, and circulatory filling). They are mediated through downregulation of β-receptor function and harmful biologic effects on the cardiomyocyte and structural end-organ damage such as cardiac enlargement, hypertrophy and fibrosis begin to develop, secondary to permanently elevated levels of catecholamines, renin, angiotensin, and aldosteron.[6] Also,

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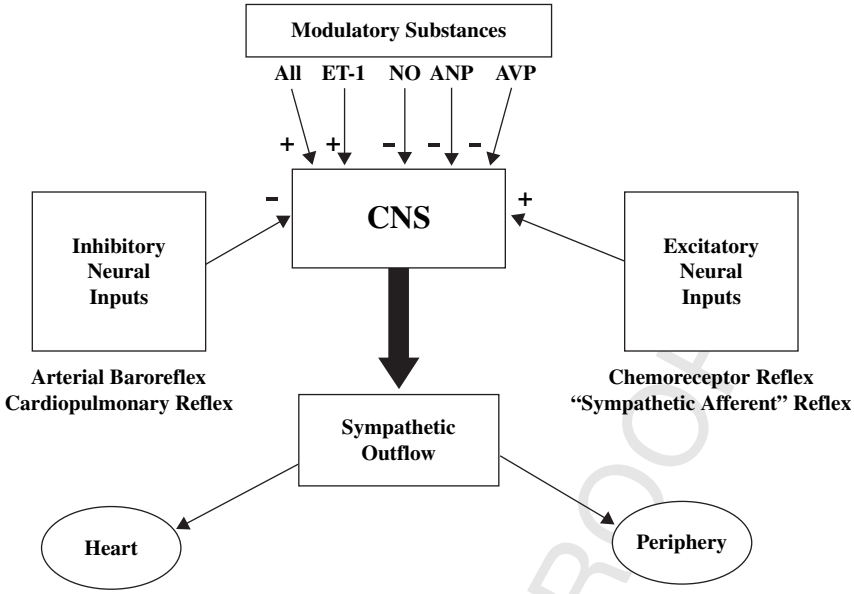

Fig. 1. Neurohumoral excitation depicted as a process consisting of primary sympathetic excitation with neural and humoral feedback at the level of the brainstem. In heart failure, hormonal compounds such as angiotensin-II, endothelin-I, nitric oxide, atrial natriuretic peptide, and arginine-vasopressin in the circulation are dysregulated, as are the concentrations of these modulatory substances at the level of the brainstem. Obviously, the active function of the blood-brain barrier and local production at the level of the brain result in differences in the peripheral and central concentrations of these compounds. Hence the levels measured in blood are not fully representative of the concentrations in the brain. However, there is good evidence to support that peripheral and central concentrations parallel each other, thus making the peripherally measured concentrations at least indicative for the degree of feedback inhibition/excitation at the central level.[54,55] Figure reproduced from Zucker et al,[4] with permission.

neurohumoral activation is a possible trigger for the heart failure related inflammatory response and its effect on cytokines.[7,8]

Besides the negative effects of persistent neurohumoral activation on the heart, peripheral musculature undergoes detrimental structural and functional changes as well,[9,10] and the rise in neurohormones is paralleled by an increase in the degree of exercise intolerance.[11] Moreover, there is a more prominent role of the ergoreflex in CHF patients compared with healthy subjects; indirectly, by increased stimulation of the ergoreceptors by lactate accumulation in peripheral muscle, or directly, by increased reflex gain.[12]

Pharmacological Approach

Attempts have been made to assist or repair the heart by mechanical[13] and electrical devices or surgical intervention.[14] A major component of CHF pharmacologic therapy is, however, the suppression of the detrimental influences of neurohumoral activation. Although diuretics, digoxin, adrenergic receptor agents, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone receptor antagonists have greatly reduced mortality,[15,16] even with optimal treatment mortality rates remain high. Surveys show that 45% to 65% of CHF patients die within 5 years.[17,18] This underscores the importance of the ongoing quest to improve current therapy and to develop new therapeutic modalities.

Patients with the highest sympathetic activation and patients with the lowest BRS have the poorest survival rate.[19,20] Lowering of plasma catecholamine concentrations and increasing BRS seem logical therapeutic goals, as, in CHF, over time lowered plasma neurohormones and increased BRS are associated with decreased morbidity and mortality.[20] Optimal treatment with adrenergic receptor blockers and angiotensin-converting enzyme inhibitors lowers plasma neurohormones but, unfortunately, the levels remain elevated with respect to normal.[15,21] β-blockade may also increase BRS;[22,23] however, BRS in CHF patients remains lower than normal.

Exercise Training

European and American guidelines[14,24] recommend exercise training in addition to pharmacotherapy. Exercise training lessens dyspnea and fatigue,[25,26] improves quality of life, improves New York Heart Association (NYHA) class,[27–32] decreases morbidity and, likely, also mortality.[33–36] The beneficial effects of exercise training in CHF have been documented at various functional and structural levels. Although the Exercise in Left Ventricular Dysfunction and Chronic Heart Failure (ie, ELVD-CHF) trial[37] reports a slightly increased left ventricular ejection fraction, most studies report hardly any change in this parameter.[38] The generally observed exercise training induced increase in peak oxygen consumption[35] is presumably mainly

attributable to an increase in peak heart rate, an increase in stroke volume during exercise, and peripheral muscular adaptations such as increased capillary density, blood flow, mitochondrial volume density, fibre size, slow twitch fibers, and decreased lactic acidosis and vascular resistance.[26,39–43]

In addition to these functional and clinical effects, exercise training in CHF also appears to reduce autonomic derangement and neurohumoral excitation at rest.[44] The mechanisms by which these effects are accomplished are [Q1] incompletely known; in part, it may be ascribed to nNOS formation in the paraventricular nucleus.[45] By lowering neurohormone plasma concentrations and by reinforcing the arterial baroreflex, exercise training acts in concert with pharmacotherapy in the treatment of CHF patients. Unfortunately, the effects of exercise training on autonomic derangement and neurohumoral excitation in CHF patients at rest have not been studied or reviewed to the extent of the effects of pharmacologic therapy. Only 1 review,[46] merely reiterating the 1 by Braith and Edwards,[44] has appeared since 2003. A total of 16 original studies, of which 10 were published after the review by Braith and Edwards,[44] were not included in either review article (Table 1). Hence a recent overview with the merit to update readers and with educational potential to readers not familiar with this topic is necessary. The recent studies have confirmed and nuanced earlier findings and demonstrated new information in the field, notably the effect of exercise on resting BRS, on resting muscle sympathetic nerve activity (MSNA), and on resting plasma renin, endothelin, and brain natriuretic peptide (BNP) concentrations in heart failure. Of these, BRS and BNP have a high prognostic value in CHF and have substantial importance for clinical evaluation and treatment of CHF patients.

Reviewed Studies

We searched MEDLINE and www.scholar.google.com, using the following terms: chronic heart failure, exercise, training, rehabilitation, physical activity, neurohumoral, neurohormones, catecholamines, epinephrine, norepinephrine, angiotensin, aldosterone, brain natriuretic peptide, atrial natriuretic peptide, baroreflex, endothelin, vasopressin, muscle sympathetic nerve activity, heart rate variability. We found 23 original studies addressing the effects of exercise training on autonomic derangement and neurohumoral activation in CHF patients with systolic failure measured at rest. The main methodologic characteristics of all 23 studies are listed in Table 1. Seventeen studies had a control group; 14 of these were randomized controlled trials, whereas in the other 2 studies, no explicit statement about randomization was made. Six studies had no control group, 3 of these were case series and 3 were crossover trials. In the 23 reviewed studies, 849 patients (550/299 exercise/control) were included. Nineteen studies enrolled NYHA Class II-III patients; Hambrecht et al,[26] Passino et al,[47] and the European heart failure training group[48] included NYHA Class I-III patients, whereas Yeh et al[49] included NYHA Class I-IV patients. In the latter study, training was done by Tai Chi, which is to be classified as exercise with moderate intensity, requiring energy expenditure of approximately 3 to 5 metabolic equivalent tasks.[50] In the publication by Yeh et al,[49] there is no explicit statement about the training intensity, but it is doubtful whether the Tai Chi was applied at a 3 to 5 metabolic equivalent intensity level, because NYHA Class IV patients are already symptomatic at rest. Among the reviewed articles, the exercise training programs varied considerably in intensity, training frequency (2 to 7 sessions/week), session duration (15 to 60 minutes), program duration (8 weeks to 6 months), and training modality. The observed effects of exercise on autonomic derangement and neurohumoral excitation, summarized in Tables 2 through 5, are discussed in the following sections.

Results

Baroreflex and Heart Rate Variability

Baroreceptors are stretch-sensitive receptors located in the aortic wall, the wall of the pulmonary artery, and the carotid sinuses. Every blood pressure pulsation elicits an afferent baroreceptor burst, of which the intensity varies from 0 to average to maximum when the systolic blood pressure of the given heart beat is very low, equal to, or very high respectively, relative to the average blood pressure level. The afferent baroreceptor burst constitute neural information for the vasomotor center in the medulla oblongata.[51] Here, the efferent reflex output is generated, both in the form of a vagal burst (more intense with a higher blood pressure pulsation) and in the form of a brief episode of sympathoinhibition (the degree of inhibition increasing with blood pressure). Thus the baroreflex is a negative feedback loop in the neurohumoral excitation process in CHF. Baroreflex vigor is usually characterized in terms of the extent of bradycardia that occurs when blood pressure increases, and is indicated by the BRS. BRS is expressed as the increase of the interval between heart beats (in ms) per mm Hg systolic blood pressure rise and is usually determined during rest. Lowered BRS sensitivity in CHF parallels deterioration of clinical and hemodynamic status and is significantly associated with poor survival.[52]

Exercise training increases BRS in healthy subjects[53] and in patients with myocardial infarction.[54,55] A significant positive relation was also found between individual exercise-induced BRS improvement and survival.[54] Only 1 study examined the effect of exercise training on resting BRS in patients with CHF (Table 2),[56] but unfortunately, this study lacked a control group. The study comprised a small training group (13 patients), but managed to find a significant training-induced increase in BRS. Controlled studies should verify this interesting finding. Heart rate variability (HRV) is intimately related to BRS, because it gives a qualitative and quantitative description of the variations in the instantaneous heart rate that are mainly the result of

Table 1. Methodologic Characteristics of the Included Studies

Study	RCT	N (C/T)	M/F		EF% Inclusion Criteria	EF%		NYHA	Intensity	Days/ Week	Duration per Session	Duration Training Program	Exercise Modality
			T	C		T	C						
Adamopouos, 1995	No	12	12/0	—	—	19 ± 2	—	II/III	70−80% max HR	5	?	8 weeks	Cycling
Belardinelli, 1995	No	27 (9/18)	16/2	7/2	30 ± 5%	31 ± 5	29 ± 4	II/III	40% VO2 peak	3	30−40 min	8 weeks	Cycling
Braith, 1999	Yes	19 (9/10)	?	?	<40%	30 ± 7	30 ± 7	II/III	70−80% VO2 peak	?	30−40 min	16 weeks	Walking
Coats, 1992	No	17	17/0	—	—	20 ± 2	—	II/III	60−80% max HR	5	20 min	8 weeks	Cycling
Conraads, 2004[11]	No	49 (22/27)	21/6	15/7	<35%	26 ± 1	26 ± 1	II/III	90% of VT/50−60 1RM	3	10 min cycling 40 min resistance	4 months	Cycling/resistance
European HF training Group 1998[11]	No	134*/43†/ 11‡/57δ	126/8	—	—	25 ± 9	—	I/II/III	70−80% max HR	4−5	25 min cycling 12 min calisthe-netics	6−16 weeks	Cycling/calisthenics optional
Gordon, 1997[11]	No	20 (7/13)	13/0	7/0	—	28 ± 3	27 ± 3	II/III	65−75% VO2 peak	3	20 min	8 weeks	Knee extensor
Hambrecht, 1995	Yes	22 (10/12)	12/0	10/0	<40%	26 ± 9	27 ± 10	II/III	70% VO2 peak	6−7	Two 20-min sessions a day	6 months	Cycling/walking/ calisthenics/ball games
Hambrecht, 2000[11]	Yes	73 (37/36)	37/0	36/0	<40%	27 ± 9	27 ± 9	I/II/III	70% VO2 peak	7	20 min	6 months	Cycling/walking/ calisthenics/ball games
Jónsdóttir, 2005[11]	Yes	43 (22/21)	16/5	18/4	—	42 ± 14	41 ± 14	II/III	50% VO2 peak/20− 40% 1RM	2	50 min	5 months	Cycling/thera-bands/ resistance
Keteyian, 1999	Yes	51 (25/26)	25/0	26/0	<35%	22 ± 8	22 ± 7	II/III	50−80% HR-reserve	3	33 min	24 weeks	Treadmill/walking/ ArmergoMeter
Kiilavuori, 1999	Yes	22 (10/12)	12/0	14/1	<40%	24 ± 5	25 ± 7	II/III	50−60% VO2 peak	3	30 min	6 months	Cycling
Kobayashi, 2003[11]	Yes	28 (14/14)	12/2	8/6	<40%	33 ± 2	29 ± 2	II/III	VT	2−3	Two 15-min sessions a day	3 months	Cycling
Larsen, 2004[11] Franco, 2006	No	12	12/0	—	—	32 ± 6	—	II/III	80% max HR below VT	3	30 min	12 weeks supervised, 4 months at home	Cycling
Passino, 2006[11]	Yes	85 (41/44)	39/5	35/6	<45%	35 ± 2	32 ± 2	I/II/III	60% VO2 peak	3	30 min	9 months	Cycling
Pietilä, 2002[11]	No	13	12/1	—	—	36 ± 5	—	II/III	60−85% max HR	6	Minimal 30 min	6 months	Light anaerobic muscle training, walking, aerobic, step board, cycling
Roveda, 2003[11]	Yes	16 (9/7)	5/2	6/3	<40%	35 ± 3	35 ± 3	II/III	90% of VT	3	60 min	4 months	Cycling/ground exercise
Sarullo, 2006[11]	Yes	60 (30/30)	23/7	22/8	<40%	29 ± 5	30 ± 4	II/III	60−70% VO2 peak	3	30 min	3 months	Cycling
Selig, 2004[11]	Yes	39 (20/19)	15/4	18/2	<40%	27 ± 7	28 ± 6	II/III	< within 5 beats/min max HR	3	—	3 months	Resistance
Tyni-Lenne, 1999[11]	Yes	24 (8/8+8)	T:5/3 KT:4/4	4/4	<40%	T:29 ± 13 KT: 31 ± 9	30 ± 11	II/III	50−80% HR-reserve	3	30 min	8 weeks	Cycling/knee extensor
Tyni-Lenne, 2001[11]	Yes	24 (8/16)	8/8	5/3	<40%	30 ± 9	30 ± 10	II/III	?	3	60 min	8 weeks	Cycling/knee extensor
Yeh, 2004[11]	Yes	30 (15/15)	10/5	9/6	<40%	24 ± 7	22 ± 8	I/II/III/IV	Tai Chi	5	35−60 min	12 weeks	Tai Chi

RCT, randomized controlled trial; C, control group; T, exercise training group; M, male; F, female; KT, knee extension training group; EF, ejection fraction; max HR, heart rate; VT, ventilatory threshold; 1RM, 1-repetitive maximum; unknown; [11], not reviewed before.

*Total number of patients.

†Number of patients with noradrenaline measurement.

‡Number of patients with adrenaline, plasma renin activity, aldosteron and atrial natriuretic peptide measurement.

δNumber of patients with heart rate variability measurement.

Table 2. The Effect of Exercise Training in CHF on Baroreflexsensitivity (BRS), Heart Rate Variability (HRV) at Rest

	BRS			HRV		
Study	T vs C	T	C	T vs C	T	C
Adamopoulos, 1995				—	↑*18%	—
Coats, 1992				—	↑*15%	—
European HF training Group 1998				—	↑*13%	—
Pietilä, 2002	—	↑*74%	—			
Selig, 2004				5%↓	5%↓	↔

T vs C, change (baseline vs intervention) in the exercise training group relatively to the change (baseline vs placebo) in control group; T, relative change (baseline vs intervention) in the training group; C, relative change (baseline vs placebo) in the control group; ↓, decrease; ↑, increase; ↔; no changes were found; ?, unknown significance level; *, significant change, $P < .05$.

baroreflex-mediated spontaneous blood pressure fluctuations.[57,58] Decreased HRV in CHF patients is likely to be attributed to decreased vagal involvement in cardiovascular control (59). Reduced HRV (eg, a reduced standard deviation of the intervals between normal beats, SDNN) has a strong prognostic value and is related to increased mortality in CHF.[60]

Because SDNN is 1 of the most commonly computed HRV parameters, and has the advantage that is not sensitive to algorithmic variants as seen in spectral HRV analysis,[61] we have searched the literature for studies toward the influence of exercise training on SDNN in rest in CHF patients. Four such studies[48,62–64] were found (Table 2). Three studies[48,62,63] reported a significant increase in SDNN at rest after exercise training. Selig et al[64] did not find any difference after exercise training; however, in this study, the training regimen was restricted to resistance training. In conclusion, aerobic exercise training increases SDNN at rest in CHF patients.

Sympathetic Nervous System

Circulating catecholamines originate from the adrenal medulla, in the form of epinephrine and norepinephrine in a ratio of about 80%/20%. Catecholamine secretion occurs when the innervating preganglionic sympathetic nerves are activated during times of stress. Circulating catecholamines also originate from spilled-over norepinephrine produced at sympathetic nerve endings throughout the body.[65] In addition to measuring catecholamines in blood, sympathoexcitation can also be assessed by measuring MSNA (eg, in the peroneal nerve); catecholamine levels and MSNA are well correlated during enhanced sympathetic drive.[66] Thirteen studies[26,31,47–49,63,67–73] comprising 481 patients (239/199 exercise/control) investigated the effect of exercise on plasma norepinephrine levels or norepinephrine spillover levels at rest (Table 3). Coats et al[63] found a significant decrease in whole-body norepinephrine spillover in the exercise group, when compared with the control group. Likewise, 4 other studies found significant reduction of norepinephrine plasma resting levels.[31,47,68] Tyni-Lenné et al,[72] in a study with 2 different exercise groups, found a significant decrease in norepinephrine plasma resting levels in the knee extensor training group, but not in the cycling group. None of the 13 studies found a significant increase of norepinephrine in rest. Kobayashi et al[71] and Yeh et al[49] found a trend toward an increase in plasma norepinephrine at rest in the training groups,[49,71] but, as stated before, the Tai Chi training intensity in the study by Yeh et al may have been low, whereas

Table 3. The Effect of Exercise Training in CHF on Norepinephrine (NE), Epinephrine (E), and Muscle Sympathetic Nerve Activity (MSNA) at Rest.

	NE			E			MSNA		
Study	T vs C	T	C	T vs C	T	C	T vs C	T	C
Belardinelli, 1995	—	↓16%	↔	—	↓21%	↔			
Coats, 1992	—	↓*16%	—						
European HF training Group 1998	—	↓*23%	—	—	↓*53%	—			
Gordon, 1997	—	↓10%	—	—	↑25%	—			
Hambrecht, 1995	↓*52%	↓*52%	↔	↓*	↓*50%	↔			
Hambrecht, 2000	↓31%	↓31%	↔	↓*	↓?	↑?			
Keteyian, 1999	↓18%	↓17%	↑1%						
Kiilavuori, 1999	—	↓19%	↓						
Kobayashi, 2003	↑16%	↑37%	↑21%						
de Mello Franco, 2006							45%S↓* 33%H↓	29%S↓* 17%H↓	16%↑
Passino, 2006	↓44%	↓*26%	↑18%						
Roveda, 2003							↓*46%	↓*48%	↓2%
Tyni-Lenne, 1999	—	↓knee* ↔Cycling	—						
Tyni-Lenne, 2001	↓*32%	↓*26%	↑6%						
Yeh, 2004	↑29%	↑46%	↑17%						

T vs C, change (baseline vs intervention) in the exercise training group relatively to the change (baseline vs placebo) in control group; T, relative change (baseline vs intervention) in the training group; C, relative change (baseline vs placebo) in the control group; ↓, decrease; ↑, increase; ↔; no changes were found; ?, unknown significance level; *, significant change, $P < .05$.

Table 4. The Effect of Exercise Training in CHF on Plasma Renin Activity, Angiotensin II, Aldosterone, Vasopressin, and Endothelin at Rest

	Plasma renin activity			Angiotensin II			Aldosterone			Vasopressin		
Study	T vs C	T	C	T vs C	T	C	T vs C	T	C	T vs C	T	C
Braith, 1999				↓?30%	↓*26%	↑4%	↓?34%	↓*30%	↑4%	↓?34%	↓*30%	↑4%
European HF training Group 1998	—	↓12%	—				—	↓1%	—			
Passino, 2006	↑1%	↓3%	↓4%				↓17%	↓6%	↑11%			

T vs C, change (baseline vs intervention) in the exercise training group relatively to the change (baseline vs placebo) in control group; T, relative change (baseline vs intervention) in the training group; C, relative change (baseline vs placebo) in the control group; ↓, decrease; ↑, increase; ?, unknown significance level; *, significant change, $P < .05$.

Kobayashi et al used the shortest session duration of all studies. Possibly a longer session duration and a higher training intensity are needed to lower norepinephrine plasma concentrations at rest. Five studies measured the effect of exercise on plasma epinephrine at rest (Table 3).[26,48,67,68,73] Three studies[26,68] showed a significant reduction of plasma epinephrine in the exercise group; in 1 controlled study, there was a nonsignificant trend of plasma epinephrine reduction in the exercise group.[67] Gordon et al[73] found in an uncontrolled study a nonsignificant upward trend in plasma epinephrine at rest. Two studies[74,75] investigated the effect of exercise on MSNA at rest and found a substantial decrease in resting MSNA after exercise training. Roveda et al[75] even found that resting MSNA levels in trained heart failure patients were even comparable to MSNA levels in trained healthy controls (Table 3). In conclusion, the controlled studies report a significant decrease in sympathoexcitation at rest, with the exception of the studies by Kobayashi[71] and Yeh.[49] Because the latter 2 studies used very brief training sessions or very low intensity exercise, respectively, we conclude that exercise training with reasonable frequency, duration, and intensity decreases sympathoexcitation at rest in CHF patients.

Renin-Angiotensin-Aldosterone System. The renin-angiotensin-aldosterone system (RAAS) is the primary mechanism for volume control.[76] Sympathetic stimulation increases the formation of renin (mainly produced by the juxtaglomerular kidney cells), that stimulates the formation of angiotensin I from angiotensinogen (produced in the liver). Then, A-II is formed from angiotensin I by angiotensin converting enzyme (produced in the lungs). Finally, A-II enhances the release of aldosterone from the adrenal glands.[77] In addition to acting on circulating volume and vascular resistance, A-II and aldosterone are involved in hypertrophy and collagen synthesis in the heart.[78]

One important effect of A-II with respect to the process of neurohumoral activation is that it facilitates the production of norepinephrine, and, at the level of the central nervous system, has a sympathoexcitatory action.[4] In addition, aldosterone inhibits nitric oxide production[79] and the arterial baroreflex;[80] both would, at the central level, result in additional sympathoexcitation.[4] Hence, the RAAS acts as a positive feedback loop in the process of neurohumoral activation.

Three studies[47,48,81] examined the effect of exercise on resting RAAS parameters (Table 4). Braith et al[81] found

Table 5. The Effect of Exercise Training in CHF on Endothelin, Brain Natriuretic Peptide (BNP), and Atrial Natriuretic Peptide (ANP) at Rest

	Endothelin			BNP/NT-proBNP			ANP/NT-proANP		
Study	T vs C	T	C	T vs C	T	C	T vs C	T	C
Braith, 1999							↓?33%‡	↓*27%‡	↑6%‡
Conraads, 2004				↓*21%†	↓*23%†	↓*2%†			
European HF training Group 1998							—	↓7%[3]	—
Gordon, 1997							↓27%‡	↓*27%‡	↔0%‡
Jónsdóttir, 2005				↓3%*	↓1%*	↑2%*	↑3%‡	↑5%‡	↑2%‡
Kiilavuori, 1999								↔‡	
Kobayashi, 2003	↓20%	↓4%	↑16%	↓5%*	↓5%*	↔0%*			
Larsen, 2004							—	↑10%δ	—
Passino, 2006				↓*41%*	↓*34%*	↑7%*			
				↓*38%†	↓*32%†	↑6%†			
Sarullo, 2006				↓*49%†	↓*58%†	↓9%†			
Yeh, 2004				↓*47%*	↓15%*	↑32%*			

T vs C, change (baseline vs intervention) in the exercise training group relatively to the change (baseline vs placebo) in control group; T, relative change (baseline vs intervention) in the training group; C, relative change (baseline vs placebo) in the control group; ↓, decrease; ↑, increase; ↔; no changes were found; ?, unknown significance level; *, significant change, $P < .05$.

*BNP; †NT-proBNP; ‡ANP; δNT-proANP.

a significant decrease in A-II and aldosterone plasma levels at rest in the exercise group, reaching values comparable to those of sedentary healthy subjects. Although this study had a randomized controlled setup, no explicit information about the statistical comparison between the RAAS parameter changes in the exercise training group as compared with the changes in the control group was presented. Passino et al[47] and the European Heart Failure training Group[61] did not find any significant differences in plasma renin activity or aldosterone plasma levels.

In conclusion, the available data are controversial and more research is necessary to verify the effect of exercise on resting RAAS activity in CHF.

Arginine-Vasopressin

Arterial underfilling, low cardiac output, rising osmolarity, and increased A-II levels activate the hypothalamo-pituitary-adrenal axis that interacts with the sympathetic nervous system-RAAS axis to maintain cardiovascular and metabolic homeostasis.[82] As a consequence, arginine-vasopressin (AVP) is released from the posterior pituitary. AVP increases water reabsorption by the kidneys, and, in high concentrations, constricts arterial blood vessels. CHF patients may have 2- to 3-fold elevated AVP plasma levels,[83] causing the already increased systemic vascular resistance to rise even further. The feedback action of AVP in neurohumoral activation process is not completely elucidated. Predominantly negative feedback effects by AVP have been described at the central level. Stimulation of V1b receptors in the medulla causes catecholamine secretion (positive feedback),[84] whereas AVP produces adrenocorticotropic hormone and β-endorphins at the pituitary level[82,85] and AVP increases BRS.[86] β-endorphins and the arterial baroreflex suppress sympathetic activity (negative feedback).[87] The study by Braith et al[81] (Table 4) is the only study that addresses the effect of exercise on resting AVP levels in CHF. That article reports a significant AVP reduction in the exercise group, whereas levels in the control group remained unchanged.

Endothelin

Hypoxia, shear stress, catecholamines, and A-II stimulate endothelial cells to release endothelin.[88] Endothelin levels are considerably increased in patients with NYHA Class III-IV.[89] Endothelin causes arterial vasoconstriction, myocardial and vascular cell hypertrophy, and aldosterone release; endothelin diminishes sodium excretion and leads to sympathoexcitation. As such, endothelin closes a positive feedback loop in the process of neurohumoral excitation. Kobayashi et al[71] examined the effect of exercise on endothelin (Table 5). Resting endothelin plasma concentrations showed a nonsignificant decreasing trend (−4%) in the training group, and a nonsignificant increasing trend (16%) in the control group, with no significant difference between the 2 groups. The number of patients enrolled in this study was small (n = 28), and new studies should verify the effect of exercise training on resting endothelin concentrations in patients with CHF.

Natriuretic Peptides

When the compensatory actions of the sympathetic nervous system-RAAS and hypothalamo-pituitary adrenal axes lead to a state of cardiac overload, the humoral emergency system of the natriuretic peptides is activated. Release of atrial natriuretic peptide (ANP) and BNP occurs under influence of increased preload and afterload, contractility, heart rate, catecholaminergic stimulation, A-II, and endothelin.[90,91] Natriuretic peptides have diuretic and vasodilatory activity and inhibit aldosterone secretion. Also, ANP attenuates norepinephrine release from sympathetic nerve terminals as well as (by central action) sympathetic outflow. As such, the natriuretic peptides form a negative feedback loop in the process of neurohumoral activation in CHF. As an emergency system, elevation of ANP (atrial volume overload), and certainly elevation of BNP (ventricular pressure overload) have a strong predictive value: a 100 pg/mL increase of BNP plasma levels results in a 35% higher risk of death.[92] Some investigators prefer the measurement of NT-proBNP/ NT-proANP over the BNP or ANP plasma levels because of their larger half-life. The effect of exercise on BNP/NT-proBNP resting levels in plasma was investigated in 6 of all reviewed studies (Table 5).[47,49,71,93–95] Yeh et al[49] found a decreasing trend in plasma BNP resting levels in the training group and an increasing trend in the control group, resulting in a significant difference between the 2 groups. Conraads et al,[93] Sarullo et al,[95] and Passino et al[47] found a significant decrease of NT-proBNP resting levels in the training group and the difference between the training group and the control group was also significant, whereas Passino et al[47] found the same results also for BNP resting levels. Finally, Kobayashi et al[71] and Jónsdóttir et al[94] found no significant effect of exercise training on resting BNP levels. These differences might be explained by the larger half-life of NT-proBNP. In 6 studies, the effect of exercise on resting ANP/NT-proANP levels in plasma was investigated (Table 5).[48,70,73,81,94,96] Two studies[73,81] found in the training group a significant decrease in resting ANP levels to within the reference interval (ANP <32 pmol/L). Four studies[46,48,70,94] found no significant differences in resting ANP or NT-proANP levels; in 2 of them[70,94] the training intensity applied in these studies was lower than that employed in the studies of Braith et al[81] and Gordon et al,[73] respectively 50% to 60% of VO2 peak against 65% to 85% of VO2 peak. A higher training intensity may be needed for lowering resting ANP levels. In conclusion, training had no adverse effects on resting levels of natriuretic peptides. The available data on ANP/NT-proANP are controversial and more research is necessary to verify the effect of exercise on resting RAAS activity in CHF. Also exercise training decreased resting NT-pro-BNP levels

in patients with CHF, although BNP resting levels did not always decrease after exercise training.

Conclusion

In conclusion, exercise training has beneficial direct and reflex sympathoinhibitory effects in CHF. Also, evidence exists for the normalization of other components of neurohumoral excitation as a consequence of exercise training. Thus exercise training directly competes with the pathophysiologic afferent stimuli from the failing heart that tend to permanently increase sympathetic outflow, leading to autonomic derangement and neurohumoral activation. Therefore exercise training is an important complementary therapy for CHF patients on stable medication. The mechanism responsible for the normalization of the neurohumoral activation and autonomic derangement by exercise training is not yet clarified. Knowledge of the key elements of an exercise program that are responsible to achieve a training effect would allow designing training programs specific for CHF patients, with maximal efficacy at minimal work load, to meet their limited exercise tolerance. Also, follow-up studies are needed to determine whether normalization of exercise induced neurohumoral excitation and autonomic derangement in CHF patients is associated with improved prognosis.

Uncited references

The following references were uncited: 59.

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