

Thermal hydrotherapy improves quality of life and hemodynamic function in patients with chronic heart failure

Andreas Michalsen, MD,^a Rainer Lüdtke, PhD,^c Malte Bühring, MD,^b Günther Spahn, MD,^a Jost Langhorst, MD,^a and Gustav J. Dobos, MD^a Essen and Berlin, Germany

Background Chronic heart failure is characterized by increased peripheral vascular resistance and reduced peripheral perfusion due to adrenergic and renin angiotensin activation and impaired endothelial function. Recent studies have shown that nonpharmacological peripheral vasodilation with thermal therapy by means of warm-water baths and sauna has beneficial effects in chronic heart failure. European hydrotherapy (according to Kneipp) additionally uses short cold water stimuli, which lead to prolonged vasodilation and adaptive responses. Studies on the efficacy of hydrotherapy in chronic heart failure are lacking.

Methods We studied 15 patients (5 men, 10 women, mean ($\pm$ SD) age 64.3 ± 1.8 years) with mild chronic heart failure (NYHA functional class II to III, ejection fraction 30%–40%). Patients were randomly assigned to 6 weeks of intensive home-based hydrotherapy or 6 weeks restriction in a crossover intervention trial. Quality of life and heart-failure-related symptoms were assessed by means of a validated questionnaire (PLC). Graded bicycle exercise test with incremental workloads (0, 50, 75, 100 watts) was performed at the end of each treatment period. The hydrotherapeutic program consisted of a structured combination of daily home-based external warm- and cold-water applications.

Results Baseline characteristics were balanced between the groups. With hydrotherapy, a significant ($P \leq .05$) improvement in 3 of 6 dimensions of quality of life (mood, physical capacity, enjoyment) and a significant reduction in heart-failure-related symptoms was found. Heart rates at rest and at 50-Watt workload were significantly reduced by hydrotherapy; blood pressure decreased nonsignificantly at rest and during exercise. The hydrotherapeutic treatment was well accepted and no relevant adverse effects were observed.

Conclusions A home-based hydrotherapeutic thermal treatment program improves quality of life, heart-failure-related symptoms and heart rate response to exercise in patients with mild chronic heart failure. The results of this investigation suggest a beneficial adaptive response to repeated brief cold stimuli in addition to enhanced peripheral perfusion due to thermal hydrotherapy in patients with chronic heart failure. (Am Heart J 2003;146:e11.)

The systemic response in chronic heart failure (CHF) is characterized by generalized neurohumoral excitation in order to compensate for reduced cardiac output.¹ Increased peripheral vascular resistance and reduced peripheral perfusion due to sympathetic and renin angiotensin activation and endothelial dysfunction contribute mainly to leading clinical symptoms such as acrocyanosis, muscle fatigue, cold feet, heavy-

ness in the limbs, and constipation.² Afterload reduction by means of pharmacological vasodilators, such as angiotensin-converting enzyme inhibitors, improves hemodynamic function, symptoms, and prognosis in CHF.^{3,4} However, vasodilation is also inducible nonpharmacologically by warm environment and warm thermal therapies.⁵ Accordingly, improved cardiovascular hemodynamics with reduction of cardiac afterload and increased subjective well-being were found in patients with chronic CHF after sauna and warm-water baths.⁶ Moreover, an improvement in vascular endothelial function has been demonstrated with repeated warm thermal treatments in healthy volunteers and patients with CHF.^{7,8}

Thermally induced peripheral vasodilation can also be achieved by cold water stimuli with subsequent vasodilation.^{5,9} Thermoregulatory mechanisms induce a reactive prolonged peripheral vasodilation after cold

From the ^aKliniken Essen Mitte, Department of Internal Medicine V, Essen, ^bFree University of Berlin, Klinikum Benjamin Franklin, Immanuel Hospital, Department of Internal Medicine, Berlin, and the ^cKarl and Veronica Carstens Foundation, Essen, Germany. Submitted August 7, 2002; accepted January 28, 2003.

Reprint requests: Gustav Dobos, MD, Kliniken Essen Mitte, Department of Internal and Integrative Medicine; Am Deimelsberg 34 a; 45276 Essen, Germany.

E-mail: gustav.dobos@uni-essen.de

© 2003, Mosby, Inc. All rights reserved.

0002-8703/2003/\$30.00 + 0

doi:10.1016/S0002-8703(03)00314-4

water immersions, cold water pourings, and showers.^{10,11} After serial cold water applications, a physiologic cold adaptation with consecutive attenuated catecholamine response was observed.^{12,13}

In central-European physical therapy, warm-water baths and sauna are commonly supplemented by repeated cold water stimuli with peripheral cold water immersions and cold water pourings (hydrotherapy according to Kneipp).¹⁴ Serial hydrotherapeutic cold- and warm-water applications are also used as a supportive treatment for patients with coronary artery disease and patients with CHF in cardiological rehabilitative facilities. The beneficial effects of hydrotherapy in patients with CHF, hypertension, and coronary artery disease have been described in some empirical and observational reports.¹⁴⁻¹⁶ However, its efficacy has never been tested in controlled trials. The current study was designed to test whether a specific and intensive home-based hydrotherapeutic treatment program, consisting of a structured combination of warm and cold thermal applications, can induce improvements in exercise performance, quality of life (QOL), and heart-failure-related symptoms in patients with mild CHF.

Methods and patients

Participation in the study was offered by advertisement in cooperating cardiological outpatient facilities. Of 30 patients screened, 17 patients (6 men, 11 women, mean ($\pm$ SEM) age 66.2 ± 1.6 years) met the inclusion criteria and consented to participate in the study after complete protocol information. Two patients (one in each group) dropped out before the end of the first study period and were not included in the further data analysis. The remaining study subjects were 15 patients (5 men, 10 women, mean ($\pm$ SEM) age 64.3 ± 1.8 years) with a history of mild CHF. Analysis was performed regardless of adherence with the study treatment (intention to treat). Etiology of heart failure was classified as idiopathic dilated cardiomyopathy in 3 patients, ischemic heart disease in 8 patients, and chronic hypertension in 4 patients. The criteria for heart failure were clinical and included dyspnea at exertion, fatigue, or fluid retention, with objective confirmation by an echocardiographic or ventriculographic ejection fraction $<40\%$, documented within the last 6 months before study entry. To achieve a homogeneous study group, we recruited only patients in sinus rhythm with New York Heart Association (NYHA) functional class II to III and an ejection fraction between 30% to 40%. No patient had evidence of exercise-induced arrhythmias or symptomatic myocardial ischemia at baseline.

Exclusion criteria were myocardial infarction or unstable angina within the previous 6 months. Other ex-

clusion criteria were chronic obstructive pulmonary disease, peripheral vascular disease, hemodynamically significant valvular heart disease, orthopedic limitation, and neurologic disease.

Informed consent was obtained from all patients before they entered the study, which was approved by the local ethics committee. No patient had a change in his or her medical regimen for the duration of the study.

The study was designed as a random-order crossover comparison of 6 weeks of intensive hydrotherapy and 6 weeks of restricted therapy (control phase). Patients were not told to expect hydrotherapy to be better for them, merely that we were trying to find out objectively the effects of hydrotherapy in heart failure. Data analysis was performed for all patients with at least one follow-up examination, independent of treatment adherence (intention to treat).

The exercise test was carried out on an upright bicycle ergometer with 2-minute incremental-stage work loads of 0, 50, 75, and 100 watts (w). All tests were done at the same time in the morning after an overnight fast. Heart rate was recorded from the 12-lead electrocardiogram and blood pressure measured by cuff sphygmomanometer every minute. Rate-pressure product (double product) was derived as systolic blood pressure times heart rate.

QOL was assessed by means of a validated inventory: the quality of life profile for chronic diseases (PLC).¹⁷ The PLC is based on 40 items, which are grouped to 6 functional or symptom dimensions: physical capacity (8 items), positive mood (5 items), negative mood/depression (8 items), ability to enjoy and relax (8 items), social well-being (5 items) and social functioning/contact ability (6 items). Each item is a question that has to be answered on a 5-point-rating scale (0-4). High internal consistency ($\alpha > 0.75$) and retest-reliability have been demonstrated for the scales in different populations.^{18,19} A relevant increase in QOL is defined as a procedure-related significant increase in at least 2 of the 6 dimensions. Heart-failure-related symptoms were measured by an additional 5-point Likert-scaled symptom questionnaire with 17 items.

Generally, results are expressed as mean $\pm$ SEM. According to the recommendations for the analysis of crossover trials,²⁰ we fitted split-plot ANOVA models to the data. Group (= carryover effect) was modeled as a between-subject factor; time point and treatment as within-subject factors. Tests for treatment effects are valid if no carryover effects can be assumed. Effects were assumed to be statistically significant with P values $\leq .05$.

Hydrotherapeutic program

At the start of the hydrotherapy period, patients were instructed, over 90 minutes, in the common

Table I. Baseline characteristics by treatment order

	Hydrotherapy first (n = 8)	Restriction first (n = 7)
Age (y)	67.3 ± 2.3	61.0 ± 2.2
Sex (M/F)	3/5	2/5
Weight (kg)	74.4 ± 4.5	79.6 ± 3.9
Body mass index (kg/m ²)	26.4 ± 1.3	28.3 ± 1.3
No in NYHA II/III	7/1	6/1
Ejection fraction (%)	35.4 ± 1.4	35.3 ± 0.8
Resting heart rate (beats/min)	78.4 ± 6.1	81.0 ± 4.2
Heart failure etiology		
Hypertension (n)	2	2
Ischemic heart disease (n)	4	4
Dilative cardiomyopathy (n)	2	1
ACE inhibitors (n)	6	5
Diuretics (n)	3	4
Digitalis (n)	4	4
β-Blockers (n)	3	5

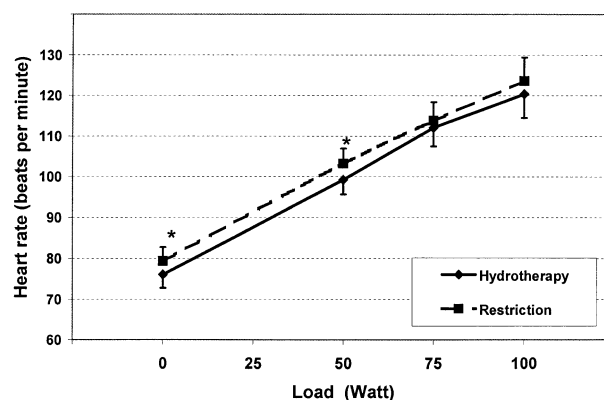
Results are given as mean ± SEM or in absolute numbers. NYHA, New York Heart Association Class; ACE, angiotensin-converting enzyme inhibitors.

techniques of thermal therapy and hydrotherapy by an experienced physician. Patients were advised to practice warm and cold applications at least 3 times a day to a total maximum of 30 minutes daily. Warm thermal applications consisted of peripheral warm water baths (arm baths, foot baths) with incremental temperature (maximum 40°C) and warm sheet packs. For cold applications, short-term arm or foot baths and peripheral water pourings with a water temperature below 18°C were taught. Patients were instructed to apply the hydrotherapeutic applications long enough to induce a postprocedural reactive feeling of warmth with respective mild redness of the treated skin area, but no longer than 15 minutes for baths and 5 minutes for cold pourings. The instructions were completed by a practical demonstration. For each patient, an individual home-based combination program was developed at the end of the instruction.

Results

The baseline characteristics of the patients are given in Table I. Drug treatment did not change during the 3-month study period. Both groups were statistically similar with regards to ejection fraction, age, body mass index, and pharmacological treatments. Of 17 randomized patients, 2 (one in each group) dropped out before the end of the first study period and were not included in the presented data analysis. Causes for study termination were not related to the intervention (acute coronary bypass operation in one patient; acute surgery of the prostate because of newly diagnosed cancer in the other). All other subjects completed the trial. The hydrotherapeutic program was well tolerated. Adherence, assessed by interview, was excellent

Figure 1



Heart rate at rest and in response to graded bicycle exercise workloads (0, 50, 75, 100 W) after 6 weeks of hydrotherapy (solid line) or restriction (dashed line); pooled data for n = 15. * $P \leq .05$ for between group difference ($P = .003$ at 50 W; 0.016 at rest).

in 14 of 15 study subjects. One patient did not practice the hydrotherapeutic applications because of lack of motivation, but was included in the data analysis.

QOL and symptoms

Baseline values for QOL and heart-failure-related symptom scores were balanced between the hydrotherapy-first and restriction-first group; in the dimension "depression," the restriction-first patients had a nonsignificant lower initial level of depression. With hydrotherapy, the values in all dimensions of QOL increased in both groups. With restriction, levels decreased in all dimensions. Baseline values were not reached in 4 dimensions; however, no significant carryover effects were detected. Complete data for QOL in both groups are given in Table II. With pooling of the data according to hydrotherapy/restriction levels of all dimensions, QOL was increased with hydrotherapy (Table III). Significant increases were observed in the dimensions of positive mood, physical capacity, and enjoyment/relaxation. Additionally, heart-failure-related symptoms were significantly reduced after 6 weeks of hydrotherapy.

Hemodynamic data

Exercise tests were completed in all 15 patients. All patients reached a 75-W load as maximum exercise; 8 patients reached 100-W load. Heart rate at rest and the rate-pressure product at rest were significantly lower after the hydrotherapeutic program. Blood pressure at rest was nonsignificantly reduced after hydrotherapy (Table IV).

Table II. Descriptive statistics of quality of life and heart-failure-related symptoms during study period by treatment order

Dimension	Group	Baseline	6 Weeks	12 Weeks
Positive mood	Hydrotherapy first	1.9 ± 0.2	2.3 ± 0.2	2.1 ± 0.2
	Restriction first	1.9 ± 0.2	1.7 ± 0.3	2.1 ± 0.3
Depression	Hydrotherapy first	2.1 ± 0.3	2.5 ± 0.3	2.4 ± 0.2
	Restriction first	2.8 ± 0.1	2.5 ± 0.3	2.9 ± 0.1
Physical capacity	Hydrotherapy first	2.1 ± 0.3	2.2 ± 0.2	1.8 ± 0.1
	Restriction first	2.0 ± 0.3	1.7 ± 0.3	2.2 ± 0.2
Enjoyment/relaxation	Hydrotherapy first	2.2 ± 0.2	2.5 ± 0.2	2.3 ± 0.1
	Restriction first	2.3 ± 0.2	2.1 ± 0.3	2.4 ± 0.2
Social wellbeing	Hydrotherapy first	2.5 ± 0.3	3.1 ± 0.2	3.0 ± 0.2
	Restriction first	2.4 ± 0.4	2.4 ± 0.3	2.7 ± 0.3
Social functioning	Hydrotherapy first	2.6 ± 0.2	2.7 ± 0.2	2.6 ± 0.1
	Restriction first	2.6 ± 0.3	2.1 ± 0.4	2.5 ± 0.3
Heart failure-related symptoms	Hydrotherapy first	18.0 ± 2.7	13.6 ± 2.5	17.1 ± 2.8
	Restriction first	18.1 ± 5.1	19.6 ± 4.0	13.4 ± 3.7

Table III. Quality of life and heart-failure-related symptoms

Dimension	Hydrotherapy	Restriction	P (hydrotherapy vs restriction)
Positive mood	2.2 ± 0.2	1.9 ± 0.2	.050
Depression	2.7 ± 0.2	2.5 ± 0.2	.122(NS)
Physical capacity	2.2 ± 0.1	1.8 ± 0.1	.033
Enjoyment/relaxation	2.5 ± 0.2	2.2 ± 0.1	.022
Social wellbeing	2.9 ± 0.2	2.7 ± 0.2	.053(NS)
Social functioning	2.6 ± 0.2	2.3 ± 0.2	.073(NS)
Heart-failure-related symptoms	13.5 ± 2.1	18.3 ± 2.3	.028

Pooled data after 6 weeks of hydrotherapy versus 6 weeks of restriction.

Figure 1 shows the effect of hydrotherapy compared to restriction on heart rate with incremental workloads. With hydrotherapy, heart rate at the 50-W load was significantly reduced ($P = .003$); there was a trend towards a lower heart rate at 75 W ($P = .10$) and 100 W ($P = .09$). There was a modest but nonsignificant reduction in blood pressure during exercise with hydrotherapy compared to restriction. Rate-pressure product was nonsignificantly reduced at both the 50-W and 75-W workload and significantly reduced at the 100-W workload. In interviews at the end of the study, 14 of 15 patients rated hydrotherapy as generally beneficial for wellbeing.

Discussion

Hydrotherapy has a long tradition in central Europe and is established in some rehabilitative cardiological clinics for the adjunctive nonpharmacological treatment of patients with cardiovascular disease and heart failure.¹⁶ The current study, for the first time, investigated the clinical and hemodynamic effects of serial

hydrotherapy in CHF by means of a randomized, controlled trial. Our data indicate that an intensive 6-week hydrotherapy program according to Kneipp improves QOL, as well as heart-failure-related symptoms, and reduces resting heart rate and heart rate exercise response to a clinically relevant extent.

There are several potential mechanisms that could be responsible for the observed beneficial effects of intensive hydrotherapy on clinical symptoms and hemodynamic function in CHF. Hydrotherapy consists of serial thermal warm- and cold-water applications. Whereas warm-water applications and immersions directly lead to peripheral vasodilation,⁵ cold immersions and pourings provoke immediate vasoconstriction with reactive prolonged vasodilation and subsequent cold adaptation with serial treatment.¹¹

Thermal therapy, by means of sauna and warm-water baths, has been shown to reduce cardiac afterload and preload and to increase cardiac output in CHF.⁶ Moreover, repeated sauna treatments improved peripheral vascular endothelial function and decreased brain natriuretic peptide concentrations in patients with chronic mild heart failure.⁷ Experimental studies have demonstrated that CHF impairs endothelial-dependent vasodilation in response to acetylcholine,²¹ and in humans, peripheral resistance vessels are largely impaired by CHF.²² This may occur because of decreased shear stress due to reduced peripheral perfusion.²³ Because shear stress is an important stimulus for the peripheral vascular production of endothelium-derived nitric oxide (NO),²⁴ treatments that improve peripheral perfusion, like thermal therapy and hydrotherapy, could induce NO production by the vessels.

Besides, serial immersions and pourings with cold water induce physiologic adaptive mechanisms. During cold stimulation, adrenaline and noradrenaline increases are provoked; with serial treatments, an attenu-

Table IV. Hemodynamic data at rest at baseline and after 6 weeks of restriction or hydrotherapy

	Baseline	Hydrotherapy	Restriction	P (hydrotherapy vs restriction)
Blood pressure at rest				
Systolic	142.3 ± 4.5	137.5 ± 3.7	143.3 ± 5.0	.207 (NS)
Diastolic	84.7 ± 1.4	83.3 ± 2.1	85.7 ± 2.1	.195 (NS)
Resting heart rate (beats/min)	79.6 ± 3.4	76.1 ± 3.4	79.4 ± 3.3	.016
RPP (beats/min × mm Hg)	11406 ± 714	10491 ± 577	11369 ± 692	.024

Pooled data; n = 15. RPP, Rate-pressure product.

ated catecholamine response as well as diminished catecholamine resting levels were found.^{11,12,25} Further adaptations relate to cytokine production, circulating cortisol concentrations, and increased antioxidative capacity.^{26,27} In summary, these adaptive mechanisms can be interpreted as an increased tolerance to environmental stress and show similarities to some effects of physical exercise in CHF.²⁸

Overall, the treatment program was well accepted and no patient had worsened clinical symptoms during hydrotherapy. Compliance, a major problem in CHF therapy,²⁹ was excellent, presumably because of the short treatment period and because hydrotherapy was perceived as generally enjoyable and refreshing.

The current data must be interpreted in the context of some important limitations of the study. We applied hydrotherapy only to a limited number of patients from outpatient facilities with mainly NYHA functional class II and a modestly impaired ejection fraction. Only half of the population received diuretics, and we cannot rule out the possibility that the observed symptomatic improvement is partly due to nonspecific treatment effects. Being overweight was common in the studied patients, but no weight changes were induced by the treatment. Due to the recruitment strategy, the ratio of women to men in the study population was unusual for heart failure trials, which reduces the external validity of our results.

The current study tested the efficacy of hydrotherapy by means of a crossover design. As no significant carryover effects could be detected, we assume that the beneficial effects of thermal hydrotherapy are not maintained with restriction and, consequently, the applications need to be applied continuously by the patient for sustained benefit. Therefore, the long-term effects of hydrotherapy may be compromised by decreasing adherence, as is commonly seen with other self-care interventions, such as exercise training. Thus, assessment of long-term adherence remains critical in future studies with hydrotherapy.

Finally, an important limitation results from the unblinding of the intervention; however, blinding is not

feasible in a self-care based physical therapy approach. Besides the nonspecific effects due to unblinding, the ritualistic component of serial hydrotherapy might further contribute to the improvement in QOL. Assessment of outcome expectations, as well as comparison of 2 differentially scheduled treatment programs, could be useful for further evaluation of these subjective components.

Our findings imply that an appropriately performed home-based hydrotherapeutic program may provide a practical, salutary, nonpharmacological therapy for patients with CHF without the need for expensive rehabilitation facilities. Furthermore, this therapy approach may be applicable in patients who are unable to participate in exercise training.

We conclude that a simple, home-based, hydrotherapeutic program is feasible and effective in improving symptoms, QOL, and hemodynamics of patients with nonsevere CHF. Further studies are needed to investigate the effects of hydrotherapy in patients with larger populations and more severe heart failure, and to clarify the mechanisms behind this nonpharmacological therapy approach.

References

1. Benedict CR, Johnstone DE, Weiner DH, et al. Relation of neurohumoral activation to clinical variables and degree of ventricular dysfunction: a report from the registry of studies on left ventricular dysfunction. *J Am Coll Cardiol* 1994;23:1410–20.
2. Floras JS. Clinical aspects of sympathetic activation and parasympathetic withdrawal in heart failure. *J Am Coll Cardiol* 1993;22:72–84A.
3. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med* 1992;327:669–77.
4. Pouleur H. Results of the treatment trial of the studies of left ventricular dysfunction (SOLVD): the SOLVD investigators. *Am J Cardiol* 1992;70:135–6C.

5. Rowell LB, Brengelmann GL, Blackmon JR, et al. Redistribution of blood flow during sustained high skin temperature in resting man. *J Appl Physiol* 1970;28:415–20.
6. Tei C, Horikiri Y, Park J-C, et al. Acute hemodynamic improvement by thermal vasodilation in congestive heart failure. *Circulation* 1995;91:2582–90.
7. Kihara T, Biro S, Imamura M, et al. Repeated sauna treatment improves vascular endothelial and cardiac function in patients with chronic heart failure. *J Am Coll Cardiol* 2002;39:754–9.
8. Imamura M, Biro S, Kihara T, et al. Repeated thermal therapy improves impaired vascular endothelial function in patients with coronary risk factors. *J Am Coll Cardiol* 2001;38:1083–8.
9. Kirsch KA, Rocker DL, von Ameln H, et al. The cardiac filling pressures following exercise and thermal stress. *Yale J Biol Med* 1986;59:257–65.
10. Cordes J. Die thermische Hautreaktion in der Hydrotherapie. *Z. Physiother* 1972;24:241–5.
11. Hildebrandt G. Therapeutische Physiologie. In: Amelung G, Hildebrandt G, editors. *Balneologie und Klimatologie*. Berlin: Springer; 1985. p. 328–56.
12. Huttunen P, Rintamäki H, Hirvonen J. Effect of regular winter swimming on the activity of the sympathoadrenal system before and after a single cold water immersion. *Int J Circumpolar Health* 2001;60:400–6.
13. Cordes J. Aktuelle Erkenntnisse zu theoretischen Grundlagen und zur Praxis der Hydrotherapie. *Z Physiother* 1984;36:415–23.
14. Bühring M. Die Kneippsche Hydrotherapie in der Praxis. *Therapeutikon* 1988;2:80–6.
15. Gutenbrunner C, Ruppel K. Zur Frage der adaptiven Blutdrucknormalisierung im Verlauf von Bädern unter besonderer Berücksichtigung von Homogenisierungseffekten und Lebensalter. *Phys Rehab Kur Med* 1992;2:58–64.
16. Brüggemann W. *Hydrotherapie*. Berlin: Springer; 1986. p. 8–36.
17. Siegrist J, Broer M, Junge A. PLC-Profil der Lebensqualität chronisch Kranker. Göttingen: Beltz-Test GmbH; 1996.
18. Junge A, Fünfstück G, Siegrist J. Ein Fragebogen zur Erfassung der Lebensqualität - erste teststatistische Ergebnisse am Beispiel von Hypertonikern. *Diagnostika* 1990;36:353–8.
19. Goldbeck L, Schmitz TG. Comparison of three generic questionnaires measuring quality of life in adolescents and adults with cystic fibrosis: the 36-item short form health survey, the quality of life profile for chronic diseases, and the questions on life satisfaction. *Qual Life Res* 2001;10:23–6.
20. Jones B, Kenward MG. *Design and analysis of cross-over trials*. London: Chapman and Hall; 1989.
21. Kaiser L, Spickard RC, Olivier NB. Heart failure depresses endothelium-dependent responses in canine femoral artery. *Am J Physiol* 1989;256:H962–7.
22. Kubo SH, Rector TS, Bank AJ, et al. Endothelium-dependent vasodilation is attenuated in patients with heart failure. *Circulation* 1991;84:1589–96.
23. Drexler H. Hypertension, heart failure, and endothelial function. *Am J Cardiol* 1998;82:20–2S.
24. Buga GM, Gold ME, Fukuto JM, et al. Shear stress-induced release of nitric oxide from endothelial cells grown on beads. *Hypertension* 1991;17:187–93.
25. Budd GM, Brotherhood D, Thomas DW, et al. Cardiovascular and metabolic responses to noradrenaline in men acclimatized to cold baths. *Eur J Appl Physiol* 1993;67:450–6.
26. Dugue B, Leppanen E, Leppanen E. Adaptation related to cytokines in man: effects of swimming in ice-cold water. *Clin Physiol* 2000;20:114–21.
27. Siems WG, Brenke R, Sommerburg O, et al. Improved antioxidative protection in winter swimmers. *QJM* 1999;92:193–8.
28. Kiilavuori K, Naveri H, Leinonen H, et al. The effect of physical training on hormonal status and exertional hormonal response in patients with chronic congestive heart failure. *Eur Heart J* 1999;20:456–64.
29. Michalsen A, König G, Thimme W. Preventable causative factors leading to hospital admission with decompensated heart failure. *Heart* 1998;80:437–41.