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Effect of an exercise training program on endothelial dysfunction in diabetic and non-diabetic patients with severe chronic heart failure

Auswirkung eines Trainingsprogramms auf die Endotheldysfunktion bei Diabetikern und Nicht-Diabetikern mit schwerer chronischer Herzinsuffizienz

Zusammenfassung *Hintergrund* Eine endotheliale Dysfunktion wird sowohl bei Patienten mit chronischer Herzinsuffizienz als auch bei Patienten mit insulinpflichtigem Diabetes mellitus gefunden. Diese Endotheldysfunktion führt zu einer deutlichen Reduktion der endothelvermittelten Vasodilatation. Körperliches Training kann einen positiven Effekt auf die gestörte Endothelfunktion bei koronarer Herzerkrankung, chronischer Herzinsuffizienz und Diabetes mellitus ausüben. Unklar ist allerdings, ob ein Trainingsprogramm auf die Endothelfunktion bei Diabetikern mit chronischer Herzinsuffizienz Einfluss hat. Somit war Ziel unserer Arbeit zu überprüfen, ob ein spezielles Trainingsprogramm Auswirkung auf die Endothelfunktion hat. Die Untersuchung wurde vergleichend bei insulinpflichtigen Typ-2-Diabetikern und Nicht-Diabetikern mit schwerer chronischer Herzinsuffizienz durchgeführt. *Methodik* 42 Patienten mit schwerer chronischer Herzinsuffizienz (LVEF ≤ 30%), insulinpflichtige Typ-2-Diabetiker (n = 20, Durchschnittsalter 67 ± 6 Jahre, 16 männlich, 4 weiblich), Nicht-Diabetiker (n = 22, Durchschnittsalter 68 ± 10 Jahre, 20 männlich, 2 weiblich) nahmen an einem vierwöchigen Trainingsprogramm bestehend aus Ergometer- und speziellem Muskelaufbautraining teil. Vor Beginn (T1) und am Ende (T2) des Trainingsprogramms wurden mittels Durchmesserbestimmung der Arteria brachialis die endothelabhängige und endothelunabhängige Vasodilatation erfasst. *Ergebnisse* Am Ende des Trainingsprogramms zeigten sich innerhalb der beiden Gruppen keine signifikanten Veränderungen. Die endothelabhängige Vasodilatation veränderte sich zwischen den Zeitpunkten T1 und T2 wie folgt: In der Gruppe der Diabetiker lag zu Beginn (T1) und am Ende (T2) die endothelabhängige Vasodilatation bei 5,1 ± 3,6 vs. 4,9 ± 2,5%. Für die Nicht-Diabetiker betrug die endothelabhängige Vasodilatation zu T1 und T2 6,8 ± 4,5 vs. 7,6 ± 4,0%. Die endothelunabhängige Vasodilatation lag bei den Diabetikern zu Beginn (T1) bei 10,5 ± 5,6 und fiel am Ende (T2) auf 8,7 ± 4,1% ab. Die Ergebnisse der Nicht-Diabetiker lagen für die Untersuchungszeitpunkte T1 und T2 bei 13,2 ± 5,8 vs. 12,3 ± 6,3%. Die LVEF betrug bei den Diabetikern zu Beginn (T1) 24,2 ± 3,4% und nahm am Ende (T2) auf 27,8 ± 5,8% zu. Bei den Nicht-Diabetikern lag die LVEF bei T1 22,9 ± 3,8 vs. T2 28,6 ± 6,9%. Zu Beginn (T1) und am Ende (T2) lag die maximale Sauerstoffaufnahme (VO_2max) in der Gruppe der Diabetiker bei 10,3 ± 3,9 vs. 11,4 ± 2,8 ml/kg/min und in der Gruppe der Nicht-Diabetiker bei 10,0 ± 3,1 vs. 13,5 ± 5,0 ml/kg/min. Korrelationen zwischen der prozentualen Veränderung der endothelabhängigen Vasodilatation und der Zunahme der Sauerstoffaufnahme wurden nicht gefunden. *Schlussfolgerung* In unserer Untersuchung hatte bei insulinpflichtigen Typ-2-Diabetikern und Nicht-Diabetikern mit deutlich eingeschränkter Auswurffraktion ein Trainingsprogramm keinen Einfluss auf die endothelabhängige

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und -unabhängige Vasodilatation. Jedoch zeigte sich in beiden Gruppen ein trainingsabhängiger Einfluss auf medizinische Parameter und körperliche Leistungsdaten.

Schlüsselwörter Endothel – Vasodilatation – Diabetes mellitus – chronische Herzinsuffizienz – Training

Summary *Background* Endothelial dysfunction is found both in patients with chronic heart failure and in patients with insulin-treated type 2 diabetes mellitus. This endothelial dysfunction leads to a significant reduction in endothelium-derived vasodilation. Physical exercise can have a positive effect on endothelial dysfunction in patients with coronary artery disease, chronic heart failure and diabetes mellitus. It is not clear, however, whether an exercise program influences endothelial function in diabetics with chronic heart failure. Our study was thus aimed at investigating whether a special exercise program would affect endothelial function. Comparisons were made with insulin-treated type 2 diabetics and with non-diabetics suffering from chronic heart failure. *Methods* 42 patients with severe chronic heart failure (LVEF ≤ 30%), insulin-dependent diabetics (n = 20, mean age 67 ± 6 yrs, 16 male, 4 female), non-diabetics (n = 22, mean age 68 ± 10 yrs, 20 male, 2 female) participated in a 4-week exercise program consisting of ergometer and special muscle strength training. Before (T1) and at the end (T2) of the training program endothelium-dependent and endothelium-independent vasodilatory capacity were assessed by brachial artery diameter measurement. *Results* At the end of the training program, there were no significant results within the two groups. The endothelium-dependent vasodilation changed between T1 and T2 as follows: In the diabetic group, the endothelium-dependent vasodilation at T1 and T2 was 5.1 ± 3.6 and 4.9 ± 2.5%, respectively. For the non-diabetics, the endothelium-dependent vasodilation was 6.8 ± 4.5 and 7.6 ± 4.0% at T1 and T2, respectively. The endothelium-independent vasodilation in the diabetics was 10.5 ± 5.6 at T1 and dropped to 8.7 ± 4.1% at T2. The results for the non-diabetics were 13.2 ± 5.8 and 12.3 ± 6.3% at T1 and T2, respectively. The LVEF in the diabetics was 24.2 ± 3.4% at T1, increasing to 27.8 ± 5.8% at T2. In the non-diabetics, the LVEF was 22.9 ± 3.8 at T1 vs. 28.6 ± 6.9% at T2. In the groups of diabetics, the maximum oxygen uptake (VO_{2}-max) was 10.3 ± 3.9 at T1 vs. 11.4 ± 2.8 ml/kg/min at T2 and in the group of non-diabetics 10.0 ± 3.1 vs. 13.5 ± 5.0 ml/kg/min. No correlations were found between the change in endothelium-dependent vasodilation and the increase in oxygen uptake. *Conclusion* In our study, a program of physical exercise had no influence on endothelium-dependent or endothelium-independent vasodilation in insulin-treated type 2 diabetics or in non-diabetics with considerably reduced ejection fraction. In both groups, however, an exercise-related influence on medical parameters and physical performance could be observed.

Key words Endothelium – vasodilation – diabetes mellitus – heart failure – exercise

Introduction

There is various evidence that endothelium-derived vasodilators and vasoconstrictors regulate the balance of vascular tone [3]. An important physiological vasodilator released by endothelial cells is nitric oxide (NO). The release of NO triggers a flow-dependent, endothelium-mediated vasodilation (FDD). Its production and release are influenced by endocrine mediators like acetylcholine (ACh) [6] and bradykinin [1] as well as changes in blood-flow velocity and wall shear stress [22].

In patients with chronic heart failure (CHF) a peripheral vasoconstriction may be observed due to activation of the sympathetic nervous system and the renin-angiotensin system [24]. Due to the impaired NO release, the FDD is severely restricted [15]. Likewise an impaired endothelial function is found in patients with arterial hypertension [12], coronary artery disease [23] and diabetes mellitus [27]. A correlation between endothelial dysfunction and cardiovascular risk factors influences the development and prognosis of atherosclerosis [9]. Insulin resistance in patients with type 2 diabetes also appears to influence endothelial function [5].

Many studies have investigated endothelial function to date, some focusing on the ways in which it is influenced by various drug treatments [4, 14], others concentrating on the influence of physical exercise on endothelial function in patients with cardiovascular diseases [10, 11, 13, 17]. Physical exercise leads to improved endothelial function both in patients with normal and with restricted left-ventricular ejection fraction [13, 17]. The degree of endothelium function is possibly dependent on the release of progenitor cells [16].

Physical training also leads to significantly improved FDD in patients with type 2 diabetes mellitus and without manifest coronary artery disease [18].

To date there have been no comprehensive reports about the influence of physical exercise on endothelial function in patients with diabetes and CHF, however. Thus we investigated the effect of a standardized 4-week training program on endothelial function in diabetic (IDDM) and non-diabetic patients with severe chronic heart failure.

Methods

Study group

A total of 42 patients took part in a special training program, 20 of whom had insulin-treated type 2 diabetes mellitus. The mean age of the diabetics at the start of rehabilitation was 67 ± 6 yrs, the proportion of males was 80%, females 20%. The mean age of the non-diabetics was 68 ± 10 yrs, 91% male and 9% female. In 72% of the diabetics, the CHF was due to coronary artery disease, in 28% other causes were responsible. In the group of non-diabetics 81% had coronary artery disease and 19% other causes (Table 1). There were no significant differences between the two groups with regard to baseline parameters. Preexisting medication was maintained throughout the rehabilitation and supplemented as required. For medication at the start of rehabilitation Table 2.

Tab. 1 Baseline data: patient characteristics

	Diabetic group (N = 20)	Non-diabetic group (N = 22)
Mean age (years)	67 ± 6	68 ± 10
Male (%)	80	91
Female (%)	20	9
Comorbidity (%)		
Hypertension	85	72.7
Hyperlipidemia	55	54.5
Family history	10	27.3
NYHA functional class (%)		
I	55	43
II	15	43
III	30	14
IV	–	–
Cause of CHF (%)		
Ischemic heart disease	72.2	81
Other	27.8	18
BMI	26.4 ± 3.1	25.2 ± 4.0

Tab. 2 Medication at the beginning of the training program

	Diabetic group		Non-diabetic group	
	%	n	%	n
ACE inhibitors	65	13	40	8
Beta-blockers	65	13	60	12
Diuretics	65	13	80	16
Digitalis	35	7	30	6
Statins	60	12	35	7
Anticoagulation	25	5	25	5

Study design

The exercise program was carried out over a period of 4 weeks during in-hospital rehabilitation. We excluded patients with severe pulmonary diseases, considerable cognitive deficits and/or physical disabilities which prevented them from participating. The program consisted of ergometric, muscle strength and walking exercises [19]. Before (T1) and at the end (T2) of the program endothelium-dependent and endothelium-independent vasodilatory capacity were assessed by brachial artery diameter measurement. Further data recorded included echocardiographic determination of left-ventricular ejection fraction (LVEF), spiroergometric measurement of maximum work load and ascertainment of CHF severity using the NYHA class system. Clinical parameters for both groups (diabetic and non-diabetic) are shown in Table 3.

Measurement of endothelium-dependent and endothelium-independent vasodilation

Before and after the training program endothelium-dependent and endothelium-independent vasodilatory capacity was assessed by brachial artery diameter measurement [2]. All cardiovascular medications were withheld for 24 h before assessment of endothelium vasodilation. Alcohol and caffeine were pro-

Tab. 3 Baseline data: clinical parameters at the beginning

	Diabetic group (N = 20)	Non-diabetic group (N = 22)
LVEF (%)	24.2 ± 3.4	22.9 ± 3.8
LVEDV (ml)	137 ± 34	166 ± 46
LVESV (ml)	102 ± 25	129 ± 37
VO_2max (ml/kg/min)	10.3 ± 3.9	10.0 ± 3.1
Max. work load (W)	60 ± 32	71 ± 32

LVEF left ventricular ejection fraction, *LVEDV* left ventricular end-diastolic volume, *LVESV* left ventricular end-systolic volume, *VO_2max* maximum oxygen uptake, *Max. work load* maximum work load

hibited within the 12 hours before investigation. The assessment was performed in a fasting condition before breakfast. Brachial artery diameter was measured 8–12 cm above the cuff using a 7 MHz linear array transducer. Arterial occlusion was produced by cuff inflation above 30 mmHg systolic blood pressure for five minutes. Following release of the occlusion a reactive hyperemia with increased blood flow can be observed. The flow-mediated dilator response was used as a measure of endothelium-dependent vasodilation. The endothelium-independent vasodilation was assessed 4 minutes after application of 0.4 mg nitroglycerin.

Echocardiography

Left-ventricular function was analyzed at the beginning and the end of the program using two-dimensional echocardiography (Acuson Aspen) according to the recommendation by the American Society of Echocardiography [25]. Left-ventricular end-diastolic volume (LVEDV) and left-ventricular end-systolic volume (LVESV) were obtained from the apical 4 and 2-chamber views. Simpson's formula was used to calculate left-ventricular ejection fraction.

Cardiopulmonary exercise test

A bicycle ergometer (Ergoline 900, Marquette/Hellige) was used to collect cardiopulmonary exercise data. The gas exchange parameters and maximum oxygen uptake (VO_2max) were collected using an automated breath-by-breath system (Ganshorn, Ergoscope). We carried out a ramp-like test on the bicycle ergometer. Following an initial warm-up of three minutes without work load, a starting level of 25 Watts was selected, increasing by 10 Watts every two minutes. In this way even patients with considerable muscle wasting were able to perform well enough on the ergometer to produce the exercise test data required. An oscillometric instrument measured blood pressure automatically every 2 minutes. Exercise test data were monitored during the 3-minute recovery time. A cardiopulmonary exercise test was performed, symptom-limited by dyspnea, physical exhaustion and fatigue. Criteria for prematurely stopping exercise tests were additionally adhered to. Maximum oxygen uptake (VO_2max) was determined using the V-Slope method [26].

Exercise training

The 4-week exercise program comprised ergometer training (three times), a 6-minute walk test (twice) and muscle strength training (twice) every week throughout the rehabilitation period [19].

Bicycle ergometer training was carried out under standardized conditions. The maximum work load for the bicycle ergometer was defined by cardiopulmonary exercise test results (60–80% of VO_2max). The maximum performance possible per training unit was individual and symptom-limited.

In order to train the lower limb muscles we included a muscle strengthening by shuttle training. Following a warm-up phase on the bicycle ergometer at a low work load, patients underwent a session on a shuttle exercising device. Patients stretch their legs against an adjustable resistance and move along tracks in a semi-supine position. The adjustable resistance enables the required exertion to be tailored individually to the performance of each patient. See previous publications [19, 21] for an exact description and definition of this technique.

A 6-minute walk test was used as a training unit [8]. Following brief instruction, patients were requested to walk briskly down a set path for six minutes. The distance covered was measured in meters.

Statistical analysis

Statistical comparisons for endothelial vasodilation, medical parameters and physical performance data were obtained by general linear model (GLM) for repeated measurements. All data are expressed as mean ± SD. Normal distribution was tested using the Kolmogorov-Smirnov Goodness of Fit Test. A value of $p \leq 0.05\%$ was established for all tests. Relationships between variables were determined by bivariate correlations. This calculation was supplemented by new differentials for the endothelium-dependent variable in the context of cardiopulmonary capacity.

Results

All 42 patients took part in the training program and completed it to the end of the rehabilitation. None of them showed any immediate adverse effects related to the training program.

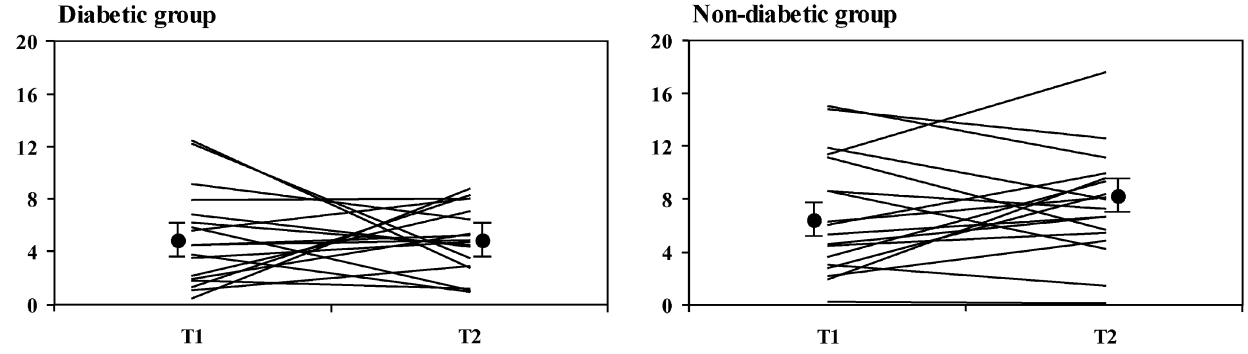

Fig. 1 1 Change in endothelium-dependent vasodilatory capacity at the beginning (T1) and at the end (T2) of the training program for the diabetic group (left diagram) and the non-diabetic group (right diagram). There were no significant changes within or between the two groups (p = n.s.)

Endothelial function

Before and after the training program there were no significant changes in FDD measurement (%) of the brachial artery in either group (diabetic group: T1 5.1 ± 3.6 vs. T2 4.9 ± 2.5%; non-diabetics T1 6.8 ± 4.5 vs. T2 7.6 ± 4.0%). Data are shown in Fig. 1.

Neither were any significant training-related effects measured for endothelium-independent vasodilatory capacity in the diabetic or the non-diabetic group (diabetic group: T1 10.5 ± 5.6 vs. T2 8.7 ± 4.1; non-diabetics T1 13.2 ± 5.8 vs. T2 12.3 ± 6.3%).

Echocardiography

For the diabetic group LVEF significantly increased from 24.2 ± 3.4% at the beginning (T1) to 27.8 ± 5.8% at the end of the program (T2). In the group of non-diabetics, this parameter was 22.9 ± 3.8% at T1 and increased significantly to 28.6 ± 6.9%. In both groups, left-ventricular end-diastolic volume (LVEDV) did not change between the beginning and end of the program (diabetic group: T1 138 ± 35 vs. T2 135 ± 32 ml; non-diabetics T1 165 ± 47 vs. T2 159 ± 54 ml). In the diabetic group, left-ventricular end-systolic volume (LVESV) was 104 ± 26 and 96 ± 24 ml at T1 and T2, respectively. In the non-diabetic group LVESV significantly diminished from 128 ± 38 to 115 ± 43 ml. There were significant differences between the two groups for LVEF ($p \leq 0.01$) and LVESV ($p \leq 0.01$), but not for LVEDV (p = n.s.). All clinical data results are shown in Table 4.

Tab. 4 GLM for the within-subjects factors (T1/T2), the between-subject factors (diabetes) and interaction terms for the clinical parameters

Measure: clinical parameters Source	df	F	p-value
LVEF (within groups)	1	0.001	*
Diabetes (between groups)	1	0.88	n.s.
LVEF * Diabetes	1	0.28	n.s.
LVEDV (within groups)	1	0.22	n.s.
Diabetes (between groups)	1	0.08	n.s.
LVEDV * Diabetes	1	0.66	n.s.
LVESV (within groups)	1	0.004	*
Diabetes (between groups)	1	0.07	n.s.
LVESV * Diabetes	1	0.46	n.s.
VO_2max (within groups)	1	0.002	*
Diabetes (between groups)	1	0.84	n.s.
VO_2max * Diabetes	1	0.22	n.s.
Work load (within groups)	1	0.02	*
Diabetes (between groups)	1	0.28	n.s.
Work load * Diabetes	1	0.37	n.s.

GLM general linear model, *LVEF* left ventricular ejection fraction, *LVEDV* left ventricular end-diastolic volume, *LVESV* left ventricular end-systolic volume, *VO_2max* maximum oxygen uptake, *df* degrees of freedom, *F* exact F distribution, *p-value* $p \leq 0.05$

Cardiopulmonary exercise capacity and exercise measurement

At the beginning (T1), VO_2max for the diabetic group was 10.3 ± 3.9 ml/kg/min; by the end of the program it had increased significantly to 11.5 ± 3.1 ml/kg/min ($p \leq 0.01$). Similar results could be observed for the non-diabetic group. VO_2max improved significantly from T1 10.0 ± 3.1 ml to T2 13.5 ± 5.0 ml/kg/min ($p \leq 0.05$). The maximum symptom limited work load (W) increased significantly in both groups (diabetic group: T1 60 ± 32 vs. T2 67 ± 19 W; non-diabetics T1 71 ± 32 vs. T2 85 ± 32 W). The results within and between groups, as well as the interaction terms are shown in Table 4.

Tab. 5 GLM for the within-subjects factors (T1/T2), the between-subject factors (diabetes) and interaction terms of the training-related data

Measure: training-related data Source	df	F	p-value
6-min walk test (within groups)	1	0.001	*
Diabetes (between groups)	1	0.45	n.s.
6-min walk test * Diabetes	1	0.36	n.s.
MST (within groups)	1	0.001	*
Diabetes (between groups)	1	0.36	n.s.
MST * Diabetes	1	0.18	n.s.

GLM general linear model, *6-min walk test* 6-minute walk test, *diabetes* diabetic and non-diabetic group, *MST* muscle strength training units, *df* degrees of freedom, *F* exact F distribution, *p-value* $p \leq 0.05$

The exercise-related performance data included the results from the 6-minute walk test and the muscle strengthening exercises. At the beginning the 6-minute walk test was 311 ± 96 m in the diabetic group, rising significantly to 407 ± 102 m at the end of the program (T2) ($p \leq 0.01$). At the beginning the non-diabetics walked a distance of 333 ± 102 m, improving by the end to 452 ± 95m ($p \leq 0.01$). In the diabetic group muscle strength training units (MST) were 2.3 ± 1.0 at T1 and 5.4 ± 1.7 MST at T2 ($p \leq 0.01$). The non-diabetic group had similar results, from 2.3 ± 0.9 to 6.2 ± 2.5 MST. Table 5 shows the results within and between groups, as well as the interaction terms. There was no significant correlation between the change in FDD response (ΔE_d) and the change in maximum oxygen uptake (ΔVO_2max). Correlations between the changes are shown in Fig. 2.

Discussion

The results of our study showed that a special 4-week training program including endurance and muscle strength training had no statistically significant effect on endothelium function. However, the special physical training program was found to be effective in improving medical parameters such as LVEF, LVESV, VO_2max and maximum work load in Watts. There was no statistically significant result for the correlation between the change in endothelium-dependent vasodilatory capacity and the change in cardiopulmonary capacity.

A number of studies have demonstrated the influence of physical exercise on endothelial function [11, 17]. But no results had been published to date regarding the influence of physical training on diabetics with heart failure. This study therefore set out to investigate the effect of a training program on endothelial function in patients with chronic heart failure and insulin-dependent diabetes. Our results showed no influence of training on endothelial function in the participating groups. Hornig et al. [13] showed that patients with CHF had a baseline endothelial function of $8.6 \pm 0.9\%$, increasing to $13.6 \pm 0.9\%$ after physical exercise. Six weeks after the training period, however, this effect could no longer be observed. We were unable to detect an increase in FDD after training. It should be noted that Hornig et al. [13] measured FDD via the radial artery.

Due to the fact that diabetes mellitus and CHF are associated with endothelial dysfunction, exercise training is often recommended. In the study by Maiorana et al. [18], patients with type 2 diabetes without IDDM or cardiac insufficiency took part in an 8-week physical exercise program. Endothelium-dependent and endothelium-independent vasodilation was measured before and after the training period. In this randomized, controlled, crossover trial brachial artery endothelium-dependent vasodilation significantly increased from 1.7 ± 0.5 to $5.0 \pm 0.4\%$.

In a patient population with diverse cardiovascular risk factors, exercise-induced improvements in endothelial dysfunction were observed, but this was not mediated by changes in cardiovascular risk factors [7]. Just as was the case for Green et al. [7], we were also unable to find any correlation between the

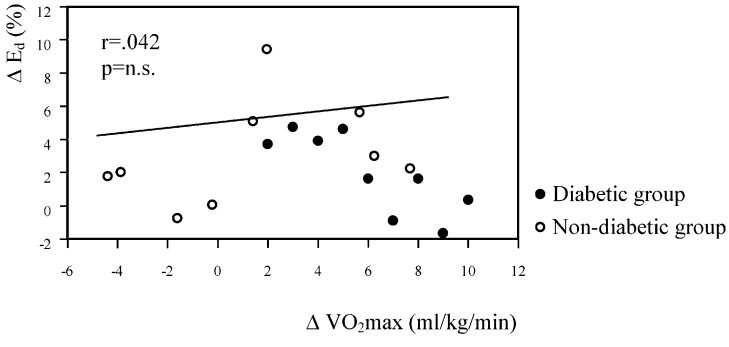

Fig. 2 Relationship between change in endothelium-dependent vasodilatory capacity (ΔE_d %) and change in cardiopulmonary capacity (ΔVO_2max ml/kg/min). The black dots (●) represent patients from the diabetic group. The white dots (○) represent patients from the non-diabetic group

change in endothelium-dependent vasodilation and the change in cardiopulmonary capacity. This was not the case for Nakamura and team [20], who ascertained a positive correlation in patients with CHF between the cumulative changes in forearm blood flow after intra-arterial infusion of ACh and maximum oxygen uptake. Linke et al. [17] observed an improvement in endothelial function, measured via the intra-arterial infusion of ACh, in patients with CHF during lower limb exercise training. They were also able to show that this was associated with a correlation between change in vasodilation and increase in functional work capacity.

Study limitations

The short duration (four weeks) of the training program may not have been long enough to show positive effects on endothelium function. In addition, changes in medication during the study might have influenced the results. Different methods of measurement of FDD might explain our findings of the non-significant correlation between the changes in endothelium vasodilation and increase in cardiopulmonary capacity.

Conclusion

In patients with insulin-treated type 2 diabetes mellitus and severe CHF, endothelial function is severely impaired compared to healthy subjects. In our study, endothelial dysfunction could not be positively influenced by physical exercise, unlike the training-related data. This result could affect the risk stratification and unfavorable prognosis for diabetics with CHF.

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