CHAPTER 6

THE EFFECT OF EXERCISE TRAINING ON THE OXYGEN UPTAKE-WORK RELATION IN CHRONIC HEART FAILURE

Maaike G.J. Gademan
Luc J.S.M. Teppema
Joris C.W. Haest
Harriette F. Verwey
Henk J. van Exel
Carolien M. H. B. Lucas
Martin J. Schalij
Ernst E. van der Wall
Cees A. Swenne

1Department of Cardiology, Leiden University Medical Center, Leiden
2Department of Anesthesiology, Leiden University Medical Center, Leiden
3Department of Cardiopulmonary Rehabilitation, Rijnland Rehabilitation Center, Leiden
4Heart Failure Outpatient Clinic, Rijnland Hospital, Leiderdorp

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ABSTRACT

Background. The oxygen uptake-work relation (ΔVO₂/ΔW) has predictive value in chronic heart failure (CHF) and the reduction in ΔVO₂/ΔW reflects the severity of this disease. Exercise training improves prognosis in CHF patients. Exercise training also improves several cardiopulmonary exercise testing variables in these patients. It is, however, unknown if exercise training improves ΔVO₂/ΔW in CHF patients with subnormal ΔVO₂/ΔW.

Methods. We studied 36 New York Heart Association (NYHA) class II-III CHF patients, randomized into an exercise training group T (n=18; 15M/3F; age 60 ± 11 yrs; LVEF 32 ± 7%) and a control group C (n=18; 17M/1F; age 63 ± 9 yrs; LVEF 33 ± 7%). A progressive workload exercise test was done at baseline and repeated after four weeks (group C) or after completion of the training program (group T).

Results. Exercise training improved VO₂peak by 23% (P(TvsC)=0.0001), oubs by 18% (P(TvsC)=0.01), w₅₀m by 17% (P(TvsC)=0.01) and VO₂/VO₂slope by 10% (P(TvsC)=0.02). Exercise training did not improve ΔVO₂/ΔW (P(TvsC)=0.86). However, 33% of T and 50% of C had a relatively normal ΔVO₂/ΔW (≥10 (ml/min)/Watt) at baseline. ΔVO₂/ΔW improved in the population with subnormal baseline ΔVO₂/ΔW values from 8.91 ± 0.90 to 9.14 ± 0.78 (ml/min)/Watt (P(TvsC)=0.04).

Conclusions. Exercise training improved VO₂peak, VO₂/VO₂slope, w₅₀m and oubs. In patients with subnormal ΔVO₂/ΔW exercise training improved ΔVO₂/ΔW. Further research has to reveal the prognostic significance of exercise-induced ΔVO₂/ΔW improvements.

CHAPTER 6 | THE EFFECT OF EXERCISE TRAINING ON THE OXYGEN UPTAKE-WORK RELATION IN CHF

METHODS

Patients. Our institutional Medical Ethics Committees approved the protocol of this study. All participants gave written informed consent. Eligible patients (NYHA class II or III CHF with systolic dysfunction and left ventricular ejection fraction < 45%) were scheduled for cardiopulmonary rehabilitation. Patients with pulmonary hypertension and/or chronic obstructive pulmonary disease were excluded from the study.

Patients were randomized to a control (C) and an exercise training group (T). Patients performed exercise tests before commencing their exercise training program and within one week after their final training session. Patients performed two exercise tests, four weeks apart, before starting their actual training program.

Exercise testing. The symptom-limited exercise tests were done with respiratory gas exchange analysis (Oxycon Pro, Jaeger). Exercise intensity started at 5 Watts and was increased by 5 Watts every 30 seconds. Maximal work rate (Wmax) was defined as the highest obtained workload minimally maintained for 30 seconds. Subjects exercised to their self-determined maximal capacity or until the supervising physician stopped the test because of adverse symptoms, e.g., chest pain, dizziness, potentially dangerous arrhythmias or ST-segment deviations, or marked systolic hypotension or hypertension. Breath-by-breath respiratory gas analysis was done throughout the entire test.

Exercise testing variables. Oxygen uptake (VO₂) values were determined over every 30 second period and over the final measurement period at peak exercise when this was more than 15 seconds long. The last valid VO₂ value was taken as peak VO₂ (VO₂peak). ΔVO₂/ΔW was calculated by linear regression of VO₂ on work rate, from 1 minute after the beginning to 80% of the total exercise test duration. VO₂/VO₂slope was obtained by linear regression of minute ventilation (V̇E) on carbon dioxide output (V̇CO₂) over the entire exercise test. VO₂ was computed by a linear least squares regression from VO₂ on the logarithm of the minute ventilation (V̇E) over the entire exercise test.

Exercise training. T-patients performed 30 exercise training sessions, which were held 2 to 3 times a week. The initial 20 minutes of a training session consisted of cycling. Exercise intensity during the first session was 50% of the maximal load attained during the baseline exercise test, preceded by warming up and followed by cooling down. Per session, this load was increased, until the attained heart rate was equal to the heart rate at the anerobic threshold as estimated during the baseline test. Subsequent rowing or walking during 15 minutes was optional. Additionally, light resistance training was performed, consisting of 1 series of 25 repetitions of each of: flies, rowing, chest press, shoulder press, leg extension, leg curl, leg press and pull down. Resistance training intensity was adjusted in such a way that the patient experienced nearly-complete exhaustion of the involved muscle group after 25 repetitions.

Statistics. Data are expressed as mean ± standard deviation. Baseline characteristics were evaluated by using Mann-Whitney U test or chi-square tests with Yates correction. An unpaired Student’s t-test was used to compare baseline values between the training and the control groups, and to test on changes in VO₂peak, ΔVO₂/ΔW, VO₂/VO₂slope, VO₂ and maximal workload (Wmax). Changes in NYHA class within group T were evaluated with a Wilcoxon signed rank test. Linear regression analyses were performed to evaluate the relationship between ΔVO₂/ΔW and the baseline values of the other cardiopulmonary oxygen uptake variables (VO₂peak, oubs and VO₂/VO₂slope). Linear
regression was also performed to assess the relationship between $\Delta V_O₂/\Delta W$ baseline values and $\Delta V_O₂/\Delta W$ changes.

**RESULTS**

**Patient characteristics**

Characteristics of the patients in group T (n=18) and group C (n=18) groups are summarized in Table 1. No significant differences were found between any of the characteristics of the patients in the T and C group. There were also no significant differences in baseline exercise testing variables (Table 2). Throughout the study, medication remained the same for all patients.

**New York Heart Association classification**

NYHA class improved after exercise training (P<0.01): 8 patients improved one NYHA class, while 8 patients remained in their NYHA class. NYHA class values after exercise training were missing for 2 patients.

**Exercise capacity**

Exercise training improved $V_O₂_{peak}$, $W_{max}$ and $V̇E/V̇CO₂$ slope, but it did not improve $\Delta V_O₂/\Delta W$ (P>0.05, Table 2). However, 50% of group C and 33% of group T had relatively normal $\Delta V_O₂/\Delta W$ values ($\Delta V_O₂/\Delta W$>10 (ml/min)/Watt). We divided group T and group C in a population with $\Delta V_O₂/\Delta W$>10 (normal) and a population with $\Delta V_O₂/\Delta W$<10 (subnormal). Exercise training improved $\Delta V_O₂/\Delta W$ in the population with $\Delta V_O₂/\Delta W>$10 (n=12) from 8.71±0.90 to 9.14±0.78 (ml/min)/Watt (Table 3). In this population all other exercise testing variables also improved (Table 3). Furthermore, baseline $\Delta V_O₂/\Delta W$ was related with the exercise-induced change in $\Delta V_O₂/\Delta W$, r=0.60 (Figure 1).

There was only a weak correlation in baseline values between $\Delta V_O₂/\Delta W$ and $V_O₂_{peak}$ (r=0.12, P=0.02), and between $\Delta V_O₂/\Delta W$ and $OUES$ (r=0.10, P=0.01, Figure 4). No correlation was found between $\Delta V_O₂/\Delta W$ and $V̇E/V̇CO₂$ slope (r=0.02, P=0.41, Figure 1). There was no significant difference between the $\Delta V_O₂/\Delta W$ baseline values of CHF patients with NYHA class II and of patients with NYHA class III (9.74±0.93 versus 9.28±1.41 (ml/min)/Watt, P=0.25).

**DISCUSSION**

Exercise training improved $V_O₂_{peak}$, $V̇E/V̇CO₂$ oues and $W_{max}$. In 42% of our study population, $\Delta V_O₂/\Delta W$ baseline values were normal. In patients with subnormal $\Delta V_O₂/\Delta W$ baseline values, exercise training improved $\Delta V_O₂/\Delta W$. The amount of exercise-induced change in $\Delta V_O₂/\Delta W$ was related to baseline $\Delta V_O₂/\Delta W$.

To our knowledge, this is the first study demonstrating the effect of exercise training on the oxygen uptake-work relation in CHF. $\Delta V_O₂/\Delta W$ is often seen as an aspect of the $V_O₂$ kinetics as $\Delta V_O₂/\Delta W$ determines the amplitude of the oxygen response on exercise in a constant workload test. It is, however, not identical to the $V_O₂$ time constants measured during a constant workload test. Only one previous study has reported on the effect of exercise training on the $V_O₂$ time constants. In contrast with our study, they found that exercise training improved $V_O₂$ kinetics in CHF irrespective of their baseline values. This discrepancy can be explained by the fact that $\Delta V_O₂/\Delta W$ measures another aspect of the $V_O₂$ kinetics than the $V_O₂$ time constants.

Subnormal $\Delta V_O₂/\Delta W$ in CHF can be attributed to components of both oxygen delivery and oxygen utilization systems. Recently, Kemps and colleagues suggested that in CHF the delay in $V_O₂$ is primarily due to limitations in oxygen delivery systems. In healthy persons cardiac output time constants are larger than $V_O₂$ time constants, indicating that, during exercise onset, oxygen delivery to skeletal muscles is in excess of the metabolic demand. Kemps and colleagues demonstrated that in CHF patients no clear difference between the $V_O₂$ and cardiac output time constants existed. This would imply that oxygen delivery is the limiting factor for $V_O₂$. kinetics, hence, limitation in oxygen delivery systems could also be the limiting factor of $\Delta V_O₂/\Delta W$ in CHF.
Induced vasodilatation in the working muscle, hereby causing blood flow redistribution at the sacrifice of other organs. Hence, work efficiency is increased, a mechanism that compensates for the limited oxygen supply in CHF patients.

Cardiac output is an important variable in oxygen delivery. CHF patients have an attenuated cardiac output response to exercise, which also can be seen as a major cause of a decreased ΔVO_{2}/ΔW. Unfortunately, our exercise testing protocol does not allow for differentiation between cardiac and peripheral training effects. Several studies showed that exercise training improves the cardiac output response to exercise. Also, Roditis and colleagues showed that exercise training increases VO_{2} kinetics particularly in phase 1 (the exercise phase in which cardiac output increases considerably) and speculated that this might imply cardiac function improvement. However, it is known that exercise training also reduces vasoconstriction, improves endothelial dysfunction, decreases tissue inflammation and improves intrinsic skeletal muscle properties. Likely, training effects will also occur within these systems. Also, these systems all influence each other. E.g., an increased cardiac output response may improve pulmonary gas exchange. Further research has to reveal to which extent each of the codeterminants of ΔVO_{2}/ΔW affects the degree of response to exercise training.

Normal ΔVO_{2}/ΔW values are around 10 (ml/min)/Watt 

Different from the other exercise testing variables, VO_{2peak}, VE/VO_{2}, W_{max} and OUES, 42% of our study population had normal baseline ΔVO_{2}/ΔW values. Cohen-Solal and colleagues reported that ΔVO_{2}/ΔW values were significantly reduced in severely impaired (VO_{2peak} <16 ml/kg/min) CHF patients. According to this definition, greater values, one may assume that patients improved in work efficiency, therefore, the actual improvement in aerobic metabolism may even be higher than the measured increase in ΔVO_{2}/ΔW.

As ΔVO_{2}/ΔW is likely not sensitive enough to assess changes in exercise capacity in mild CHF patients and as ΔVO_{2}/ΔW is influenced by external work efficiency, evaluation of the severity of the disease or the effectiveness of an exercise training program in CHF patients cannot be performed properly by only assessing ΔVO_{2}/ΔW. However, as all exercise testing parameters reflect different aspects of the
cardiopulmonary system during exercise, we think it is still of importance to assess $\Delta VO_2/W$ in combination with other cardiopulmonary exercise training variables like $VO_2 peak/VE/VO_2 slope$ and $OUES$. We are of opinion that assessing all exercise testing variables together for each individual will make it possible to establish a more reliable representation of the patient’s individual capabilities and drawbacks. Also, exercise testing variables have all individually important prognostic value and, combining these variables might lead to a powerful prognostic tool. Further research to investigate this, and to investigate if exercise-induced $\Delta VO_2/W$ improvements are associated with improved prognosis, is needed.

**Limitations**

Although the time interval between the initial and second symptom-limited exercise tests is probably not of utmost importance, it is a limitation that there is a discrepancy in time between the performance of the first and second symptom limited exercise test between the C and T groups. This difference was a result caused by our principle that the start of the rehabilitation program of the control patients should not be delayed by our study.

Also, as mentioned in the discussion, it is a limitation that $\Delta VO_2/W$ is not uniquely determined by the aerobic metabolism, as it is also codetermined by the external work efficiency.

**CONCLUSIONS**

Exercise training improved $VO_2 peak$, $VE/VO_2$, $w_{max}$ and $OUES$. In half of our population $\Delta VO_2/W$ baseline values were normal. In patients with decreased $\Delta VO_2/W$ exercise training improved $\Delta VO_2/W$. Follow-up studies are needed to demonstrate if exercise-induced $\Delta VO_2/W$ improvements are associated with improved prognosis.

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**REFERENCE LIST**

training on the kinetics of oxygen uptake in patients with chronic heart failure.


