Exercise Training in Patients With Chronic Heart Failure Delays Ventilatory Anaerobic Threshold and Improves Submaximal Exercise Performance

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We have recently demonstrated that exercise training can induce important hemodynamic and metabolic adaptations in patients with chronic heart failure due to severe left ventricular dysfunction. This study examines the accompanying changes in submaximal exercise performance and the ventilatory response to exercise in these patients. Before and after 16–24 weeks of exercise training, subjects underwent two symptom-limited bicycle exercise tests, one with an incremental graded workload, and one with a constant workload that represented 79±11% of the pretraining peak oxygen consumption. Breath-by-breath expired gas analysis was performed continuously during each test, and central hemodynamic, leg blood flow, and blood lactate measurements were obtained during the incremental protocol. The ventilatory anaerobic threshold was determined during the incremental exercise study from coplotted breath-by-breath ventilatory data with standard criteria by observers who were unaware of patient identity or training status. As previously reported, exercise training increased peak oxygen consumption by 23% from 16.8±3.8 to 20.6±4.7 ml/kg/min and reduced blood lactate levels during submaximal exercise. The training-induced decrease in lactate accumulation was accompanied by a decrease in carbon dioxide production, respiratory exchange ratio, and ventilation during submaximal exercise. The ventilatory anaerobic threshold was delayed from 284±43 to 352±91 seconds of exercise (p=0.02), and it occurred at an increased oxygen consumption (10.1±1.2 vs. 12.1±2.6 ml/kg/min, p=0.01). Exercise duration during the constant workload protocol increased from 938±410 to 1,429±691 seconds (p<0.01). Thus, exercise training improved submaximal and maximal exercise performance in patients with chronic heart failure. The present study provides further evidence of a close physiologic link between the ventilatory and metabolic responses to exercise in patients with chronic heart failure, which is similar to that previously described in normal subjects, and demonstrates that an intervention that causes a significant delay in lactate accumulation during exercise can be accompanied by an appropriate change in the ventilatory anaerobic threshold. (Circulation 1989;79:324–329)

Exercise intolerance is a major component of the symptom complex in patients with chronic heart failure. Recent studies have focused on the importance of early skeletal muscle anaerobic metabolism in limiting exercise in this disorder.1–7 Weber and Janicki4 have demonstrated that the onset of lactate accumulation is an important predictor of submaximal exercise tolerance in chronic heart failure. Although the precise mechanisms responsible for early lactate production in chronic heart failure have not been clearly defined, studies in our laboratory8 and others9–11 have demonstrated that the ventilatory anaerobic threshold (Vt) is a reproducible noninvasive index of the rise in blood lactate during exercise in normal subjects and in patients with chronic heart failure. Studies in

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normal subjects have demonstrated that changes in the Vt after an intervention reflect changes in blood lactate accumulation and are linked to changes in exercise tolerance.12–15 Although a similar response may be assumed to be present in patients with chronic heart failure, studies examining the relation of changes in blood lactate, submaximal exercise tolerance, and the Vt after an intervention have not been published regarding patients with this disorder.

Exercise training is known to delay the Vt and decrease blood lactate levels and ventilation during submaximal exercise in normal subjects.16–18 Our laboratory recently reported that long-term exercise can lead to a training effect in patients with chronic heart failure and severe left ventricular dysfunction.19 We demonstrated that training increased peak VO2 (16.8±3.8 vs. 20.6±4.7 ml/kg/min, p<0.01), peak leg blood flow (2.5±0.7 vs. 3.0±0.8 l/min, p<0.01), and peak central arteriovenous oxygen difference (13.1±1.4 vs. 14.6±2.3 ml/dl, p<0.05). During submaximal exercise, arterial and femoral venous blood lactate levels and leg lactate production were markedly decreased, whereas cardiac output, pulmonary capillary wedge pressure, and leg blood flow were unchanged. These results suggest that long-term exercise significantly delays skeletal muscle anaerobic metabolism during exercise. The present study focuses on the effects of exercise training on the ventilatory and metabolic responses to exercise in this same patient group. Our primary aim was to determine whether or not the decrease in blood lactate induced by long-term exercise was reflected by a change in the Vt. A secondary aim of the study was to determine whether or not changes in the Vt were accompanied by changes in submaximal exercise tolerance in these patients.

Methods

The patient population, exercise training methodology, and procedures for incremental bicycle exercise testing were described in the initial report from this investigation19 and will be summarized. Sixteen patients were initially enrolled in the study; four did not complete exercise training and were excluded from analysis.19 The 12 patients who completed training form the basis of the present study; the hemodynamic and metabolic responses to long-term exercise were reported previously in these patients19 but will be included in the “Discussion” of the present study to provide a better understanding of the factors underlying changes in ventilation and submaximal exercise capacity after training in patients with this disorder.

Study Population

Twelve patients with chronic heart failure due to left ventricular dysfunction (ejection fraction, 24±10%) and peak VO2 16.8±3.8 ml/kg/min completed 16–24 weeks of aerobic exercise conditioning. Subjects were 57±10 years old and were New York Heart Association functional Class I–III (mean patients, 2.4±0.6). Patients did not have pulmonary rales and were clinically stable for at least 3 months before the study. All were limited by dyspnea or fatigue during exercise. Eleven patients were taking digoxin, 12 were taking diuretics, and three were taking stable dosages of captopril for more than 4 months before the study. Four patients occasionally took short-acting nitrates for mild angina. Captopril was discontinued during training in two patients; all other medication dosages were unchanged.

Study Protocol

All studies were performed under a research protocol approved by the Institutional Review Boards of the Duke University and the Durham Veterans Administration Medical Centers, Durham, North Carolina. All subjects underwent a familiarization bicycle exercise test with incremental difficulty 2–14 days before the study. Expired gas analysis was performed during all exercise tests with a commercially available Sensormedics 4400 unit (Anaheim, California) that was calibrated before each study as previously described.19 Exercise testing to a symptom-limited maximum was performed on an isokinetic bicycle. Heart rate was measured by continuous electrocardiographic monitoring, and blood pressure was measured by direct intraarterial recording or by a sphygmomanometer.

Incremental Maximal Protocol

Exercise began at 150 kilopond-meters (kpm)/min and advanced 150 kpm/min in 3-minute intervals. One hour before the incremental exercise test, catheters were inserted for direct measurement of resting and exercise central hemodynamic variables and leg blood flow as previously described in our laboratory.3,19,20 The lactate concentration of arterial and femoral venous blood was determined at rest and at each workload with a Calbiochem-Behring (San Diego, California) rapid lactate kit.

Constant Workload Exercise

Two to 5 days after the maximal incremental exercise test, subjects reported to the laboratory at least 2 hours after eating. Exercise was performed at a constant workload that was 150 kpm/min less than the maximal workload that could be sustained for more than 1 minute during the pretraining incremental protocol. This constant workload was identical for the studies before and after training. Expired gases and heart rate were continuously monitored, and blood pressure was recorded every 3 minutes. Exercise continued until a symptom-limited maximum was reached or until 30 minutes had elapsed.

Exercise Training

Subjects exercised in a supervised cardiac rehabilitation program for 3–5 hr/wk (mean, 4.1±0.6 hours) for 16–24 weeks. The exercise intensity was gradually increased during the first 3 weeks until subjects exercised at a heart rate corresponding to 75% of
peak \( \dot{V}O_2 \). Exercise consisted of stationary bicycle
ergometry, stair climbing, walking, and jogging.

**Determination of the Ventilatory Anaerobic Threshold**

With an on-line computer, the Sensormedics 4400 provides coplotted graphs of ventilatory variables. Previous studies in our laboratory\(^8\) demonstrated that the \( V_t \) could be identified in 16 of 18 subjects with chronic heart failure by examining coplots of the ratio of ventilation (\( V_e \)) to \( \dot{V}O_2 \) (\( V_e/\dot{V}O_2 \)) and the ratio of \( V_e \) to carbon dioxide production (\( V_{\text{CO}_2} \)). As described by Wasserman,\(^12\) the \( V_t \) was identified as the point at which the \( V_e/\dot{V}O_2 \) initially increased during exercise without a concomitant increase in the \( V_e/V_{\text{CO}_2} \), and it was expressed as the corresponding \( \dot{V}O_2 \) (ml/kg/min) in the 30-second time interval in which the \( V_t \) occurred. Paired determinations of the \( V_t \) on separate days in our laboratory in 18 normal subjects and 18 patients with chronic heart failure showed a good correlation \( (r=0.91, p<0.01) \) with a standard error of the estimate of 1.74 ml/kg/min.\(^8\) Coplots of \( V_e/\dot{V}O_2 \) with \( V_e/V_{\text{CO}_2} \) for each patient before and after training were randomly numbered and read by the consensus of two investigators who were unaware of the subject’s identity or training status.

**Statistical Analysis**

Intragroup comparisons were made with Wilcoxon’s signed-rank test to avoid potential errors from nonnormal distribution of data. Submaximal exercise data for each variable during the maximal graded test at 150, 300, and 450 kpm/min and during the constant workload exercise protocol from submaximal time periods where data were available before and after training were combined by an area-under-the-curve technique before paired analysis was performed. Linear regression analysis by the least-squares method was used to determine the relation of changes of submaximal exercise hemodynamic variables with changes in the \( V_t \) after training. To determine training-induced changes in hemodynamic and ventilatory responses at the \( V_t \), individual regression equations were determined for each patient for each variable versus \( \dot{V}O_2 \). The correlation coefficient of each individually derived relation was greater than 0.80. With the derived equations, values for each variable were then calculated at the \( \dot{V}O_2 \) at which the \( V_t \) occurred for each patient before and after training. A \( p \) value less than 0.05 was considered to be statistically significant. Group data for each variable are mean ± SD.

**Results**

**Incremental Exercise Study**

Ventilatory response to exercise. Rest and submaximal exercise \( \dot{V}O_2 \) were unchanged by training. Ventilation, respiratory exchange ratio, and \( V_{\text{CO}_2} \) at rest were also unchanged after training (Figures 1A–1C). However, submaximal exercise values for these variables were all significantly reduced after training. Maximal respiratory exchange ratio (Figure 1B) was unchanged, whereas peak exercise ventilation (Figure 1A) and \( V_{\text{CO}_2} \) (Figure 1C) were increased, reflecting attainment of a higher workload. The \( V_e/V_{\text{CO}_2} \) ratio, an index of ventilatory drive,\(^3\) was unchanged during the incremental study at rest or at peak exercise (Figure 1D). A comparison of the integrated area for all three submaximal workloads revealed that \( V_e/V_{\text{CO}_2} \) was unchanged at submaximal exercise. However, pairwise comparison of \( V_e/V_{\text{CO}_2} \) at 450 kpm/min showed a decrease after training \( (p<0.05) \), whereas this variable was unchanged at the lower workloads. Tidal volume and respiratory rate were unchanged at rest; at maximal exercise, tidal volume increased from 1.61 ± 0.36 to 1.83 ± 0.58 l \( (p<0.05) \), whereas respiratory rate was unchanged. Submaximal exercise respiratory rate and...
tidal volume tended to decrease although neither change reached statistical significance.

Ventilatory anaerobic threshold. The Vt could not be identified in two patients during both exercise studies because the initial rise in Ve/VO2 was accompanied by a rise in the Ve/VCO2 ratio, indicating hypocapnic hyperventilation. The VO2 at which the Vt occurred increased from 10.1 ± 1.2 to 12.1 ± 2.6 ml/kg/min (p = 0.01) (Figure 2) or from 284 ± 43 to 352 ± 91 seconds of exercise (p = 0.02). There was no relation between the change in the Vt and the change in submaximal exercise (300 kpm/min) leg blood flow (r = 0.38, p = 0.21), cardiac output (r = 0.46, p = 0.16), or femoral venous oxygen saturation (r = 0.08, p = 0.69) after training. The change in peak VO2 after training, was not related to the change in the Vt (r = 0.13, p = 0.90). The derived values for hemodynamic and ventilatory variables at the Vt before and after training are shown in Table 1. The absolute blood lactate level at the Vt tended to decrease after training, but the change in lactate from rest to the Vt was not altered because resting lactate decreased slightly after training. The VCO2 and cardiac output at the Vt were unchanged after training, whereas femoral venous oxygen saturation at the Vt tended to decrease from 28 ± 8% to 22 ± 8% (p = 0.06).

Constant Workload Protocol

Submaximal endurance exercise testing was performed before and after training in the last nine patients entered into the study. The constant workload represented 79 ± 11% of the peak VO2 before and 68 ± 10% of the peak VO2 after training. Exercise time increased from 938 ± 410 to 1,429 ± 691 seconds (p < 0.01), and three subjects had exercise stopped at 30 minutes after training. Rest and exercise heart rate was reduced after training (Figure 3A). The VO2 was unchanged at rest and at matched submaximal exercise times (Figure 3B). At peak exercise, the VO2 tended to decrease from 1.16 ± 0.33 to 1.08 ± 0.30 l/min after training (p = 0.06). Respiratory exchange ratio, VCO2, and ventilation were unchanged at rest but were significantly reduced at matched submaximal exercise times (Figures 3C–3E). The Ve/VCO2 ratio was decreased during exercise after training (Figure 3F) at the relatively intense workload used for this exercise protocol, but it was unchanged at rest.

Discussion

This study demonstrates that exercise training can improve submaximal exercise performance in patients with severe left ventricular dysfunction. As has been demonstrated in normal subjects,16–18,21,22 long-term exercise in our patients resulted in a delay in the Vt and a decrease in submaximal exercise VCO2, ventilation, and respiratory exchange ratio. These results, when coupled with the previously reported observations that exercise training decreases blood lactate levels during submaximal
exercise in our patients, support the concept that the ventilatory response to exercise is closely related to exercise metabolism in the presence of chronic heart failure. These data suggest that the physiologic basis for the Vt is similar in patients and in normal subjects: lactate production and buffering during exercise cause the \( V_{\text{CO}_2} \) to increase faster than \( V_{\text{O}_2} \), and because \( V_{\text{E}}/V_{\text{CO}_2} \) is unchanged, \( V_{\text{E}}/V_{\text{O}_2} \) increases.\(^{14,15}\) This is consistent with our previous findings that pulmonary dead space decreases in patients and in normal subjects during exercise (initially decreasing \( V_{\text{E}}/V_{\text{CO}_2} \) and that ventilation is closely related to \( V_{\text{CO}_2} \) in both groups.\(^3\)

Studies in our laboratory,\(^8\) by Weber et al,\(^9\) and by Matsumura et al\(^{11}\) have demonstrated that the ventilatory anaerobic threshold is a reproducible phenomenon in patients with chronic heart failure. It has been suggested that the Vt may serve as a useful index of submaximal exercise tolerance in these patients and may be useful in determining the effects of long-term interventions. The present study demonstrates that a long-term intervention that alters lactate metabolism can alter the Vt in patients with heart failure. However, the changes in the Vt in our patients were associated with marked reductions in submaximal exercise lactate levels (femoral venous lactate decreased from 4.3 ± 1.6 to 2.5 ± 1.6 mM/l at 300 kpm/min, \( p < 0.01 \),\(^9\) indicating that the delayed Vt reflected relatively large changes in exercise metabolism. Although our results support the current physiologic concept of the Vt in chronic heart failure,\(^3,8,11,14,15\) they do not establish the usefulness of serial measurements of the Vt in monitoring the response to pharmacologic interventions in this disorder. Although Weber and Janicki\(^4\) have demonstrated that some interventions that increase exercise cardiac output may decrease blood lactate accumulation during exercise in this disorder, studies by Wilson et al\(^23\) indicate that improvements in central hemodynamic measurements and leg blood flow do not necessarily translate into delayed lactate production. Thus, interventions that improve hemodynamic variables but do not alter lactate metabolism would not be expected to be reflected by a change in the Vt in this disorder.

As has been previously demonstrated in normal subjects,\(^12,13\) the delayed Vt in our patients was accompanied by an improvement in submaximal exercise tolerance, which was indicated by increased exercise duration coupled with decreased exercise respiratory exchange ratio, \( V_{\text{CO}_2} \), ventilation, and heart rate. This finding and the observation that pulmonary capillary wedge pressure was unchanged by training in our patients\(^19\) would support the conclusion of Weber and Janicki\(^4\) that skeletal muscle anaerobic metabolism, and not increased pulmonary capillary wedge pressure, is the major limiting factor during submaximal endurance exercise in stable patients with chronic heart failure. Although the mechanisms underlying this improved endurance exercise capacity are not clearly defined in the present study, normal subjects delay anaerobic metabolism after training through increased free fatty acid utilization and increased oxidative enzyme and mitochondrial content of skeletal muscle.\(^{24,25}\) It is possible that similar changes may have occurred in our patients. Thus, although leg blood flow abnormalities are important in determining the metabolic response to exercise in this disorder,\(^4\) skeletal muscle biochemical and, possibly, vascular factors\(^25\) may also play a role in determining the onset of lactate production in the presence of chronic heart failure.

Controversy exists as to the precise physiologic meaning of the ventilatory anaerobic threshold and whether or not the adjective “anaerobic” should be used to describe this ventilatory phenomenon. Wasserman\(^12,14\) has reviewed several studies demonstrating that hypoxia increases lactate production during exercise and has postulated that the Vt occurs when lactate production accelerates because a critical level of cellular \( \text{PO}_2 \) is reached during exercise. Although oxygen delivery can play an important role in determining lactate production during exercise, Davis\(^13\) has suggested that several other factors may play an important role, including skeletal muscle fiber type and motor unit recruitment patterns, glycogen stores, adrenergic stimulation, and skeletal muscle aerobic enzyme content. Although cellular \( \text{PO}_2 \) was not measured in the present study, our findings that femoral venous oxygen saturation at the Vt tended to be lower after training and that submaximal exercise leg blood flow was unchanged by training suggest that alterations in the Vt may have occurred independent of skeletal muscle oxygen delivery. These findings are consistent with the findings of Connett et al\(^26\) that lactate efflux in working skeletal muscle is not related to intracellular \( \text{PO}_2 \), in a canine model and support the conclusion of Ivy et al\(^24\) that skeletal muscle aerobic enzyme capacity, and not maximal central hemodynamic function, is the primary determinant of the Vt in normal subjects.

Previous investigators have demonstrated a decrease in the ventilatory response to submaximal exercise after training in normal subjects,\(^17,21,22\) Casaburi et al\(^21\) have proposed that this decreased ventilation is related to decreased blood lactate levels. Our findings that training decreased blood lactate levels, \( V_{\text{CO}_2} \), and ventilation in our patients support this conclusion and extend our previous observations that ventilation is closely related to \( V_{\text{CO}_2} \) in this disorder.\(^3\) However, the \( V_{\text{E}}/V_{\text{CO}_2} \) ratio was also decreased during intense submaximal exercise after training in our patients. This was clearly demonstrated during the constant workload protocol that represented 144 ± 58% of the Vt before training and 123 ± 34% of the Vt after training. Normal subjects demonstrate a hypoxic ventilatory response at workloads above the Vt at near maximal exercise,\(^3,12\) which has also been demonstrated in patients with chronic heart failure in our laboratory.\(^3,8\) A likely explanation for
the decreased Ve/VCO₂ after training during the constant workload protocol was that this workload was above this “hyperventilation” threshold before training and tended to be below the “hyperventilation” threshold after training. Thus, two mechanisms may have acted to reduce ventilation during submaximal exercise after training in our subjects: 1) reduced VCO₂ levels and 2) an apparent increased threshold for hypocapnic hyperventilation during intense exercise.

In conclusion, this study demonstrates that exercise training in patients with left ventricular dysfunction increases submaximal, as well as maximal, exercise performance. Training delayed lactate accumulation and decreased VCO₂, ventilation, and respiratory exchange ratio during submaximal exercise. These changes were associated with an increase in the VO₂ at which the Vt occurred without a significant alteration in ventilatory control at this level of exercise, indicating that the Vt is linked to lactate production in patients with chronic heart failure. As has been demonstrated in normal subjects, the delay in the Vt was associated with improved submaximal exercise performance in our patients. This finding, when coupled with the observation that training did not alter submaximal hemodynamic variables, indicates that the metabolic response to exercise may play a primary role in determining day-to-day exercise performance in stable ambulatory patients with chronic heart failure. Our results suggest that the Vt may be useful in observing the response to long-term interventions that have an important effect on the peripheral metabolic response to exercise in patients with chronic heart failure.

References


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