Aerobic Conditioning: An Effective Therapy in McArdle's Disease

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Objective: Susceptibility to exertional cramps and rhabdomyolysis in myophosphorylase deficiency (McArdle's disease [MD]) may lead patients to shun exercise. However, physical inactivity may worsen exercise intolerance by further reducing the limited oxidative capacity caused by blocked glycogenolysis. We investigated whether aerobic conditioning can safely improve exercise capacity in MD.

Methods: Eight MD patients (4 men and 4 women; age range, 33–61 years) pedaled a cycle ergometer for 30 to 40 minutes a day, 4 days a week, for 14 weeks, at an intensity corresponding to 60 to 70% of maximal heart rate. We monitored serum creatine kinase levels; changes in peak cycle work, oxygen uptake, and cardiac output; presence and magnitude of a spontaneous and glucose-induced second wind; and citrate synthase and β-hydroxyacyl coenzyme A dehydrogenase enzyme activities in quadriceps muscle.

Results: The prescribed exercise program increased average work capacity (36%), oxygen uptake (14%), cardiac output (15%), and citrate synthase and β-hydroxyacyl coenzyme A dehydrogenase enzyme levels (80 and 62%, respectively) without causing pain or cramping or increasing serum creatine kinase. A spontaneous and glucose-induced second wind was present and was of similar magnitude in each patient before and after training.

Interpretation: Moderate aerobic exercise is an effective means of improving exercise capacity in MD by increasing circulatory delivery and mitochondrial metabolism of bloodborne fuels.

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Blocked glycogen breakdown in myophosphorylase deficiency (McArdle's disease [MD]) results in severe limitations in both anaerobic (glycogen metabolized to lactic acid; adenosine triphosphate produced via substrate-level phosphorylation) and aerobic (glycogen metabolized to carbon dioxide and water; adenosine triphosphate produced via oxidative phosphorylation) metabolism.[1] The result is a complex pattern of exercise intolerance, in which moderate exercise taxes oxidative capacity, causing fatigue, tachycardia, and breathlessness, whereas more strenuous activities, which normally would engage anaerobic glycogenolysis, may trigger muscle cramps (contractures), rhabdomyolysis, and myoglobinuria. Because of the severe and potentially dangerous consequences of physical exertion in MD, affected patients often choose or are advised by caregivers to avoid exercise and adopt a sedentary lifestyle. Habitual physical inactivity promotes deconditioning and a decline in circulatory capacity, which could limit the delivery of bloodborne fuels, primarily glucose and free fatty acids, on which muscle oxidative metabolism critically depends when glycogen breakdown is blocked.[2] Deconditioning also reduces levels of muscle mitochondria and of mitochondrial enzymes that are necessary for metabolizing these fuels.[3] Thus, habitual physical inactivity in MD may compound the energy limitation caused by mutations in the myophosphorylase gene by restricting access to and the capacity to metabolize alternative fuels. In effect, habitual avoidance of physical activity to avoid muscle injury may promote a vicious downward spiral of exercise tolerance in which deconditioning diminishes aerobic capacity, and thus lowers the threshold of physical activity necessary to provoke muscle cramping and injury.

These considerations suggest that regular exercise could benefit MD patients by augmenting circulatory capacity, increasing mitochondrial enzyme levels, or both. Accordingly, we evaluated the effect of a program of regular aerobic exercise on exercise and oxidative capacity, and we assessed the effect of training on circulatory and muscle metabolic capacity. In addition, we evaluated the effect of exercise training on the presence

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and magnitude of the spontaneous second wind, which is the characteristic increase in oxidative and exercise capacity that occurs after 8 to 10 minutes of sustained exercise in MD patients that is attributable to increased oxidation of blood glucose or blood glucose and free fatty acids.[2,4] We also assessed the effect of training on the ability of intravenous glucose administered after the spontaneous second wind to further increase muscle oxidative capacity.[2]

Patients and Methods

Patients

Eight unrelated MD patients participated in the study: 4 men aged 33, 38, 42, and 52 years and 4 women aged 33, 42, 45, and 61 years. The diagnosis in each patient was established by biochemical analysis demonstrating complete myophosphorylase deficiency, and each had a flat lactate response to ischemic forearm exercise. None of the patients performed regular exercise training before participating in the study, though the four men engaged in occasional strenuous activity in the course of work or hobbies. The 38-year-old man in particular was active in rock climbing and had participated in recreational dancing.

The research protocol was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center at Dallas and Presbyterian Hospital of Dallas.

Exercise Training

Training consisted of exercise performed on a stationary cycle 4 times a week for 14 weeks. During each training session, patients cycled for 30 to 40 minutes (30 minutes per session for the first 7 weeks, 40 minutes per session for the last 7 weeks) at an exercise intensity eliciting a heart rate corresponding to 60 to 70% of maximum as determined by prior exercise testing. Patients were instructed to exercise within a 20-beat/min heart rate range, which varied from 95 to 115 beats/min for the oldest subject to 110 to 130 beats/min for the younger subjects. Aerobic exercise capacity in MD patients is particularly low in the first 5 to 8 minutes of exercise. However, after 8 to 10 minutes of exercise, patients develop a distinctive second wind attributable to a marked increase in muscle oxidative capacity that is associated with a proportional fall in exercise heart rate.[2,5,6] Accordingly, we instructed patients to increase the exercise intensity as needed to maintain the prescribed heart rate after achieving a second wind. Heart rate was displayed and recorded during each exercise session utilizing a Polar NV chest band and watch (Polar Electro, Finland). Heart rate records were downloaded using a Polar/PC computer interface to monitor each exercise session. Initial training sessions were conducted in the exercise physiology laboratory. The five patients who lived within the greater Dallas metropolitan area performed one exercise session per week in the Neuromuscular Center of the Institute for Exercise and Environmental Medicine of Presbyterian Hospital, Dallas. At the time of these tests, heart rate data from the prior week's training session were collected. In the three patients who lived elsewhere, heart rate monitors were shipped by overnight mail at biweekly intervals to ensure compliance with the exercise-training regimen.

Pretraining and Posttraining Evaluation

CREATINE KINASE MONITORING. Serum creatine kinase (CK) levels were assessed at one or more clinic visits before training was begun and weekly during training in the first six patients. To provide a more discriminating evaluation of the effect of individual training sessions, we assessed CK before and 24 hours after some of the weekly training sessions in five of these patients.

PHYSIOLOGY. Before and after training, patients underwent exercise testing after an overnight fast to determine the effect of training on peak work, oxidative capacity, and cardiac output; to determine the presence and magnitude of a spontaneous second wind; and to determine the ability of intravenous glucose administered after the spontaneous second wind to further increase work and oxidative capacity. A previously described protocol was used.[2] In brief, patients cycled continuously for approximately 40 minutes with peak work capacity determined before the onset of a spontaneous second wind (at 6–8 minutes of exercise), after the onset of a spontaneous second wind (at 20–25 minutes of exercise), and after an intravenous infusion of glucose sufficient to increase blood glucose approximately 3-fold (at 35–40 minutes of exercise).[2] Heart rate was monitored continuously during testing. Gas exchange and cardiac output were measured at rest and during peak exercise within the initial 6 to 8 minutes of exercise (initial), after patients achieved a spontaneous second wind, and after glucose infusion following the spontaneous second wind. Ventilation (V_E) was measured utilizing Douglas bags (Warren E. Collins, Inc.) and a Tissot spirometer (Warren E. Collins). Fractions of O_2, CO_2, and N_2 in expired air were determined with a mass spectrometer (Marquette 1100, Marquette Medical Systems); and oxygen uptake (VO_2), carbon dioxide production (VCO_2), ventilatory equivalent for oxygen (V_E/VO_2), and respiratory exchange ratio (VCO_2/VO_2) were calculated. Cardiac output was measured utilizing acetylene rebreathing in which the rate of disappearance of C_2H_2 from a rebreathing bag is proportional to pulmonary blood flow and cardiac output (Q).[7,8] Systemic arteriovenous O_2 difference was calculated from the Fick equation: VO_2 = cardiac output × systemic arteriovenous O_2 difference. The relation between peak oxygen utilization and peak cardiac output was determined as the ratio VO_2/Q and by linear regression analysis of VO_2/Q among subjects.

ASSAYS. Blood was obtained from a forearm vein during peak exercise to coincide with gas exchange and cardiac output determinations during the initial 6 to 8 minutes of exercise, after patients achieved a spontaneous second wind, and after glucose infusion after the spontaneous second wind. Whole-blood samples were assayed for lactate and glucose utilizing a commercially available analyzer (Yellow Springs Instruments, Youngston, OH).

In each patient, needle muscle biopsy of the vastus lateralis muscle was performed before training and of the opposite vastus lateralis muscle after training for determination of muscle enzymes representative of mitochondrial volume (citrate synthase) and of β oxidation (β-hydroxyacyl coenzyme A dehydrogenase) by spectrophotometric assays with enzy-

matic activity expressed per unit of muscle dry weight, as described previously.[9]

Statistics

The significance of differences between preexercise and postexercise results was assessed utilizing a paired t test; $p \leq 0.05$ was considered significant.

Results

Creatine Kinase Levels during Training

All patients completed the training program without symptoms of muscle pain or cramping related to the prescribed exercise, and none experienced episodes of pigmenturia during the 14 weeks of training. Serum CK levels varied substantially before and during training among patients. In general, blood CK levels were similar before and 24 hours after individual training rides (Fig 1), indicating that exercise within the prescribed guidelines did not provoke muscle injury. In one patient, postexercise training samples were higher in the first 2 weeks of training. Evaluation of heart rate records indicated that this patient's heart rate had increased to 157 beats/min (prescribed heart rate range, 110–130 beats/min) in the first 10 minutes of one of the preceding training sessions. In another patient, an increase in CK from 771IU before a training ride in week 8 to 10,580IU the following day was likely attributable to muscle injury sustained while working on his car.

Work, Heart Rate, and Oxygen Consumption in Exercise

The change in work capacity and corresponding heart rate response during prolonged exercise before and after 14 weeks of conditioning exercise in a 42-year-old woman is shown in Figure 2. Before exercise training, exercise capacity in this patient was remarkably low. A workload of only 10 watts caused fatigue and a heart rate of 162 beats/min in the first 5 to 6 minutes of exercise. By minute 15, she had developed a spontaneous second wind and was able to exercise briefly at 20 watts at a heart rate of 167 beats/min. After intravenous glucose, she was able to achieve a further increase in peak work rate to 30 watts at a heart rate of 162 beats/min (see Fig 2). After 14 weeks of exercise training, her exercise and oxidative capacity increased dramatically so she was able to cycle at 30 watts in the first 6 to 7 minutes of exercise, at 40 watts after a spontaneous second wind, and at 50 watts after glucose.

Each patient had an exercise response similar to the patient shown in Figure 2 in which peak work capacity was lowest in the first 5 to 6 minutes of exercise, increased with the onset of a spontaneous second wind, and increased further after glucose infusion. In each patient, work capacity under each condition of exercise was higher after 14 weeks of training (Fig 3). Training increased peak work capacity as measured in the first 5 to 8 minutes by approximately 50% ($p < 0.002$). Work capacity after the spontaneous second wind was

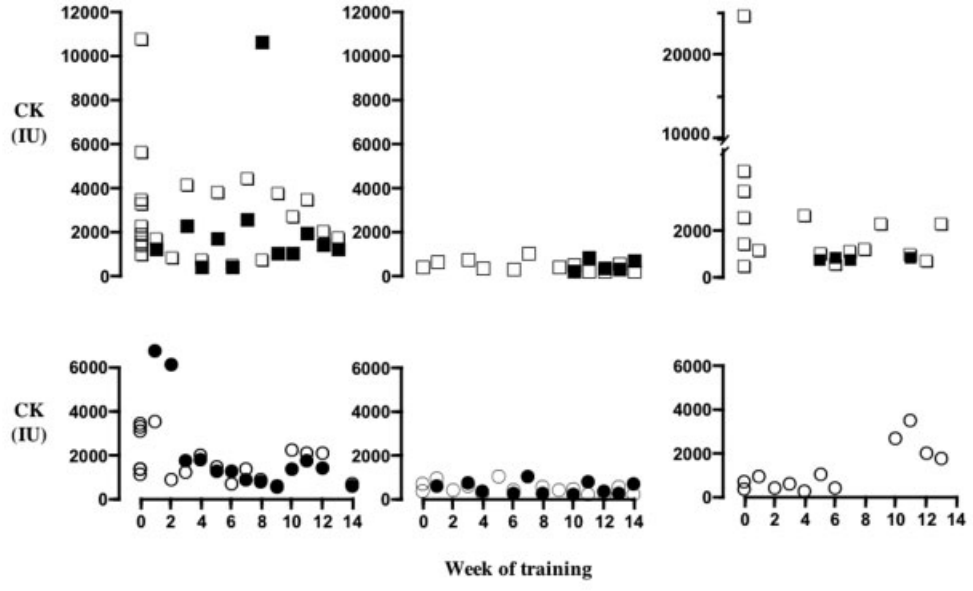

Fig 1. Serum creatine kinase (CK) levels before (week 0) and at weekly intervals during exercise training in six patients (three men, squares; *three women,* circles*). In three patients, multiple pretraining CK values determined in clinic visits over a period of 4 to 18 months were available. In five patients, serum CK was determined before (*open squares *and* open circles*) and 24 hours after (*solid squares *and* solid circles*) some training sessions.*

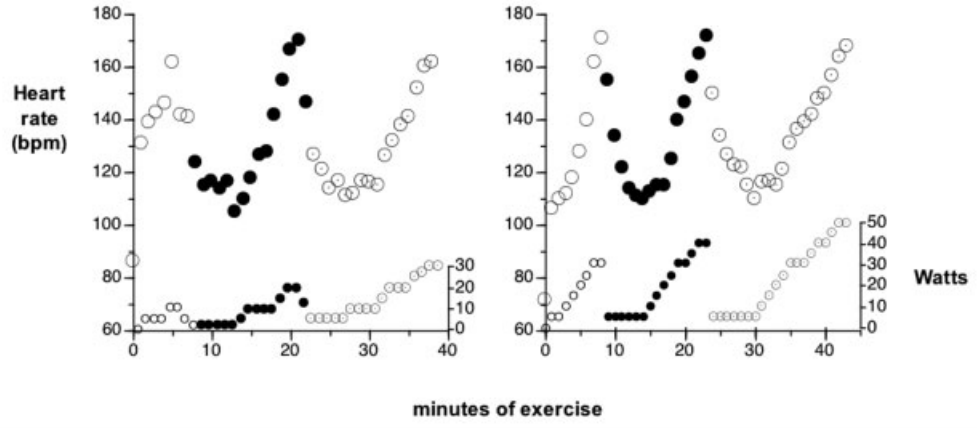

Fig 2. Heart rate (large symbols) *and workload (measured in watts;* smaller symbols*) in a 42-year-old woman (homozygous for the common R49X mutation) before (left) and after (right) 14 weeks of exercise training.* Open circles *correspond to workload and heart rate in the first 8 minutes of exercise before the onset of a spontaneous second wind;* solid circles *correspond to workload and heart rates during and after the onset of a spontaneous second wind (minutes 9–22 of exercise);* circles with centered dot *(minutes 23–39 of exercise) correspond to workload and heart rate during glucose infusion to achieve a glucose-induced second second wind.*

increased more than 30% by training ($p < 0.002$), and peak work capacity after glucose was more than 25% higher after training ($p < 0.001$). Improved work capacity under each exercise condition after training was associated with increased oxidative capacity (see Fig 3).

Cardiac Output and Oxygen Utilization

Training increased peak cardiac output approximately 15% (mean peak Q for all patients before training = 13.8 ± 1.2L/min; posttraining = 15.8 ± 1.2L/min). There were minor, insignificant differences in peak cardiac output as assessed in the first 6 to 8 minutes of exercise, after a spontaneous second wind, and after glucose before and after training (Fig 4); but under each condition of exercise, peak cardiac output was significantly higher after training. In contrast with the significant increase in cardiac output, peak systemic arteriovenous O_2 difference was unchanged by training. Before and after training, peak arteriovenous O_2 difference was lowest in the first 6 to 8 minutes of exercise and substantially higher after the onset of a spontaneous second wind and after glucose infusion (see Fig 4). Peak VO_2 and cardiac output as determined in the first

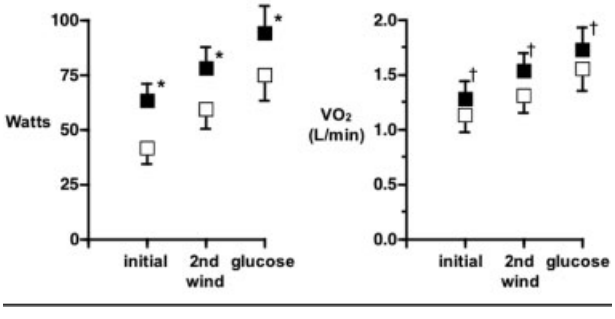

Fig 3. Mean ± standard error for peak work levels (left) and peak oxygen uptake (right) during prolonged exercise for eight patients with McArdle's disease before (open squares) *and after* (solid squares) *14 weeks of cycle exercise training. On the x-axis, "initial" corresponds to peak exercise capacity as determined in the first 6 to 8 minutes of exercise, before the onset of a spontaneous second wind; "2nd wind" corresponds to peak exercise capacity determined at 20 to 25 minutes of exercise, after the onset of a spontaneous second wind; and "glucose" refers to peak capacity determined at 35 to 40 minutes of exercise and approximately 2 minutes after the infusion of glucose sufficient to increase blood glucose about 3-fold preinfusion levels. Symbols denote statistically significant differences between pretraining and posttraining values: *p < 0.01; †p < 0.02.*

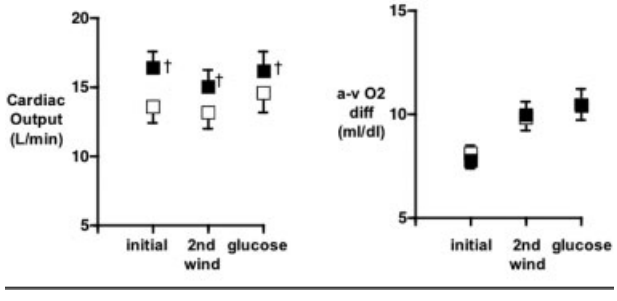

Fig 4. Mean ± standard error for peak cardiac output (left) and peak systemic arteriovenous O_2 (a-v O_2) difference (right) during prolonged exercise for the McArdle's disease patients before (open squares) *and after* (solid squares) *14 weeks of cycle exercise training. Cardiac output and systemic arteriovenous O_2 differences were measured during peak exercise during the initial 6 to 8 minutes of exercise before the spontaneous second wind (initial), after patients achieved a spontaneous second wind (2nd wind), and after glucose infusion after the spontaneous second wind (glucose). Symbols denote statistically significant differences between pretraining and posttraining values: †p < 0.02.*

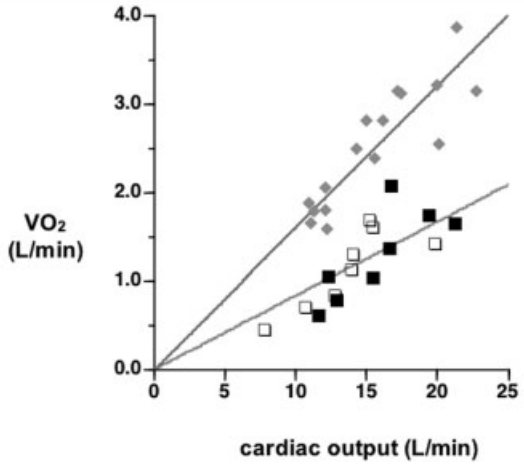

*Fig 5. Relation between peak oxygen uptake and peak cardiac output as assessed in the first 6 to 8 minutes of exercise in healthy subjects (*diamonds*; healthy subject data from previously published results[30,31]) and in McArdle's disease patients before* (open squares) *and after* (solid squares) *14 weeks of exercise training.*

6 to 8 minutes of exercise were related linearly in healthy subjects and in patients (Fig 5). In patients, the slope VO_2/Q was similar before (0.084; $R^2 = 0.69$) and after (0.083; $R^2 = 0.62$) training. The VO_2/Q slope for healthy subjects under comparable conditions is approximately twofold greater (slope = 0.160; $R^2 = 0.77$), indicating higher levels of O_2 utilization for a given level of cardiac output when glycogen availability does not limit muscle oxidative phosphorylation.

Glucose Availability and Utilization

Glucose and lactate levels were similar before and after training, consistent with similar levels of glucose availability and utilization (Table). The level of ventilation relative to O_2 utilization (VE/VO_2) and respiratory exchange ratio also were similar under each condition of exercise before and after training, consistent with similar patterns of ventilation and similar proportions of fat and carbohydrate contributions to muscle metabolism.

Muscle Enzyme Levels

Aerobic training resulted in a marked increase in mitochondrial enzyme levels. Citrate synthase levels increased from 20 ± 2 to 36 ± 5μmol/min ṡ gm^{-1} dry weight ($p < 0.005$), and β-hydroxyacyl coenzyme A dehydrogenase levels increased from 19 ± 3 to 31 ± 4μmol/min ṡ gm^{-1} dry weight ($p < 0.01$).

Discussion

The major new findings of our study are that moderate aerobic exercise is well tolerated and, when performed regularly, leads to adaptations that substantially increase oxidative and work capacity in patients with MD disease. These results support the view that regular exercise is an effective therapy for this disorder. A corollary conclusion is that habitual physical inactivity increases the severity of exercise limitations in MD by further diminishing the limited oxidative capacity that results when glycogen metabolism is blocked.

MD (glycogen storage disease type V) is the most common inborn error of muscle carbohydrate metabolism and one of the most common causes of recurrent myoglobinuria.[10] Although understanding of pathophysiology and genetics of the disease has progressed substantially since the original description of MD,[11,12] identification of effective therapy has remained elusive.[13] Studies of a high-protein diet or of creatine supplements have yielded meager evidence of improved muscle energy availability that have not translated into consistent clinical benefits[14–16]; attempted treatment with branched-chain amino acids, high-dose creatine, pyridoxine, and D-ribose have been proved ineffective[17–20]; despite encouraging in vitro results, gene replacement therapy in human myophosphorylase deficiency is not currently a therapeutic option[21]; and short-term treatment with intravenous gentamicin to attempt to read through the common R49X stop codon mutation has been ineffective.[22] Although most dietary interventions have been ineffective, recent results indicate that a sucrose-containing meal consumed 40 minutes before exercise substantially improves exercise capacity by increasing levels of blood glucose, on which muscle metabolism critically depends when glycogen is unavailable.[23] However, the applicability of this treatment is limited by a restricted time frame of benefit and by the potential for weight gain. Our results suggest that exercise training has the capability to provide a robust improvement in exercise capacity regardless of diet, and that this enhanced exercise capacity complements the energetic benefit of increased fuel availability.

A major concern about advising patients to exercise is their susceptibility to exertional muscle contractures, rhabdomyolysis and myoglobinuria. Although the precise conditions of exercise necessary to provoke muscle cramping and necrosis are incompletely defined, activities that normally would engage anaerobic glycogenolysis typically are involved. Thus, ischemic, isometric, and maximal effort dynamic exercises are the usual triggers for muscle injury. In contrast, clinical experience suggests, and our study confirms, that submaximal exercise fueled by oxidative metabolism is well tolerated and does not promote muscle injury. Heart rate closely parallels exercise intensity expressed as a percentage of maximal oxidative capacity; therefore, the use of a heart rate monitor during exercise provides a valuable tool for patients to identify and maintain lev-

Table. Metabolites and Ventilation During Exercise

Metabolites/ventilation	Initial	Second Wind	Glucose
Lactate, mmol/L			
Pretraining	0.60 ± 0.07	0.70 ± 0.08	1.18 ± 0.12
Posttraining	0.63 ± 0.07	0.71 ± 0.06	1.18 ± 0.08
Glucose, mg%			
Pretraining	76.2 ± 2.8	69.6 ± 2.7	262 ± 32.5
Posttraining	77.0 ± 2.4	76.1 ± 3.8	271 ± 39.5
Respiratory exchange ratio (VCO_2/O_2)			
Pretraining	0.872 ± 0.035	0.892 ± 0.028	0.915 ± 0.030
Posttraining	0.878 ± 0.039	0.864 ± 0.021	0.899 ± 0.012
Ventilatory equivalent for oxygen (V_E/VO_2)			
Pretraining	45.6 ± 5.8	43.6 ± 5.9	41.1 ± 3.1
Posttraining	44.9 ± 5.4	41.5 ± 2.8	40.1 ± 2.6

els of aerobic exercise that are submaximal (≤70% of maximal) and safe.

The logic for exercise training in MD is to increase the range of oxidative capacity and raise the threshold at which dynamic exercise risks muscle injury. Complicating this effort is that muscle phosphorylase deficiency restricts oxidative metabolism by limiting oxidative substrate availability. Muscle glycogen is required for peak rates of muscle oxidative phosphorylation.[24–26] Without glycogen, the capacity for aerobic exercise is both greatly reduced and varies with the availability of blood glucose and free fatty acids. The combination of blocked glycogenolysis and low FFA and glucose availability severely limits cellular levels of oxidative substrate in the first 5 to 10 minutes of exercise in MD.[2] Accordingly, peak oxygen utilization and the level of oxygen extraction from blood (systemic arteriovenous O_2 difference) are most limited (see Figs 3 and 4), and the mismatch between oxygen delivery and oxygen utilization, as indicated by low O_2 utilization relative to cardiac output (see Fig 5), is most marked in that time period. Consequently, in the first minutes of exercise, walking at a modest pace may cause fatigue and tachycardia, and walking faster or up an incline may tax oxidative capacity and trigger muscle injury. Our study indicates that exercise training substantially increases work and oxidative capacities in the first 5 to 10 minutes of exercise, and thus may increase the level of exercise that can be undertaken without promoting muscle fatigue or injury. After training, oxidative metabolism remained limited by substrate availability since work and oxidative capacity increased progressively with a spontaneous second wind and after glucose infusion. The relative magnitude of improvement in work and oxidative capacity with the spontaneous second wind and glucose-induced second wind was similar before and after training, but the absolute level of work and oxygen utilization achieved under each condition was consistently higher after training. These results indicate that regular exercise is capable of expanding the range of exercise that MD patients can sustain under a variety of exercise and dietary conditions that modify fuel availability.

Training adaptations underlying this improved exercise capacity include an increase in peak exercise cardiac output of 2L/min, which likely increases the capacity to deliver bloodborne fuels to working muscle. Training also increased the activity of the mitochondrial enzymes, citrate synthase and hydroxyacyl coenzyme A dehydrogenase, by 60 to 80%, consistent with an enhanced capacity to oxidize available fuels. The relative contribution of enhanced systemic blood flow versus higher mitochondrial enzyme activity to improved exercise capacity cannot be stated with certainty. Despite these training adaptations, fuel availability continued to limit oxygen utilization, as indicated by the observation that peak oxygen utilization and peak arteriovenous O_2 difference increased to a similar extent with spontaneous and glucose-induced second winds before and after training.

Clinical evidence supports the view that the severity of exercise intolerance and susceptibility to exertional pain and cramping vary considerably among MD patients. All mutations in the myophosphorylase gene currently described cause a similar complete loss of enzymatic activity; thus, no genotype has yet been identified to explain more severe phenotypes. Our study indicates that the level of aerobic fitness of patients is an important determinant of the severity of exercise limitations in MD. Interestingly, Martinuzzi and coworkers[27] found a correlation between severity of exercise intolerance as assessed by clinical histories and the frequency of an insertion/deletion polymorphism of angiotensin-converting enzyme (ACE). Compared with the ACE deletion, the ACE insertion polymorphism has been suggested to correlate with enhanced responses to aerobic training in healthy individuals and was found to be the predominant ACE form in patients with less severe symptoms of exercise intolerance.[27] Based on patient questionnaires that surveyed

clinical symptoms and daily energy expenditure, Ollivier and coworkers[28] suggested that patients who were more physically active experienced a lesser severity of muscle pain in the preceding 3 months, though no correlation was found between habitual activity levels and episodes of muscle cramps or pigmenturia. Preliminary results from these investigators also indicate improved tolerance of submaximal exercise after 8 weeks of training.[29] Our study strongly supports the conclusion that regular aerobic exercise improves and that habitual inactivity worsens exercise tolerance by increasing and decreasing, respectively, muscle oxidative capacity, and thus the level of exercise necessary to trigger muscle symptoms. We conclude that regular exercise should be a consistent component of therapy for MD patients.

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