

# Spontaneous “Second Wind” and Glucose-Induced Second “Second Wind” in McArdle Disease

## Oxidative Mechanisms

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**Background:** Blocked glycogen breakdown in McArdle disease impairs oxidative as well as anaerobic metabolism, but the contribution of impaired oxidative phosphorylation to everyday symptoms of McArdle disease remains poorly defined.

**Objective:** To evaluate the oxidative implications of the spontaneous second wind and variables that influence the development of this typical feature of McArdle disease.

**Design:** Assessment of exercise and oxidative capacity ( $\dot{V}O_2$ ) before and after the spontaneous “second wind” and with a glucose infusion after a spontaneous second wind.

**Patients:** Eight patients with complete myophosphorylase deficiency and 1 unique patient with 3% of normal myophosphorylase activity.

**Main Outcome Measures:** Work capacity,  $\dot{V}O_2$ , heart rate, cardiac output.

**Results:** All patients with complete myophosphorylase deficiency (1) had low peak  $\dot{V}O_2$  (mean  $\pm$  SD,  $13.0 \pm 2.0$  mL  $\cdot$  kg $^{-1}$   $\cdot$  min $^{-1}$ ) in the first 6 to 8 minutes of exercise; (2)

achieved a spontaneous second wind with increased exercise capacity between 8 and 12 minutes of exercise due to a more than 25% increase in peak  $\dot{V}O_2$  ( $16.5 \pm 3.1$  mL  $\cdot$  kg $^{-1}$   $\cdot$  min $^{-1}$ ); and (3) with glucose infusion after a spontaneous second wind, experienced a further more than 20% increase in oxidative capacity ( $\dot{V}O_2$ ,  $19.9 \pm 3.9$  mL  $\cdot$  kg $^{-1}$   $\cdot$  min $^{-1}$ ). In the patient with residual myophosphorylase,  $\dot{V}O_2$  ( $22.2$  mL  $\cdot$  kg $^{-1}$   $\cdot$  min $^{-1}$ ) in the first 6 to 8 minutes of exercise was approximately 2-fold higher than the mean of patients lacking myophosphorylase, and no significant improvement in exercise and oxidative capacity accompanied prolonged exercise or glucose infusion.

**Conclusions:** First, the spontaneous second wind and the glucose-induced second second wind in McArdle disease are due to substrate-dependent increases in muscle oxidative capacity. Second, by providing glycogen-derived pyruvate, a small amount of residual myophosphorylase activity normalizes the oxidative deficit of complete myophosphorylase deficiency and virtually eliminates the spontaneous second wind and glucose-induced second second wind.

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**A**BSENCE OF the muscle form of glycogen phosphorylase (myophosphorylase deficiency or McArdle disease) blocks the breakdown of intramuscular glycogen. The major energetic consequence traditionally has been considered to be an absence of anaerobic glycogenolysis (glycogen metabolized to lactic acid), and the clinical observation that ischemic exercise produces muscle contractures and rhabdomyolysis confirms the role of impaired anaerobic production of adenosine triphosphate (substrate-level phosphorylation) in the generation of these typical symptoms of McArdle disease. Blocked glycogen breakdown also has been shown to impair muscle aerobic metabolism (glycogen metabolized to carbon dioxide and water).<sup>1-3</sup>

However, the clinical correlates of impaired oxidative metabolism are not well defined.

A typical feature of McArdle disease that is likely attributable to glycogen-limited oxidative metabolism is the “second wind” phenomenon. As first described by Pearson and coworkers,<sup>4</sup> the second wind denotes a sudden, marked improvement in exercise capacity in which exercise that previously produced muscle fatigue, tachycardia, and often breathlessness becomes easily tolerated.<sup>4-7</sup> Pearson et al identified 2 varieties of second wind—one that could be induced by the infusion of carbohydrate or lipid fuels and one that occurred spontaneously.<sup>4</sup> Evidence has now accumulated that the second wind that can be induced in the laboratory by infusing various fuels is due to an in-

crease in muscle capacity for oxidative phosphorylation.<sup>1,2,8</sup> However, no studies have directly addressed the oxidative implications of the more clinically relevant spontaneous second wind or variables that might influence the occurrence of this classic clinical feature of McArdle disease.

We investigated the hypothesis that the spontaneous second wind is a direct consequence of restricted oxidative fuel availability when glycogenolysis is blocked, and represents a transition from low to a higher capacity for oxidative phosphorylation as the availability of extramuscular fuels increases. Furthermore, we investigated whether oxidative metabolism remains limited by fuel availability after the development of a spontaneous second wind by assessing the effect of a glucose infusion on oxidative capacity. Finally, we examined whether residual muscle phosphorylase activity would augment muscle oxidative capacity and, by reducing muscle dependence on blood-borne fuels, blunt or eliminate the spontaneous second wind.

## SUBJECTS AND METHODS

### SUBJECTS

We studied 9 patients: 2 brothers, aged 39 and 42 years, and 7 additional, unrelated patients, 3 men aged 50, 37, and 27 years and 4 women aged 42, 40, 33, and 29 years. Eight of the patients had complete myophosphorylase deficiency. One patient (a 37-year-old man) had 3% of control values for biochemically determined myophosphorylase activity. This patient is unique among more than 40 patients with McArdle disease whom we have personally examined both with respect to the residual enzyme activity and in that venous effluent lactate in this patient approximately doubled after ischemic forearm exercise. This is in contrast to the complete absence of lactate production in typical patients with McArdle disease, including the 8 patients in this report, and to a 4- to 5-fold lactate increase in control subjects.<sup>9</sup> This patient experienced premature fatigue and sometimes cramps with intense exercise such as weightlifting and rope climbing, and had experienced an episode of myoglobinuria and renal failure triggered by weightlifting to "get in shape," but tolerated moderate exercise such as walking at a brisk pace without fatigue. Screening for the 2 most common myophosphorylase gene mutations (R49X and G204S) in 8 of our patients showed that the 2 brothers and the 42-year-old woman were homozygous and 3 additional patients were heterozygous for the R49X mutation.<sup>10</sup> Two were heterozygous for the G204S mutation, including the patient with residual myophosphorylase activity. The mutations in the remaining alleles were not identified. One patient was unavailable for genetic testing.

The research protocol was approved by the institutional review board of The University of Texas Southwestern Medical Center at Dallas. Each subject's consent was obtained according to the Declaration of Helsinki.

### EXERCISE

Patients were tested after an overnight fast. Intravenous catheters were placed for blood sampling and, in the opposite arm, for infusion of glucose. Subjects cycled continuously (CPE 2000; Medical Graphics Corp, St Paul, Minn) for about 40 minutes. Initial work capacity was determined in the first 6 to 8 minutes of exercise. Then the workload was reduced for 5 to 10

minutes, similar to the strategy patients use to facilitate achieving a spontaneous second wind.<sup>11</sup> The workload was again progressively increased to determine peak work capacity at approximately minute 25 of exercise. Immediately thereafter, 50 mL of 50% glucose was infused during a period of 1 to 2 minutes, followed by a continuous, 6-mL/min infusion of 10% glucose for the duration of exercise. The exercise workload was maintained or transiently reduced and then increased to assess peak work capacity at approximately 40 minutes of exercise. Because of substantial differences in the exercise responses of the patient with residual myophosphorylase activity compared with typical patients with McArdle disease, 3 separate exercise tests were performed during a span of 24 months in this patient. Since there were only minor and inconsistent differences between these tests, results for this patient are presented as the mean of the 3 tests.

### PHYSIOLOGICAL MONITORING

Heart rate was monitored continuously with a 12-lead electrocardiogram. Gas exchange and cardiac output were measured at rest and during peak exercise within the initial 6 to 8 minutes of exercise, after patients achieved a spontaneous second wind, and after glucose infusion following the spontaneous second wind. Ventilation was measured by means of ventilation bags (Douglas bags; Warren E. Collins Inc, Baintree, Mass) and a spirometer (Tissot; Warren E. Collins Inc); fractions of oxygen, carbon dioxide, and nitrogen in expired air were determined with a mass spectrometer (Marquette 1100; GE Marquette, Milwaukee, Wis); and oxygen uptake ( $\dot{V}O_2$ ), carbon dioxide production, ventilatory equivalent for oxygen (ventilation divided by  $\dot{V}O_2$ ), and respiratory exchange ratio (carbon dioxide production divided by  $\dot{V}O_2$ ) were calculated. Cardiac output was measured with acetylene rebreathing in which the rate of disappearance of acetylene from a rebreathing bag is proportional to pulmonary blood flow and cardiac output ( $\dot{Q}$ ).<sup>12</sup> Systemic arteriovenous (AV) oxygen difference was calculated from the Fick equation:  $\dot{V}O_2 = \text{cardiac output} \times \text{systemic AV oxygen difference}$ . The increase in cardiac output ( $\Delta\dot{Q}$ ) relative to the increase in  $\dot{V}O_2$  ( $\Delta\dot{V}O_2$ ) from rest to exercise was determined as the ratio  $\Delta\dot{Q}/\Delta\dot{V}O_2$ .

### ASSAYS

Blood was obtained from a forearm vein at rest and during peak exercise under initial, spontaneous second wind, and glucose infusion conditions. Whole-blood samples were assayed for lactate and glucose by means of a commercially available analyzer (YSI Incorporated, Yellow Springs, Ohio) and for free fatty acids by means of a commercially available kit (Wako Chemicals GmbH, Neuss, Germany).

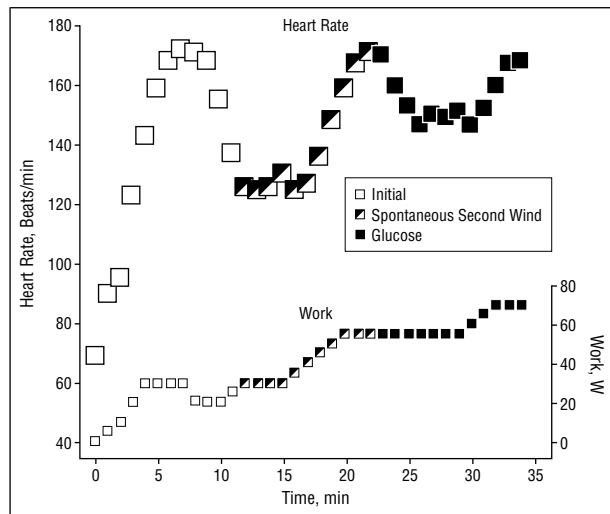
### STATISTICS

The statistical significance of differences among resting, fasting, second wind, and glucose conditions was evaluated by means of a Newman-Keuls multiple comparisons test or a paired *t* test. Differences were considered significant when  $P \leq .05$ . Data are reported as mean  $\pm$  SD, unless otherwise indicated.

## RESULTS

### WORK CAPACITY DURING CONTINUOUS EXERCISE

A typical exercise response in a patient with complete myophosphorylase deficiency is indicated in **Figure 1**.



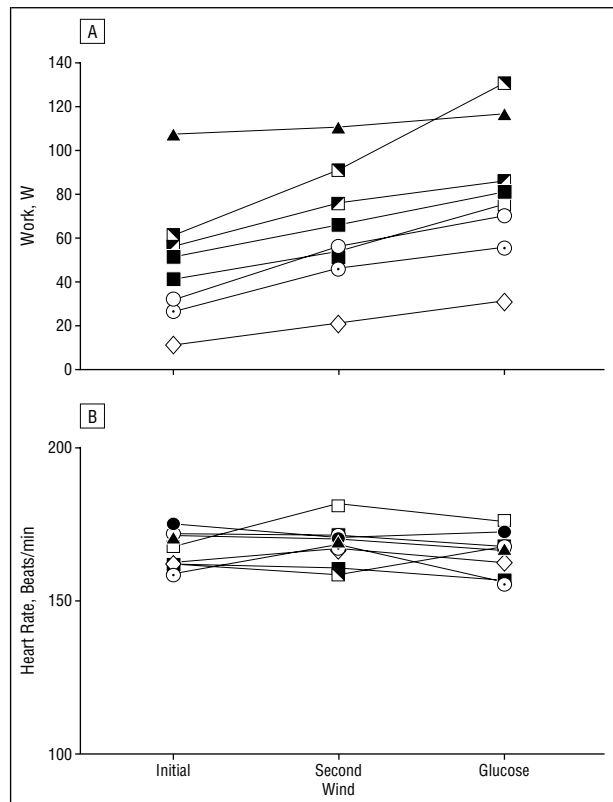
**Figure 1.** Heart rate during continuous cycle exercise in a 29-year-old woman with complete myophosphorylase deficiency under conditions corresponding to initial, spontaneous second wind, and glucose conditions, as described in the text.

Peak work at 7 minutes of exercise was 30 W with a heart rate of 172 beats/min. As the workload was reduced, between minutes 8 and 10, the patient experienced the onset of a second wind marked by decreasing exercise effort and a falling heart rate. By minute 12, the 30-W workload that had caused fatigue and tachycardia was easily tolerated, and the heart rate had fallen to 126 beats/min. The heart rate was stable while the workload remained at 30 W for the next 5 minutes; then the workload was able to be increased to 55 W, corresponding to a heart rate of 171 beats/min, in minute 22 of exercise. Then, 50 mL of 50% dextrose was infused while the workload remained at 55 W. Shortly after the glucose bolus, the patient experienced a second second wind associated with decreased effort and a fall in heart rate to 147 beats/min during approximately 3 minutes. The heart rate was stable for the next 5 minutes. Then the workload again was able to be increased to a new peak of 70 W, corresponding to a heart rate of 168 beats/min at minute 34 of exercise.

All 8 patients with complete myophosphorylase deficiency had a similar response (**Figure 2**). Peak work rose from  $39 \pm 17$  W at  $7 \pm 1$  minutes of exercise to  $57 \pm 21$  W ( $P < .001$ ) after achieving a second wind. After glucose infusion, work capacity further increased to  $74 \pm 28$  W ( $P = .002$ ). The patient with residual myophosphorylase cycled at 100 W in the first 7 minutes of exercise, a level 2.5-fold higher than the mean of patients with complete myophosphorylase deficiency and, in contrast to all of the other patients, did not demonstrate substantial improvement in exercise capacity as exercise was prolonged or after glucose infusion (Figure 2 and **Figure 3**).

#### OXYGEN UTILIZATION AND DELIVERY IN EXERCISE

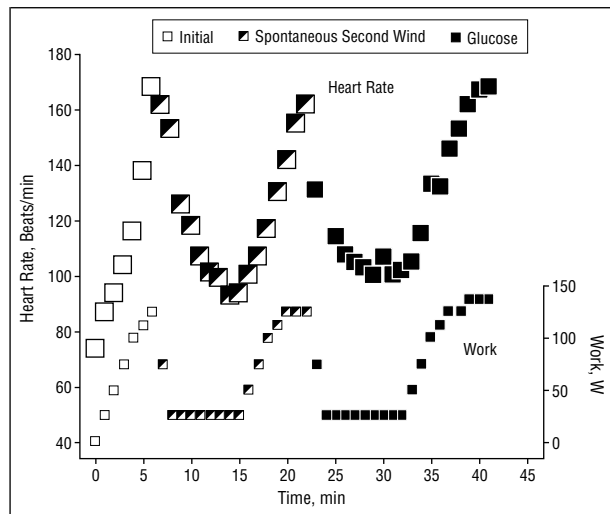
Increased work capacity with the spontaneous second wind and the glucose-induced second wind was attributable to progressive increases in peak rates of muscle



**Figure 2.** Peak workload (A) and corresponding peak heart rates (B) determined at 3 points during continuous cycle exercise: "initial" denotes peak work capacity determined at  $7 \pm 1$  minutes of exercise, mean  $\pm$  SD (before the onset of the second wind); "second wind" corresponds to peak work capacity determined after the onset of a spontaneous second wind, at  $23 \pm 2$  minutes of exercise; and "glucose" denotes peak exercise determined after glucose infusion, at  $39 \pm 3$  minutes of exercise. Symbols correspond to individual patients; squares represent men, and circles and diamond represent women with typical McArdle disease with no residual myophosphorylase activity. The triangles represent results from the patient with partial myophosphorylase deficiency. Note the substantially higher work capacity in this patient compared with the other patients with McArdle disease in the first 6 to 8 minutes of exercise.

oxidative phosphorylation. Initial peak  $\dot{V}O_2$  in typical patients with McArdle disease was  $1.02 \pm 0.33$  L/min ( $13.0 \pm 2.0$  mL  $\cdot$  kg $^{-1}$   $\cdot$  min $^{-1}$ ). With the spontaneous second wind, oxidative capacity increased more than 25%, with peak  $\dot{V}O_2$  rising to  $1.28 \pm 0.39$  L/min ( $16.5 \pm 3.1$  mL  $\cdot$  kg $^{-1}$   $\cdot$  min $^{-1}$ ;  $P < .001$ ), and with the glucose-induced second wind,  $\dot{V}O_2$  rose more than 20% further to  $1.55 \pm 0.50$  L/min ( $19.9 \pm 3.9$  mL  $\cdot$  kg $^{-1}$   $\cdot$  min $^{-1}$ ;  $P < .001$ ) (**Figure 4**). Peak cardiac output was similar during each exercise condition (Figure 4). In contrast, peak systemic AV oxygen difference rose progressively, from  $6.8 \pm 1.0$  mL/dL at  $7 \pm 1$  minutes of exercise, to  $8.6 \pm 1.7$  mL/dL ( $P < .001$ ) after a spontaneous second wind, and to  $9.8 \pm 1.5$  mL/dL ( $P < .001$ ) after a glucose-induced second wind (Figure 4) consistent with enhanced oxidative phosphorylation attributable to improved substrate availability.

In the patient with residual myophosphorylase, peak  $\dot{V}O_2$  in the first 6 to 8 minutes of exercise was 2.22 L/min ( $22.3$  mL  $\cdot$  kg $^{-1}$   $\cdot$  min $^{-1}$ ), almost 2 times the mean level of patients with complete myophosphorylase deficiency (Figure 4). The difference in initial oxidative capacity between this patient and those with complete myophos-



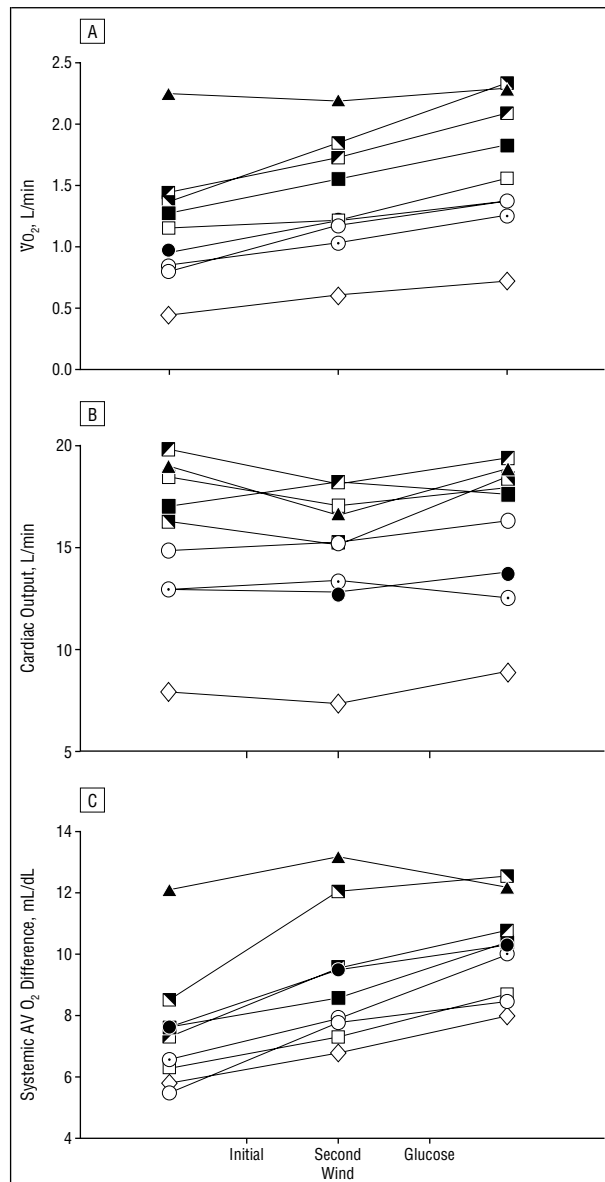
**Figure 3.** Heart rate during continuous cycle exercise in a 37-year-old man with partial myophosphorylase deficiency under conditions that corresponded to fasting, spontaneous second wind, and glucose conditions in patients with complete myophosphorylase deficiency. Note the absence of a change in work capacity with prolonged exercise and glucose, in contrast to the results for a typical patient with McArdle disease in Figure 1.

phorylase deficiency is evident in comparing the relationship between oxygen uptake and cardiac output (**Figure 5**). In patients with complete myophosphorylase deficiency, there is a significant linear relationship ( $R^2=0.82$ ) between oxygen uptake and cardiac output. However, the level of increase in oxygen utilization relative to oxygen delivery by the circulation is low compared with that of the patient with residual myophosphorylase activity whose  $\dot{V}O_2$ - $\dot{Q}$  relationship is similar to that of healthy subjects (Figure 5). This difference is attributable to an almost 2-fold higher level of muscle extraction of available oxygen (peak systemic AV oxygen difference, 12.0 mL/dL) compared with patients with complete enzyme deficiency (peak AV oxygen difference,  $6.8 \pm 1.0$  mL/dL) and is consistent with enhanced availability of substrate for oxidative phosphorylation attributable to residual glycogenolysis.

In contrast to all individuals with complete enzyme deficiency, neither sustained exercise nor glucose infusion substantially affected peak  $\dot{V}O_2$  or AV oxygen difference in this patient (Figure 4).

#### HEART RATE, VENTILATION, AND CARDIAC OUTPUT RESPONSES TO EXERCISE

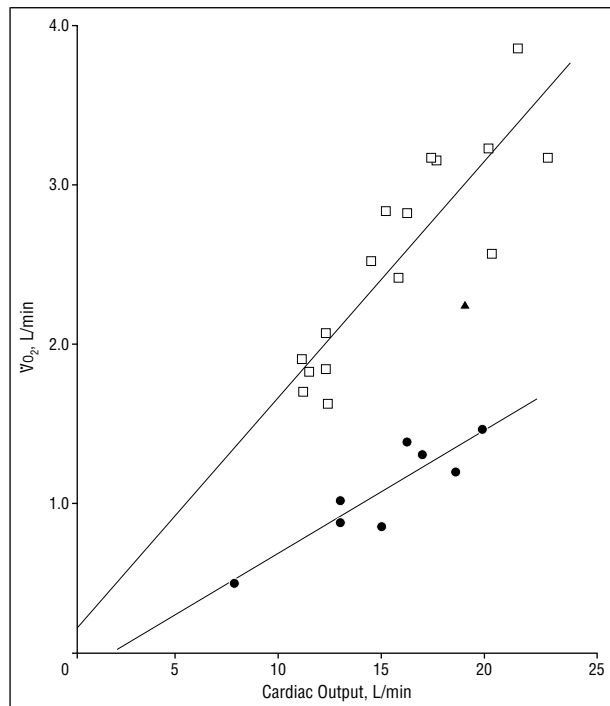
In patients with complete myophosphorylase deficiency, heart rate at the workload that was maximal in the first 6 to 8 minutes of exercise was  $36 \pm 8$  beats/min lower after the spontaneous second wind, and heart rate at the workload that was maximal after the spontaneous second wind was  $25 \pm 5$  beats/min lower after the glucose-induced second wind. Correspondingly, the ventilatory equivalent for oxygen fell from  $49 \pm 14$  to  $34 \pm 12$  ( $P < .001$ ) after the spontaneous second wind but did not change after the glucose-induced second wind. In the first minutes of exercise,  $\dot{Q}$  was high relative to oxygen uptake ( $\Delta\dot{Q}/\Delta\dot{V}O_2$ ,  $12.2 \pm 1.9$ ), indicating that the level of oxygen delivery by the circulation in relation to oxygen up-



**Figure 4.** Oxygen uptake ( $\dot{V}O_2$ ) (A) and the physiological components of oxygen uptake, cardiac output (B) and systemic arteriovenous (AV) oxygen difference (C) corresponding to the time and conditions of exercise as indicated in Figure 2. Symbols are the same as in Figure 2. Note the far higher oxidative capacity and peak AV oxygen difference in the first 6 to 8 minutes of exercise in the patient with residual enzyme activity. In contrast, peak cardiac output is similar in all subjects.

take by working muscle was more than twice the normal value of approximately 5 (ie, 5 L of increase in cardiac output per 1 L of increase in  $\dot{V}O_2$ ).<sup>15</sup> The  $\Delta\dot{Q}/\Delta\dot{V}O_2$  fell to  $9.1 \pm 1.5$  ( $P < .001$ ) after the spontaneous second wind and to  $7.9 \pm 1.0$  ( $P = .03$ ) during peak exercise after the glucose-induced second wind (**Figure 6**).

In contrast to each patient with complete myophosphorylase deficiency, prolonged exercise and glucose did not substantially influence the relationship between heart rate, ventilation, and workload in the patient with residual enzyme activity (Figure 3 and **Table**). The initial  $\Delta\dot{Q}/\Delta\dot{V}O_2$  in this patient was virtually normal ( $6.2$ ) and did not change with prolonged exercise or glucose (Figure 6).

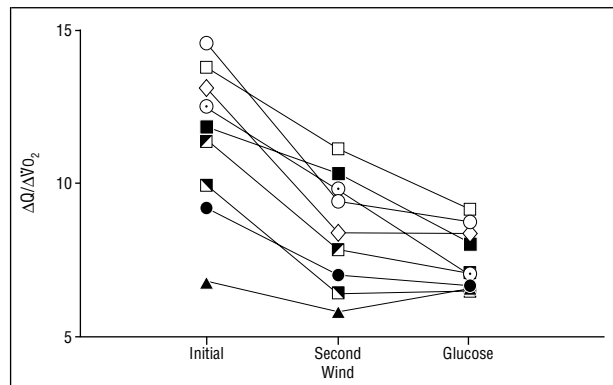


**Figure 5.** Relationship between peak cardiac output and peak oxygen uptake ( $\dot{V}O_2$ ) in the first 6 to 8 minutes of cycle exercise in 8 patients with McArdle disease associated with a complete absence of myophosphorylase (open squares), the patient with residual myophosphorylase (closed triangle), and healthy subjects (closed circles; healthy subject data from previously published results<sup>13,14</sup>). Regression analysis of data from both healthy control subjects and patients with McArdle disease showed a significant linear correlation for  $\dot{V}O_2$ –cardiac output (healthy subjects,  $R^2=0.77$ ; patients with McArdle disease,  $R^2=0.82$ ), but the slope of increase in  $\dot{V}O_2$  relative to cardiac output in healthy subjects (0.15) is approximately 2-fold higher than in patients with McArdle disease (0.08). The  $\dot{V}O_2$  relative to cardiac output relationship in the patient with McArdle disease with residual enzyme activity is similar to that of healthy subjects and much higher than in typical patients with McArdle disease.

## FUEL AVAILABILITY AND UTILIZATION

In patients with complete myophosphorylase deficiency, free fatty acid levels were lowest during peak exercise at  $7 \pm 1$  minutes of exercise and were similar during peak exercise after a spontaneous second wind and after glucose infusion. Lactate levels fell from rest and were lowest at  $7 \pm 1$  minutes of exercise ( $P < .05$ ). The spontaneous second wind was associated with a small but consistent increase in lactate levels from  $5.1 \pm 1.4$  mg/dL ( $0.57 \pm 0.16$  mmol/L) to  $6.1 \pm 1.2$  mg/dL ( $0.67 \pm 0.13$  mmol/L) ( $P = .003$ ), implying increased availability of blood glucose–derived pyruvate. The glucose-induced second wind was associated with a further increase in lactate level to  $10.9 \pm 2.6$  mg/dL ( $1.21 \pm 0.29$  mmol/L) ( $P < .001$ ), consistent with a further increase in glucose-derived pyruvate. Fuel mix as indicated by the respiratory exchange ratio was similar during peak exercise under each condition (Table). After the spontaneous second wind, exercise at the workload that was maximal at 7 to 8 minutes of exercise resulted in a fall in the respiratory exchange ratio from  $0.98 \pm 0.09$  to  $0.80 \pm 0.05$ .

In the patient with residual myophosphorylase activity, high oxidative capacity in the first 6 to 8 minutes of exercise was associated with an increase in blood lac-



**Figure 6.** Increase in cardiac output ( $\Delta\dot{Q}$ ) relative to the increase in oxygen uptake ( $\Delta\dot{V}O_2$ ) from rest to peak exercise at the 3 times and conditions of exercise indicated in Figure 2. Symbols are the same as in Figure 2.

tate levels, in contrast to every patient with complete phosphorylase deficiency (**Figure 7**). Increased carbohydrate oxidation in this patient was indicated by the fact that the respiratory exchange ratio was substantially higher than in patients with complete myophosphorylase deficiency (Table). Blood levels of glucose and free fatty acids at rest and during exercise were similar to those of other patients with McArdle disease (Table).

## COMMENT

The major findings of our study are as follows: (1) The spontaneous second wind phenomenon in McArdle disease is attributable to a limitation in muscle oxidative phosphorylation that is most severe in the first 6 to 8 minutes of exercise and to a substantial increase in muscle oxidative capacity that occurs as exercise is prolonged. (2) A glucose-induced second second wind exists that is due to a further increase in the peak rate of muscle oxidative phosphorylation. (3) The oxidative deficit that accompanies complete myophosphorylase deficiency is largely normalized in a patient with a small amount of residual enzyme activity. (4) This normalization of oxidative capacity in the first minutes of exercise virtually abolishes the spontaneous second wind and glucose-induced second wind responses.

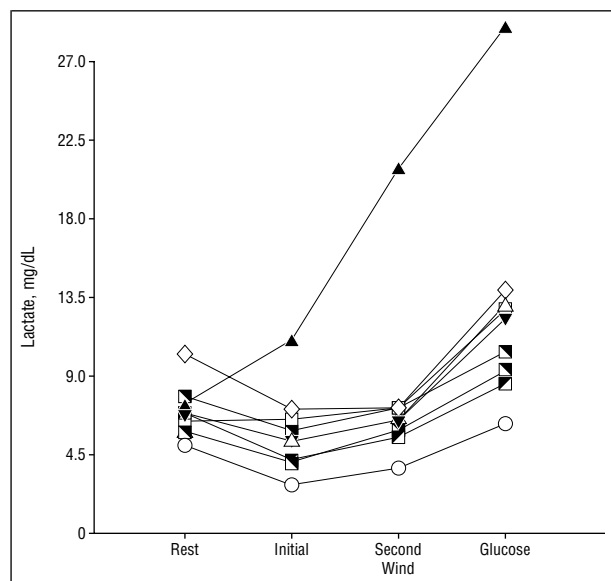
Since its initial description by Pearson and colleagues,<sup>4</sup> the spontaneous second wind has been recognized to be a typical clinical feature of McArdle disease<sup>11</sup> that is characterized by low exercise capacity in the first minutes of sustained exercise followed by an abrupt improvement in exercise tolerance so that exercise that produced fatigue and tachycardia only moments before can be sustained virtually indefinitely.<sup>6,7</sup> This phenomenon has generally been interpreted to be a consequence of impaired anaerobic glycolysis and to represent a transition from impaired anaerobic to normal oxidative metabolism.<sup>4,7</sup> However, our results indicate that the spontaneous second wind relates specifically to the fact that blocked glycogenolysis eliminates a fuel that is critical for normal oxidative metabolism and makes muscle oxidative capacity dependent on and fluctuate with changing availability of extramuscular fuels. In patients with typical McArdle disease with a complete absence of muscle phosphorylase, a nadir of fuel availability and oxi-

### Fuel Availability and Metabolism at Rest and During Peak Exercise\*

Myophosphorylase	Measurement†	Rest	Exercise		
			Initial	Second Wind	Glucose
8 Patients with McArdle disease with complete myophosphorylase deficiency	Glucose, mg/dL	73.9 ± 5.4	73.9 ± 3.6	66.7 ± 7.2	245.0 ± 27.0
	Free fatty acids, mmol/L	0.70 ± .09	0.49 ± 0.12	0.73 ± 0.14	0.72 ± 0.30
	Lactate, mg/dL	6.9 ± 1.6	5.1 ± 1.4	6.0 ± 1.2	10.9 ± 2.6
	RER	...	0.98 ± 0.09	0.93 ± 0.08	0.91 ± 0.08
	$\dot{V}_E/\dot{V}O_2$	...	49.0 ± 14.5	45.0 ± 15.5	39.1 ± 12.0
Patient with 3% residual myophosphorylase	Glucose, mg/dL	72.1	73.9	64.9	196.4
	Free fatty acids, mmol/L	0.44	0.22	0.45	0.47
	Lactate, mg/dL	7.4	11.0	20.9	29.0
	RER	...	1.10	1.08	1.09
	$\dot{V}_E/\dot{V}O_2$	...	39.1	36.2	35.6

\*RER indicates respiratory exchange ratio;  $\dot{V}_E/\dot{V}O_2$ , ventilatory equivalent for oxygen; and ellipses, not applicable.

†To convert glucose to millimoles per liter, multiply by 0.0555. To convert lactate to millimoles per liter, multiply by 0.1110.



**Figure 7.** Venous lactate levels at rest and during peak exercise at the times and conditions indicated in Figure 2. Symbols are the same as in Figure 2.

ductive capacity occurs in the first 6 to 8 minutes of sustained exercise. Our patients developed fatigue and tachycardia at low levels of exercise because of a peak oxygen utilization of only  $13.0 \pm 2.0 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ —a level that is similar to that in patients with mitochondrial myopathies.<sup>16,17</sup> This illustrates the critical role of glycogen as an oxidative fuel in the transition from rest to exercise. Healthy subjects achieve maximal rates of oxygen utilization within 3 to 5 minutes of sustained exercise by increasing systemic AV oxygen difference (ie, the extraction of available oxygen from blood) 3-fold from resting levels of 4 to 5 mL/dL to about 15 mL/dL in concert with maximally increasing systemic oxygen transport (cardiac output).<sup>18,19</sup> In our patients, although peak cardiac output was achieved by  $7 \pm 1$  minutes of exercise, peak AV oxygen difference was only 6.8 mL/dL, ie, approximately half that of healthy subjects, consistent with a severely restricted capacity of muscle to extract available oxygen from blood because of substrate-limited oxidative phosphorylation.

Between minutes 8 and 15 of sustained cycle exercise, each patient with complete myophosphorylase deficiency developed a spontaneous second wind with an increase in exercise capacity and a fall in exercise heart rate.<sup>4,5,7</sup> A level of exercise that initially produced fatigue and a heart rate of  $166 \pm 6$  beats/min became easily tolerated and produced a heart rate of  $130 \pm 12$  beats/min after the second wind. Increased work capacity and the fall in heart rate were due to an approximately 25% increase in peak oxygen utilization. Exercise heart rate is directly proportional to relative exercise intensity expressed as a percentage of maximal oxidative capacity.<sup>19</sup> Thus, heart rate is maximal at maximal oxidative capacity, 75% of maximal at 75% of maximal oxidative capacity, and so on. Accordingly, an increase in muscle oxidative capacity results in a proportional fall in exercise heart rate. The 36-beat/min drop in heart rate in our patients after the onset of the spontaneous second wind corresponds closely to that predicted from the measured increase in oxidative capacity. Improved oxidative capacity with a fall in exercise heart rate at a given absolute exercise workload occurs in healthy subjects after prolonged exercise conditioning. However, the predominant physiological mechanism is a higher cardiac stroke volume and a higher peak level of cardiac output.<sup>18</sup> In the second wind phenomenon, peak cardiac output is unchanged, whereas muscle capacity for extracting available oxygen increases, consistent with an increased level of fuel availability and oxidation.

Although the onset of a spontaneous second wind has been interpreted to signify a transition to normal muscle metabolism and normal exercise capacity,<sup>7</sup> our results demonstrate that exercise and oxidative capacity remain limited by fuel availability. This is evident in the fact that glucose administration resulted in an additional second wind attributable to a more than 20% increase in peak oxygen uptake above the level achieved after a spontaneous second wind. Exercise that caused fatigue and tachycardia after a spontaneous second wind was more easily tolerated at a heart rate  $25 \pm 6$  beats/min lower after glucose.

Our results indicate that the fundamental oxidative limitation in complete myophosphorylase defi-

ciency is absence of glycogen-derived pyruvate to support oxidative phosphorylation and that the spontaneous and glucose-induced second winds represent improved oxidative capacity that results from increased availability of extramuscular fuels. The fuel crisis is maximal in the transition from rest to exercise because of the combination of absent glycogenolysis and low availability of free fatty acids and of glucose-derived pyruvate,<sup>20</sup> as indicated by low blood levels of free fatty acids and of lactate in the first minutes of exercise (Table and Figure 7). Increased oxidative capacity in a spontaneous second wind has been correlated with increased availability and oxidation of free fatty acids,<sup>5,6</sup> and our results confirm higher free fatty acid levels with the onset of a second wind (Table). However, we believe that enhanced utilization of blood glucose may also be critical. This conclusion is supported by previous observations by our group that glucose uptake during exercise is substantially higher in patients with McArdle disease than in control subjects.<sup>21</sup> In addition, this study provides the novel observation that blood lactate level increases with the onset of the second wind (Figure 6), implying that increased availability of glucose-derived pyruvate is an important contributor to the spontaneous second wind. The further increase in muscle oxidative capacity after glucose administration correlates with increased cellular availability of glucose-derived pyruvate as indicated by a further increase in blood lactate levels (Figure 7). The fact that the respiratory exchange ratio remains low after glucose administration suggests that the metabolic benefit may involve pyruvate-mediated expansion of the tricarboxylic acid cycle via anaplerosis with resultant enhanced oxidation of noncarbohydrate fuels.<sup>22</sup>

Despite the increased oxidative rate achieved with a glucose-induced second wind, peak  $\dot{V}O_2$  and systemic AV oxygen difference remained low compared with those of healthy subjects, indicating that blood-borne fuels cannot fully substitute for glycogen in oxidative metabolism. This accords with the observation that complete glycogen depletion in healthy humans causes fatigue and a dramatic 40% to 50% decrease in maximal aerobic capacity.<sup>20,23,24</sup> The unique role of glycogen in muscle oxidative metabolism is underscored by our findings in an unusual patient with a small amount of residual myophosphorylase activity.

Peak work and oxygen uptake and the level of oxygen utilization relative to oxygen delivery by the circulation within the first 6 to 8 minutes of exercise in this patient were far higher than in patients with McArdle disease with complete myophosphorylase deficiency (Figures 4 and 5). This difference in oxidative capacity from patients with complete myophosphorylase deficiency was accounted for by the fact that systemic AV oxygen difference (12.0 mL/dL) was almost double that of other patients with McArdle disease during the first minutes of exercise ( $6.8 \pm 1.0$  mL/dL) and was approximately 25% greater than the mean of typical patients with McArdle disease under conditions of a glucose-induced second wind ( $9.8 \pm 1.5$  mL/dL), consistent with enhanced availability of substrate for oxidative phosphorylation. We suggest that this enhanced substrate availability is a consequence of the small level of preserved glycogenolysis in

this patient. Consistent with this interpretation is the finding of an increase in blood lactate levels in the first 7 to 8 minutes of exercise in this patient in contrast to all patients with complete myophosphorylase deficiency (Figure 7). Furthermore, increased oxidative capacity was associated with an increased level of carbohydrate oxidation as indicated by a higher respiratory exchange ratio in this patient compared with those with complete myophosphorylase deficiency (Table), indicating increased availability of carbohydrate for oxidation. Blood glucose and free fatty acid levels were similar to those of patients with typical McArdle disease, and differences in the turnover and transport of these fuels are unlikely to account for this difference in substrate availability. That so small a residual capacity for glycogenolysis is able to meet oxidative fuel requirements may seem surprising but is consistent with the observation that muscle oxidative capacity in healthy humans is maintained until glycogen depletion is complete.<sup>23,25</sup> The fact that residual glycogenolysis in McArdle disease at once enhanced oxidative rate and virtually abolished the second wind phenomenon confirms the conclusion that the spontaneous second wind and the glucose-induced second wind are the direct result of glycogen-limited oxidative metabolism.

These results provide a framework for differentiating symptoms related to impaired aerobic from deficient anaerobic glycogenolysis in McArdle disease. They indicate that fatigue and tachycardia with moderate exercise and fluctuations in exercise capacity and in cardiopulmonary responses that are characteristic of the second wind phenomenon are consequences of substrate-limited oxidative phosphorylation. They confirm that glycogen-derived pyruvate is required both to fuel maximal rates of muscle oxidative phosphorylation and to buffer oxidative metabolism during fluctuations in the availability of extramuscular fuels, especially in the transition from rest to exercise.<sup>26</sup> They also suggest that premature muscle fatigue, cramping, and rhabdomyolysis with intense exercise are attributable to limited substrate-level phosphorylation when glycogenolysis is either blocked or severely limited. Furthermore, since anaerobic energy demands increase when oxidative capacity is low, the combined deficit in aerobic and anaerobic glycogenolysis results in a vicious cycle of impaired energy availability to account for the spectrum of exercise intolerance in McArdle disease.

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