

No spontaneous second wind in muscle phosphofructokinase deficiency

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Abstract—Objective: The spontaneous second wind in myophosphorylase deficiency (MD, McArdle's disease) represents a transition from low to a higher exercise capacity attributable to increased oxidation of blood-borne fuels, principally glucose and free fatty acids. Muscle phosphofructokinase deficiency (PFKD) blocks the metabolism of muscle glycogen and blood glucose. The authors inquired whether the additional restriction in glucose metabolism in PFKD prevents a spontaneous second wind. **Methods:** The authors compared the ability of 29 patients with MD and 5 patients with muscle PFKD to achieve a spontaneous second wind during continuous cycle exercise after an overnight fast. Patients cycled at a constant workload for 15 to 20 minutes (3 MD patients, 3 PFKD patients) and at variable workloads in which peak exercise capacity was determined at 6 to 8 minutes of exercise and again at 25 to 30 minutes of exercise (29 MD patients, 4 PFKD patients). Heart rate was monitored continuously, and perceived exertion (Borg scale) was recorded during each minute of exercise. Oxygen utilization and blood levels of lactate and ammonia were determined at rest and during peak workloads. **Results:** All variables in both patient groups were similar at 6 to 8 minutes of exercise. Thereafter exercise responses diverged. Each MD patient developed a second wind with a decrease in heart rate and perceived exertion and an increase in work and oxidative capacity. In contrast, no PFKD patient developed a spontaneous second wind. **Conclusions:** Patients with muscle phosphofructokinase deficiency are unable to achieve a spontaneous second wind under conditions that consistently produce one in patients with McArdle's disease. The authors conclude that the ability to metabolize blood glucose is critical to the development of a typical spontaneous second wind.

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Muscle phosphofructokinase deficiency (PFKD, Tarui's disease) prevents the metabolism of muscle glycogen and blood glucose, whereas the isolated block in the breakdown of glycogen in myophosphorylase deficiency (MD, McArdle's disease) preserves the ability to use blood glucose. Despite this fundamental difference in availability of substrates to fuel muscle contraction, many clinical features of PFKD and MD are similar, including exercise-induced premature muscle fatigue, cramps (contractures), and rhabdomyolysis.¹ Another similarity is restricted oxidative metabolism that results in a low capacity for dynamic exercise, so that even modest exertion such as walking on level ground at a moderate pace may cause fatigue, tachycardia, and breathlessness.^{2,3} Our previous studies indicate that this oxidative limitation relates primarily to the inability to generate glycogen-derived pyruvate necessary for substrate flux through the tricarboxylic acid cycle to support a normal rate of electron transport and oxidative phosphorylation.^{4–7} As a result, PFKD patients and MD patients depend on extramuscular substrates to fuel muscle oxidative metabolism and experience marked fluctuations in exercise capacity attributable to changing availability of these blood-borne fuels.

The primary example of this effect is the sponta-

neous second wind in patients with MD. As originally described,⁸ activity that produces muscle fatigue during the first minutes of exercise in MD patients often becomes easily tolerated as exercise is sustained or resumed after a brief rest.^{9,10} Although the spontaneous second wind is now recognized to be a classic feature of MD, the incidence of this phenomenon remains unsettled and, based primarily on patient histories, has been estimated to occur in only approximately 50% of MD patients.⁹ Patients with PFKD also have been reported to achieve a second wind;^{11,12} however, the incidence of a second wind has been considered to be less frequent than in patients with MD, and some investigators have argued that a second wind is not a feature of PFKD.¹³

We have shown that the metabolic basis of the spontaneous second wind in MD is an exercise-related increase in the peak capacity for muscle oxidative phosphorylation that correlates with increased availability of blood-borne fuels.¹⁰ Although some investigators have suggested the improved exercise capacity in MD with a spontaneous second wind relates primarily to increased availability of free fatty acids,^{14,15} our studies suggest that increased mobilization and utilization of blood glucose are critical to the metabolic adaptation that en-

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ables the rate of muscle oxidative phosphorylation to increase.^{10,16} This view predicts that the inability to use blood glucose in PFKD may impair or eliminate the ability of affected patients to achieve a spontaneous second wind. We evaluated this hypothesis by assessing the ability of patients with PFKD compared with a large number of patients with MD to develop a spontaneous second wind during sustained exercise.

Methods. *Subjects.* We studied 5 unrelated patients with muscle PFKD: 4 men aged 23, 29, 34, and 55 years, and 1 woman aged 53 years. The responses of these patients were compared with those of 29 patients with MD (16 men and 13 women) of similar age (mean, 37 years; range, 12 to 61 years). All patients had typical complete deficiency of myophosphorylase or of muscle phosphofructokinase activity as determined biochemically and had a complete absence of lactate production during forearm exercise. Patients were selected for inclusion in the study based solely on the diagnosis of PFKD or MD without regard to whether patients reported having experienced a second wind. Approximately half of the MD patients were aware of sometimes experiencing a substantial improvement in exercise capacity after the initial minutes of physical activity. None consistently achieved a second wind, however, and several had noted a decrease in frequency in this phenomenon with aging. All of the PFKD patients reported fluctuations in exercise capacity but without a clear relationship to preceding exercise.

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

Exercise. Patients were tested after an overnight fast. An IV catheter was placed in a forearm vein for blood sampling. Subjects cycled continuously (Medgraphics 2000, Medical Graphics Corporation, St. Paul, MN) for 15 to 30 minutes using one or both of two exercise paradigms that have been used to demonstrate the spontaneous second wind in patients with MD.^{9,10} In the first protocol, patients cycled at a constant workload for approximately 15 minutes.⁹ In the second protocol, the work level was varied during continuous exercise to assess work and oxidative capacity before and after the onset of a spontaneous second wind.¹⁰ In this protocol, peak work capacity was determined during the first 6 to 8 minutes of exercise (initial peak). Then the workload was reduced for approximately 10 minutes to facilitate attainment of a spontaneous second wind. The workload was then increased to the level that corresponded to the initial peak exercise capacity to assess the effect of sustained exercise on heart rate and perceived exertion. For patients who experienced a second wind, the workload was again increased to determine peak exercise capacity at approximately 25 minutes of exercise (second wind peak).

Perceived exertion. Each patient's relative perceived exertion (RPE) was obtained using the Borg scale, in which patients choose a number between 6 (no effort) and 20 (maximal effort) to estimate their level of exertion.¹⁷

Physiologic monitoring. Protocol 1. Heart rate was monitored continuously with a 12-lead EKG. Gas exchange was determined at rest and at 5-minute intervals during constant workload exercise. RPE was determined at 1-minute intervals.

Protocol 2. Heart rate was monitored continuously. Gas exchange was determined at rest and during peak exercise within the first 6 to 8 minutes of exercise (initial peak) and at the same workload after exercise had been sustained for 15 to 20 minutes. For patients who experienced an improvement in work capacity, a new peak work capacity was determined for minutes 25 to 30 of exercise (second wind peak). Ventilation (V_E) was measured using Douglas bags and a Tissot spirometer. Fractions of O_2 , CO_2 , and N_2 in expired air were determined with a mass spectrometer (Marquette 1100, Marquette Electronics, Milwaukee, WI), and oxygen uptake (VO_2) was calculated.

Assays. In protocol 2, blood was obtained at rest, during the initial peak exercise (initial peak), with repetition of that workload at 15 to 20 minutes of exercise, and, for patients whose exercise capacity improved with prolonged exercise, at peak work capacity after the spontaneous second wind (second wind peak). Blood samples were assayed for lactate using a commercially

available analyzer (Yellow Springs Instruments, Yellow Springs, OH) and for ammonia using a commercial enzymatic method (Kodak, Rochester, NY).

Statistics. The statistical significance of differences between patient groups was evaluated with an unpaired *t*-test. Differences within patient groups were compared using a paired *t*-test. For analysis of differences in relative perceived exertion, a Mann-Whitney test was used. Differences were considered significant when $p \leq 0.05$.

Results. *Heart rate and perceived exertion during constant workload exercise: protocol 1.* Patients with MD displayed a stereotyped response to constant workload exercise consisting of an increase in heart rate that peaked between minutes 6 and 9 of exercise and then decreased steadily during the next 4 to 5 minutes to a stable lower heart rate between 12 and 15 minutes of exercise (figure 1). The decrease in exercise heart rate corresponded to a decrease in perceived exertion characteristic of a second wind that paralleled the change in heart rate. In contrast, patients with muscle PFKD showed no evidence of a second wind using the heart rate and perceived exertion criteria. Heart rate plateaued or increased gradually throughout 15 minutes of exercise. Correspondingly, perceived exertion plateaued or gradually increased through the same period of exercise. In no instance was there a decrease of heart rate or exercise effort as in MD patients.

Prolonged exercise—effects on peak work and oxidative capacity: protocol 2. Peak work capacity at 6 to 8 minutes of exercise in MD patients (peak work = 36 ± 3 W, mean \pm SE) was virtually identical to that of PFKD patients (peak work = 39 ± 6 W) (figure 2). Similarly at 6 to 8 minutes of exercise, peak oxygen consumption (MD = 13.2 ± 0.7 mL/kg/min, PFKD = 14.0 ± 1.2 mL/kg/min), heart rate (MD = 162 ± 2 vs 154 ± 7 beats/min), and level of perceived exertion (16 ± 1 vs 17 ± 1) did not differ between MD and PFKD patients (see figure 2). When the exercise workload was then transiently reduced, each MD patient developed a second wind so that exercise at the workload that previously was fatiguing was able to be performed with far less perceived effort (see figure 3). The level of perceived exertion decreased from 16 ± 1 to 12 ± 1 ($p < 0.05$). Correspondingly, the heart rate response decreased an average of 31 beats/min, from 162 ± 2 to 131 ± 3 beats/min. After the onset of the spontaneous second wind, each MD patient was able to exercise at a higher peak workload (53 ± 3 W) attributable to a higher peak VO_2 (16.2 ± 0.8 mL/kg/min) at a peak heart rate (162 ± 3 beats/min) that was the same as that achieved during the first 6 to 8 minutes of exercise.

In contrast, no patient with PFKD experienced a decrease of exercise effort, and no PFKD patient was capable of exercising at a higher rate. Relative perceived exertion that was 17 ± 1 after 6 to 8 minutes of exercise increased to 19 ± 1 with peak exercise at approximately 25 minutes of exercise. Although perceived exertion was equal to or greater than that with initial peak exercise, patients with PFKD were able to achieve a maximal heart rate of only 135 ± 6 beats/min, i.e., 19 beats/min less than with initial peak exercise.

Blood lactate levels at rest and during exercise were similar in MD and PFKD patients (data not shown). Resting blood ammonia levels also did not differ (MD = 18 ± 4 μ mol/L, PFKD = 29 ± 10 μ mol/L). During initial peak exercise, venous ammonia levels were higher ($p < 0.05$) in

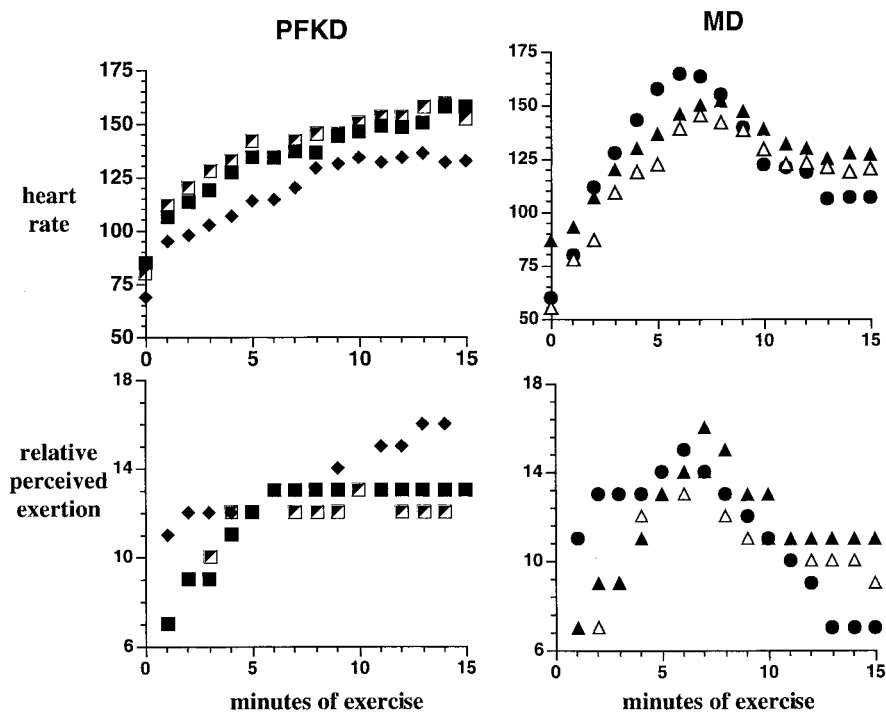


Figure 1. Heart rate responses (upper graphs) and patient rating of relative perceived exertion (lower graphs) during constant workload exercise in three patients with muscle phosphofructokinase deficiency (left) and in three patients with muscle phosphorylase deficiency (right).

PFKD patients ($173 \pm 46 \mu\text{mol/L}$) compared with MD patients ($82 \pm 17 \mu\text{mol/L}$); with repetition of the initial peak workload at 15 to 20 minutes of sustained exercise, blood ammonia was dramatically higher ($p < 0.01$) in PFKD patients ($387 \pm 65 \mu\text{mol/L}$) compared with MD patients ($165 \pm 32 \mu\text{mol/L}$).

Discussion. The principal new finding of our study is that none of the 5 PFKD patients developed a spontaneous second wind under the conditions of

prolonged exercise that consistently resulted in improved exercise and oxidative capacity in 29 MD patients.

The energy defect in MD and muscle PFKD classically has been attributed to impaired anaerobic glycogenolysis and glycolysis, respectively. However, our studies indicate that MD and PFKD have severely restricted oxidative metabolism and that this oxidative deficit is a major contributor to exercise limitations.^{2,6} The basis of the oxidative deficit is limited availability of substrate to fuel oxidative metabolism. The close similarity clinically and physiologically between MD and PFKD implies that the metabolic limitation common to both—namely a block in availability of glycogen-derived pyruvate—is the major mechanism of impaired oxidative phosphorylation. Blocked glycogenolysis increases muscle dependence on extramuscular fuels—principally glucose and free fatty acids—to support oxidative metabolism. The availability of these extramuscular fuels varies with conditions of diet and exercise, which influence the mobilization, blood levels, delivery, and uptake of these fuels. Changes in cellular availability of glucose and free fatty acids result in characteristic fluctuations in the capacity for aerobic exercise that depend on the ability of these fuels to bypass the metabolic block in PFKD and MD. Increased glucose availability increases exercise capacity in MD. In contrast a carbohydrate meal or IV glucose in PFKD patients causes a characteristic decrease in work and oxidative capacity that is the result of the inability of PFKD muscle to metabolize glucose combined with a glucose-mediated decrease in availability of free fatty acids on which oxidative metabolism in PFKD critically depends.⁶ We have termed this distinctive

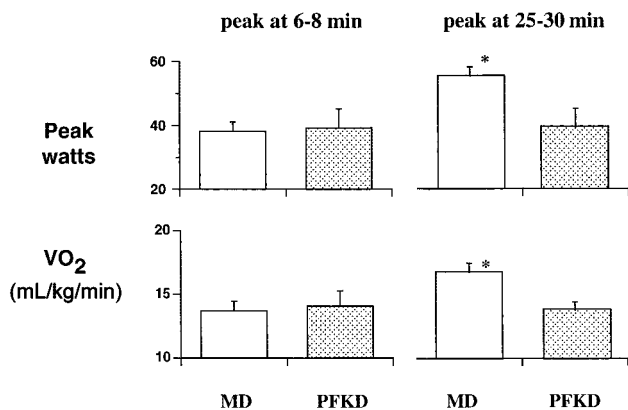


Figure 2. Peak work (in watts, mean \pm SEM) and peak oxygen uptake (mL/kg/min) determined at 6 to 8 minutes of cycle exercise (as shown on the left) and at 25 to 30 minutes of exercise (shown on the right) in 29 patients with muscle phosphorylase deficiency (open bars) and in 4 patients with muscle phosphofructokinase deficiency (shaded bars). *Indicates significant difference in results at 25 to 30 minutes compared with those at 6 to 8 minutes of exercise for peak work ($p < 0.0001$) and peak VO_2 ($p < 0.0001$) in patients with myophosphorylase deficiency.

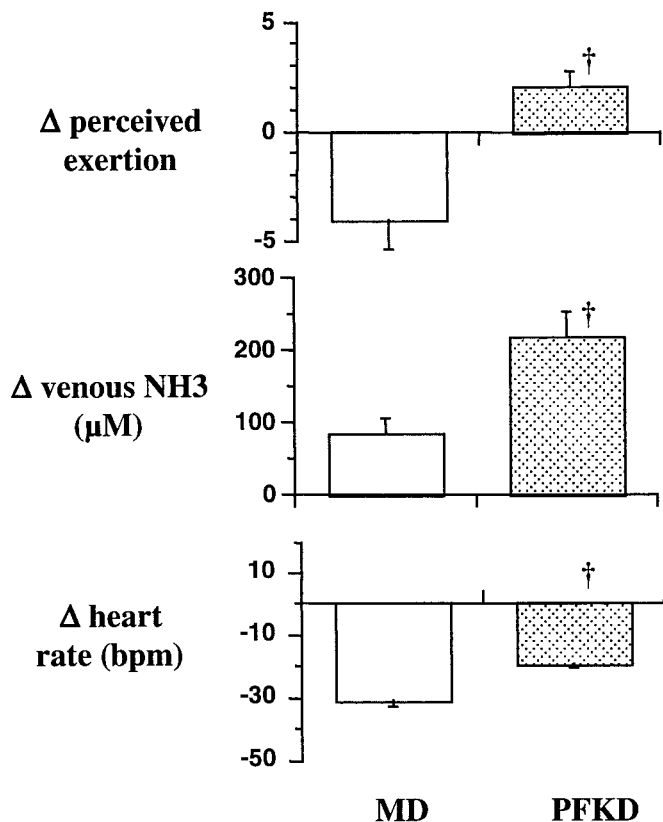


Figure 3. Change (Δ) in perceived exertion (upper panel), venous ammonia (NH₃) (middle panel), and heart rate (lower panel) when the workload that represented each patient's peak exercise capacity when performed at 6 to 8 minutes of exercise was repeated at 15 to 20 minutes of exercise in patients with myophosphorylase deficiency (MD; open bars) compared with those with muscle phosphofructokinase deficiency (PFKD; shaded bars). †Indicates significant differences between MD and PFKD responses for changes in perceived exertion ($p < 0.01$), venous NH₃ ($p < 0.01$), and heart rate ($p < 0.05$).

response in PFKD patients the "out of wind" phenomenon.⁶

Exercise also alters the availability of extramuscular fuels by increasing rates of glycogenolysis in liver and of lipolysis in adipose tissue. Increased cellular availability and oxidation of these fuels are responsible for the spontaneous second wind in patients with MD.¹⁰ As first described in the 1960s, the spontaneous "second wind" denotes a change in exercise tolerance such that activity that initially produces muscle fatigue, tachycardia, and often breathlessness becomes easily tolerated as exercise is prolonged.⁸ The spontaneous second wind typically occurs between 8 and 12 minutes of exercise and is attributable to a transition from a low capacity for oxidative phosphorylation to a higher work and oxidative capacity that accompanies increased availability of blood-borne fuels.¹⁰ Whether increased availability of fatty acids, blood glucose, or both is necessary for the spontaneous second wind is not known with certainty. Evidence that increased glu-

cose utilization is critical in this response includes the finding that rates of hepatic glucose production and glucose uptake during exercise are exaggerated in MD patients compared with control subjects in the time frame corresponding to the onset of a second wind.¹⁶ In addition, we have shown that the increase in oxidative capacity that is the basis of the spontaneous second wind in MD is associated with an increase in blood lactate levels consistent with increased glucose utilization in working muscle.¹⁰ The comparison of responses to prolonged exercise in patients with MD vs PFKD provides an opportunity to further evaluate the role of muscle glucose metabolism in this response.

Our results indicate that exercise responses of both patient groups were virtually identical during the first 6 to 8 minutes of exercise as indicated by similar peak work and VO₂ capacity, heart rate responses, and ratings of perceived exertion. These results indicate that the oxidative fuel crises in MD and muscle PFKD is similar in the first minutes of exercise and relates to the combined effect of absent glycogenolysis or glycolysis and low availability of blood-borne fuels. As exercise was prolonged, exercise responses in these two conditions dramatically diverged.

Each of the MD patients studied during constant workload exercise developed a classic spontaneous second wind associated with a decrease in exercise heart rate and perceived exertion that typically occurred between minutes 8 to 12 of exercise (see figure 1). In contrast, in each of the PFKD patients evaluated with this protocol, heart rate and perceived exertion remained elevated or increased further.

When exercise that caused fatigue during the first 6 to 8 minutes of exercise was repeated at 15 to 20 minutes of exercise, perceived exertion was lower in each of 29 MD patients but was rated as equal or greater in each PFKD patient. Furthermore, the metabolic stress of such exercise was greater in PFKD patients compared with MD patients as indicated by higher blood ammonia levels. The major mechanism of exaggerated ammonia production in PFKD and MD during brief intense exercise is an abnormal increase in cellular ADP attributable to impaired ADP phosphorylation via glycolysis and to relative inhibition of proton-dependent ADP phosphorylation via creatine kinase caused by the absence of exercise-related muscle acidosis when glycogenolysis or glycolysis is blocked.¹⁸ Increased ADP levels in turn result in increased production of AMP and ammonia because of AMP deamination via myoadenylate deaminase. Therefore, the level of ammonia increase in muscle and blood parallels the energy crises in working muscle and reflects the level of mismatch between ADP production and ADP phosphorylation in exercise. Curiously, despite maximal perceived exertion and severe energy crises as reflected by high blood ammonia levels, PFKD patients were not able to achieve as high a heart rate

with peak exercise at 25 minutes of exercise as compared with that achieved at 6 to 8 minutes of exercise. This contrasts with the sustained high heart rates in PFKD patients during less intense, constant workload exercise as illustrated in figure 1. This raises the possibility that the level of inorganic phosphate in active muscle may participate in the regulation of exercise heart rate. A consequence of maximal exercise in PFKD is the trapping of inorganic phosphate produced in the hydrolysis of ATP and phosphocreatine as sugar phosphates as indicated by the accumulation of an anomalous, large phosphomonoester peak that can be detected by magnetic resonance spectroscopy.^{19,20} Clearance of this phosphomonoester peak after heavy exercise requires 30 minutes or more, so the increase in inorganic phosphate with subsequent exercise within this time frame is blunted.

We infer that the inability of PFKD patients to achieve a spontaneous second wind under conditions of exercise that consistently produce this phenomenon in MD patients is attributable specifically to the inability of PFKD muscle to metabolize glucose. Increased availability and oxidation of free fatty acids have been postulated to be the basis of the spontaneous second wind in patients with MD, but differences in fatty acid availability between MD and PFKD patients are unlikely to be responsible for our results. Exercise was undertaken after an overnight fast to optimize the availability of free fatty acids in both patient groups, and previous studies of substrate mobilization and turnover indicate that free fatty acid availability is similar in MD and PFKD patients during these conditions of exercise.^{16,21} However, it should be noted that glucose may enhance muscle oxidative phosphorylation in MD patients in part via pyruvate-mediated anaplerosis, thereby increasing availability of oxaloacetate and augmenting the rate of oxidation of acetyl CoA derived from either pyruvate or fatty acids.^{7,10} Therefore, the ability of MD muscle to metabolize glucose may also enhance fat oxidation as suggested by the adage that “fats burn in the flame of carbohydrate.” Additional experiments will be required to determine whether glucose-dependent fat oxidation contributes to the

differential capacity of MD vs PFKD to achieve a spontaneous second wind.

References

1. DiMauro S, Tsujino S. Nonlysosomal glycogenoses. In: Engel AG, Franzini-Armstrong C, eds. *Myology*. New York: McGraw Hill, 1994: 1554–1579.
2. Haller RG, Lewis SF, Cook JD, et al. Myophosphorylase deficiency impairs muscle oxidative metabolism. *Ann Neurol* 1985;17:196–199.
3. Lewis SF, Vora S, Haller RG. Abnormal oxidative metabolism and O₂ transport in muscle phosphofructokinase deficiency. *J Appl Physiol* 1991;70:391–398.
4. Lewis SF, Haller RG. The pathophysiology of McArdle's disease: clues to regulation in exercise and fatigue. *J Appl Physiol* 1986;61:391–401.
5. Sahlin K, Areskog N-H, Haller RG, et al. Impaired oxidative metabolism increases adenine nucleotide breakdown in McArdle's disease. *J Appl Physiol* 1990;69:1231–1235.
6. Haller RG, Lewis SF. Glucose-induced exertional fatigue in muscle phosphofructokinase deficiency. *N Engl J Med* 1991;324:364–369.
7. Sahlin K, Jorfeldt L, Henriksson K-G, et al. Tricarboxylic acid cycle intermediates during incremental exercise: attenuated increase in McArdle's disease. *Clin Sci* 1995;88:687–693.
8. Pearson C, Rimer D, Mommaerts WF. A metabolic myopathy due to absence of muscle phosphorylase. *Am J Med* 1961;30:502–517.
9. Braakhekke JP, deBruin MI, Stegeman DF, et al. The second wind phenomenon in McArdle's disease. *Brain* 1986;109:1087–1101.
10. Haller RG, Vissing J. Spontaneous “second wind” and glucose-induced second “second wind” in McArdle disease: oxidative mechanisms. *Arch Neurol* 2002;59:1395–1402.
11. Agamanolis DP, Askari AD, DiMauro S, et al. Muscle phosphofructokinase deficiency: two cases with unusual polysaccharide accumulation and immunologically active enzyme protein. *Muscle Nerve* 1980;3:456–467.
12. Rowland L, DiMauro S, Layzer R. Phosphofructokinase deficiency. In: Engel AE, Banker BQ, eds. *Myology*. New York: McGraw-Hill, 1986: 1603–1617.
13. Tarui S, Mineo I, Shimizu T, et al. Muscle phosphofructokinase deficiency and related disorders. In: Serratrice G, Desnuelle C, Pellissier J, et al., eds. *Neuromuscular Diseases*. New York: Raven Press, 1984: 71–77.
14. Porte D Jr, Crawford DW, Jennings JB, et al. Cardiovascular and metabolic responses to exercise in a patient with McArdle's syndrome. *N Engl J Med* 1966;275:406–412.
15. Pernow BB, Havel RJ, Jennings DB. The second wind phenomenon in McArdle's syndrome. *Acta Med Scand* 1967;472(suppl):294–307.
16. Vissing J, Lewis SF, Galbo H, et al. Effect of deficient muscular glycogenolysis on extramuscular fuel production in exercise. *J Appl Physiol* 1992;72:1773–1779.
17. Borg G. Perceived exertion as an indicator of somatic stress. *Scand J Rehabil Med* 1970;2:92–98.
18. Radda GK. The use of NMR spectroscopy for the understanding of disease. *Science* 1986;233:640–645.
19. Duboc D, Jehenson P, Dinh S, et al. Phosphorus NMR spectroscopy study of muscular enzyme deficiencies involving glycogenolysis and glycolysis. *Neurology* 1987;37:663–674.
20. Bertocci LA, Haller RG, Lewis SF, et al. Altered high energy phosphate metabolism during exercise in muscle phosphofructokinase deficiency. *J Appl Physiol* 1991;70:1201–1207.
21. Vissing J, Galbo H, Haller RG. Paradoxically enhanced glucose production during exercise in humans with blocked glycolysis due to muscle phosphofructokinase deficiency. *Neurology* 1996;47:766–771.