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# A Diagnostic Cycle Test for McArdle's Disease

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**We investigated whether the second wind phenomenon (ie, a decrease in heart rate and perceived exertion during exercise) is pathognomonic for McArdle's disease. Twenty-four patients with McArdle's disease, 17 healthy subjects, and 25 patients with other inborn errors of muscle metabolism cycled a constant workload for 15 minutes. In McArdle's disease patients, heart rate consistently decreased by 35 ± 3 beats per minute from the 7$^{th}$ to the 15$^{th}$ minute of exercise, whereas heart rate increased progressively with exercise in all 42 control subjects. The findings indicate that cycling at a moderate, constant workload provides a specific, sensitive, and simple diagnostic test for McArdle's disease.**

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In McArdle's disease, muscle glycogen breakdown is typically blocked completely because of absence of myophosphorylase activity. The presence of a metabolic myopathy, particularly the most common defect of muscle carbohydrate metabolism, McArdle's disease, should always be considered in patients with complaints of exercise intolerance, exercise-induced muscle pain, and cramps, but a simple screening procedure that can unequivocally confirm or exclude such a diagnosis is not available.

Muscle glycogen is the most important fuel for working muscle early during exercise and at high work intensities.[1] McArdle's disease patients therefore experience severe exercise intolerance, and intense exercise provokes cramps, muscle injury, and myoglobinuria.[2,3] Diagnosis can be suggested by a forearm exercise test, but final diagnosis rests on either molecular genetic investigations or histochemical or biochemical demonstration of absent myophosphorylase activity in muscle.

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After 8 minutes of exercise, McArdle's disease patients typically experience improved exercise tolerance with a decrease in perceived exertion and heart rate, so that exercise that previously was exhausting can be performed with ease.[4–6] This phenomenon, originally described and termed the *second wind phenomenon* by Pearson and colleagues,[4] is attributable to a marked increase in muscle oxidative capacity.[6] Based on anecdotal evidence, it has been assumed that patients with other disorders of muscle carbohydrate metabolism, particularly phosphofructokinase deficiency (PFKD), also experience a second wind during exercise.[2]

To potentially establish a new, simple diagnostic test for McArdle's disease, we investigated whether the second wind phenomenon is pathognomonic for McArdle's disease.

## Subjects and Methods

### *Subjects*

Twenty-four patients with McArdle's disease were studied. Findings in 24 McArdle's disease patients were compared with those in 25 patients with other inborn errors of muscle metabolism and 17 age- and sex-matched, healthy subjects. The other inborn errors of metabolism were phosphoglycerate mutase deficiency (one patient), PFKD (three patients), the myopathic form of very long-chain acyl-CoA dehydrogenase deficiency (two patients), the adult-onset myopathic form of carnitine palmitoyltransferase II deficiency (five patients), and 14 patients with mitochondrial myopathy. One McArdle's disease patient was on metoprolol XL (25mg every day) for hypertension and one McArdle's disease patient took glimepiride tablets and a mitochondrial myopathy patient received insulin for diabetes mellitus.

Diagnosis in all patients was confirmed by biochemical demonstration of the relevant enzyme defect in muscle or by molecular genetic analysis.[7] All patients had exercise intolerance, and all patients with defects of carbohydrate and lipid metabolism had experienced repeated episodes of exercise-induced myoglobinuria and muscle pain. The study was approved by the Scientific-Ethical Committee of Copenhagen (no. KF 01-046/01) and the institutional review board of the University of Texas, Southwestern Medical Center at Dallas. All subjects were informed about the nature and risks of the study, and all gave written consent to participate.

### *Experimental Protocol*

All subjects had eaten breakfast 2 to 3 hours before testing and were studied between 9 AM and noon. The subjects were studied on a cycle ergometer (MedGraphics CPE 2000) operated via a cardiopulmonary exercise test system (MedGraphics CPX/D, St. Paul, MN) that measured gas exchanges, workload, and heart rate. A catheter was inserted in the median cubital vein. The subjects cycled at a constant workload that elicited a heart rate corresponding to 60 to 70% of the predicted maximal heart rate (based on 220-age in years) within the first 5 to 7 minutes of exercise. Heart rate and rate of perceived exertion, assessed by the Borg rating scale,[8] were monitored every minute. All subjects cycled for 15 minutes to evaluate the potential occurrence of a second wind. McArdle's disease patients continued to exercise after the 15th minute, where the workload was increased. A bolus of glucose (139mmol) was administered intravenously during the 20th minute of exercise to investigate whether a second, "second wind" could be induced.

Values are expressed as mean ± SE. A $p$ value of 0.05 or less (two-tailed testing) was considered significant. Differences among groups were assessed by an unpaired Student's $t$ test.

## Results

### *Heart Rate and Borg Scale Ratings*

Fifteen minutes of cycling at a constant workload of approximately 40 watts consistently resulted in a marked second wind in all 24 McArdle's disease patients, with a decrease in heart rate of 35 ± 3 bpm (range of decrease, 20–69 bpm; Fig 1). The diabetic and metoprolol-treated McArdle's disease patients had a normal decrease in heart rate of 28 and 29 bpm. Borg ratings closely mirrored changes in heart rate (see Fig 1). In contrast, a second wind could not be observed in any of the 42 control subjects. Heart rate in the 7th minute of exercise was on average 133 ± 2 bpm in all control subjects and increased ($p$ <0.0005) to 141 ± 3 bpm in the 15th minute of exercise (Fig 2). The range of change was 0 to 21 bpm. In line with the heart rate increase, Borg ratings increased ($p <$ 0.0005) during exercise in the control group.

The bolus infusion of glucose consistently induced a second, "second wind" in all McArdle's disease patients ($p <$ 0.0005), with a decrease in heart rate from 151 ± 4 bpm in the 20th to 133 ± 3 bpm in the 25th minute of exercise. Borg ratings mirrored these changes (see Fig 1).

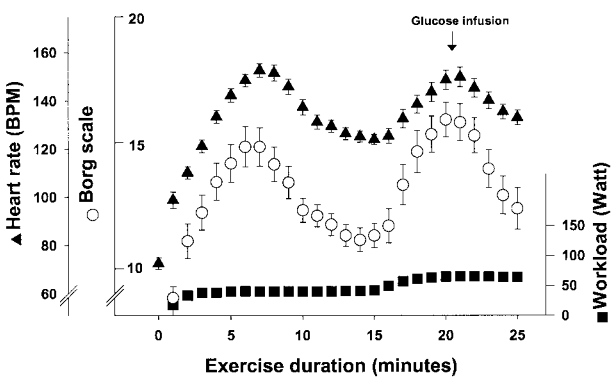


*Fig 1. Heart rate* (triangles), *Borg ratings* (circles), *and workload* (squares) *in 24 patients with McArdle's disease during 25 minutes of cycle exercise. A glucose infusion was administered intravenously at 20 minutes of exercise. Values are mean ± SE. Where not shown, error bars are smaller than symbol size.*

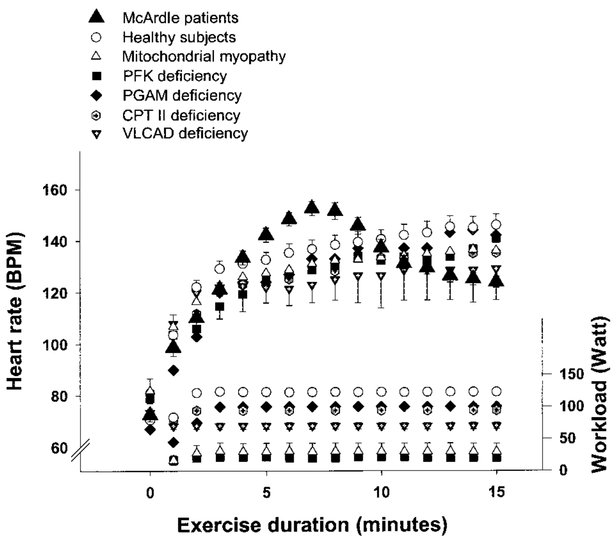


*Fig 2. Heart rate (seven upper curves) and workload (six lower curves) during 15 minutes of constant workload exercise at 65% of $VO_{2max}$ in 17 healthy subjects, 14 patients with mitochondrial myopathy, 3 with phosphofructokinase (PFK) deficiency, 1 with phosphoglycerate mutase (PGAM) deficiency, 5 with carnitine palmitoyltransferase II (CPT II deficiency), and 2 patients with very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency. The heart rate trace of the 24 patients with McArdle's disease are shown in the large, filled triangles for comparison. Values are mean ± SE. Where not shown, error bars are smaller than symbol size.*

## Discussion

McArdle's disease usually is screened for by the ischemic forearm exercise test. The test requires insertion of a venous catheter for blood sampling and invariably results in muscle cramps that may cause muscle injury in McArdle's disease patients.[9–11] Although unpleasant side effects can be avoided by performing a modified aerobic exercise test,[11] the test can be technically difficult because it ideally requires monitoring of the force output and immediate analysis of plasma ammonia, due to the labile nature of this compound.

Findings in this study suggest that a simple cycle test can be a useful diagnostic screening procedure for McArdle's disease, based on the absence or presence of the second wind phenomenon. In all 24 patients with McArdle's disease, but in none of 42 control subjects, did a second wind occur during cycle exercise, indicating that a second wind is a 100% sensitive and specific phenomenon for McArdle's disease. Demonstration of a second, "second wind" by glucose infusion can further confirm the diagnosis but is unnecessary for the diagnosis, because the diagnostic value of the heart rate response during the spontaneous second wind is sufficient.

The findings suggest that a diagnostic test can be conducted in McArdle's disease patients regardless of sex and age. McArdle's disease patients generally have decreased insulin sensitivity, probably related to the sedentary lifestyle.[12] One patient had type II diabetes mellitus but still had a strong second wind, suggesting that contraction-induced, and not insulin-mediated, glucose uptake mechanisms prevail during exercise. Several other conditions, however, may complicate interpretation of heart rate findings during exercise. Although the patient on metoprolol treatment had a normal second wind response, caution should be exercised in the interpretation of findings in subjects treated with drugs that may influence heart rate. Patients with cardiac arrhythmias are not eligible for the test.

It is well known that heart rate increases progressively during exercise at a constant workload in healthy subjects, because working muscles gradually fatigue.[13] This is so because heart rate is closely related to the relative, and not the absolute workload performed by an individual.[14] It is therefore not surprising that healthy subjects in this study did not experience a second wind during exercise, but why is the second wind phenomenon pathognomonic for McArdle's disease and not present in other metabolic myopathies? The second wind in McArdle's disease is attributable to an increase in muscle glycolysis, brought about by a high uptake of glucose from the blood stream.[6] In line with this, glucose utilization has been shown to be enhanced during exercise in McArdle's disease.[15,16] The second wind in McArdle's disease occurs at a time when blood flow and enhanced delivery of extramuscular fuels to the working muscle can partially compensate for the block in muscle glycogenolysis. We believe that the unique metabolic situation of completely blocked muscle glycogenolysis, but preserved capacity for glycolysis in conjunction with enhanced glucose uptake in McArdle's disease provides the metabolic basis of the second wind phenomenon,[6] and explains why this phenomenon is pathognomonic for McArdle's disease. According to this, enzyme defects that directly affect glycolysis, such as PFKD, should not be subject to a second wind. In PFKD, increased glucose mobilization is useless for muscle because of the complete block in muscle glycolysis, and futile recycling of glucose therefore occurs during exercise.[17] The increased fat mobilization that accompanies exercise in PFKD patients is not as effective a fuel as glucose to provide energy to working muscle, because anaplerosis (expansion) of the tricarboxylic cycle requires glycosyl units derived from pyruvate to spark the cycle.[6] The different findings in McArdle's disease and PFKD patients constitute a physiological experiment of nature that illustrates the adage that "fat burns in the flame of carbohydrate." The absence of a second wind in PFKD, carnitine palmitoyltransferase II deficiency, and mitochondrial myopathy patients in this study is supported by similar findings in earlier studies of these patients.[18–20]

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# Retinal Involvement in Dementia with Lewy Bodies: A Clue to Hallucinations?

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**Visual hallucinations are a core feature of dementia with Lewy bodies. Their pathophysiology is not well understood, because neither clinical nor histological data have shown their basic mechanisms. Here, we report the presence of pale inclusions in the outer plexiform layer of the retina in a patient with dementia with Lewy bodies. These inclusions are related to cytoskeletal disorganization of the cones at ultrastructural level and modifications of the immunohistochemical pattern of distribution of synucleins in the retina. These modifications may participate in the visual impairment in dementia with Lewy bodies.**

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Dementia with Lewy bodies (DLB) is characterized by the presence of LB inclusions in the brainstem and in the cortex.[1]

One of the main components of LBs is α-synuclein (αS).[2] αS, β-synuclein (βS), and γ-synuclein (γS) are members of the same protein family which is involved in synaptic function, neuronal plasticity, and neurodegeneration.[3]

Clinically, visual hallucinations (VHs) are considered as an essential feature of DLB.[4] Because VH may be observed in patients with ocular impairment,[5] and synucleins are expressed in the ocular tissues,[6] we used electron microscopy and synuclein immunohistochemistry to study the retina of a patient with pathologically proven DLB. We observed modifications that could have been involved in the appearance of VHs. These

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