Diagnostic exercise tests and treatment options in McArdle disease

John Vissing

Neuromuscular Clinic and Research Unit, Department of Neurology, University of Copenhagen, Rigshospitalet, Copenhagen
Exercise testing is a mainstay in neuromuscular diseases

Muscle glycogenoses are unique in that the metabolic defects in glycolysis provides an opportunity to monitor physiologic and metabolic abnormalities during exercise.
What kind of symptoms could prompt exercise testing?

• Exercise-induced cramps and pain
• Low lactate levels during exercise
• Exertional myoglobinuria
• Severe exercise intolerance
• History of second wind phenomenon
MUSCLE cramps?? Are you kidding?
Exercise tests in muscle McArdle disease

- Handgrip exercise
- Cycle ergometry
- $^{31}$P-MR spectroscopy
Handgrip test for muscle glycogenoses

- Catheter i vena cubiti *mediana*
- Measure plasma lactate and ammonia before and after handgrip exercise
Handgrip test for muscle glycogenoses

• Exercise test: Maximal handgrip contractions every other second for 1 min (30 contractions)

• The test is performed under aerobic conditions (No cuff)
Plasma lactate response to forearm exercise in McArdle disease

Lactat response to forearm exercise in “classical” McArdle disease, and two patients with variant McArdle disease.

![Graph showing lactate response to forearm exercise](image)

- Healthy subjects
- Mean/range for MPD (no phosphorylase)
- Patient A (trace phosphorylase)
- Patient W (trace phosphorylase)
Pitfalls using the forearm exercise test

- Low lactate and ammonia responses
  - Wrong catheter placement
  - Low effort (measure force output)

- Flat ammonia, normal lactate responses
  - Myoadenylate deaminase deficiency
Cycle ergometry in McArdle disease

- A diagnostic test
- A test to determine efficacy of therapeutic interventions
Cycle ergometry as a diagnostic test in McArdle disease

• Low maximal oxidative power (1/2-1/3 of normal)
• A decrease in plasma lactate during exercise
• A second wind phenomenon
• A hyperkinetic circulatory response with increased cardiac output/oxygen consumption ratio
Practical approach to cycle ergometry testing in McArdle

• Determine VO$_{2\text{max}}$ (start at 0 watts and apply 5-10 watts increments every other minute until exhaustion).

• Monitor heart rate, (plasma lactate, cardiac output), watts

• Expected maximal VO$_2$ is 14-28 ml O$_2$ min$^{-1}$ kg$^{-1}$, and workload is 25-60 watts
Practical approach to cycle ergometry testing in muscle glycogenoses

• If there is a significant increase in plasma lactate and a normal age- and gender-matched VO$_{2\text{max}}$ (or workload), then discontinue further cycle testing

• Otherwise, continue to a constant workload test
Practical approach to cycle ergometry testing in McArdle

- A steady-state workload test for 15 min at 65% of VO$_{2\text{max}}$ (usually around 35 watts)
- Monitor HR, perceived exertion, (plasma lactate, cardiac output), watts
Second wind phenomenon in McArdle disease
Second wind phenomenon in McArdle disease
A glucose-induced second wind

Circulatory response to exercise in "Classical" and "variant" McArdle patients

\[ \text{VO}_2 \quad (\text{L/min}) \]

\[ \text{Cardiac Output (L/min)} \]

- Healthy Subjects
- MYPD (no phosphorylase) n=48
- Patient A (trace phosphorylase)
- Patient W (trace phosphorylase)
Circulatory response to exercise in "Classical" and "variant" McArdle patients.
Conclusions: Diagnostic validity of cycle testing in McArdle disease

• The second wind phenomenon is pathognomonic for McArdle disease and, together with a decrease in plasma lactate, is diagnostic for the condition
Cycle ergometry: Efficacy measures that can be used for clinical trials

- Plasma lactate and glucose levels
- Maximal oxygen uptake (and workload) before and after the 2\textsuperscript{nd} W
- The cardiac output/oxygen uptake ratio
- Levels of plasma CK
- The magnitude of the 2\textsuperscript{nd} W
- The average HR and Borg scale at a constant workload
$^{31}$P-MR spectroscopy:
Muscle glycogenoses

Variables of interest for diagnosis:

- Muscle acidification
- Demonstration of phosphomonoesters
$^{31}$P-MR spectroscopy

MRS features:
- $\text{Pi:PCr} = 1:10$
- $\text{pH}$
- $\text{PCr recovery}$
Concluding remarks:
Exercise tests in muscle glycogenoses

- Handgrip exercise and cycle ergometry are sensitive and specific tests to diagnose muscle glycogenoses with dynamic symptoms, but should be performed by experienced investigators.

- $^{31}$P-MR spectroscopy is also sensitive and specific, but expensive, technically complicated and inaccessible. Should be reserved for research purposes.
Do carriers of *PYGM* mutations have symptoms of McArdle disease?
Oxidative capacity and changes in plasma lactate during exercise in McArdle patients and carriers of *PYGM* mutations

Andersen, Dunø, Schwartz, Vissing. Do carriers of *PYGM* mutations have symptoms of McArdle disease? *Neurology* 2006; 67: 716-718.
Dietary treatments in McArdle disease
Intravenous glucose in McArdle disease

It is has been known for 45 years that IV glucose improves exercise tolerance in McArdle disease (Pearson et al. Am J Med 1961;30:502-17)


Oral sugar in McArdle disease

The notion that oral glucose will help McArdle patients can be questioned because:

• Oral glucose produces hyperinsulinemia that blocks mobilization of fats, and thus fat combustion.

• IV, but not oral glucose improves exercise tolerance in CPT II deficiency

Glycogen → Glucose-6-P → Pyruvate → Acetyl-CoA → Krebs’ cycle

McArdle disease (myophosphorylase deficiency)

Blood glucose
Oral sucrose-loading before exercise in 12 McArdle patients

• 75g of sucrose or placebo, 30-40 min before exercise

• Exercise at a constant workload (65% of \( VO_{2\text{max}} \) for 15 minutes)
The Effect of Oral Sucrose on Exercise Tolerance in Patients with McArdle’s Disease

John Vissing, M.D., Ph.D., and Ronald G. Haller, M.D.

Copyright © 2003 Massachusetts Medical Society.
Oral glucose treatment in McArdle disease

Conclusions

- Pre-exercise oral glucose effectively improves exercise tolerance and may prevent muscle injury in McArdle disease.
- The treatment should be used with caution, because of the high intake of calories.
- The treatment may be inconvenient because of the 30-40 minutes waiting period.
Oral sucrose-loading shortly before exercise in McArdle disease

- 37g of sucrose or placebo, 5 min before exercise
- Exercise at a constant workload (65% of $VO_{2\text{max}}$ for 15 minutes)
Andersen ST, Haller, RG, Vissing J. Effect of oral sucrose shortly before exercise on work capacity in McArdle disease. Arch Neurol 2008; 65: 786-789
Conclusions

A low dose of oral glucose immediately before exercise;

• is more effective in improving exercise tolerance compared with a double-dose of sucrose administered 40 min before exercise
• is convenient for the patient (no waiting time)
• has a better metabolic profile than delivery 40 minutes before exercise (glucose is absorbed during exercise, and not stored as fat)
• Cuts down the amount of calories ingested
Fat metabolism during exercise in patients with McArdle disease.

Effect of manipulating fat availability on exercise capacity in McArdle disease
Effect of diet on exercise tolerance in McArdle disease

• Based on single-patient case studies, it has been postulated that a protein-rich diet is beneficial in McArdle disease based on;

• $^{31}$P-MRS-assessed biochemical changes
  

• Endurance after protein and training
  
Effect of diet on exercise tolerance in McArdle disease

*Why should protein be beneficial?*

- Proteins/amino acids contribute very little to energy metabolism

- Branched chain amino acids, do not improve exercise tolerance in McArdle disease

Effect of diet on exercise tolerance in McArdle disease

- Eight McArdle patients were investigated in a cross-over study with either:
  - Carbohydrate-rich diet
    - 20% fat, 15% protein, 65% carbohydrate
  - Protein-rich diet
    - 15% fat, 55% protein, 30% carbohydrate
- Careful instructions about diet (15-page description of recipes with weights of ingredients).
- Patients weighed the food and registered the food intake on a form.
- Each diet was followed for 3 days prior to testing.
Experimental protocol

Constant workload at 65% of VO$_{2\text{max}}$ for 15 min

Followed by 5 min incremental workload until exhaustion

Monitor HR, perceived exertion, plasma lactate and glucose, peak VO$_2$
Conclusion

• A protein-rich diet does not improve exercise tolerance in McArdle disease

• A carbohydrate-rich diet ensures sufficient liver glycogen stores, and thus glucose delivery during exercise
Aerobic training in McArdle disease

Treatment recommendations for patients with McArdle disease

• Keep a high-carbohydrate diet to maintain hepatic glycogen stores
• Use oral sucrose loading shortly before exercise when strenuous exercise that elicits symptoms is anticipated
• Engage in supervised, aerobic conditioning to increase maximal oxidative capacity