The Ischamic Lactate Test

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McArdle Disease GSDV

- Incidence 1:100,000
- Autosomal recessive mutations in PYGM
- Absent or severely reduced muscle phosphorylase
- Failure to produce lactate during ischaemic exercise

Features	N=59	%
Exercise Related Pain/ Fatigue	59	100
Second wind	51	86
Myoglobinuria	36	61
Renal Failure	6	10
Hyperuricaemia	8	13
Muscle Hypertrophy	24	41
Muscle wasting Paraspinal, shoulder, Peri-scapular	16	27
Muscle weakness MRC 4 Shoulder girdle Axial	12	20

McArdle Disease

Age yrs	<10	10-19	20-29	30-39	40-49	>50
Age at onset of symptoms n=65	54 87%	6 9.6%	0	2 3.2%	0	
Age at diagnosis N=60	6 10%	11 18.3%	12 20%	12 20%	13 21.6%	7 11.6%

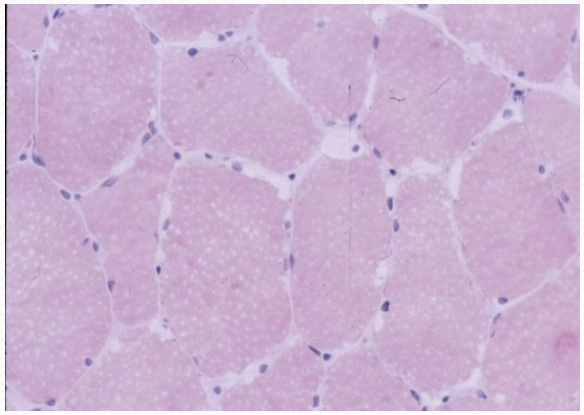
96% onset <20 years
28% diagnosed <20 years

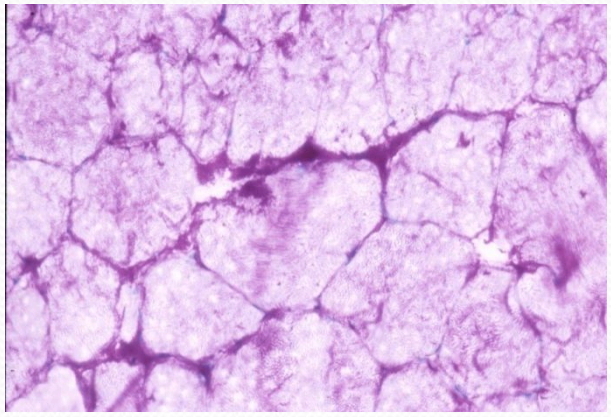
Differential Diagnosis

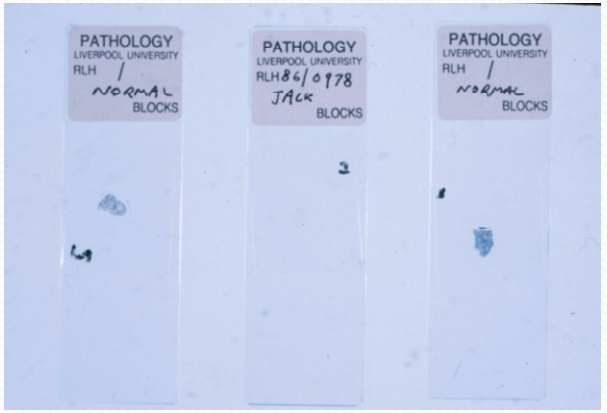
- Other glycolytic disorders
- Muscular Dystrophies
- Fatty acid oxidation defects
- Mitochondrial disorders

Investigations

- Creatine kinase
  - Average 2,700 iu/l (range 230-13,000)
- Muscle biopsy







Muscle biopsy: caution

- Phosphorylase is unstable and fades quickley
- Regenerating muscle expresses the foetal isoenzyme
- Glycogen depletion (critical illness) phosphorylase histochemistry will not work
- 18% of patients previously diagnosed by muscle biopsy did NOT have McArdle disease

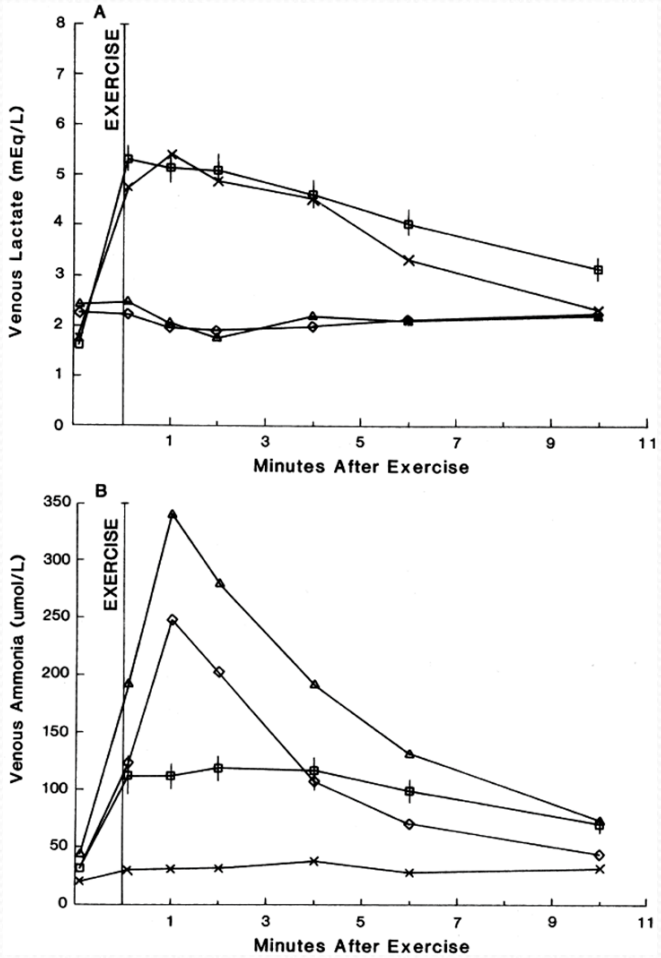
Ischaemic Lactate test: Equipment

- Cannula
- Sphygmomanometer cuff and bulb
- 8 Fluoride oxalate tubes (lactate)
- 8 EDTA tubes for (ammonia)
- Ice
- Fasting patient

Protocol

- Baseline Blood sample
  - Lactate
  - ammonia
- Inflate Sphygmomanometer cuff >systolic BP
- Patient rapidly grips repetitively for 1 minute (some protocols say 2 minutes)
- After two minutes, when patient fatigues cuff is deflated
- Blood is taken at 1, 2, 3, 5, 7, 10 and 12 minutes
  - Lactate
  - Ammonia
- Blood samples must be kept in ice

Normal result: 3-5 fold increase in lactate and ammonia



A failure for both Lactate and Ammonia to rise indicates a failed test

Problems with the test

- Protocol not standardised
- Healthy individuals can't exercise for more than a minute
- GSD V patients often can't exercise for a minute
- False results
  - Ipsilateral ante-cubital vein not used
  - Blood taken before cuff is deflated
  - If ammonia not simultaneously measured
  - Samples not put in ice
- Potential adverse events
  - Severe cramping/ discomfort
  - Myoglobinuria
  - Compartment syndrome

Non-ischaemic forearm exercise test Hogrel et al Neurology 2001

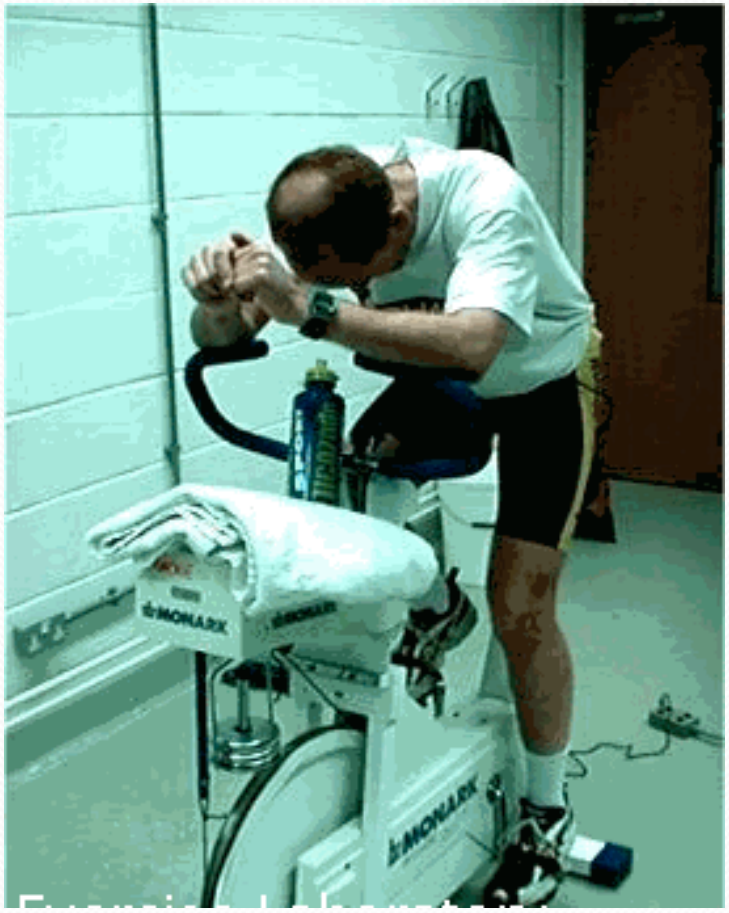
- 26 healthy controls and 32 patients with a metabolic myopathy
- Aerobic forearm exercise at 70% maximum voluntary contraction for 30 seconds
- Discriminates GSDV from normal

Kasemi-Esfarjarni et al Ann Neurology 2002

- 9 GSDV patients and 1 phosphoglycerate mutase deficiency
- Identical protocol to ischaemic forearm test without ischaemia
- Similar results with both protocols
- No cramps with non-ischaemic test
- Four patients could not complete ischaemic forearm test

Diagnostic cycle test
Vissing and Haller 2003

- 24 GSD V
- 17 normal controls
- 25 other metabolic myopathies
- Cycled at constant workload
- for 15 minutes
  Heart rate and respiratory gas exchange measured
- Second wind 7-15 minutes in McArdle subject



12 minute shuttle test

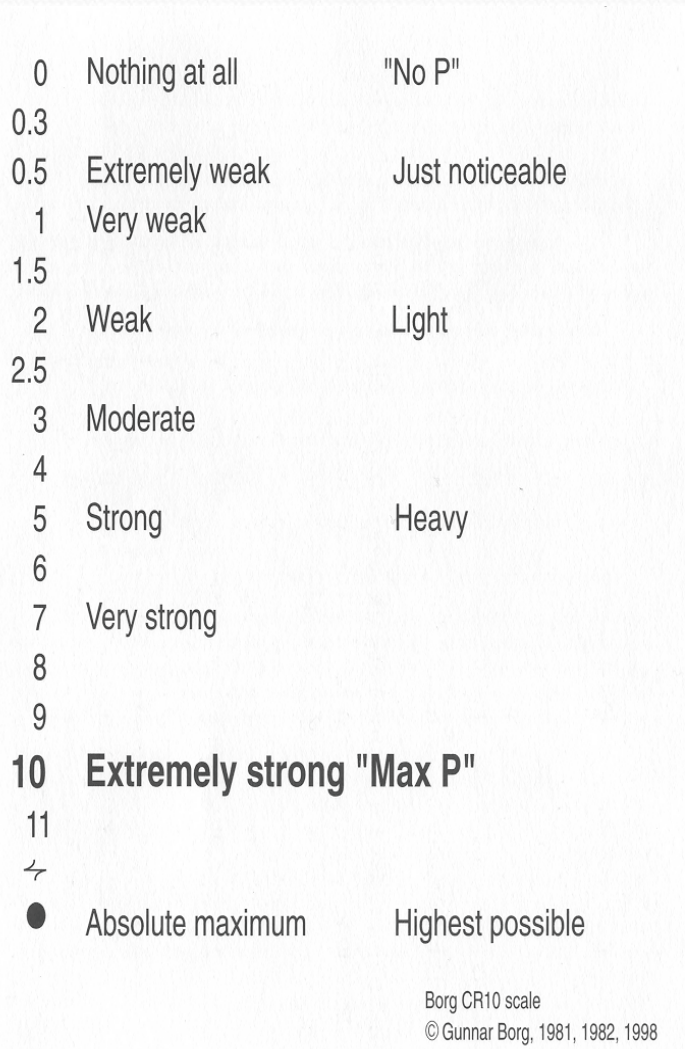
- Patient walks as far as possible in 12 minutes
- Borg RPP must not exceed 4
- Every one minute record
  - Heart rate
  - RPP
  - Distance travelled (walking speed)

12 minute walk test
Quinlivan et al JNNP 2010

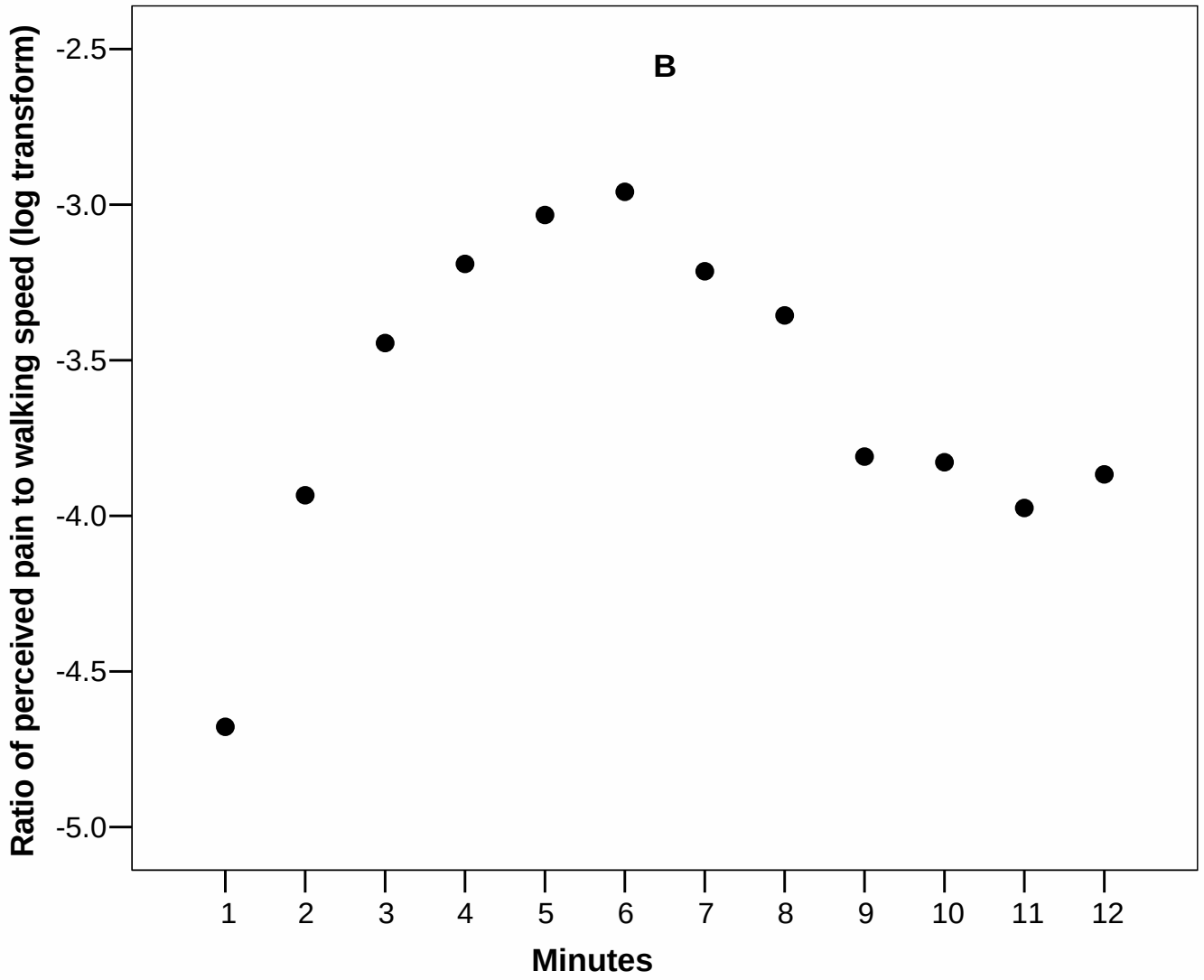
- 36 patients studied on more than one occasion for baseline assessment
- Second wind identified in 100%
  - For some it was the first time
- Pain and heart rate increase at 2-3 minutes
- Pain and Heart rate ratio peak at 5 – 6 minutes
- Second wind at 6-8 minutes

12 minute walking assessment

Minutes	Heart Rate	Walking speed km/hr	RPP
1	90	4.0	0
2	117	5.5	0.5
3	140	5.5	5.0
4	144	4.5	3.0
5	142	4.5	3.0
6	152	4.5	3.0
7	143	4.5	3.0
8	134	4.5	2.0
9	116	4.5	2.0
10	122	5.5	2.0
11	131	5.5	2.0
12	133	5.5	2.0



Rating of Pain as a ratio to walking speed
Group Mean (n = 20) (John Buckley)



DNA analysis

R50X/ R50X	R50X/ other	R50X/ G205s	G205s/ G205s	Other
41/75	21/75 c2430C>T,G810G C2386_2387delG c1129A>T,N377Y c808C>T, R270X c1345G>A,G449R c2465C>A,G133R c2465C>A,A822D c403G>A,A822D c403G>A,Gi33R c279C>T,R94W c1466C>G, P489R c107T>C, L36P 3xPro489Arg	9/75	2/75	4/75 Pakistani male: Homozygous exon 1 c.14delT Caucasian female: Compound Heterozygote 1x L36p/ c1239A+1G>A Pakistani Sibs Arg576x/Arg576x
54.6%	28%	12%	2.6%	5.3%

R50X, G205S 70% diagnostic, 95% at least one allele mutated

Summary

- Forearm exercise test is not essential for the diagnosis of McArdle disease
- Ischaemia is not necessary
- Protocol must be standardised open to error
- The test should not be performed by inexperienced individuals without supervision
- Useful test normal result excludes glycolytic disorder
- Other forms of exercise testing may be more useful for patients with suspected McArdle disease

Acknowledgements

- John Buckley, Chester University
- Association for Glycogen Storage Disorders