Leiden University
Medical Center

Skeletal muscle MR spectroscopy at high field

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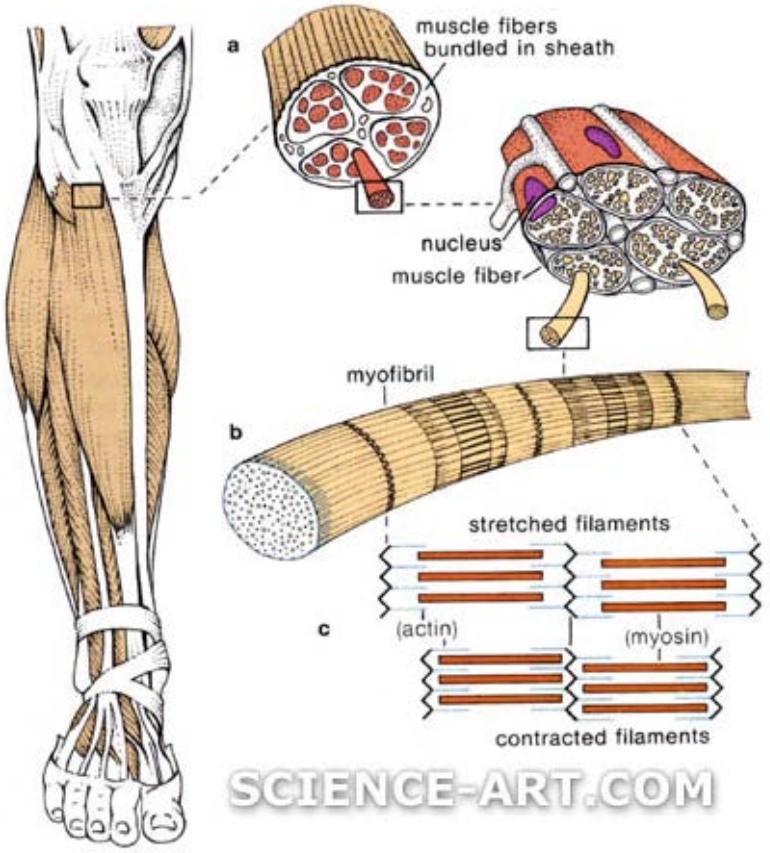
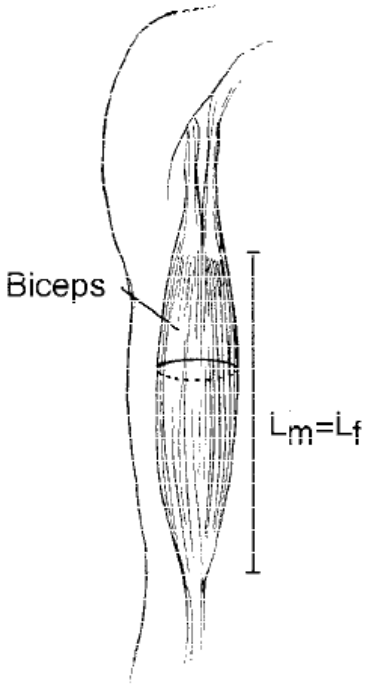
Skeletal muscle

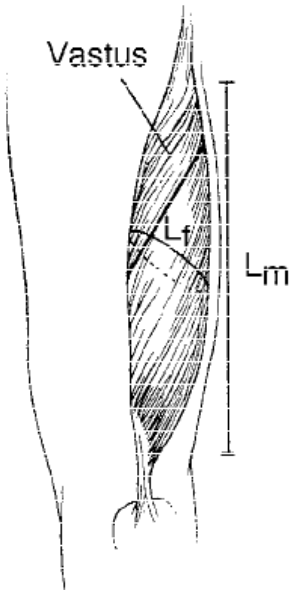
- Over 600 muscles in the body
- Function: deliver force
- Very dynamic organ
- Long cylindrical cells
- Different layers of connective tissue
- Highly structured



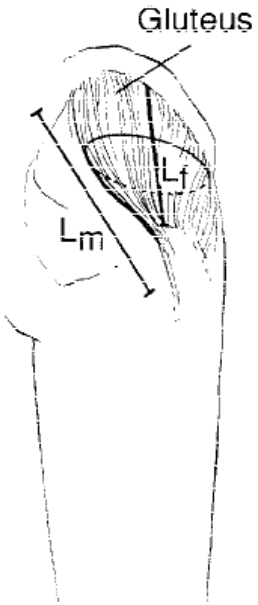
Types of muscle architecture



Parallel (fusiform)



Unipennate
Angle 0-30^o



Multi pennate

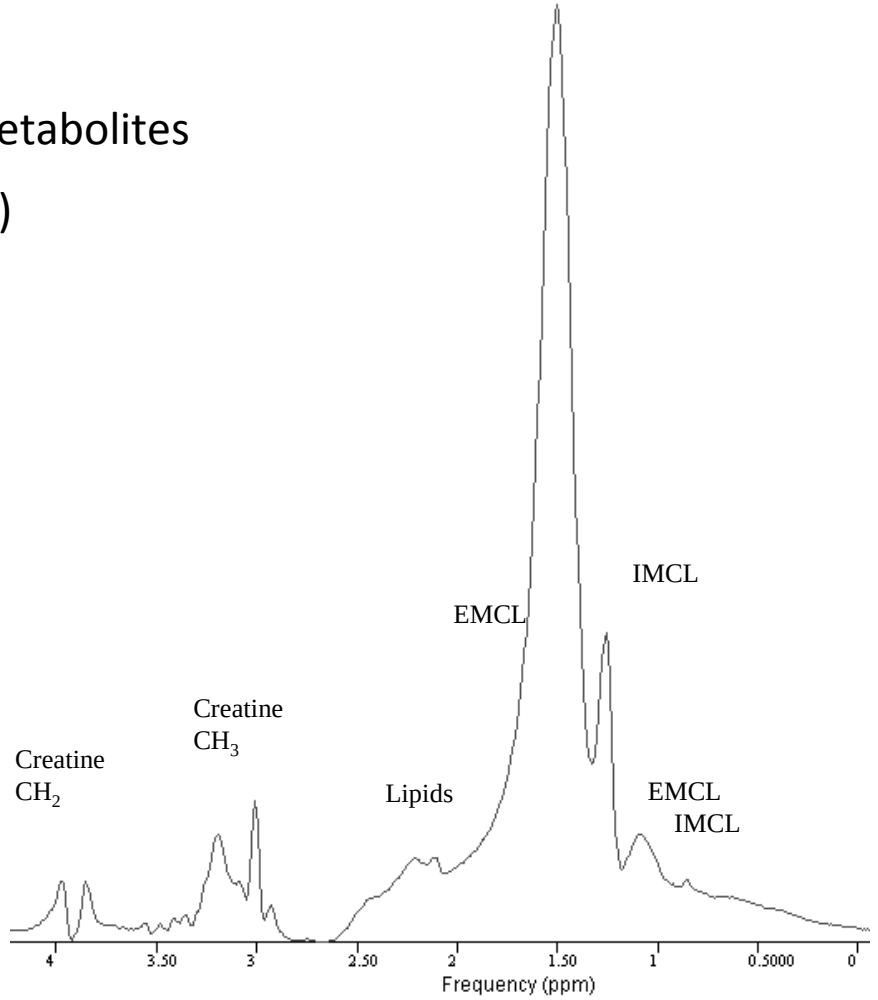
Applications

- Measurements at rest and during/after activity
- Important metabolites: lipids, phosphocreatine, ATP, glycogen
- Common applications:
  - Diabetes
  - Aging
  - Sports medicine
  - Muscular dystrophies

High field MRS

- Specific challenges of MRS:
  - Intrinsic low concentration of metabolites
  - Low gyromagnetic ratio (^{31}P, ^{13}C)
  - Overlapping signals

- Specific high field advantages:
  - Higher SNR
  - Higher spectral resolution



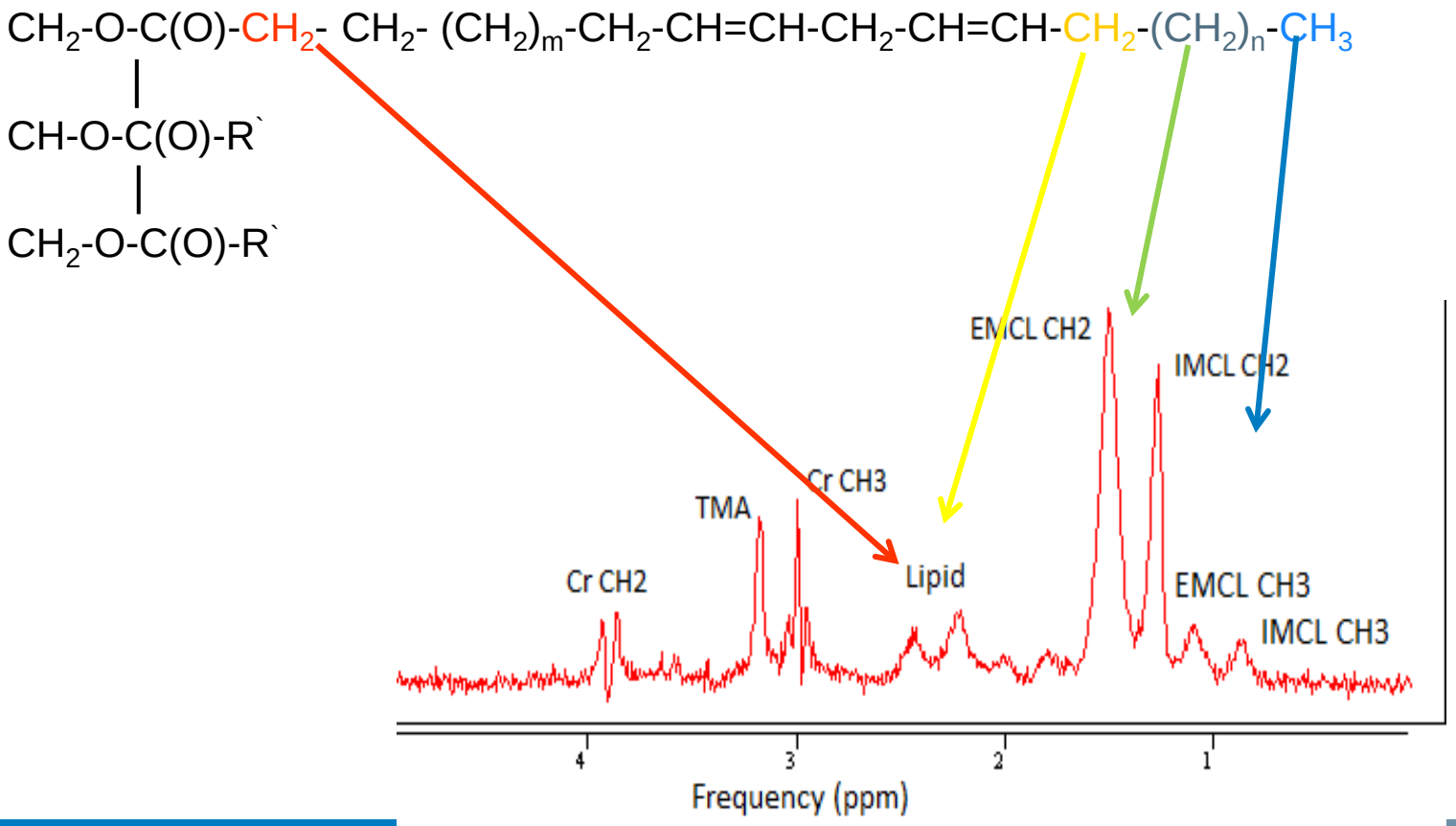
Nuclei with spin and MRS

Isotope	Spin	Gyromagnetic ratio (10^7 rad s^{-1} T^{-1})	Natural abundance (%)	Relative sensitivity
^{1}H	½	26.752	99.985	1.00
^{2}H	1	4.107	0.015	1.45×10^{-6}
^{13}C	½	6.728	1.108	1.76×10^{-4}
^{14}N	1	1.934	99.63	1.01×10^{-3}
^{15}N	½	-2.714	0.37	3.85×10^{-6}
^{19}F	½	25.181	100	0.833
^{23}Na	3/2	7.08	100	9.27×10^{-2}
^{31}P	½	10.841	100	6.65×10^{-2}

^{1}H MRS

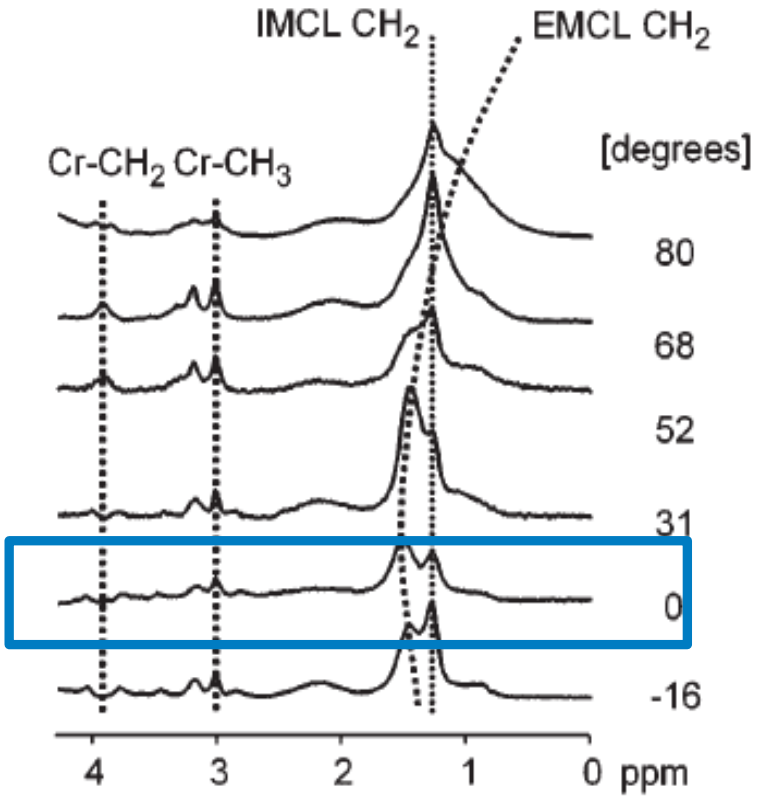
Muscle ^{1}H MRS

- Energy metabolism, diabetes
- Creatine, intra and extra myocellular lipids, carnitine, acetylcarnitine
- Dipolar couplings and bulk susceptibility effects



IMCL/EMCL: bulk susceptibility effects

- IMCL:
  - Metabolically active
  - Lipid droplets
- EMCL:
  - Not metabolically active
  - Located between fibers
  - Shift in resonance frequency
- Different spectrum for each muscle

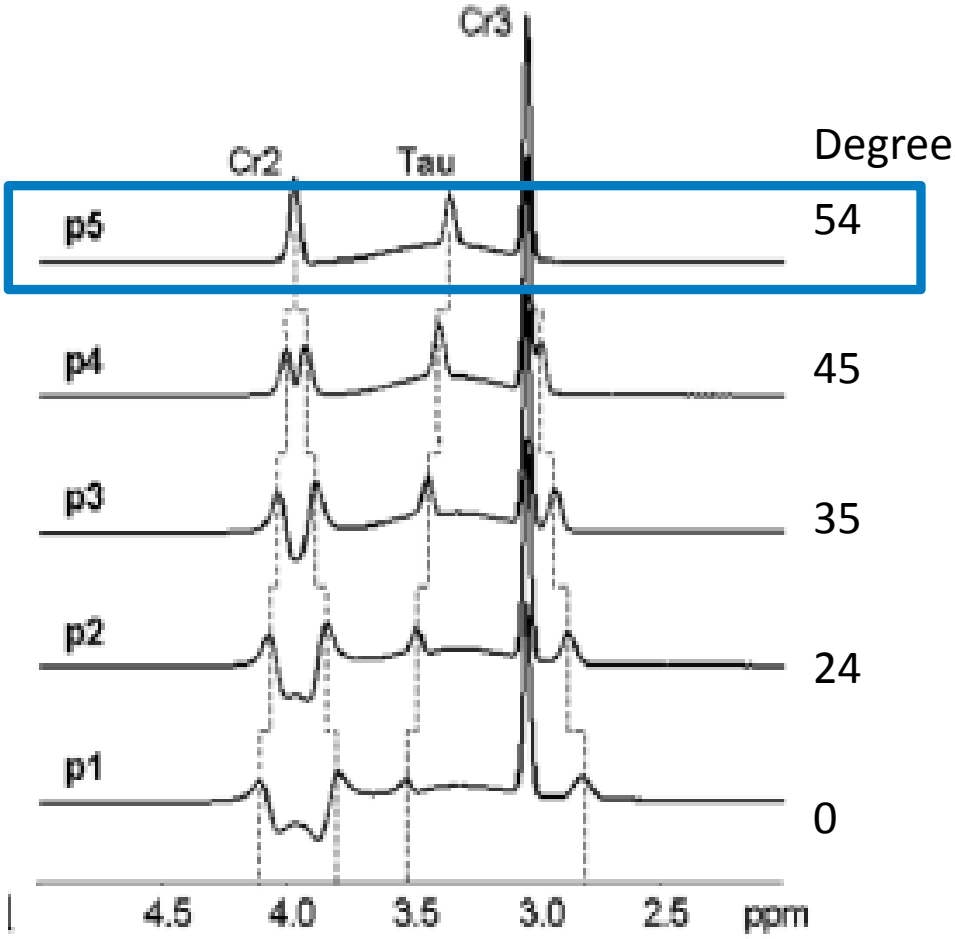


Boesch et al, NMR in Biomed 2006

Residual dipolar couplings

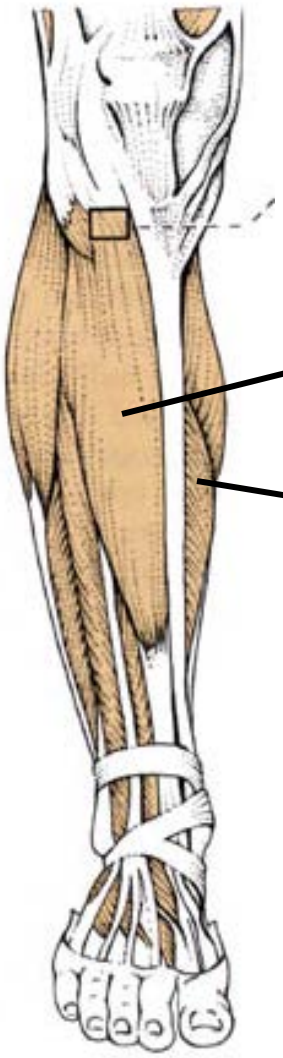
- Creatine, Carnitine, Acetylcarnitine, Carnosine, Taurine
- Singlet at the magic angle

- 'Optimal' angle for IMCL and metabolites is different!



Vermathen et al. Magn Reson Med 2003

Muscles of the calf



Tibialis anterior muscle

Fusiform

0 degrees

Optimal for IMCL

Soleus muscle

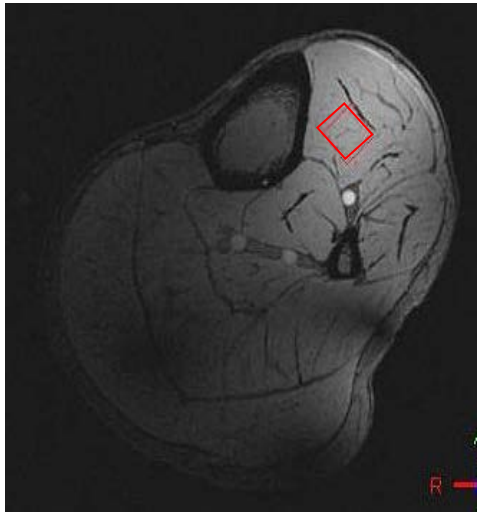
Bipennate

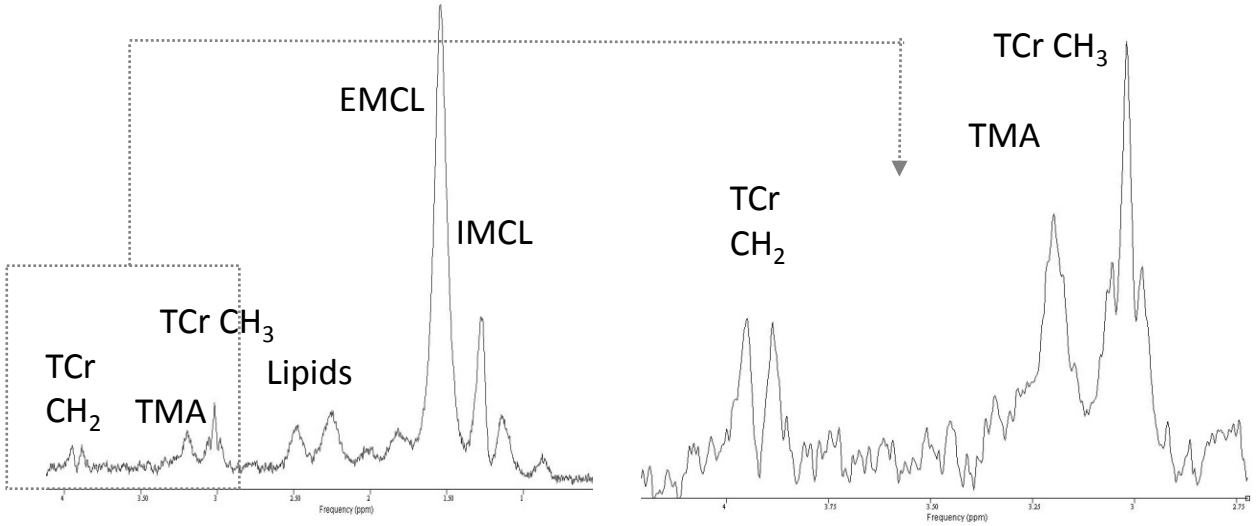
Close to magic angle

Optimal for metabolites

Added value of 7T

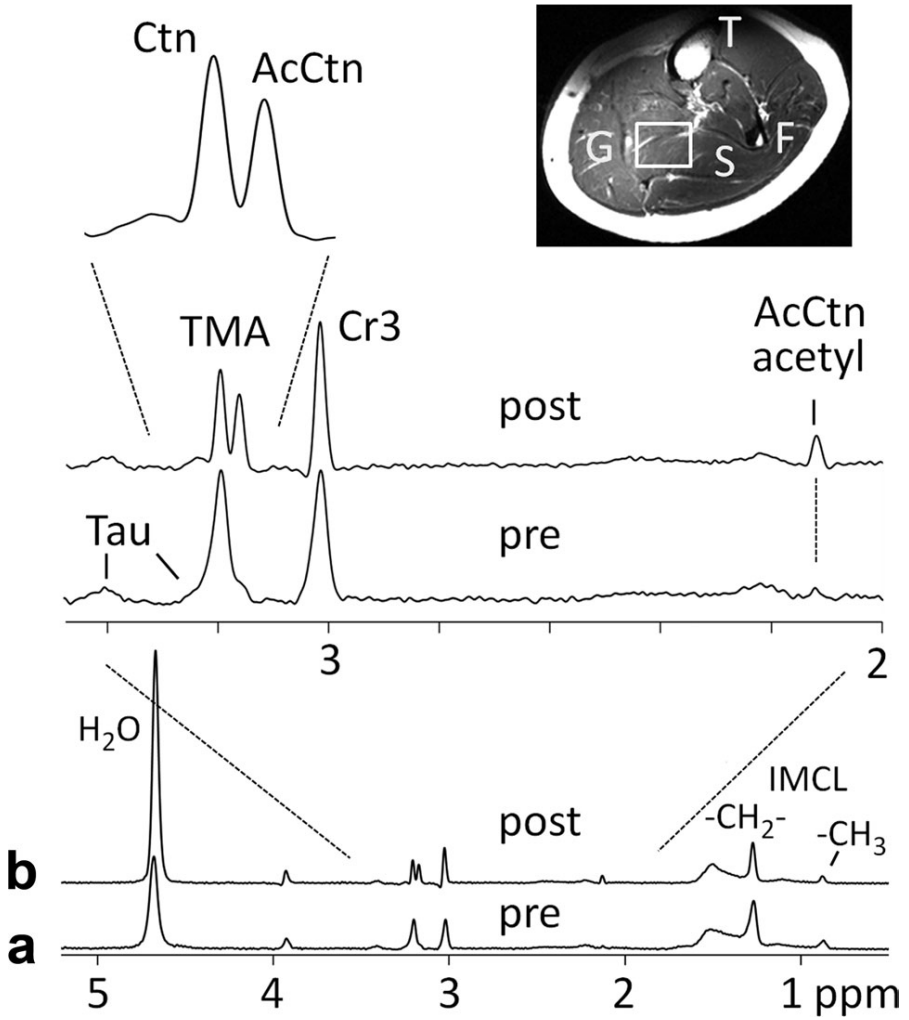
- Tibialis anterior muscle
- Creatine triplet is quantifiable at 7T





Carnitine and acetyl carnitine

- Important metabolite in energy metabolism
- Scans pre- and post exercise
- Split in TMA signal after exercise and extra resonance at 2.1 ppm
- Recovery of 2.1 and 3.17 signal are the same
- Observation of acetyl-carnitine by its TMA resonance

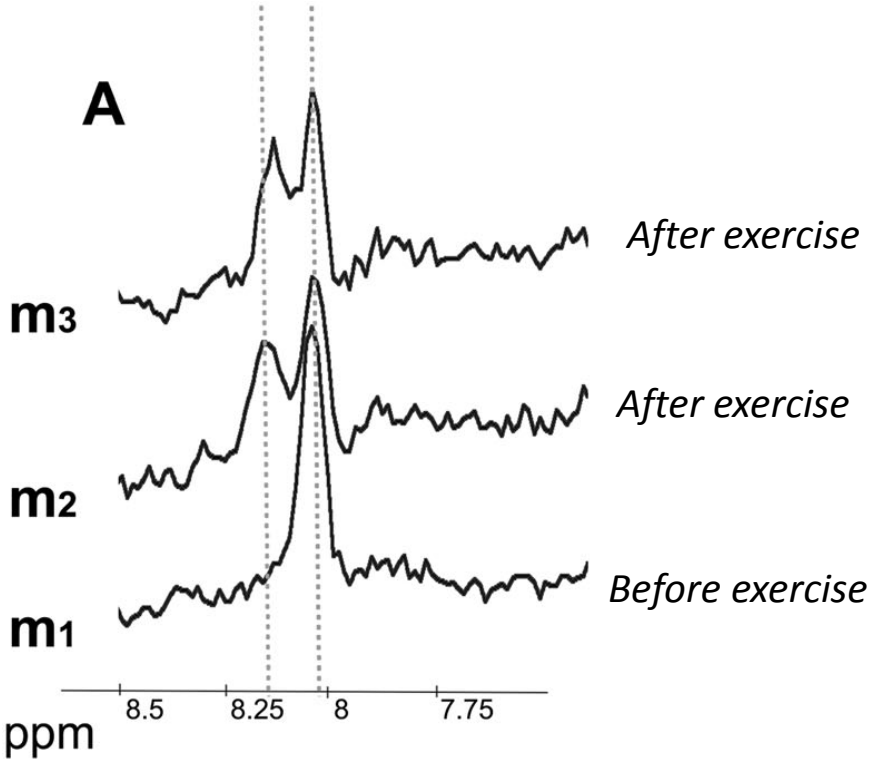


Ren et al. Magn Reson Med 2013

Carnosine

- pH buffering, anti-inflammatory function
- Dependent on fiber type, age, sex, training, nutritional intake
- Splitting of the 8 ppm resonance after exercise
- Two different pH compartments

Carnosine



Kukurova et al. NMR Biomed 2016

Summary ^{1}H MRS

- Combination of higher SNR and spectral resolution enables:
  - Fully resolved Cr CH_3 in dipolar coupled muscles
  - Assessment of acetyl carnitine by its TMA signal
  - Observation of splitting of 8 ppm carnosine signal

^{31}P MRS

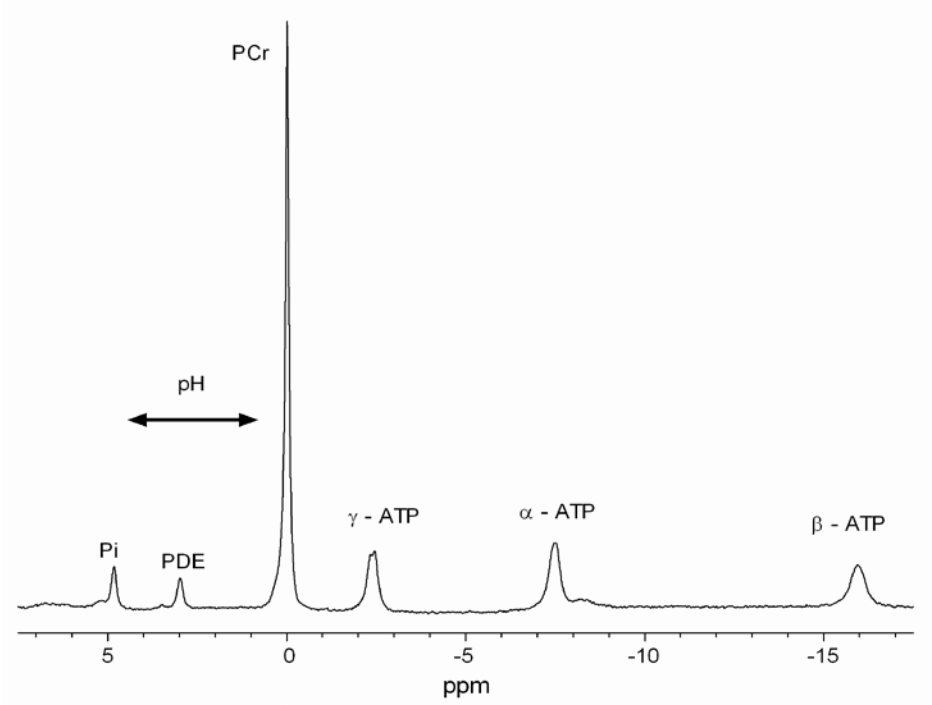
Muscle ^{31}P MR

Static measurements of energy metabolism:

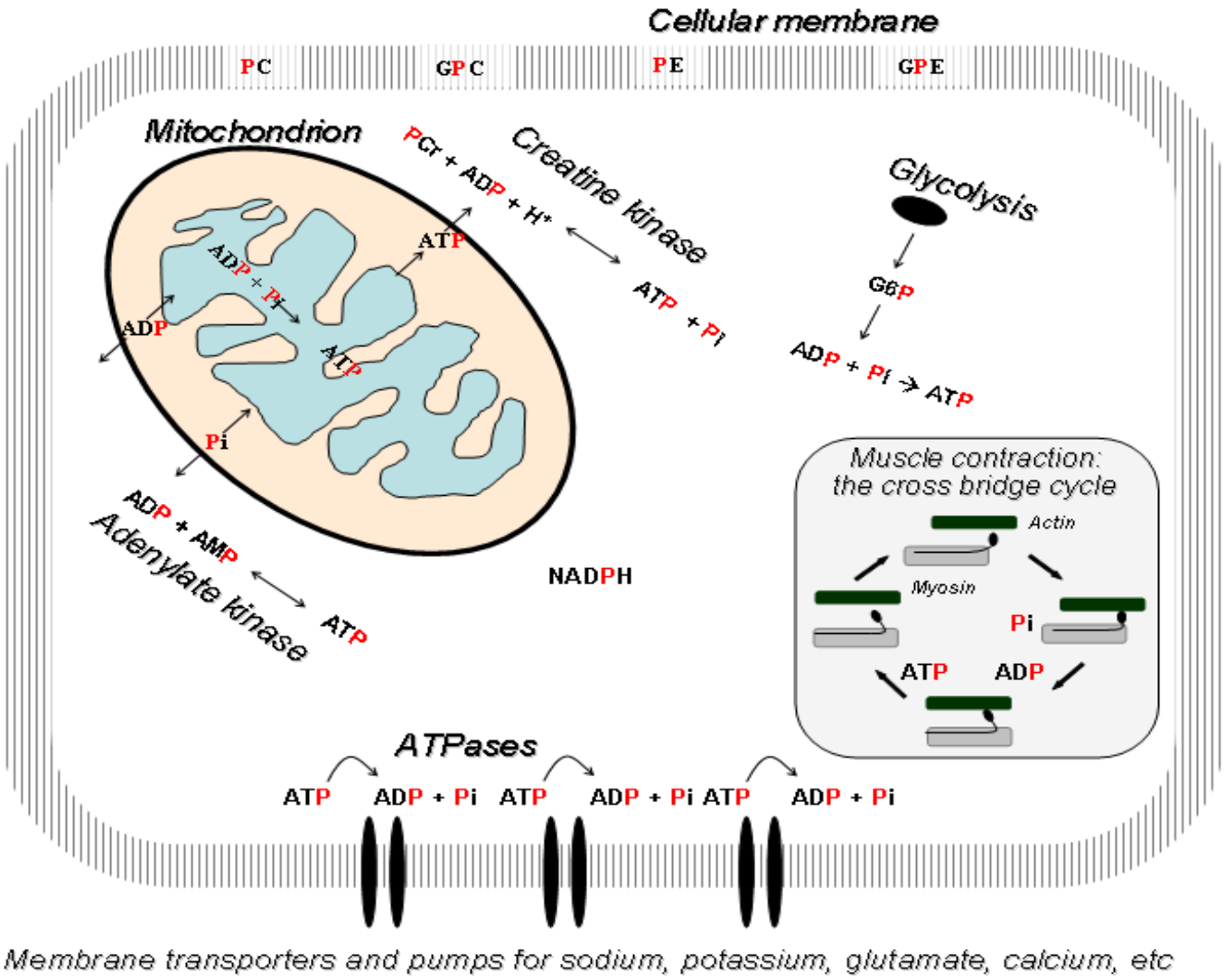
- Phosphocreatine
- Tissue pH
- ATP, phosphorylated sugars

Dynamic measurements

- Mitochondrial ‘capacity’
- pH response during exercise
- Exchange kinetics

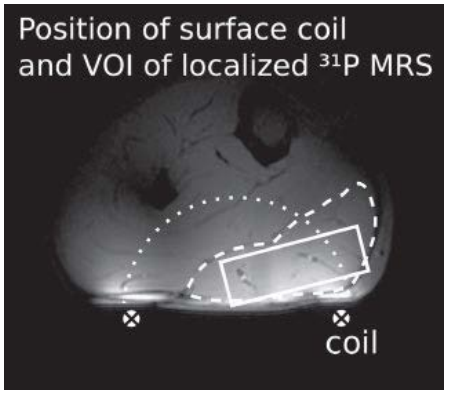


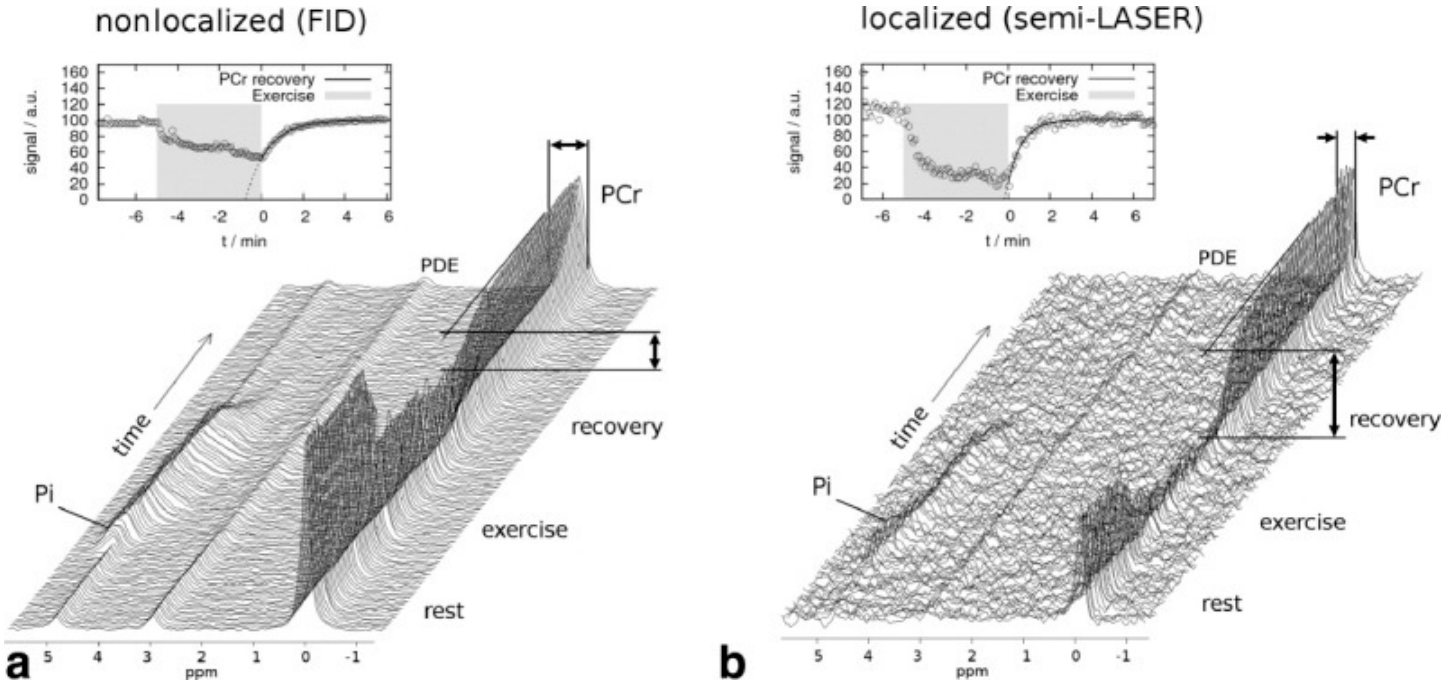
Phosphorous energy metabolism



7T facilitates use of localization

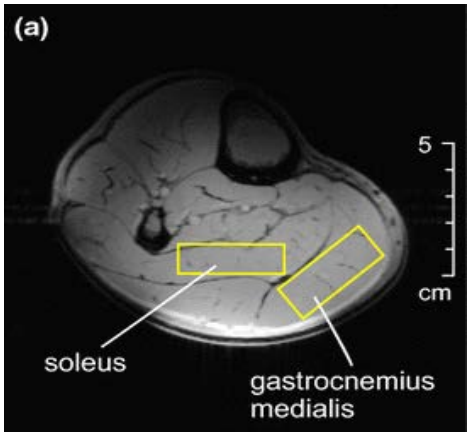
- Comparison of semi-laser vs coil-localized MRS
- More PCr breakdown and narrow line widths

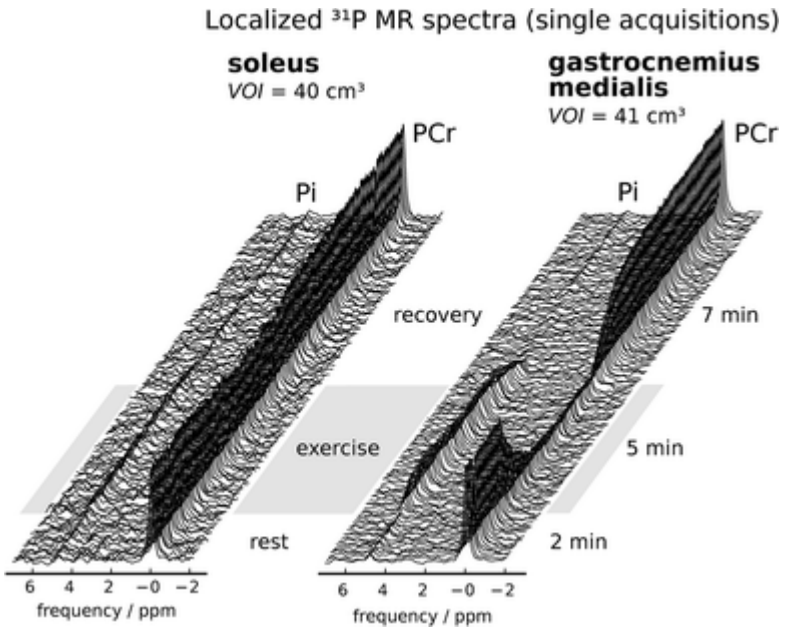


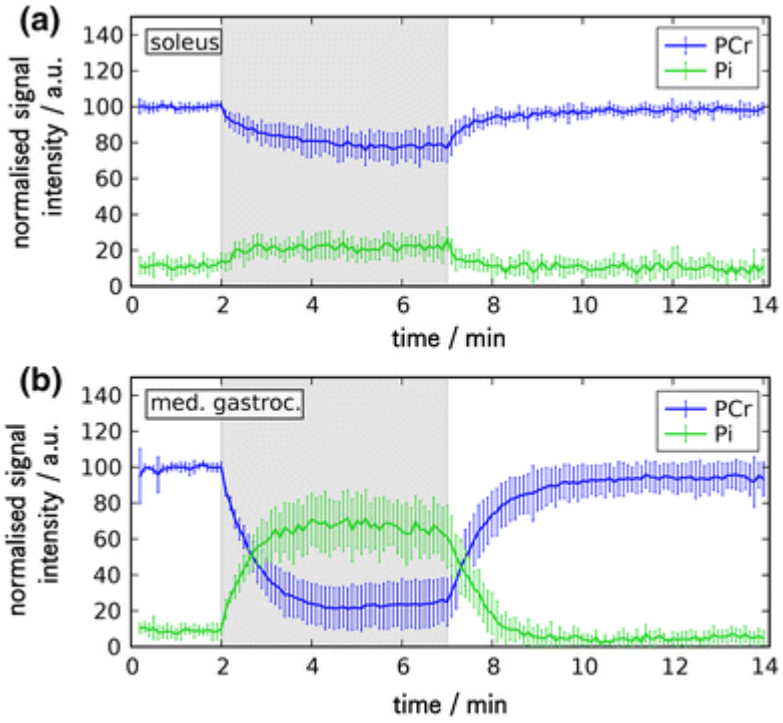


Meyerspeer et al, Magn Res Med 2012

Differences between muscles





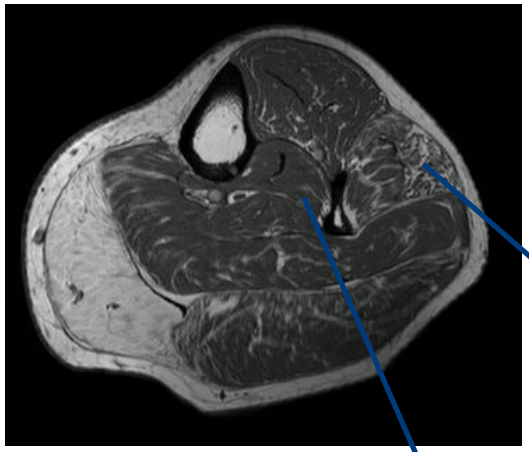


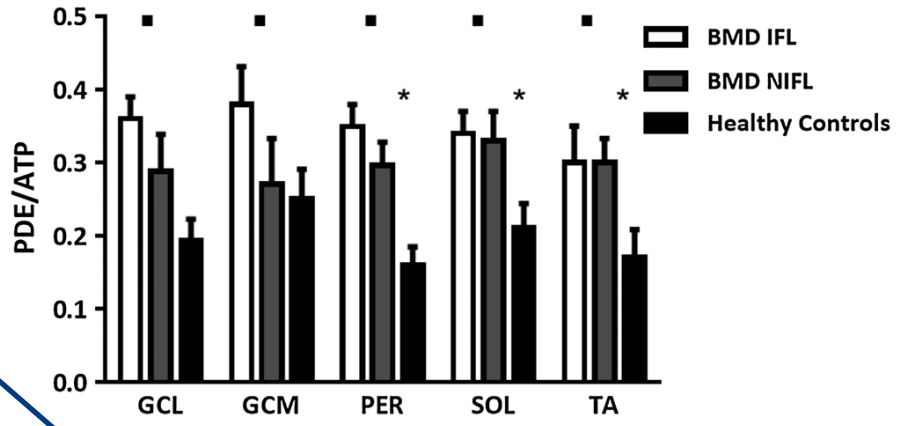
Meyerspeer et al, MAGMA 2015

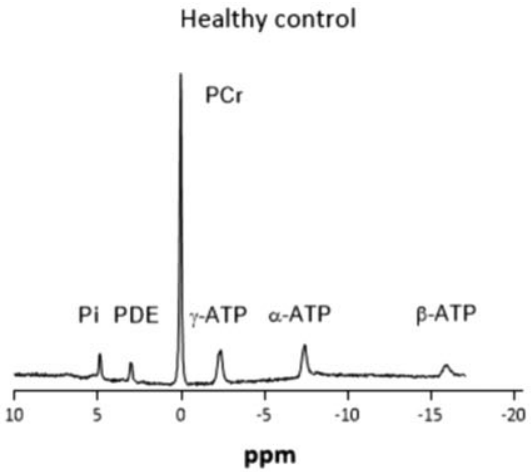
^{31}P MRS in muscular dystrophy at 7T

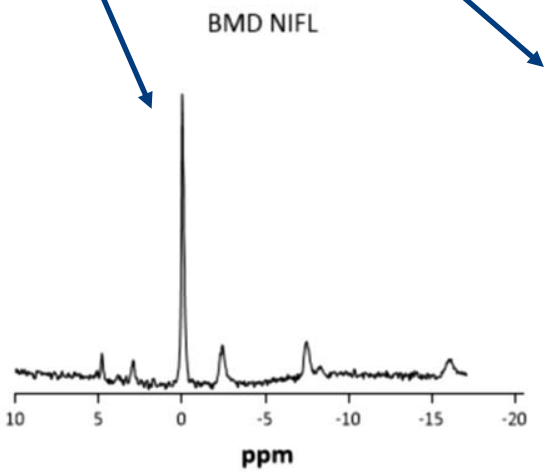
- Progressive muscle wasting
- Muscle symptoms:
  - Fatty infiltration
  - Inflammation/edema
  - Fibrosis
  - Disturbed energy metabolism
- Not all muscles affected equally
- Previous studies using surface coils: mixture of tissue types

Changes in metabolism in absence of fatty infiltration





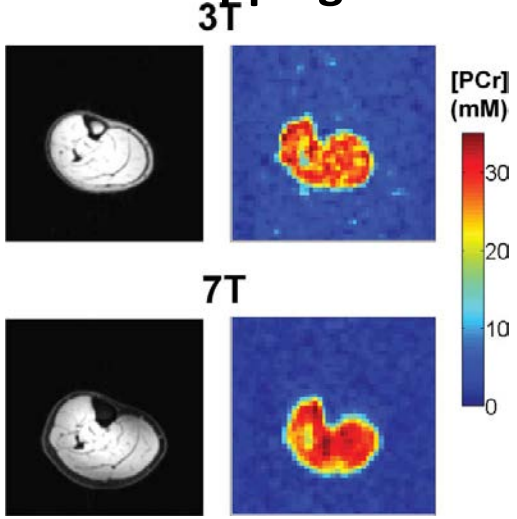




Wokke et al, NMR in Biomed 2014

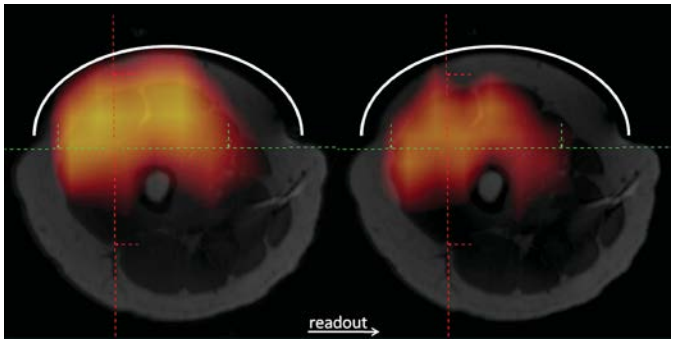
7T boosts the use of ^{31}P imaging

PCr mapping



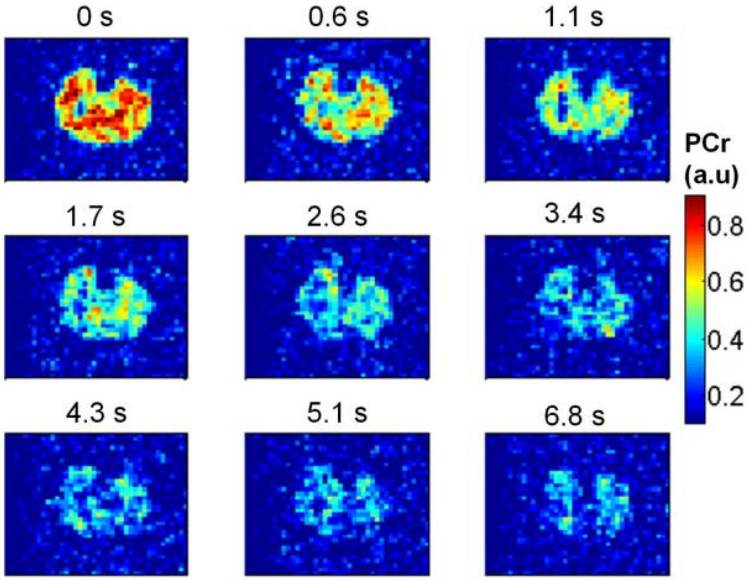
Parasoglou et al, Magn Res Med 2013

PCr and b-ATP mapping



Steinseifer et al, Magn Res Med 2013

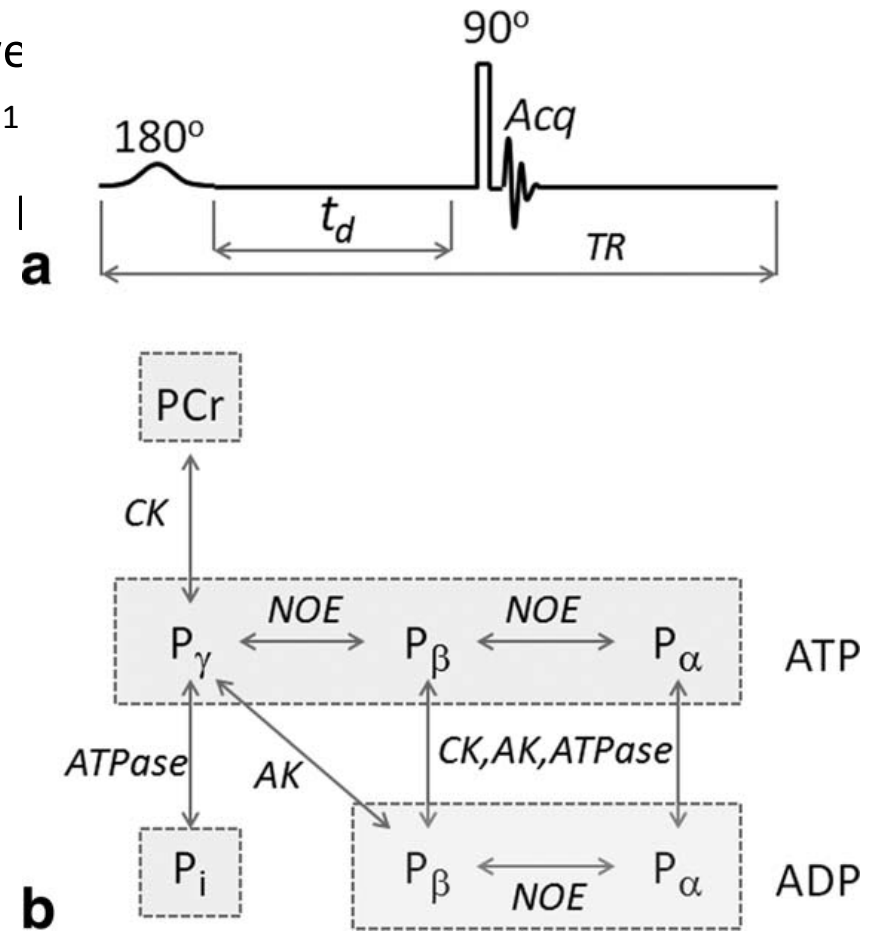
Saturation transfer



Parasoglou et al, Sci Rep 2014

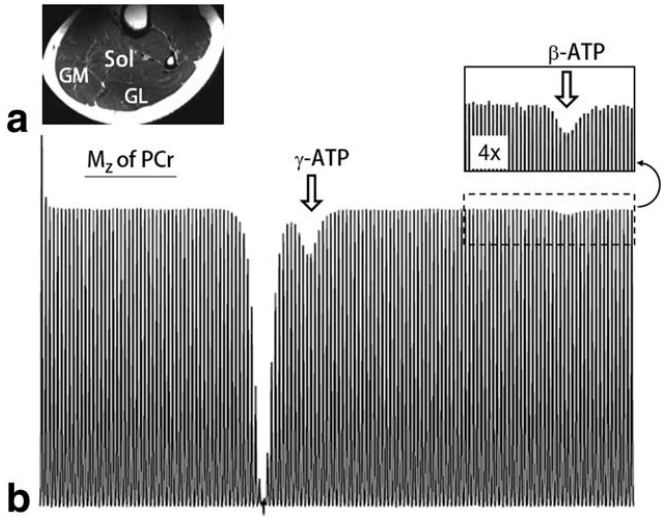
Exchange kinetics by inversion transfer

- CEST like approach using low powe
- Assessment of many exchanging [31]
- No assumptions needed on which
- Large dynamic range

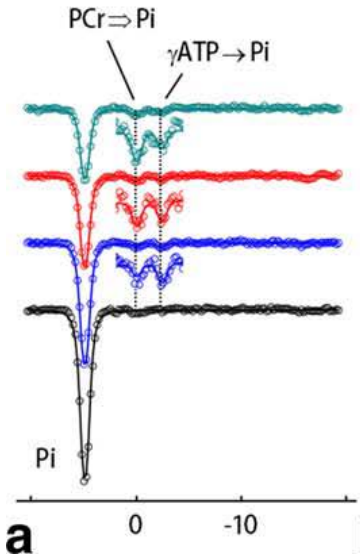


Ren et al, Magn Res Med 2015

EKIT spectrum



Ren et al, Magn Res Med 2015



t_d (sec)

3

2

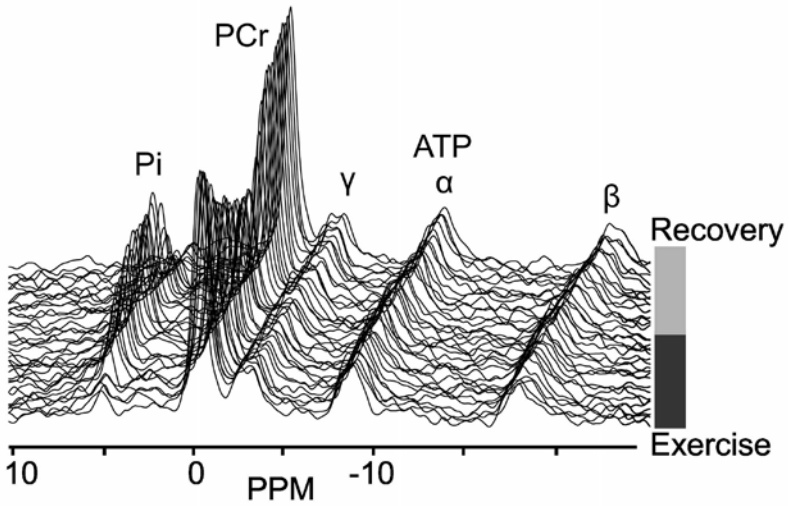
1

0

Second Pi compartment

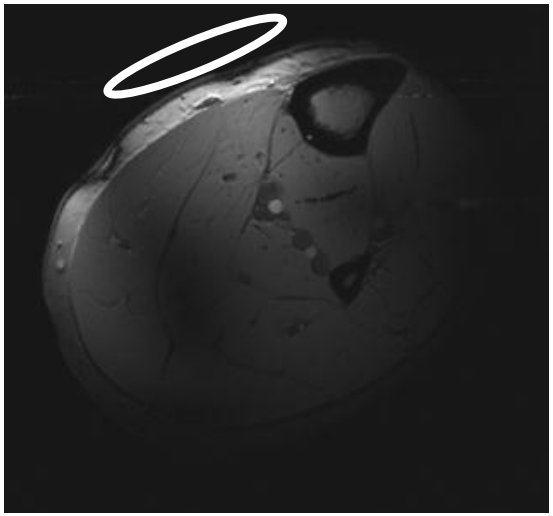
Common methods to assess mitochondrial capacity:

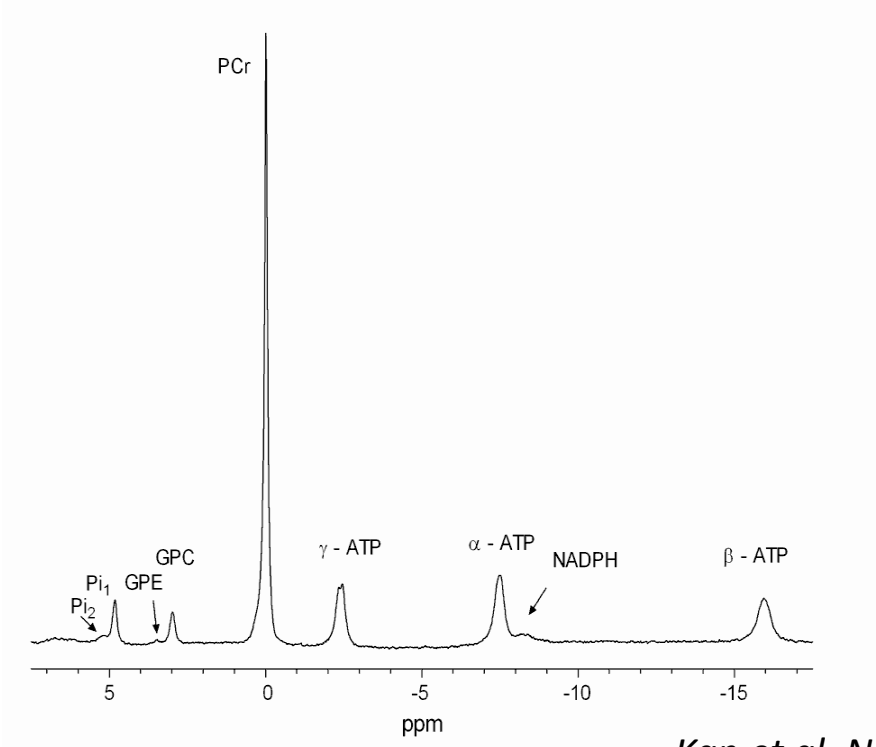
- Recovery of phosphocreatine (PCr) signal after exercise
- Saturation transfer



Alkaline Pi

- Resonance frequency of Pi depends on tissue pH
- Mitochondrial pH is 0.4 units more alkaline than cytosol
- Assessment of mitochondrial Pi possible at 7T?





Kan et al, NMR Biomed 2010

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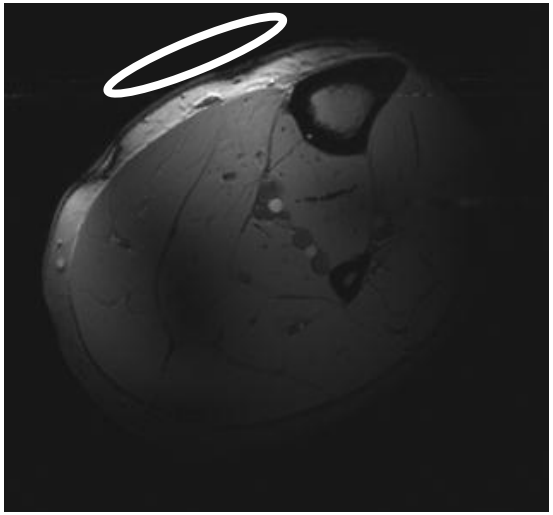
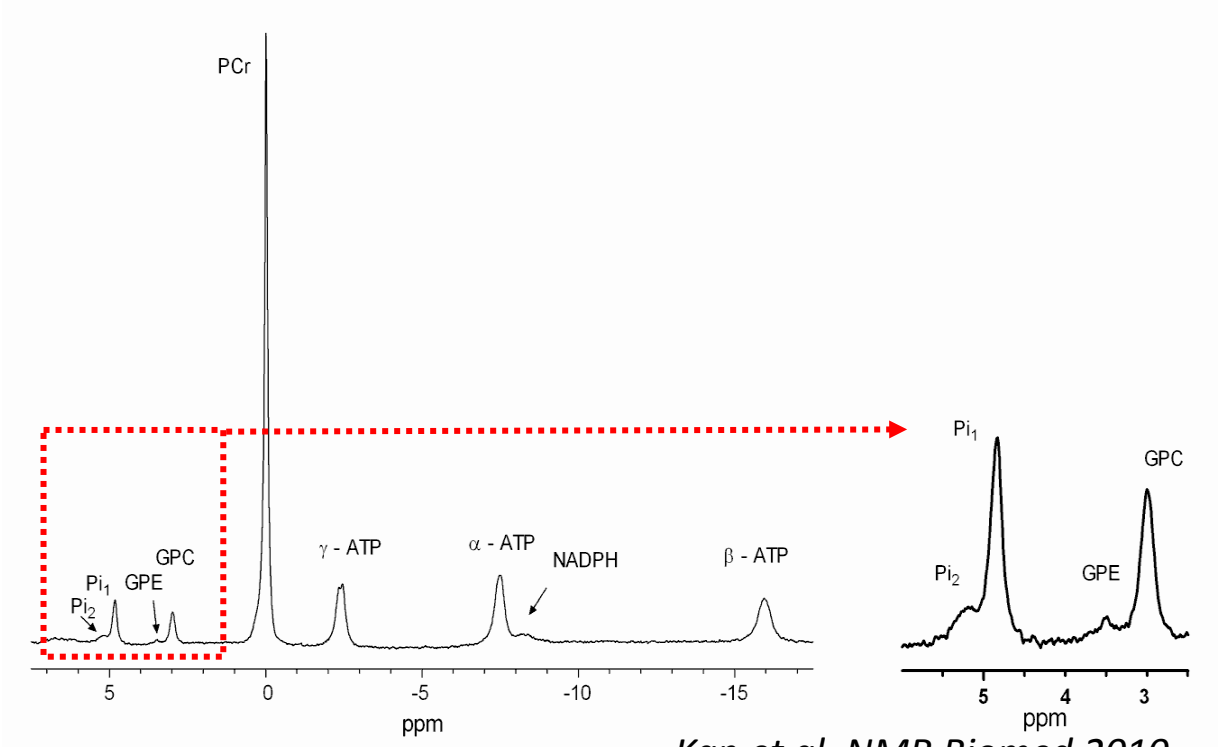
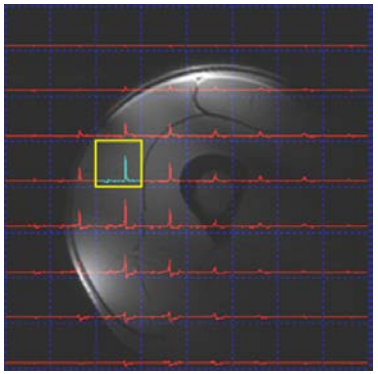


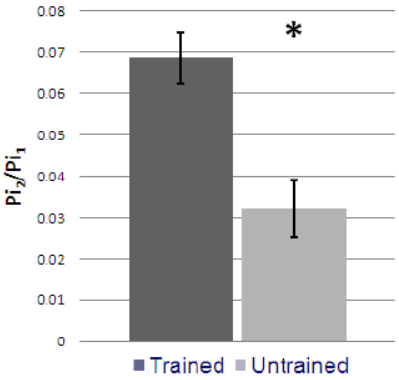


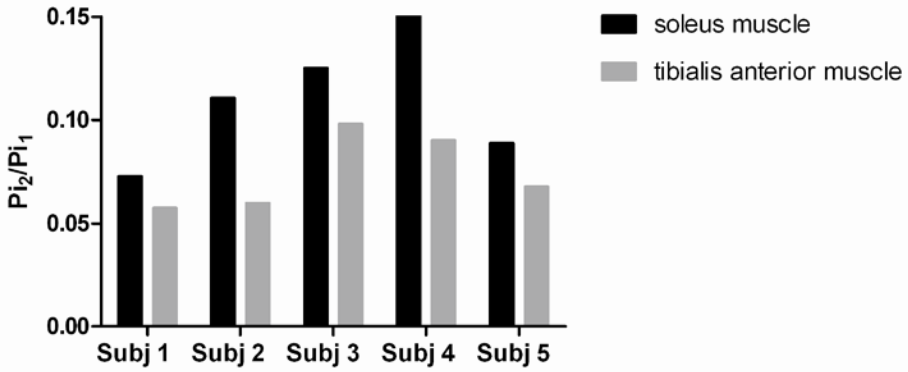
Kan et al, NMR Biomed 2010

Mitochondrial Pi?

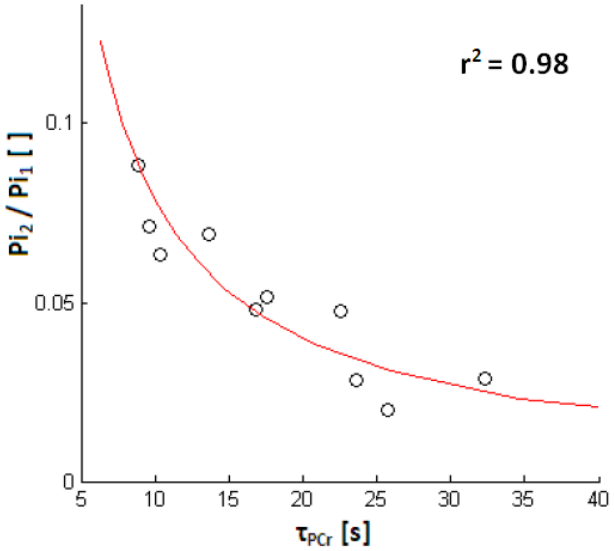
- Differences between muscles
- Differences between trained and untrained subjects
- Correlation with PCr recovery







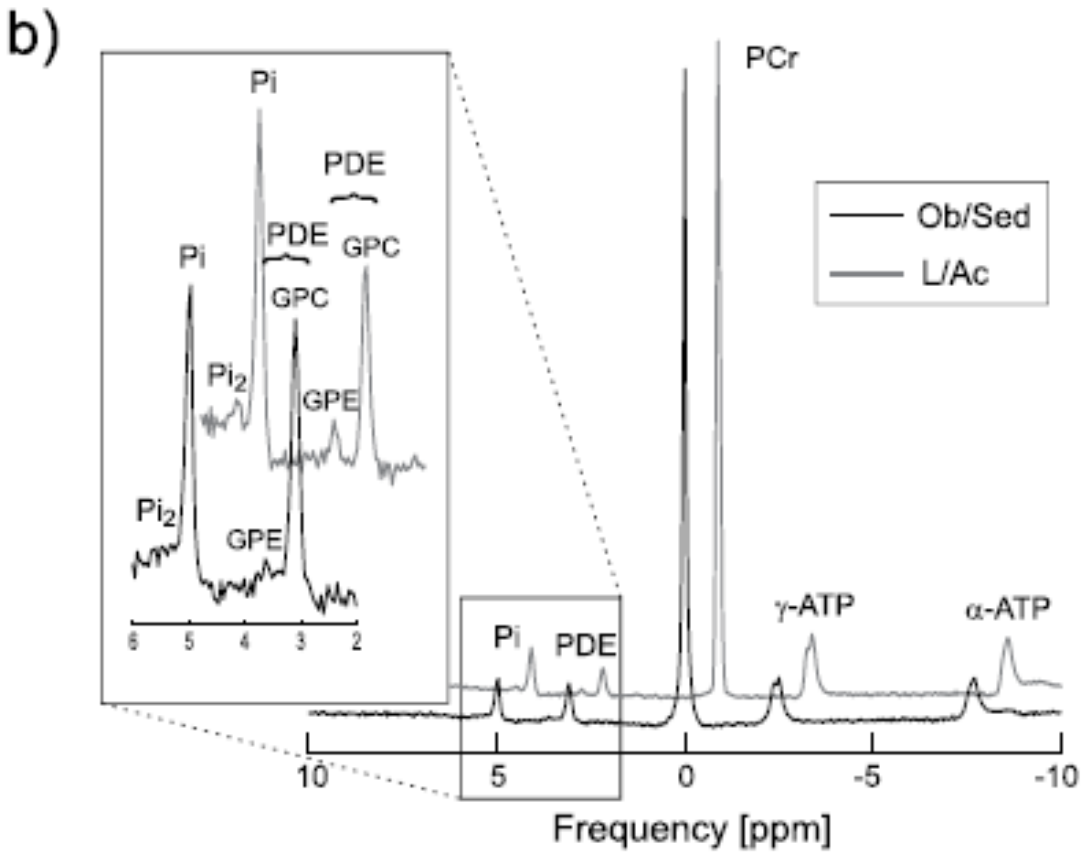
Kan et al, NMR Biomed 2010



Van Oorschot et al, PlosOne 2013

Alkaline Pi lower in overweight subjects

- Alkaline Pi most predictive of exercise capacity
- GPC also correlates with exercise capacity



Valkovic et al, Sci Rep 2016

Specific advantages of high field ^{31}P MRS

- Signal localization:
  - Assessment of individual muscles instead of mixture of tissue types
  - Imaging approaches
- Use of increased SNR and spectral resolution
  - Exchange kinetics by Inversion Transfer
  - Alkaline Pi

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Thank you for your attention