31P WIDEBAND INVERSION TRANSFER FOR MEASURING ATP SYNTHESIS RATES IN HUMAN SKELETAL MUSCLE

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There has been a long-standing interest in measuring ATP synthesis rates *in vivo*. Recent studies using ^{31}P saturation transfer (ST) suggest that the inorganic phosphate (Pi) → ATP flux in skeletal muscle may differ with age and development of insulin resistance and type 2 diabetes. Although simple in principle, ST requires prolonged saturation of γATP, typically 5 – 9 sec, which can at some fields be SAR limited. An alternative technique is inversion transfer (IT), but the conventional approach of selective inversion of γ-ATP is less efficient in reducing the Pi signal due to rapid leaking of magnetization to other spins in the exchange network, especially phosphocreatine (PCr).

PURPOSE: This study was designed to develop a magnetization transfer (MT) method that is sensitive to the γ-ATP ↔ Pi exchange pathway and that can be easily implemented on a human scanner for skeletal muscle studies.

METHODS: Wideband inversion was used to invert all major ^{31}P spins upfield of Pi, including PCr (0 ppm), γ-, α- and β-ATP (-2.4, -7.4 and -16.0 ppm) followed by a variable post-inversion delay period (t_d) to allow for chemical and spin magnetization exchanges before a hard-pulse readout. A series of ^{31}P spectra were acquired at 7T from human calf muscle of 4 healthy subjects at rest with varying t_d from 35 ms to 10 sec (12 data points) while keeping TR constant (20 sec). To correct for any partial inversion of Pi spins, ^{31}P data were also acquired using an inversion pulse with the same bandwidth (2700 Hz) but applied on the opposite side of Pi. A partial volume ^{1}H/^{31}P coil (ϕ = 10 cm) was used for ^{31}P detection. The protocol was approved by our local IRB.

RESULTS: ^{31}P spectra acquired with wideband inversion (Fig 1a) clearly showed a reduction in the intensity of Pi due to chemical exchange (Fig1b). There was a 4.5-fold increase in MT effect at Pi when using wideband inversion as compared to frequency-selective inversion of only γ-ATP (18% vs 4%, measured from Pi Mz/Mz^{max} ~ t_d curves at the maximal Mz reduction points, Fig 1b inset). The first-order rate constant for ATP synthesis calculated from these data was 0.06 ± 0.02 s^{-1} (n=4), in agreement with results by frequency-selective inversion (0.05 s^{-1}) and by ST (0.05 – 0.11 s^{-1}) in literatures.

DISCUSSION: With wideband inversion, both PCr and γ-ATP are inverted. This enables the replenishment of inverted γ-ATP by the long T_1 of PCr (Fig 1c) via creatine kinase-mediated pathway, and consequently amplifying chemical exchange effects at Pi. In comparison, using frequency-selective inversion of only γ-ATP, the inverted γ-ATP is drained by un-inverted PCr thereby attenuating the exchange effects seen at Pi (Fig 1c). For studies of γ-ATP ↔ Pi exchange kinetics, it is advantageous to choose wideband over frequency-selective inversion at high fields due to the increased T_1 value for PCr.

CONCLUSIONS: Wideband ^{31}P inversion provides an alternative approach for monitoring ATP synthesis in skeletal muscle. The single ^{31}P inversion pulse necessary for this measurement was easy to implement on the 7T scanner.

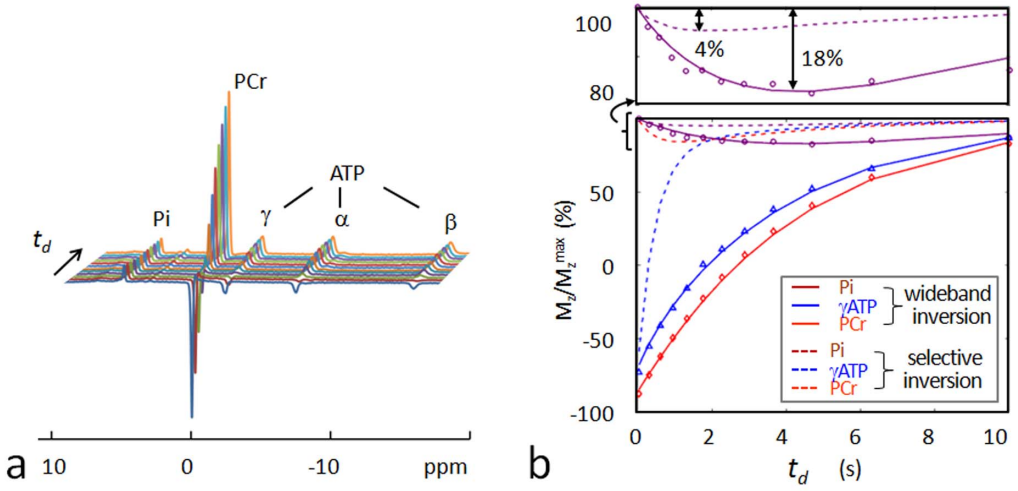

Fig.1 (a) ^{31}P MR spectra after wideband inversion at different delay times (t_d). (b) Inversion recovery data showing replenishment of the inverted γ-ATP signal and the long-T_1 PCr signal where Mz^{max} is the equilibrium Z-magnetization at TR 20 sec. Other NMR parameters: NSA = 4; excitation bandwidth 4 KHz; wideband/selective inversion bandwidth 2700/250 Hz.