European Journal of Radiology 82 (2013) 745–751

Contents lists available at SciVerse ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Time-resolved phosphorous magnetization transfer of the human calf muscle at 3 T and 7 T: A feasibility study

Ladislav Valkovič[a,b], Marek Chmelík[a], Ivica Just Kukurova[a], Martin Kršňák[c], Stephan Gruber[a], Ivan Frollo[b], Siegfried Trattnig[a,*], Wolfgang Bogner[a]

[a] MR Center of Excellence, Department of Radiology, Medical University Vienna, A-1090 Wien, Lazarettgasse 14, Austria
[b] Institute of Measurement Science, Department of Imaging Methods, Slovak Academy of Sciences, 841 04 Bratislava, Dúbravska cesta 9, Slovak Republic
[c] Department of Internal Medicine III, Medical University Vienna, A-1090 Wien, Lazarettgasse 14, Austria

ARTICLE INFO

Article history:
Received 25 August 2011
Accepted 19 September 2011

Keywords:
Magnetization transfer
Muscle metabolism
Phosphorous
Spectroscopy
7 T

ABSTRACT

Phosphorous (^{31}P) magnetization transfer (MT) experiments enable the non-invasive investigation of human muscle metabolism in various physiological and pathological conditions. The purpose of our study was to investigate the feasibility of time-resolved MT, and to compare the results of MT experiments at 3 T and 7 T.

Six healthy volunteers were examined on a 3 T and a 7 T MR scanner using the same setup and identical measurement protocols. In the calf muscle of all volunteers, four separate MT experiments (each ~10 min duration) were performed in one session. The forward rate constant of the ATP synthesis reaction (k_{ATP}) and creatine kinase reaction (k_{CK}), as well as corresponding metabolic fluxes (F_{ATP}, F_{CK}), were estimated. A comparison of these exchange parameters, apparent T_1s, data quality, quantification precision, and reproducibility was performed.

The data quality and reproducibility of the same MT experiments at 7 T was significantly higher (i.e., k_{ATP} 2.7 times higher and k_{CK} 3.4 times higher) than at 3 T ($p < 0.05$). The values for k_{ATP} ($p = 0.35$) and k_{CK} ($p = 0.09$) at both field strengths were indistinguishable. Even a single MT experiment at 7 T provided better data quality than did a 4 times-longer MT experiment at 3 T. The minimal time-resolution to reliably quantify both F_{ATP} and F_{CK} at 7 T was ~6 min.

Our results show that MT experiments at 7 T can be at least 4 times faster than 3 T MT experiments and still provide significantly better quantification. This enables time-resolved MT experiments for the observation of slow metabolic changes in the human calf muscle at 7 T.

1. Introduction

Phosphorus magnetic resonance spectroscopy (^{31}P-MRS) is a powerful tool for the noninvasive investigation of human muscle metabolism. It has been commonly used for the study of various physiological and pathological conditions [1]. Steady-state concentrations of high-energy metabolites (adenosine triphosphate [ATP] and phosphocreatine [PCr]) are very robust and do not reflect the mitochondrial activity and function of cells, i.e., the synthesis and consumption of ATP, in a broad range of pathologies. Only direct kinetic measurements by magnetization transfer (MT) ^{31}P-MRS and/or dynamic ^{31}P-MRS during the exercise and subsequent recovery provide a quantitative assessment of metabolic functions.

Metabolic fluxes measured by MT experiments provide information about the steady-state metabolite turnover, and therefore, reflect mitochondrial activity or function [2]. Another independent measure of resting-state ATP turnover is the observation of PCr depletion during ischemia [3]. In contrast, post-exercise PCr recovery in dynamic ^{31}P-MRS experiments is likely to reflect maximum mitochondrial output or capacity [1]. Although these methods do, in fact, determine different parameters, there is reported correlation between resting-state ATP turnover measured by MT and ischemic PCr depletion, as well as with PCr recovery during dynamic exercise-recovery experiments [3].

MT techniques allow the *in vivo* observation of metabolic fluxes caused by the exchange of phosphate ions between γ-ATP and inorganic phosphate (Pi) (i.e., ATPase) and between γ-ATP and PCr (the creatine-kinase [CK] reaction). The transfer of magnetization can be studied by the selective suppression of the γ-ATP resonance and simultaneous measurement of the reduction in signal strength of its

* Corresponding author. Tel.: +431 40400 6460; fax: +431 40400 7631.
E-mail addresses: siegfried.trattnig@meduniwien.ac.at (L. Valkovič), marek.chmelik@meduniwien.ac.at (M. Chmelík), ivica.kukurova@meduniwien.ac.at (I. Just Kukurova), martin.krssak@meduniwien.ac.at (M. Kršňák), stephan@nmr.at (S. Gruber), umerollo@savba.sk (I. Frollo), siegfried.trattnig@meduniwien.ac.at (S. Trattnig), wolfgang@nmr.at (W. Bogner).

0720-048X/$ – see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ejrad.2011.09.024

exchange partners (PCr, Pi) [4,5]. Many studies have used MT techniques in human skeletal muscle to study the relationship between unidirectional ATP synthesis, for example, in insulin resistance and type 2 diabetes [6], and other metabolic syndromes [7]. MT experiments are the only possible method by which to study the energy metabolism of organs that cannot be challenged by exercise in the MR scanner (for example, the liver) [8].

The utilization of MT techniques is inherently limited by the time required to perform a single experiment (~30–120 min) [6,9,10]. Thus, to date, it is not possible to observe metabolic changes on a finer time scale, such as the early effects in insulin clamp studies (<15 min) [9]. Previous MT studies of human muscles were performed at magnetic field strengths of ≤3 T. Ultra-high-field MR systems, such as 7 T, offer advantages for ^{31}P-MRS in terms of spectral quality, which has been demonstrated recently in non-localized [11] and localized [12] ^{31}P-MRS of the calf muscle. Improved spectral quality translates to an increase in measurement precision and a concurrent reduction in the overall measurement time of MT experiments. Using a higher field strength also resulted in a significant shortening of mixed T_1 relaxation times (T_1^{mix}), which could lead to a potential reduction in acquisition time [11]. Thus, we can hypothesize that a series of short MT experiments with a time resolution of <10 min could be sufficient for the observation of slow changes in human muscle metabolism.

The focus of this study was to compare the precision of MT experiments performed at 3 T and 7 T in the human calf muscle, with identical measurement protocols, and to analyze the potential time resolution of MT experiments at 7 T.

2. Materials and methods

2.1. Subjects

Six healthy, non-obese volunteers (two females; mean age, 25 years; range, 22–30) were recruited for this study. All participants fasted overnight for at least 12 h before the experiments. The study protocol was approved by the local ethics committee, and written informed consent was obtained from all subjects. All authors or authors' institutions have no conflict of interest.

2.2. ^{31}P-MRS examination

Measurements were performed consecutively on two MR scanners of different field strengths (a 3 T TIM TRIO and a 7 T Magnetom) from the same manufacturer (Siemens Healthcare, Erlangen, Germany). Dual-tuned ^{1}H/^{31}P single-loop coils of identical geometry, with a 10 cm diameter (RAPID Biomedical GmbH, Rimpar, Germany), were used on both systems. Subjects were examined in the supine position with the medial head of the right gastrocnemius muscle positioned over the surface coils. To prevent movement during each examination, the coil was fixed and the leg was secured using sandbags. Prior to all measurements, manual shimming was performed, the phosphorus reference frequency was fixed to PCr, and flip angles were adjusted. The vector size of spectral data was set to 1024 complex points and receiver bandwidth was adjusted to 3 kHz and 5 kHz for 3 T and 7 T, respectively. Rectangular excitation pulses (flip angle 90°; duration 400 μs), adiabatic inversion pulses (WURST shape; duration 5 ms), and continuous irradiation for saturation were used. Repetition time (TR), acquisition delay (TE*), inversion time (TI), and acquisition time (TA) were the same at both field strengths. The TR was set to 15 s in all ^{31}P experiments according to previous MT studies in the human calf muscle at 3 T [3,6].

Intramyocellular concentrations of ^{31}P metabolites were assessed based on non-localized spectra (TR = 15 s; TE* = 0.4 ms; 16 averages) without suppression. The γ-ATP resonance was used as an internal reference rather than the β-ATP, because the shape of the excitation pulse could have influenced the amplitude of the β-ATP at 7 T. A constant ATP concentration of 5.5 mmol/l in the skeletal muscle was assumed [13].

2.3. MT experiment

Resting-state ATP turnover was measured using a magnetization transfer experiment. The exchange between γ-ATP and Pi (ATP synthesis), and between γ-ATP and PCr (the CK reaction), were investigated [10,14] (Fig. 1). The protocol was split into four independent parts to investigate the possibility of time-resolved assessment of ATP synthesis and the CK reaction.

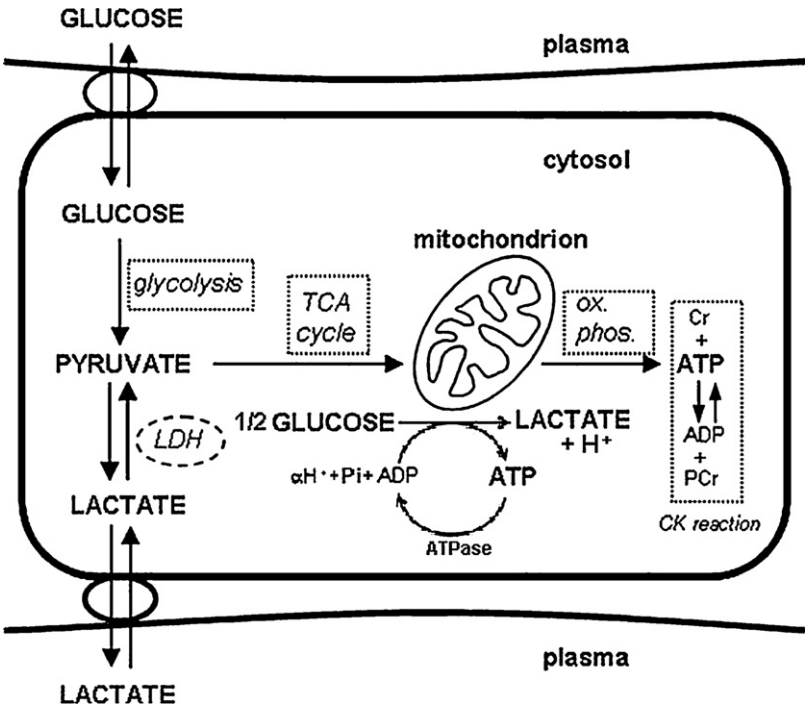

Fig. 1. Simplified scheme of the exchange system PCr ↔ ATP (CK reaction) and ATP ↔ Pi (ATPase reaction) in human muscle cells.