Metabolic Abnormalities in Patients with Mitochondrial Myopathy Evaluated by *In Vivo* ^{31}P Magnetic Resonance Spectroscopy

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Purpose : To investigate the phosphorus metabolic abnormalities in skeletal muscle of patients with mitochondrial myopathy using *in vivo* ^{31}P magnetic resonance spectroscopy (MRS).

Materials and Methods : Patients with mitochondrial myopathy (N=10) and normal control subjects (N=10) participated. All *in vivo* ^{31}P MRS examinations were performed on 1.5T whole-body MRI/MRS system by using an image selected *in vivo* spectroscopy (ISIS) pulse sequence that provided a $4\times4\times4$ cm^3 volume of interest (VOI) in the right thigh muscle tissue. Peak areas for each phosphorus metabolite were measured using a Marquart algorithm.

Results : The specific features in patients with mitochondrial myopathy were a significant increase of Pi/PCr ratio ($p=0.003$) and a significant decrease of ATP/PCr ratio ($p=0.004$) as compared with normal controls. In particular, the β-ATP/PCr ratio between controls and patients with mitochondrial myopathy was predominantly altered. No significant pH difference between patients and controls was established.

Conclusions : *In vivo* ^{31}P MRS may be a useful modality in the clinical evaluation of patients with mitochondrial myopathy based on ATP/PCr and Pi/PCr ratios in skeletal muscle tissue and provides a valuable information in further understanding disorders of muscle metabolism.

Index words : ^{31}P magnetic resonance spectroscopy ; Mitochondrial myopathy

Introduction

Mitochondrial myopathy has increasingly recognized as uncommon causes of muscle disorders characterized by disorders of mitochondrial function that result in impaired cellular adenosine triphosphate (ATP) synthesis in affected cells (1 — 2). Biochemical analysis of isolated muscle mitochondria has shown specific abnormalities of mitochondrial metabolism (3). Some cases with similar clinical features had different metabolic disturbances, while others with similar metabolic abnormality differed clinically (4). Clinical manifestations are extraordinarily variable (5) and appropriate treatment has not been fully established. In addition

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to histological identification by small muscle biopsy, diagnosis of mitochondrial myopathy can be challenging and usually requires an extensive metabolic profile of blood and muscle, and then a large biopsy specimen of muscle from which functioning mitochondria are isolated.

In vivo ^{31}P magnetic resonance spectroscopy (MRS) has been successfully used to study energy metabolism in normal and diseased human muscles *in vivo* (6—8). ^{31}P MRS has been increasingly applied to identify and quantify the levels of biochemical compounds, and to investigate the metabolism of a variety of diseases and disorders because it is a noninvasive and potentially risk-free technique (9). In addition to detection of the energy metabolism bounded with the presence of high energy phosphates [phosphocreatine (PCr), adenosin-triphosphate (ATP)] and inorganic phosphate (Pi), ^{31}P MRS is also able to estimate intracellular pH, metabolic activities of the glucogenolytic muscle fibers, enzyme activities of citric cycle, oxidative phosphorylation, pentose cycle, lipids metabolism and ATPases activity (10). A spatially localized *in vivo* MR pulse sequence, image selected *in vivo* spectroscopy (ISIS) (11), was used to improve localization and optimization of the volume of interest (VOI) in MR images. Hence, spatially localized *in vivo* ^{31}P MRS may offer a better quality of information on the biochemical alterations in the skeletal muscle tissue.

The purpose of this study was to investigate the phosphorus metabolic differences of the skeletal muscle in patients with mitochondrial myopathy compared with normal controls, and to test the possibility that ^{31}P MRS could provide neuropathologic criteria in the diagnosis of with mitochondrial myopathy. Employing *in vivo* ^{31}P MRS with an ISIS pulse sequence, we report the phosphorus metabolite ratios between normal control subjects and patients with mitochondrial myopathy.

Materials and Methods

1) Subjects

Ten patients with mitochondria myopathy (four males and six females; age range 9—53) and ten normal control subjects (five males and five females; age range 23—36) participated in this study.

Normal control subjects were recruited from the Catholic University Medical Center staff, residents, interns, and medical students. The volunteers were screened, and none of normal control subjects had a history of substance dependence or current abuse or a history of neurologic disorders.

2) MRS examination

All *in vivo* ^{31}P MRS experiments were performed on a 1.5T whole-body MRI/MRS system (GE Signa Advantage 4.8 Version; GE Medical Systems, Milwaukee, WI, USA) with use of a ^{1}H and ^{31}P dual 6 inch surface coil (Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, USA) that was tuned to two uniform RF fields (63.86 MHz for ^{1}H and 25.85 MHz for ^{31}P). T1- and T2-weighted MR images were obtained with 256×128 of acquisition matrix, 20 cm of FOV, 2 NEX of acquisition, 5mm of slice thickness. All of the ^{31}P MR spectra were obtained at ambient temperature (18—20°C). The localization was guided by T1-weighted, axial MR images (20ms TE, 400ms TR) as the first step in the MR spectroscopic examination (Fig. 1). It took approximately 25 minutes for ^{31}P MR spectrum per case. Using stimulated echo acquisition method (STEAM) pulse sequence (12), the external magnetic field B_0 was shimmed to the sensitive volume of the surface coil positioned on the right thigh muscle by means of the proton resonance from tissue water. The water line width (full width at half the maximum intensity) was typically 4—5Hz.

ISIS pulse sequence for ^{31}P MRS was employed for spatially localized volumes of 64 $(4\times4\times4)cm^3$. Spectral parameters were as follows: 256×128 of

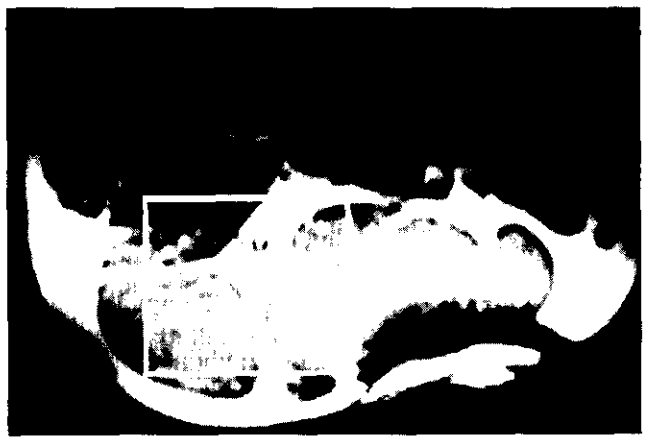

Fig. 1. T1-weighted axial MR image of a patient with mitochondrial myopathy in the right thigh muscle tissue defining the voxel selected for localized *in vivo* ^{31}P MRS.

acquisition matrix ; 8 NEX of acquisition ; 30msec of echo time ; 3secs of repetition time ; 256 of number of averaging ; 2500Hz of spectral width ; and 2048 of number of data points. Raw data were obtained from completion of scan averages per each examination, transferred to a Sun SPARC station *IPC* (Sun Microsystems, Mountain View, California) and processed by the SAGE data analysis package (GE Medical Systems, Milwaukee, WI). An exponential multiplication of line broadening 5Hz was applied for apodization to reduce the noise level. After one-dimensional Fourier transformation, the spectra were phased manually by zero- and first-order phase corrections. Frequency domain spectra were phased by hand, using frequency-independent phase corrections only. Phased absorption spectra were reported directly without baseline correction or resolution enhancement. All of the ^{31}P MR spectra were plotted and analyzed in the absorption mode, and fitted to Lorentzian lineshapes. Peak areas for each phosphorus metabolite were measured using a Marquart algorithm. ^{31}P MR resonances in the spectra were tentatively assigned on the basis of prior assignments such as PCr, Pi, phosphomonoesters (PME), phosphodiesters (PDE), and the $\alpha-$, $\beta-$, and $\gamma-$phosphorus of ATP (13). Chemical shifts in ^{31}P MR spectra were referenced to the position of PCr (δ=0.0ppm). The Pi/PCr ratio (which is an approximate index of [adenosine diphosphate : ADP]) (14) was measured to estimate the phosphorylation potential and mitochondrial activity or "energy reserve" within cells (15). The pH was calculated from the difference (δobs) between the fitted line positions of PCr and Pi using the standard formula (16).

3) Statistics

Statistical analysis was performed using SPSS (SPSS for Windows, Version 6.0, SPSS Inc., Chicago, Illinois). The data were analyzed with two-tailed t-tests, where $p<0.05$ was considered significant to account for multiple comparisons.

Results

Figure 1 shows a typical T1-weighted axial MR image from the patient with mitochondrial myopathy selected for localized in vivo ^{31}P MRS. There were no significant signal changes in the T1-weighted spin echo MR images. Typical spectra obtained

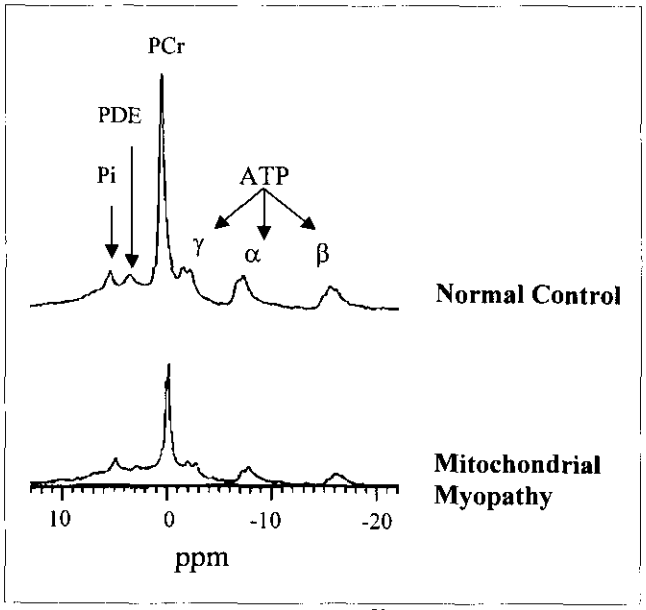

Fig. 2. Typical localized in vivo ^{31}P MR spectra obtained from the right thigh muscle tissue of a normal control and a patient with mitochondrial myopathy. Chemical shifts are indicated in parts per million (ppm). Compared with intensities of ATP, a marked decrease of the PCr signal intensity is noted in the patient with mitochondrial myopathy.

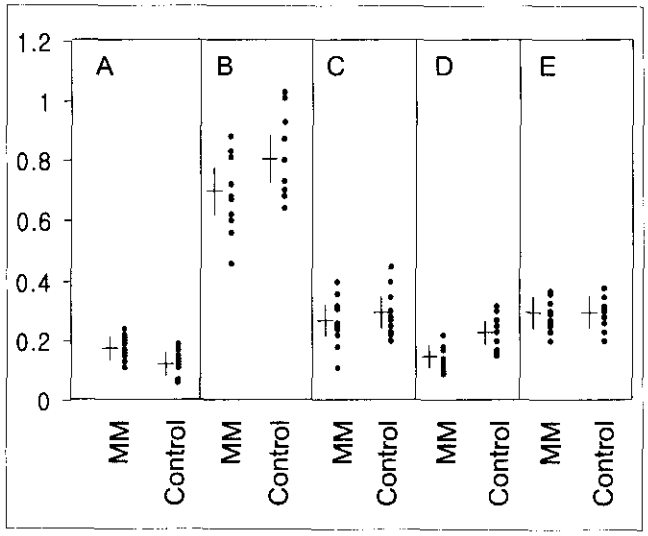

Fig. 3. Comparison of phosphorus metabolite ratios between patients with mitochondrial myopathy and normal controls. (**a**) Pi/PCr, (**b**) T-ATP/PCr, (**c**) $\alpha-$ATP/PCr, (**d**) $\beta-$ATP/PCr, (**e**) $\gamma-$ATP/PCr. Measurements from each individual subjects are plotted. Labels are : MM = mitochondrial myopathy, PCr = phosphocreatine, Pi = inorganic phosphate, ATP = adenosine triphosphate, and T-ATP = $\alpha-$ATP+$\beta-$ATP+$\gamma-$ATP. A simbol of "+" stands for mean ± standard deviation (SD).

from the patient with mitochondrial myopathy and control subjects are shown in Figure 2. The phosphate components of skeletal muscle tissue consisted of PME, Pi, PDE, PCr, and the $\alpha-$, $\beta-$, and $\gamma-$phosphorus of ATP. The resonance peaks for phosphate metabolites were assigned as followes: PME, 7.1 ppm; Pi, 5.3 ppm; PDE, 3.6 ppm; PCr, 0.0 ppm; $\gamma-$phosphorus of ATP, -2.4 ppm; $\alpha-$phosphorus of ATP, -7.7 ppm; and $\beta-$phosphorus of ATP, -16.1 ppm. Spectral patterns of the skeletal muscle tissue between patients with mitochondrial myopathy and control subjects were substantially different. The specific features in patients with mitochondrial myopathy were a significant increase of Pi/PCr ratio ($p=0.003$) and a significant decrease of ATP/PCr ratio ($p=0.004$) compared with normal controls. In particular, $\beta-$ATP/PCr ratio in patients with mitochondrial myopathy showed a marked decrease compared with that in normal control ($p=0.04$), while $\alpha-$and $\gamma-$ATP/PCr ratios in patients with mitochondrial myopathy showed no significant changes. In addition to substantial variations of PCr, Pi and ATP signals, a slight change of PDE signal was observed in several patients with mitochondrial myopathy. However, alteration of PME signal was negligible in patients with mitochondrial myopathy. Figure 3 shows a comparison of phosphorus metabolite ratios [(A) Pi/PCr, (B) T-ATP/PCr, (C) $\alpha-$ATP/PCr, (D) $\beta-$ATP/PCr, (E) $\gamma-$ATP/PCr] between patients with mitochondrial myopathy and normal controls. Comparison of phosphorus metabolite ratios and pH between patients with mitochondrial myopathy and normal controls is shown in Table 1. No significant pH difference between patients and controls was established.

Discussion

The ability of a noninvasive technique, localized *in vivo* ^{31}P MRS was demonstrated to monitor phosphate metabolic alterations of skeletal muscle tissue in patients with mitochondrial myopathy. Phosphorus containing metabolites that can be identified by ^{31}P MRS play an important role in the metabolism of both diseased tissue and normal. A ^{31}P MR spectrum obtained by ISIS pulse sequence revealed well-characterized high energy phosphates (PCr and the $\alpha-$, $\beta-$, and $\gamma-$phosphorus of ATP) that could provide energy for cellular metabolism. In addition to high energy phosphates, Pi was distinctly identified in ^{31}P MR spectrum. Muscle is known to have a high concentration of PCr. Thus, under the normal condition, PCr was dominant among the various phosphate metabolites and signal intensity of PCr was the highest in ^{31}P MR spectrum. The most striking features of spectroscopic findings in patients with mitochondrial myopathy were depletion of PCr and ATP and accumulation of Pi.

Compared with normal controls, the Pi/PCr ratio was abnormally high in patients with mitochondrial

Table 1. Comparisons of Phosphorus Metabolite Ratios and pH between Patients with Mitochondrial Myopathy and Normal Controls

	Pi/PCr	T-ATP/PCr	$\alpha-$ATP/PCr	$\beta-$ATP/PCr	$\gamma-$ATP/PCr	pH
Controls	0.14 ± 0.04	0.80 ± 0.15	0.29 ± 0.08	0.21 ± 0.10	0.30 ± 0.04	7.04 ± 0.05
Pt # 1	0.15	0.46	0.11	0.09	0.27	7.09
Pt # 2	0.24	0.56	0.18	0.14	0.25	7.05
Pt # 3	0.17	0.68	0.24	0.16	0.29	6.98
Pt # 4	0.16	0.62	0.23	0.13	0.26	7.02
Pt # 5	0.19	0.62	0.24	0.14	0.23	7.02
Pt # 6	0.27	0.81	0.32	0.12	0.37	7.02
Pt # 7	0.20	0.67	0.25	0.12	0.30	7.02
Pt # 8	0.20	0.68	0.26	0.19	0.24	6.87
Pt # 9	0.30	0.88	0.36	0.13	0.39	7.02
Pt # 10	0.21	0.83	0.31	0.16	0.36	7.09
Mean ± SD	0.18 ± 0.06	0.69 ± 0.13	0.26 ± 0.07	0.16 ± 0.07	0.30 ± 0.06	7.02 ± 0.06
P	0.003	0.004	0.087	0.048	0.960	0.317

Note : Ratios for the controls are mean ± SD (standard deviation).
T-ATP means total ATP (i.e., $\alpha-$ATP+$\beta-$ATP+$\gamma-$ATP).

myopathy. The Pi/PCr ratio is considered to be a reflection of the cellular bioenergetic state (17). However, the high Pi/PCr ratio is not disease specific and has been found in several myopathies that are associated with advanced muscle cell destruction (18). The basic mechanisms that lead to this abnormality of Pi/PCr ratio have not been clearly understood, and a variety of factors may be implicated. Among those factors, one may be due to mitochondrial malfunction (primary or secondary) that occurs in damaged muscle cells (19).

In muscle and brain, the major function of mitochondria is to provide energy in the form of ATP that enables the cells to perform a variety of energy-consuming processes. Mitochondrial energy production requires the uptake of substrates by several import systems, the conversion of these substrates to oxidizable compounds, and, finally, oxidative phosphorylation. During the latter process, electrons derived from oxidizable substrates are transported via the enzymes of the respiratory chain to oxygen (respiration), and a proton gradient is generated over the mitochondrial inner membrane. This gradient is the driving force of the production of ATP by complex V (phosphorylation). ATP produced inside the mitochondria is next transported to the cytosol by the adenine nucleotide translocator. This carrier is also responsible for the import of ADP into the mitochondria: ADP is exchanged for ATP.

Mitochondrial defects that impinge directly on mitochondrial energy metabolism can thus be based on dysfunction of one or more of the enzymes involved in the energy-consuming processes (20). In addition, many of the enzymes complexes involved in mitochondrial energy production occur as tissue-specific isoforms. For instance, muscle-specific isoforms of complex IV (cytochrome c oxidase) (21) and the adenine nucleotide translocator (22) have clearly been established. Tissue-specific mitochondrial enzyme defects are therefore also conceivable.

We have not investigated the possible significance of PME and PDE resonance intensities observed in patients with mitochondrial myopathy. Analysis of PME and PDE is somewhat difficult because the intensity of PME and PDE is low and resonances in both PME and PDE regions can arise from a variety of compounds. In normal muscle, the major PDE is glycerol-3-phosphorylcholine, but this is not the case in some pathologic states (23). The PME region includes primarily phosphorylated glycolytic intermediates, relative concentrations of which can change dramatically in disorders affecting regulation of glycolysis or glycogenolysis (24). High resolution nuclear MRS of perchlorate extracts of biopsied muscle could be used to better define contributions to these resonances in the pathologic states.

The present study showed that there was no pH difference between controls and patients with mitochondrial myopathy. There were no apparent morphologic differences in patient with mitochondrial myopathy and control subjects from MR images (Figure 1). Since a significant metabolic difference between patient with mitochondrial myopathy and normal control was demonstrated in this study, MRS may be a more sensitive modality than MRI in monitoring the progressional alterations of patient with mitochondrial myopathy.

We have found MRS to be a useful screening test for the presence of primary mitochondrial disease when used in combination with the clinical examination and routine clinical laboratory investigations. The sensitivity of MRS is at least as great as that of the current "gold standard" for diagnosis of mitochondrial myopathies: pathologic study of muscle biopsy sections. Furthermore, the test is rapid and completely noninvasive.

In conclusion, localized in vivo ^{31}P MRS with ISIS pulse sequence was employed to investigate the metabolic alterations of the skeletal muscle tissue in patients with mitochondrial myopathy. The present study demonstrated that ^{31}P MRS is a reliable method for in vivo screening for mitochondrial myopathies and offers a valuable tool in further understanding disorders of muscle metabolism. This technique will also be of value in monitoring the course of specific mitochondrial disorders, as well as responses to therapeutic trials.

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대한자기공명의과학회지 2:89-95(1998)

인 (^{31}P) 자기공명분광법을 사용하여 사립체 근질병환자와 정상인과의 대사물질 비교조사

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목 적 : 인 (^{31}P) 자기공명분광법을 사용하여 사립체 근병 (mitochondria myopathy) 환자의 대퇴부 근조직의 대사물질의 변화를 정상인과 비교조사하였다.

대상 및 방법 : 사립체 근병환자 10명과 정상인 10명을 대상으로 1.5T MRI / MRS 장비를 사용하여 인 (^{31}P) 자기공명분광법을 적용하였다. 오른쪽 대퇴부위의 근조직에 $4 \times 4 \times 4 cm^3$의 관심부위 (volume of interest : VOI)를 선정하여 image selected in vivo spectroscopy (ISIS)를 적용하였다. 인대사물질의 정량분석은 Marquart algorithm을 사용하였다.

결 과 : 사립체 근병환자의 특징은 정상인과 비교하여 Pi / PCr 대사비율이 상당히 증가하고($p = 0.003$), ATP / PCr 대사비율은 상당히 감소하였다($p = 0.004$). 특히 ATP 중 β-ATP / PCr 비율의 변화가 가장 심하게 나타났다. 환자군과 정상군의 pH 차이는 통계학적으로 큰 의의는 없었다.

결 론 : 인 (^{31}P) 자기공명분광법은 사립체 근병환자의 대퇴부 근조직의 ATP / PCr과 Pi / PCr 대사비율을 토대로 유용한 임상 평가 자료를 제공하고, 따라서 근대사물질의 질병을 이해하는데 도움을 줄 것으로 사료된다.

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