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Title: Assessment of skeletal muscle energy metabolism by 31P MRS in COVID19 and Multiple Sclerosis patients: technical and clinical insights

Antoine Naëgel¹², Jabrane Karkouri¹²³, H el ene Ratiney¹, Djahid Kennouche¹⁴, Nicolas Royer¹⁴, Guillaume Millet¹⁴, Jill Slade⁵, J er ome Morel⁶, Pierre Croisille¹, Magalie Viallon¹

¹ Universit e de Lyon, INSA-Lyon, Universit e Claude Bernard Lyon 1, UJM-Saint Etienne, CNRS, Inserm, CREATIS UMR 5220, U1206, Lyon, France, ² Siemens Healthcare SAS, Saint-Denis, France, ³ Wolfson Brain Imaging Center, University of Cambridge, Cambridge, United Kingdom, ⁴ LIBM - Laboratoire Interuniversitaire de Biologie de la Motricit e, ⁵ Department of Radiology, Michigan State University, East Lansing, USA, ⁶ anaesthetics and intensive care department, UJM-Saint-Etienne, Centre Hospitalier Universitaire de Saint- tienne, Saint-Etienne, France

Synopsis

Dynamic 31P MRS was performed during a standardized exercise of the lower leg, in patients with chronic fatigue enrolled in 2 clinical studies: multiple sclerosis patients and COVID19 patients that were hospitalized in intensive care unit and requiring respiratory assistance. In this work, we also revisit certain assumptions on the metabolite T1 and question shortcuts often made to shorten 31P protocol for a better patient's compliance.

Summary of Main Funding

Dynamic exploration by 31P MRS of chronic fatigue in 2 populations: multiple sclerosis and COVID19 patients. Significant differences were found between these populations and controls. Points of caution are reported about the deployment of 31P MRS protocol in a clinical context.

Introduction

Evaluating skeletal muscle energy metabolism is of medical interest in monitoring neuromuscular degenerative or cardiovascular diseases and evaluating muscle fatigability. 31P-MRS is a non-invasive technique of choice to dynamically assess the concentration of phosphorylated metabolites, which are directly related to the respiratory capacity of mitochondria[1,3]. However, implementing a standardized dynamic acquisition protocol that can be transposed to different longitudinal studies on large patient cohort raises methodological questions. Therefore, dynamic 31P MRS during a standardized lower leg exercise was performed in patients enrolled in 2 clinical studies, exploring chronic fatigue in, respectively, multiple sclerosis (MS) patients and COVID19 patients hospitalized in intensive care unit with respiratory assistance. This work also discusses assumptions and shortcuts often made to shorten the 31P protocol for better patient compliance.

Material & Method

NMR spectroscopy and imaging were performed on a 3T clinical MRI (MAGNETOM PRISMA, Siemens Healthineers). 31P-MRS acquisitions were performed in 36 MS patients, 18 COVID19 patients, and 35 matched controls (age/weight/sex). The non-localized MR-FID sequence implements saturation bands obtained with adiabatic pulses to minimize the signal from unstressed muscle and bone [4]. Two additional acquisitions were made with TR=30sec (12 acquisitions) and TR=4sec (32 acquisitions) at rest and before exercise to obtain spectra in the resting state. T1 was estimated with monoexponential fit, for each metabolite to determine the correction factors. The platform was equipped with an MRI-compatible ergometer (ErgoSpect), with its calf module (Trispect). Subjects were lying supine with the dual 1H/31P surface coil (Rapid GMBH) under its calf muscle. The dynamic acquisitions included the rest phase of 40s (10 acquisitions), and an exercise phase lasting 2min (30 acquisitions); the patients were asked to perform periodic ergometer-controlled plantar flexions every 4s, synchronized with the MRS acquisitions, and a final recovery and resting phase of 6min (90 acquisitions).

The data were processed using MatLab (The MathWorks) and the QUEST (QUantitation based on QUantum ESTimation) method [5]. After a manual phasing of the data using PhaseTool GUI [6], a 5 Hz

exponential apodization filter, QUEST metabolite basis set, was used as prior knowledge and was constituted with Phosphocreatine (PCr), Inorganic Phosphate (Pi), α -, β -, and γ -Adenosine Tri Phosphate (ATP). The cQUEST implementation estimated amplitude, frequency, and phase parameters for each metabolite. A mono-exponential fit was performed on the PCr amplitude recovery period to extract the rate of PCr resynthesis (τ PCr). The millimolar concentration assessment of phosphorus metabolites was based on the standard assumption that [ATP] is 8.2 mmol/L cellular water [1]. The pH was calculated from the frequency difference between PCr and Pi, as proposed in [3], [7]. The concentration of diprotonated phosphate, [H₂PO₄⁻], can be calculated according to [7]. The concentration of adenosine diphosphate (ADP) can be calculated as a function of pH and PCr, assuming creatine kinase (CK) balance [3]. We also examine PCr hydrolysis during plantar exercise. To assess the quality of the fit, the resulting residual signals (raw spectra minus estimated spectra) were used over the whole dynamic experiment. Comparisons between the three groups were performed for all measured parameters using a one-way ANOVA with Bonferroni adjusted multiple comparisons using Stata17(College Station, USA). Statistical significance was set to $p < 0.05$.

Results

We observed significant differences between the two populations and the healthy controls for the τ PCr, resting [Pi], [ADP], and [H₂PO₄] (Table). Significant differences between MS and controls were also found for the T1, resting and post-exercise [PCr]. A significant difference between COVID19 and controls was found for resting and post-exercise [PCr], post-exercise [H₂PO₄] and pH change.

Discussion

In five COVID-19 patients, metabolite concentrations (ATP, PCr) were greatly diminished during the exercise protocol initially suggesting profound metabolite depletion (cf Figure 1). More than the signature of an underlying physiological process, such abnormal behaviors, with measured amplitudes of PCr and Pi peaks that do not present the expected inverse behavior during the exercise (cf figure1 left), are likely to result from a displacement of the investigated leg during the requested effort. Our processing routine allows us to reveal these anomalies and adjust the first point of the τ PCr fit manually. The visual peak of Pi between the 39th and 42nd acquisitions serve as an objective criterion to determine the onset of the recovery phase. In case no precautions are taken, the rate of change of the τ PCr depending on the choice of the first point can vary up to 70% (cf Figure 2). Finally note that a significant difference was found between the T1PCr of MS patients and controls. This supports the choice of a protocol with long TR measurement in order to take into account metabolite T1 weighting for each subject measurement. A slight trend of increasing metabolite T1 was observed in the studied patient populations; however, this observation cannot be generalized to other populations.

Conclusion

In the context of translating a methodological protocol to a broader scale applicable in clinical studies, vigilance points are mandatory throughout the process, from acquisition to quantification. Quality control should be done during the acquisitions and processing of the data. Longitudinal studies are needed to explore the capacity of the metabolic parameters to catch disease progression in MS, or healing in COVID19, and their relationship to other functional parameters or fatigue.

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	MS		COVID19		CONTROL		P-values*		
	Mean	SD	Mean	SD	Mean	SD	MS/CONTROL	COVID19/CONTROL	COVID/MS
τPCr (s)	40.35	11.26	41.79	11.23	32.49	8.38	0.005	0.007	1.000
PCr hydrolysis %	28.78	13.14	37.00	15.06	34.79	12.49	0.181	1.000	0.105
T1 (s) PCr	6.50	0.71	6.45	0.56	6.14	0.51	0.045	0.253	1.000
T1 (s) Pi	5.92	0.99	5.78	0.67	5.46	0.75	0.072	0.587	1.000
T1 (s) ATPγ	5.39	0.55	5.30	0.58	5.15	0.62	0.268	1.000	1.000
T1 (s) ATPα	3.42	0.41	3.36	0.24	3.26	0.24	0.106	0.773	1.000
T1 (s) ATPβ	4.10	2.51	3.55	0.71	3.34	0.36	0.164	1.000	0.740
[PCr] rest (mM)	38.23	5.44	34.00	4.51	33.76	4.19	0.001	1.000	0.009
[PCr] post-ex (mM)	27.26	5.99	21.68	6.68	21.95	4.74	0.001	1.000	0.003
[Pi] rest (mM)	5.33	1.47	5.56	1.03	4.18	0.75	0.000	0.000	1.000
[Pi] mid-ex 1 (mM)	11.96	4.29	11.56	2.93	11.38	2.79	1.000	1.000	1.000
[Pi] mid-ex 2 (mM)	13.86	4.99	13.03	4.01	12.99	3.10	1.000	1.000	1.000
[Pi] post-ex (mM)	13.82	4.65	14.01	3.34	12.66	2.95	0.616	0.679	1.000
[ATP] rest (mM)	7.97	0.58	8.01	0.49	8.19	0.43	0.204	0.695	1.000
[ATP] post-ex (mM)	7.73	1.21	7.47	1.46	7.80	0.98	1.000	1.000	1.000
[ADP] rest (μM)	1.40	0.28	1.42	0.45	1.13	0.33	0.003	0.011	1.000
[ADP] post-ex (μM)	4.29	1.42	12.46	30.79	4.93	1.83	1.000	0.188	0.129
H2PO4 rest	1.72	0.47	1.74	0.35	1.35	0.23	0.000	0.002	1.000
H2PO4 post-ex	4.43	1.52	4.46	1.42	4.09	1.03	0.878	1.000	1.000
pH rest	7.07	0.03	7.09	0.02	7.07	0.02	1.000	0.001	0.006
pH post-ex	7.08	0.03	7.12	0.19	7.08	0.05	1.000	0.257	0.346
pH min	6.97	0.07	6.95	0.09	6.94	0.12	0.598	1.000	1.000
pH change	0.18	0.08	0.39	0.34	0.26	0.25	0.387	0.140	0.004

Table: Results obtained on the three patient cohorts, mean and standard deviation. *one-way ANOVA with Bonferroni adjusted multiple comparisons using Stata17(College Station, USA). Statistical significance was set to $p < 0.05$.

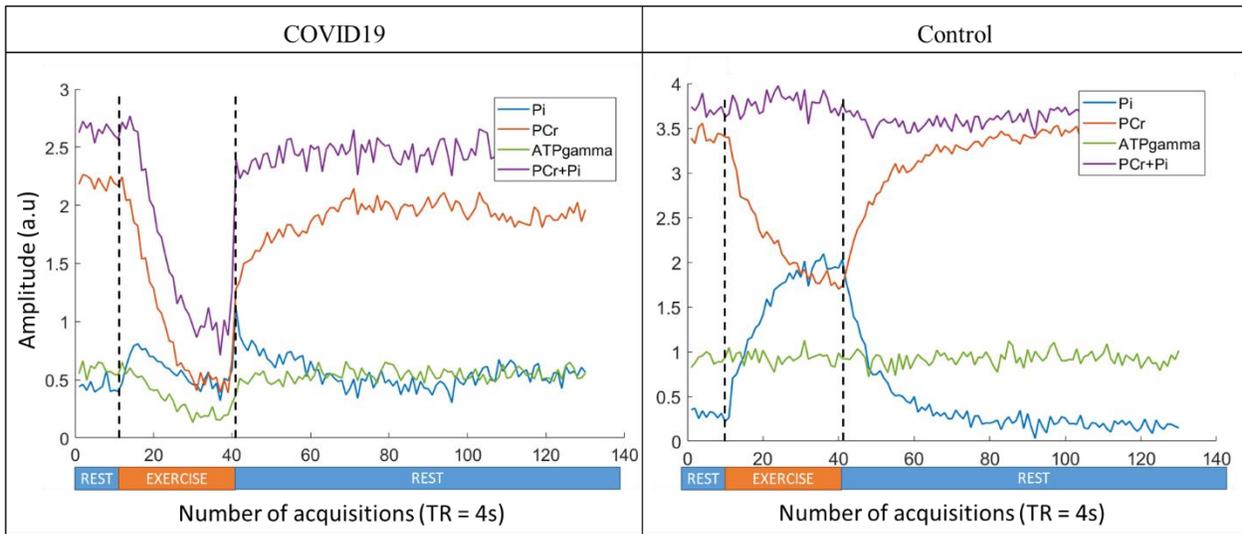


Figure 1: Metabolite amplitudes during the protocol. Left: Patient of the COVID19. Right: Control. Highlighting of the exercise and rest phases. During the exercise phase, the COVID19 patient shows abnormal attenuation of these metabolite signals.

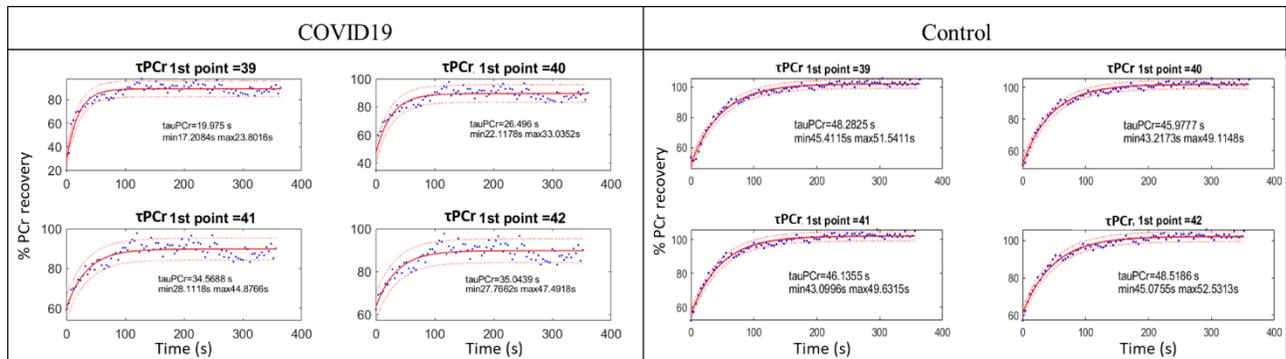


Figure 2: PCR fit procedure to trace back to τ PCr and result according to the first point considered. Left: Patient of the COVID19 cohort. Right: Control. For the COVID19 patient, the variation of the PCR rate according to the first point is consequent.

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