Post-ischemic stenosis and reperfusion studied by dynamic 31P MRS and functional imaging

A. I. Schmid[1,2], M. Andreas[3], M. Meyerspeer[2,4], E. Moser[1,4], and M. Wolzt[1]

[1]Dpt. of Clinical Pharmacology, Medical University of Vienna, Wien, Wien, Austria, [2]MR Center of Excellence, Medical University of Vienna, Wien, Wien, Austria, [3]Department of Cardiac Surgery, Medical University of Vienna, Wien, Wien, Austria, [4]Center of Biomedical Engineering and Physics, Medical University of Vienna, Wien, Austria

Introduction

Ischemia is a common clinical finding ranging from peripheral artery disease, coronary artery disease and stroke to organ transplantation. The reestablishment of blood flow is mandatory to preserve tissue but blood flow may be impaired even after vessel reopening due to pre-existing atherosclerotic stenosis, insufficient vessel dilation or insufficient reopening.

Transient limb ischemia by cuff inflation is a common model to investigate ischemic injury. Alternative reperfusion patterns like stenosis may be produced by cuff inflation to sub-systolic pressure. So far, studies using cuff-ischemia do not take the effect of stenosis into account. ^{31}P metabolites like phosphocreatine (PCr) are directly measurable in-vivo with a temporal resolution of a few seconds. While ^{31}P MRS is perfectly suited to monitor the metabolic response to alterations in oxygen supply, blood oxygen level dependent (BOLD) magnetic resonance imaging (MRI) is capable of monitoring changes in tissue oxygenation.

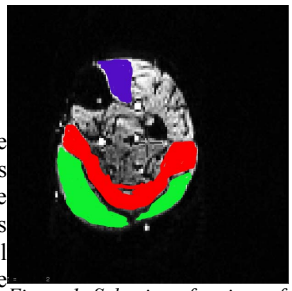

Figure 1: Selection of regions of interest. tibialis anterior T (blue), soleus S (red), gastrocnemius G (green).

Methods

11 male subjects (age 18 to 45a) were studied using a Siemens Tim Trio MR-scanner (Siemens Medical, Erlangen, Germany). The subjects lay supine in the scanner with their leg positioned in an exercise rig. A cuff was positioned on the thigh of the same leg. For either ^{31}P (pulse-acquire, T_R=4s) or BOLD (EPI; T_R=0.5s, T_E=44ms, 128x128x5 matrix, 1.4x.1.4x5mm resolution) measurements, one baseline day and one day with stenosis was prescribed. On baseline day, after correct positioning, one baseline measurement was performed, the cuff was inflated to 200mmHg by pressurized air for 20 minutes thereafter. Voluntary plantar flexions were performed during the last two minutes of ischemia every 4 seconds with half-maximal force. Cuff was deflated immediately afterwards and MR measurement was conducted for additional 30 minutes. On the second study day, the cuff was deflated to 20mmHg below systolic blood pressure during the first 5 minutes of reperfusion after exercise, followed by complete deflation.

Muscle	exercise end	Bef. recovery	hyperemia max	return to baseline
Tibialis anterior	0.83 ± 0.19		.26 ± 0.26	0.94 ± 0.17
stenosis	0.84 ± 0.21	0.64 ± 0.16*	1.22 ± 0.15	0.96 ± 0.14
Soleus	0.70 ± 0.15		1.27 ± 0.22	0.82 ± 0.14
stenosis	0.77 ± 0.12	0.56 ± 0.15*	1.34 ± 0.19	0.93 ± 0.13
Gastrocnemius	0.87 ± 0.16		1.18 ± 0.17	0.86 ± 0.13
stenosis	0.98 ± 0.11	0.72 ± 0.16	1.21 ± 0.17	0.94 ± 0.10

*Table 1: Characterisation of EPI data by picking values at different time points during stenosis and hyperemia. *: Difference between days in BOLD signal p<0.05.*

The spectra were processed and quantified in jMRUI (AMARES). The PCr recovery (non-linear least square fit) and pH were calculated. Metabolite concentrations were calculated assuming a β-ATP concentration of 5.5 mM muscle tissue.EPI were converted into the minc format for further processing. 100 images were averaged as the reference to which all EPI were registered. Manually drawn ROIs (Figure 1), covering soleus (S), gastrocnemius (G) and tibialis anterior (T), were extracted.

Results

EPI signals decreased by 15 to 20 % during ischemia compared to baseline. Signal alteration was also depending on muscle type. The soleus muscle showed the strongest signal drop. When ischemic exercise was followed by stenosis, a highly significant signal drop could be observed (Tibialis anterior (TA): p=0.03, Soleus: p=0.004, Gastrocnemius: p=0.001) (Table 1). Upon cuff release a rapid signal increase is followed by a slow return to baseline values. The gastrocnemius muscle experienced a longer hyperemic phase.

During ischemia, muscle PCr depleted by 21% on both days, and to 45 % baseline values after exercise.. During stenosis no significant change in PCr concentrations could be observed. PCr recovery rates were very similar on both days, the PCr concentration after recovery was slightly higher than at the beginning of the experiment.

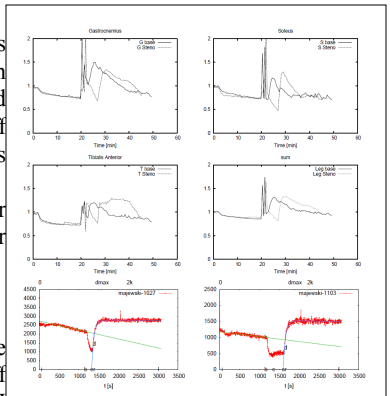

Figure 2: veraged BOLD signal evolution in different muscles of one subject as well as the PCr evolution (with (right) and without stenosis (left). With (dashed lines) and without stenosis (solid lines).

Discussion

The focus of this study was to identify a model to analyse the effect of stenosis on tissue oxygenation and metabolism. We found that restoration of arterial inflow by reducing cuff pressure below systolic values was insufficient to start PCr resynthesis. PCr and intracellular pH remained at comparable levels as at the end of ischemic exercise. Similarly, the BOLD sensitive signal decreased even further. This may be explained by the inflow of oxygenated blood that is rapidly deoxygenated and accumulated in the leg as the venous outflow is blocked. PCr recovery rates were not different whether stenosis was applied or not, neither were the PCr concentrations after recovery.

In conclusion, both BOLD sensitive NMR imaging and ^{31}P spectroscopy observe complementary aspects of ischemia-reperfusion. While the former monitors oxygen delivery, the latter directly monitors oxidative phosphorylation. The inclusion of stenosis into the paradigm is an important step to understand realistic post-ischemic conditions, especially for the development of new therapeutic approaches. The combination of ^{31}P an BOLD MRI show consistent results and that under stenosis tissue is not supplied sufficiently with oxygen to allow for complete recovery from ischemia. These findings should be considered in the context of pathologies where stenosis or transient ischemia is present.