Functional Imaging of Calf Muscle using MRI-based Tissue Oxygenation Technique

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Statement of the problem:

In western countries, atherosclerosis is associated with high morbidity and mortality[1]. As a form of atherosclerosis, peripheral arterial disease (PAD) affects approximately 8 million adult Americans, including 12-20% of Americans over 60 yrs[2]. While symptoms of early PAD are only pain caused by ischemia, at advanced stages PAD patients may require limb amputation and even have a significant risk of death[3]. Conventionally, the diagnosis of PAD relies on CT or MRI angiography imaging to detect the narrowing of peripheral arteries. However, better management of these PAD patients requires also the information on the functional status of calf muscle. In this project, we aim to test the feasibility and performance of a functional MRI technique (Blood Oxygen Level Dependent, BOLD) in assessing the function of calf muscle.

Literature Review:

BOLD signals are influenced by the amount of deoxy-hemoglobin (dHb) within voxels and can be used to estimate tissue oxygenation[4]. Oxy-hemoglobin is diamagnetic whereas dHb is paramagnetic, so the presence of dHb creates heterogeneity within the magnetic field[5]. Magnetic field heterogeneity accelerates the intravoxel spin dephasing[4]. By applying gradient echo pulses, BOLD imaging generates a set of images at different echo times (TE). The BOLD signal decays exponentially with increasing TE. From exponential fitting of the signal versus TE curves, we can get the spin-spin relaxation time (T2*)[6]. Fast BOLD signal decay implies low T2* and high level of tissue oxygenation. BOLD imaging does not require the injection of a conventional gadolinium contrast agent, which can have side effects for patients with impaired renal function. One study[7] cataloged the adverse effects of gadolinium-based contrast media over the course of approximately five years. They found that 0.48% of patients had reactions to the contrast. The severity of the reactions was largely mild (96%) with one patient who developed shortness of breath that required oxygen supplementation and steroidal intervention, and another patient who had an anaphylactic reaction[7]. While not a large percentage of patients have reactions, and they are usually minor if present, BOLD imaging does not have those risks.

Multiple previous studies have investigated the utility of BOLD in assessing muscle function in PAD patients. In a study with age-matched patients with and without PAD, BOLD scans were performed after the restriction of blood flow in the calf using a cuff for 240 seconds[8]. It was found that peak T2* value was lesser in patients with PAD and the time to peak T2* (TTP) was significantly higher with PAD. Multiple factors could cause the decrease in T2* with PAD. Firstly, blood velocity is lower in the affected arteries and capillaries of PAD patients, leading to a higher efficiency for oxygen extraction and thus more accumulated dHb in the blood, reducing the T2* level. Secondly, chronic ischemia experienced by unhealthy tissues may cause damages in capillaries and reduce capillary density, decreasing blood flow into the muscle[8]. The higher TTP was attributed to impaired blood flow and thus a hampered velocity of oxygenated blood into the capillaries[8]. BOLD imaging has also been used to test the viability of PAD treatments. Two separate studies determined the efficacy of percutaneous transluminal angioplasty (PTA) through BOLD imaging before and after the treatment. Both studies utilized the parameters denoted above, namely T2* max and TTP, to evaluate PTA[9, 10]. Both found that PTA effectively increased T2* max as well as decreased TTP[9, 10]. The results were verified by an increase of the ankle brachial index (ABI) from 0.56 ± 0.10 to 0.83 ± 0.15[10].

Activities to be taken and Timetable:

In our research team, we have collected a group of BOLD data for healthy and PAD patients, with all data acquired during exercise recovery. The first part of my project involves segmenting different muscle groups of the calf and generating their T2* versus time curves. To better localize the muscle groups, I will first study the anatomy of the calf muscle, and for each data set, view a high-resolution anatomic image. To eliminate the impact of intramuscular vessels or fat, we will also consider excluding some very bright or dark voxels. For fast processing, I will program with MatLab to perform all computations, graphing, and region-of-interest (ROI) drawing. This portion of the project should require 2 months.

In the second step in the project, we will analyze the temporal change of T2* during the exercise recovery for the cases. To quantify the change, we will find a proper mathematic function to fit the temporal curves, and use the parameters of the function for quantification. This will involve creating a MatLab program to fit the curves with optimization techniques and evaluate the curve fitting residues. This step should take [illegible]-6 months.

The final step will be to use statistical analysis to determine the optimal threshold for the curvature parameters to differentiate PAD patients and healthy subjects. This step should take until April 2016, and will include preparing all results for submitting a journal paper and/or abstracts to major national or international conferences.

Relationship of the proposed work to the expertise of the faculty member:

My mentor has extensive experience in functional MRI, both of the kidneys and of calf muscle. One ongoing project of my mentor is to quantify tissue oxygenation from BOLD MRI signals. This involves Monte Carlo simulation of the BOLD mechanism and characterization of oxygen transit in tissue. The technique has been validated in kidneys, by comparing the BOLD-estimated tissue oxygenation against measures from invasive oxygen probes in pigs. In the proposed project with calf muscle, we might consider applying the similar techniques. My mentor has been also working on quantifying muscle perfusion with different MRI techniques, including dynamic contrast enhanced MRI and arterial spin labeling MRI. As blood perfusion delivers oxygen to the tissue, the prior knowledge on muscle perfusion will be very important for interpreting muscle BOLD data in this project. Specifically, in this project, my mentor will provide guidance on image processing, mathematic modeling and statistical analysis, and also help to interpret the BOLD results. He will also guide me in writing up a journal manuscript at the end of the project.

Relationship of the proposed work to my future goals:

My long-term goal is to start an academic career in the field of medical imaging and/or computation thus improving diagnosis and treatment for major diseases. The current project is a great starting point where I get familiar with the field and learn basic skills for scientific research. Moreover, this project has promise in establishing an imaging-based method for effective evaluation of muscle function in PAD patients, which is very important for the management of PAD.

Specifically, with this project I will develop valuable research skills that will foster meticulous and critical thought, which will be very helpful for my future career. I will gain skills in idea development and presentation through scientific paper writing. These skills will be critical, given that my future profession will likely include sharing my ideas and results with coworkers in a formal setting. The proposed project will require me to acquire knowledge on fMRI techniques and PAD.

This research will improve my academic, as well as professional, resumes. If the project demonstrates that BOLD imaging can diagnose PAD, I may have the opportunity to publish the results as well as present them at a conference. Impressive research that I publish and present will gain me an edge in applying for graduate programs.

References

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