Measuring Cerebral Blood Flow Using Pseudo-Continuous Arterial Spin Labeling Perfusion Magnetic Resonance Imaging

NCT02767609

April 28, 2014

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Study Location: MRI Department
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Study Information: Expected start date: April 14th, 2014
Expected stop date: April 30th, 2016
Type of research: biomedical

Inclusion/Exclusion criteria:

Inclusion Criteria:

- Any person between the ages of 0-90 years, who is undergoing routine magnetic resonance imaging (MRI) of the head with or without contrast at LLUMC.
- Must be eligible for MRI (no electronic or metal implants that are not MR compatible)

Exclusion Criteria:

- Electronic or metal implant that is not MRI safe, pregnancy or claustrophobia

Subject recruitment and screening:

- English speaking patient populations of LLUMC with an order for a Head MRI with or without contrast between the ages of 0-90 years will be recruited. We plan to recruit 300 subjects.
- Healthy volunteers between the ages of 12-90 years will be recruited from the local population using word of mouth. We plan to recruit 50 subjects.

Informed Consent Process:

- Before participating in the study, each subject will sign an informed consent form.
- Each subject will have the right to refuse the addition of the pseudo-continuous arterial spin label (pCASL) sequence and still have their MRI as ordered.
- Consent will take place in the MRI Department, LLUMC prior to the MRI study and the consent process will be completed by the study PI or study personnel.

- All findings and documents are considered confidential. The resultant MR pCASL images will be archived as part of the patients medical record on the Radiology PACS server.

Study Design

Background

Cerebral blood flow (CBF) represents an important physiological parameter for the diagnosis and management of multiple brain disorders. The clinical need for CBF measurements is further complicated by the desire to have a non-invasive method with high temporal resolution that can measure CBF over a wide range of blood flows and in a wide range of patients. Numerous techniques are available to measure CBF. Nuclear medicine approaches, such as single positron emission computed tomography (SPECT) and positron emission tomography (PET) rely on radioisotopes which can be problematic in the pediatric population. In contrast, MRI-based methods are non-invasiveness and the CBF information can be obtained in conjunction with other MRI techniques (i.e. diffusion weighted imaging or spectroscopy) which allows for a combined longitudinal assessment of CBF, morphology, and metabolism, to provide a more complete understanding of the developing pathophysiological mechanisms.

Two distinct MRI techniques have been developed, which differ with regard to their use of contrast agents. With dynamic susceptibility contrast perfusion imaging (DSC-PWI), an injection of a gadolinium-based contrast agent is required. The use of DSC-PWI is complicated by technical difficulties in administering intravenous contrast in the neonatal and pediatric populations and by the risk of developing nephrogenic systemic fibrosis (NSF), which is increased in high-risk patients, such as those with impaired kidney function, diabetes, or over the age of 60 years (reviewed in Tepel et al 2006). In contrast, in arterial spin labeling (ASL) perfusion imaging arterial blood water is used as an endogenous diffusible tracer where radiofrequency (RF) pulses magnetically label the moving spins in flowing blood *without* the use of a contrast agent. After a time delay allowing for the magnetically labeled blow to flow into the brain, "labeled" images are acquired. Separate control images are also acquired, without labeling and the difference between the two sets of imaged provides a measure of perfusion. Since gadolinium-based contrast agents are not required, the ASL perfusion technique is completely non-invasive (Calamante et al., 1999). In addition, ASL techniques are insensitive to blood-brain barrier permeability changes, which can occur after strokes or with tumors (reviewed in Wang et al., 2012).

Because gadolinium-based contrast is not used, the ASL technique has an inherently lower sensitivity than DSC-PWI. Recent advances in MRI technology, specifically the clinical use of higher field strength MRI systems (3 Tesla), which increase the inherent signal to noise of tissues, has made this technique potentially more feasible. ASL imaging is also limited by the short tracer (labeled blood water) half-life (1-2 seconds) resulting in limited sensitivity (reviewed in Wang et al., 2012). To date, there are a number of commercially available ASL techniques that differ in their labeling schemes, which has contributed to the difficulty in obtaining consistent results across different patient populations (pediatric, elderly, stroke, tumors). The two most common labeling strategies are 1) continuous (CASL) labeling where a single, long label (1-3 seconds) is applied and 2) pulsed (pASL) labeling, where a single or a small number of pulses are applied over a shorter duration (10-20 milliseconds). More recently, pseudo-

continuous ASL (pCASL) labeling strategies, where 1000 or more pulses are applied over a long duration (1 -3 seconds) have been developed. Compared to continuous labeling (CASL), pCASL labeling strategies provide superior labeling efficiency and thus increased sensitivity (Alsop et al., 2014). A number of recent reports using pseudo-continuous ASL (pCASL) have been published and show increased reliability across different patient populations (Wang et al., 2012; Tancredi et al., 2012; White et al., 2014). Moreover, a recent consensus statement published by the International Society of Magnetic Resonance in Medicine Perfusion Study Group recommends the use of pCASL labeling strategies for clinical applications (Alsop et al., 2014). However, to date this pCASL sequence is not commercially available on the MRI systems currently used at LLUMC (Siemens Medical Solutions), while it is routinely available on General Electric and Philips Healthcare MR systems.

Objectives

The objectives of this investigator-initiated study is to determine the accuracy and reliability of a newly developed pCASL sequence and post-processing software (provided by Dr. J.J. Wang, University of California Los Angeles) across multiple patient populations (neonate to elderly) and pathological processes.

Study Procedure

Overview: Each subject will undergo a MRI study of the head with or with contrast including the pCASL sequence for a total of ~35 minutes in the MRI scanner.

Imaging: Following consent, subjects will be imaged at LLUMC using the 3T MRI scanner (Siemens Medical Solutions, Malvern, PA) after MRI safety screening questionnaire is complete. Subjects will be asked to lie on or be positioned on their backs in the MRI scanner. The coil will be placed around their head and the subject will be provided with headphones (with music) during the scan. Imaging will consist of LLUMC's routine diagnostic MR protocol for brain imaging (anatomic T1 and T2 weighted sequences, FLAIR, diffusion weighted imaging, susceptibility weighted imaging, and dynamic susceptibility contrast perfusion imaging) and the addition of the pCASL sequence to evaluate cerebral perfusion.

Data Collection and Analysis

The relative CBF in frontal, parietal, occipital gray matter and white matter regions, basal ganglia, thalami, and cerebellum will be measured using region of interest analysis obtained from both the DSC-PWI and pCASL sequences. The resultant regional CBF values will be compared between the two methods using a Mann Whitney test (SPSS, version 21). A resulting data base of institutional control values for these regional CBF will be created.

Risks

MRI related risks:

The pCASL sequence being tested is a modification of current FDA-approved and commercially available pASL sequence whose development is supported by Siemens Medical Inc. under a Master Research agreement with UCLA. The specific absorption rate (SAR, a measure of heat deposition in tissue) of pCASL is lower than with CASL sequences (Chen et al., 2011; Alsop et al., 2014); both which are within FDA specified parameters. Importantly, SAR limits are hard

coded into the MRI scanner software and cannot be overridden. In addition, before an acquisition starts, the SAR level is calculated by the scanner software using the parameters specified and if the SAR is calculated to exceed the FDA limit, a warning is generated and the acquisition will not run. Moreover, this sequence does not require the use of gadolinium contrast, thereby eliminating the risk associated with its use. All safety precautions normally used for patient scanning will be used and include the use of the standard LLUMC safety screening questionnaire to determine if the subject has MR incompatible devices or objects in the body that might cause harm such as a pacemaker, defibrillator, stents, coils, pumps, stimulators, etc. prior to having the MRI scan to determine if it is safe to scan. This form will be reviewed by MRI staff (MR Technologist and/or study Investigator) before the subject is allowed in the MRI suite.

Confidentiality or Privacy Issues

Each participant's imaging data will be archived in their medical record (Radiology PACS image archive server). To protect against a breach of confidentiality or privacy, prior to data analysis subject identifiers will be removed and replaced by a unique research identifier. The key to the research ID will be kept in a computer file on CD and locked in a file cabinet in the PI's office.

Benefits

It is not anticipated that there will be any direct benefit to most participants at the time of the study. However, should this study show that the pCASL sequence can provide an accurate and reliable measure of CBF, future use could provide additional information to Physicians in vulnerable (neonate and pediatric, elderly, diabetic, and renal-compromised) patients that would not routinely get this information.

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