IRB Protocol
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ICCR Rotation
July 21, 2008

1. Study Purpose and Rationale

1a) This study is a non-inferiority trial of cold-saline contrast MR flow thermometry against the gold standard of MR angiography in a sample of patients being evaluated for carotid stenosis.

1b) It is of practical importance to measure cerebral blood flow (CBF) accurately and non-invasively. CBF informs of the adequacy of cerebral perfusion; several other methods, such as positron emission tomography (PET), single photon emission computed tomography (SPECT) and computer tomography (CT) perfusion, have all been used to provide this vital information, but all three methods expose patients to ionizing radiation. While magnetic resonance imaging (MRI) does not involve ionizing radiation, gadolinium is the only contrast agent proven for MRI to measure cerebral blood flow; with recent discovery of the gadolinium-induced nephrogenic systemic fibrosis in renal failure patients however, it is especially important to explore safer contrast agents with which to measure CBF.

Magnetic resonance imaging (MRI) is sensitive to thermal signals [1,2,3] and has been used to non-invasively measure brain temperatures in humans [4]. The techniques over the past 20 years have been highly variable, with the measurement of the variance in the water proton resonance frequency (PRF) has been most commonly used [5]. The advantage of PRF method over other methods is that there is a nearly linear relationship between temperature and proton resonance frequency shift, and this relationship does not vary between tissue types. There are two main imaging sequences, namely phase map imaging and spectroscopy, which can measure this frequency shift. The main advantage of MR spectroscopy over phase map imaging is that the absolute tissue temperature can be measured. In contrast, phase map imaging provides the relative change in temperature in a rapid, repetitive manner [5].

Imagining with dynamic phase map sequences thus calls for the use of temperature controlled saline as a contrast agent to determine cerebral blood flow. A baseline is constructed from measurements using a body temperature saline bolus; after injection of a cold fluid bolus into the venous circulation, serial phase map imaging of cerebral circulation can be made to determine the relative temperature change for different vascular distributions. With dynamic MR phase map imaging, these changes can be graphed as regional time-temperature curves (TTCs) for every voxel. Perfusion of the vasculature is then derived from the indicator dilution principle, whereby temperature dilution occurs in a known distribution relative to the flow carrying it – in this instance, the maximum slope of the TTC is used to calculate CBF [7,8,9]. (Further description of this mathematical model can be found in the work of Klotz and Konig on CT perfusion calculations [6].)

2. Study Design and Statistical Procedures

Here it is proposed a prospective, non-inferiority study pitting MR thermometry with intravenous cold saline contrast against MR angiography in the evaluation of patients with suspected carotid stenosis. A baseline body temperature (38C) bolus injection will be performed first to determine flow and dilution-related variables with an intravenous saline bolus (50 ml). Subsequently, after

IV injection of a cold saline (4C) bolus, serial phase map imaging of cerebral circulation can be made to determine the relative temperature change for different cerebral vascular distributions, from which vascular flow rates can be derived. A conventional MR angiography of the neck will then be performed. Images will be interpreted by a panel of three neuroradiologists, who will make a determination of either >50% stenosis or <50% stenosis. The primary outcome measure is the statistical diagnostic accuracy of MR thermometry with cold-saline contrast against the gold standard of MR angiography. The threshold for non-inferiority is 90%. A sample of 183 carotid measurements is required to detect a non-inferior accuracy of 95% with 95% confidence and 80% power.

Study Procedures
Pre-study Precautions:
Before each study, an MRI safety interview (approximately 15 minutes) will be conducted over the phone, in which important safety precautions pertaining to having an MRI scan will be asked. Furthermore the safety of cold saline injection will also be explained to the volunteers. A consent form for cold saline injection and MRI will be obtained prior to the study. Interviews not completed by telephone will be completed in person before subjects enter the MRI suite.

The procedure that follows is divided into three parts:
I. Body temperature (38C) saline bolus:
Dynamic phase map imaging of the neck is obtained upon injection of a 50 cc bolus of body temperature normal saline at 10 ml/sec. The injection will be administered through a 16-gauge peripheral IV line in the cubital vein. Subjects will be asked to hold their breath for duration of 10 seconds after bolus injection so as to minimize heat exchange and to maintain cold saline temperature as much as possible.

II. Cold saline (0C) bolus:
Dynamic phase map imaging of the neck is obtained upon injection of a 50cc bolus of 4C normal saline at 10 ml/sec. The injection will be administered through a 16-gauge peripheral IV line in the cubital vein. Subjects will be asked to hold their breath for duration of 10 seconds after bolus injection so as to minimize heat exchange and to maintain cold saline temperature as much as possible. There will be a 10 minute break between Parts I and II to allow imaged tissue to return to baseline.

III. MR angiography with gadolinium contrast:
Conventional MR angiography with gadolinium contrast will be performed, with contrast administered through a 16-gauge peripheral IV line in the cubital vein.

MR angiography results will be forwarded to patient’s referring MD.

Study Drugs or Devices
Conventional gadolinium contrast

Study Questionnaires
N/A

Study Subjects
Inclusion criteria:
1. Male and nonpregnant females aged 18 or older
2. Referred for evaluation of suspected unilateral or bilateral carotid stenosis

Exclusion criteria:
1. Pregnancy
2. History of cold urticaria, cold hemoglobinuria, sensitivity to cold, or related conditions
3. At risk for fluid overload, including history of heart failure, myocardial infarction, renal disease, or diabetes
4. History of contrast-induced nephropathy of any sort, or of prior or present renal insufficiency
5. Internal placement of pacemaker or other metal materials
6. Claustrophobia
7. More than 3 of the following cardiac risk factors:
a. Smoking
b. age (male >45, female >55)
c. history of early (<age 55) cardiac death in immediate family
d. no regular exercise
e. chronic high blood pressure (>140 systolic, >100 diastolic)
f. BMI >30

Recruitment
Physicians in the Depts. of Neurology and Medicine will be notified to enroll their patients being referred for evaluation of carotid stenosis in the study. Invitation to participate in the study will also be spread by flyers posted in the MR suite waiting rooms. Participation in the study is entirely voluntary. Subjects are free to withdraw from the study at any time. Monetary reimbursement of fifty dollars will be given to the volunteers upon the completion of the study.

Confidentiality of Study Data
No personal identifier will be maintained for this subject population. The only exception is if a subject chooses to know about incidental findings on his/her MRI. In that case, the contact information of the subject and his/her primary physician (if provided by the subject) will be stored in a locked file and deleted once the subject has been notified of the findings.

Potential Risks
First, MR imaging is a noninvasive, routine, and painless procedure. It is not associated with any risks or complications to those without internal metal or electronic implants, or claustrophobia. Second, evidence from animal models and studies in humans demonstrate safety of high volume intravenous cold fluid infusions [10-16]. During prior investigation of intra-arterial cold saline infusion in 17 patients, only two patients experienced some facial shivers, which resolved spontaneously at the end of the ten minute procedure. There were no signs of microemboli, vasospasm, pain or focal neurological deficits, and all patients were discharged at scheduled time. No additional complications were demonstrated. In the intraarterial infusion experiment, approximately 300 cc of cold saline was given intraarterially through the internal carotid artery. Experience from current clinical research with cold infusions and findings from the literature

[17-21] suggest that this study is safe. As for conventional MR angiography, gadolinium-induced nephrogenic systemic fibrosis in renal-failure patients is a rare but documented complication.

Potential Benefits

There will be no direct benefit to the subjects for participating in this study, other than monetary compensation. By taking part in this study, the subject will help to increase scientific knowledge about the contrast enhancing ability of cold saline bolus and its future applications in MR-guided procedures.

Alternatives

The alternative is not to participate in this study.

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