C-arm Cone Beam CTA and CTP with Acetazolamide Challenge in Aneurysmal Subarachnoid Hemorrhage: Evaluating Predictability for Early Ischemia in Cerebral Vasospasm

NCT03377049

PI: Azam Ahmed, MD
4/28/2020

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Azam Ahmed, MD – Assistant Professor (CHS) – Principle Investigator

University of Wisconsin, School of Medicine & Public Health

Departments of Neurological Surgery and Radiology

Charles Strother, MD – Professor Emeritus

University of Wisconsin, School of Medicine & Public Health

Department of Radiology

Beverly Aagaard-Kienitz, MD – Professor (CHS)

University of Wisconsin, School of Medicine & Public Health

Departments of Radiology, Neurological Surgery, Medical Physics and Pediatrics

Mustafa Baskaya, MD – Professor (CHS)

University of Wisconsin, School of Medicine & Public Health

Department of Neurological Surgery

David Niemann, MD – Associate Professor (CHS)

University of Wisconsin, School of Medicine & Public Health

Departments of Neurological Surgery and Radiology

Demi Dawkins, MD – Neurosurgery Resident

University of Wisconsin, School of Medicine & Public Health

Department of Neurological Surgery

Project Summary

Cerebral vasospasm can be a devastating sequela of aneurysmal subarachnoid hemorrhage. Currently, there is neither a satisfactory predictor of its likelihood nor a standardized protocol for its early detection. Diagnostic methods typically employed include transcranial Doppler imaging (TCD), CT angiography (CTA), CT perfusion (CTP), and digital subtraction angiography (DSA). TCD is the least invasive technique but, has limitations because many subjects do not have an acoustical window through the skull.[1] CTP provides both volumetric imaging and well validated measurements of brain perfusion, however, its sensitivity is not adequate to detect early reductions in perfusion[1,2]. DSA allows excellent visualization of changes in large vessel caliber but often does not correlate with the degree of hemodynamic compromise; it is also a more invasive study than the other modalities[1].

Cerebral autoregulation is the inherent ability of blood vessels to keep cerebral blood flow (CBF) and cerebral blood volume (CBV) relatively constant over a wide range of systemic blood pressures by means of complex physiological mechanisms in response to changes in perfusion pressure and demand. It plays in an important role in delivering blood containing oxygen and nutrients to the brain tissue to meet its metabolic needs. This adaptation of cerebrovascular resistance through vasodilation or vasoconstriction adjusts CBF and CBV to normal values over a wide range of perfusion pressures. Below certain levels of perfusion pressure, however, autoregulation fails. This results in ischemia and injury to the brain tissue. The extent and degree of injury vary with the length of time and extent to which tissue perfusion is inadequate.

We propose a technique using cone beam perfusion (CBCTP) with an acetazolamide challenge as a potential diagnostic tool to detect a defect in cerebral autoregulation at a time when it has not yet caused clinically apparent signs or symptoms. Acetazolamide is a carbonic anhydrase inhibitor which works to increase the arterial concentrations of carbon dioxide. Carbon dioxide is an important regulator of cerebral vasculature and serves as a potent vasodilator. Acetazolamide or vasodilatory challenge should identify subjects having an abnormal cerebrovascular reactivity capacity. More specifically, after receiving the drug there will not be the expected increase CBF in some of the subjects because they are already suffering from a disturbance in the vasculature's ability to respond to the signal for vasodilation. We ultimately believe the presence of this deficit will be helpful in identifying patients who are at risk for potential brain ischemia due to this decreased capacity to autoregulate if/when clinically significant vasospasm occurs. We predict that acetazolamide-activated regional cerebral blood flow studies will be more sensitive in the detection of mild cerebral vasospasm and will not just detect changes in cerebral blood flow as does standard perfusion imaging, but will provide information regarding changes in cerebrovascular reactivity. Under these circumstances, we would have a better predictor of those patients at risk of cerebral infarction due to delayed vasospasm. Identifying this "high-risk cohort" prior to the onset of clinically apparent symptoms would result in the institution of preventative measures such as triple H therapy[3].

Background and Significance

Ruptured aneurysms are responsible for approximately 80-85% of non-traumatic subarachnoid hemorrhage and intracranial aneurysms (IAs) are present in 1-2% of adults in the United States[4]. An IA is a pathological dilation and thinning of a portion of the wall of an intracranial artery. While the overall risk of rupture of an IA is quite low, when rupture occurs the effect is devastating with mortality and morbidity rates that approach 50% and 30%, respectively. Aneurysmal subarachnoid hemorrhage is one of the most deadly and morbid types of strokes and represents approximately 3% of all strokes[5]. One third of these deaths occur in the first 30 days[6]. Cerebral vasospasm or delayed cerebral ischemia is a major cause of morbidity and mortality in patients who survive the initial hemorrhage. Angiographic vasospasm is evident in 30-70% of patients and can cause permanent morbidity or mortality in up to 20% of these patients[7]. Early prediction of patients at risk for development of cerebral vasospasm can help guide the aggressiveness of both medical and endovascular treatment to prevent irreversible cerebral infarction.

The mechanism behind cerebral vasospasm is not completely understood. It is suggested that there is global vasoconstriction in response to the presence of blood in the subarachnoid space. One theory is the degradation of hemoglobin results in formation of free radicals and consumption of nitric oxide. An environment with low concentrations of nitric oxide can produce both local and global vasoconstriction of the cerebral vessels[8]. The cerebral blood supply is unique in that is relies heavily on autoregulation. Under conditions of indiscriminate vasoconstriction there can be impaired cerebrovascular reactivity or ability to increase cerebral blood flow through vasodilation in response to either intrinsic or pharmacologic signals to increase CBF.

Posner and Plum in 1960 first incidentally observed that there is a considerable increase in cerebral blood flow after intravenous administration of acetazolamide during an investigation of the effects of acetazolamide in hepatic encephalopathy[9]. Acetazolamide is a reversible carbonic anhydrase inhibitor which prevents conversion of carbon dioxide to water and carbonic acid, resulting in an increased concentration of arterial carbon dioxide. Regulation of cerebral circulation is partly mediated by carbon dioxide which serves as a potent vasodilator resulting in increased cerebral blood flow. Under normal physiological conditions administration of acetazolamide can result in further dilation of the cerebral arterioles, therefore increasing cerebral blood flow[10]. Several studies have documented this phenomenon both in normal subjects and in patients with varying degrees of vascular pathology including subarachnoid hemorrhage and vascular insufficiency or occlusion[1,2,10–14]. However, if cerebral perfusion has been reduced due to vasospasm, the cerebral arterioles correlating to the diseased territory have already lost their ability to dilate and will not have the expected increase in cerebral blood flow as a direct response to acetazolamide administration. Simply put acetazolamide should have no additional effect on cerebral blood flow in an area where

vasoregulatory responses are impaired. In addition, acetazolamide has been reported to have been injected intravenously with no serious complications in prior CBF studies in normal subjects and in patients with vascular pathology[14].

Based on the principles of autoregulation, cerebral blood flow will not decrease until the compensatory capacity of the cerebral vasculature has been exhausted. So ideally, there is a window of opportunity for therapeutic intervention between reduction in cerebral perfusion pressure and ischemic neurological symptoms due to reduced cerebral blood flow. **We hypothesize that using CBCTP combined with an acetazolamide challenge would be able to identify abnormalities in the cerebrovascular autoregulation prior to reductions in cerebral blood flow and therefore prior to ischemic insult.** Several studies have already demonstrated a significant increase in cerebral blood flow in response to intravenous injection of acetazolamide but its application to patients with subarachnoid hemorrhage at risk of development of vasospasm has been limited[9,10,12,15,16].

C-arm CBCT is a technology that allows for CT images of the vasculature, bone, and soft tissues to be generated utilizing the flat detectors of modern angiography machines. This is accomplished with high speed rotation of the C-arm around a supinely positioned patient while collecting an array of 2-dimensional x-ray projections. Separately SMART-RECON algorithms are used to reconstruct the projections in anatomic planes comparable to CT images. With recent advances in technology the post-processing of images can provide both anatomic and physiologic (perfusion) information using an intravenous injection of contrast dye. This high-quality C-am CBCT angiography utilizes 1/3 of the radiation dose currently used in our clinical practice under conventional CT imaging technology. This technique has been validated by our previously published work[17–19].

Study Objective

The objective of this proposal is to conduct a feasibility study of acetazolamide activated C-arm CBCTP to determine its application in the prediction of symptomatic cerebral vasospasm in patients with aneurysmal subarachnoid hemorrhage. Our initial plan is to obtain C-arm CBCTP pre- and post-intravenous infusion of 1 gram acetazolamide within 24 hours of symptom onset in aneurysmal subarachnoid hemorrhage patients. Our hypothesis is that some of these patients that will later develop clinical vasospasm of a degree sufficient to cause cerebral ischemia. We believe this cohort of patients will demonstrate altered cerebrovascular reactivity during the acetazolamide challenge at a time before there is either angiographic evidence of vasospasm or clinical evidence of abnormal perfusion. Thus far in the pilot study we have enrolled a total of 10 patients and are now planning to expand enrollment to 30 patients. The data we have collected from the research scans have thus far been reproducible and collected with clinical ease. There have been no complications with imaging acquisition and there have been no safety concerns for patients. Having so far achieved our objectives with the initial 10 patients we now hope to amend the protocol to allow for the larger cohort of 30 subjects. With this larger sample size we will not only continue to assess safety and reproducibility, but also will hope to capture a large number of patients who develop vasospasm in order further assess

the utility of the research study in its application as a screening diagnostic tool to predict the subsequent occurrence of delayed vasospasm in subjects with an acute aneurysmal subarachnoid hemorrhage.

Study Methods

Inclusion criteria:

A total of 30 subjects will be enrolled in this pilot feasibility study. The following patients will be targeted for enrollment:

1. Patients with aneurysmal subarachnoid hemorrhage presenting to our institution within 24 hours of symptom onset.
2. Adults, 18 years of age or older
3. Women of childbearing potential must not be pregnant (urine pregnancy test will be required as is already done as part of standard of care)

Exclusion criteria:

Whether subjects will be invited to participate in this research will be based on the patient's medical condition and will be at the discretion of the treating physician. The following patients will be excluded automatically:

1. Contraindication to acetazolamide (i.e. sulfonamide allergy, renal or liver failure)
2. Contraindication to contrast media (Allergy or abnormal serum Cr and/or GFR based on current UW guidelines for IV contrast see Appendix A)
3. Renal insufficiency, history of renal failure or renal transplant
4. Hunt and Hess grade 1 and 5 (See Appendix B, as Grade 1 have lower yield for vasospasm and Grade 5 are by definition critically ill and unstable patients)
5. Critically ill patients who are unstable and who cannot undergo scans within the proposed timeline i.e. within 24 hours of the onset of their symptoms.

Patient identification/Recruitment/Consent:

Patients targeted for enrollment will be those referred to the Department of Neurosurgery and Neuroendovascular Surgery at University of Wisconsin meeting the inclusion criteria. Eligible candidates will be identified by the neuroendovascular or neurosurgical attending physician and will be invited to participate by a clinical care team member. If patients lack capacity to provide informed consent on their own behalf, the care team will include the next of kin in the consenting process. Subarachnoid hemorrhage patients that present with a medically unstable condition will not be considered for this study.

Capacity for providing informed consent will be determined and documented in accordance with the institutional policy for the inclusion of patients in non-therapeutic research that presents more than minimal risk. This determination will occur by direct evaluation by the clinical care team based on interaction with the patient, existing legal documentation in the

medical record in regards to a legal guardian, healthcare power of attorney, or pre-existing disease that affects decisional capacity. The University of Wisconsin Hospitals and Clinics Clinical Policy on Informed Consent will be followed (Appendix C). Those subjects lacking formal capacity will still be included in the consenting process and will be asked to provide assent to participate. Any sign of dissent by the subject will be honored by the research team even if a surrogate has provided consent on their behalf. If a subject regains capacity prior to hospital discharge, a research team member will review the consent, research procedures that have been conducted, and will obtain informed consent for continued participation in the research. For patients that have been determined to have capacity to provide informed consent, a research team member will administer a four-question assessment to confirm understanding of the implications of participating in this research (Appendix D). If the subject or legal healthcare representative is unable to provide informed consent, then the patient will be excluded from participation.

Scan procedure:

Overview of imaging protocol: Prior to catheter angiography, the diagnostic evaluations of subjects entered into this protocol will not vary from that used on others who are not eligible or who do not wish to participate in the study. Subjects entered into the study, will because of their participation, undergo only two additional DSA imaging acquisitions. These will be done in conjunction with their standard diagnostic DSA evaluation and consist of two CBCTPs, one before and one after administration of 1 g acetazolamide through a peripheral IV line. Each CBCTP will require administration of 75-100 mL iodinated contrast medium also through an IV line. Neither of these imaging studies will be used for clinical decision making, but would be processed and evaluated at later date for a formal analysis of the results. Following completion of diagnostic imaging subjects will receive the usual standard of care for treatment of their ruptured aneurysm i.e. endovascular embolization or open surgical clipping.

Details of experimental imaging: An initial CBCTP acquisition will be done in conjunction with injection of iodinated contrast medium through a peripheral IV (75-100 mL iopamidol, Isovue 370; Bracco Diagnostics, Princeton, NJ). An IV is placed for normal standard-of-care for this disease process. After this 1 g of acetazolamide will be given through the IV line. Following a 20-minute delay a second CBCTP acquisition will be completed again in conjunction with injection of iodinated contrast medium at a dose identical to that used for the first CBCTP acquisition. Each of the CBCTP acquisitions take less than 2 minutes so, except for the 20-minute period following administration of the acetazolamide there will be no delay in the subjects' diagnosis or treatment.

Contrast: C-arm CBCTP will be performed with intravenous injection of contrast dye (iopamidol, Isovue 370; Bracco Diagnostics, Princeton, NJ) at a rate of 4 mL/s and a maximum dose range of 75-100 mL. The contrast bolus may be followed by a 50-mL saline push at a rate of 4 mL/s. The delay will be calculated from the conventional CTA/CTP that was performed prior. The contrast administered during the conventional CTA head and neck with perfusion performed prior will be 120 mL. Therefore, the maximum amount of IV contrast media that would be administered

within a 24-hour period for this study is 320 mL. Contrast media administration is an important consideration as a cause of iatrogenic acute kidney injury, but it should be emphasized that the large majority of these cases are minor. Under our protocol pre- and post-procedure serum creatinine levels will be monitored closely and patients will receive adequate hydration. Iopamidol is excreted mainly through the kidneys and in the absence of renal dysfunction 35-50% of the contrast media is excreted within 60 minutes and 80-90% within 8 hours. There will be at least a 1 hour period between contrast loading from the conventional CTA/CTP and the study C-arm CBCTP scans.

SMART RECON: This software utilizes the images acquired during rotational angiography to create an angiographic CT. The volume set is reconstructed on the syngo MultiModality Workplace and available for assessment in less than 1 minute in the interventional suite.

Data Acquisition: Perfusion maps from the standard multi-row CTP will be evaluated with the Siemens CTP software after the procedure. Perfusion maps from the C-arm CBCT will be evaluated at an independent work station with SMART RECON. Matching regions of interest (ROI's) will be placed in each hemisphere in mirror image positions. The ROI's identified on each patient's standard CTP will be compared to ones selected in the post-processing phase.

Acetazolamide injection: 1 g intravenous acetazolamide will be administered by peripheral IV. Blood pressure, respiratory rate, heart rate and pulse oximetry will be monitored before, during, and after this injection by the administering nurse. The wait period after drug administration will be standardized to 20 minutes prior to obtaining the follow up perfusion study.

<u>Drug Information:</u>

Drug formulation: Solution Reconstituted, Injection
Source: Drug is on UWHC formulary and would be available through the inpatient pharmacy
Storage and stability: Store intact vials at 20-25 C (68-77 F). Store reconstituted solutions for 3 days under refrigeration at 2-8 C (36-46 F), or 12 hours at room temperature (20-25 C or 68-77 F).
Preparation: For injection reconstitute with at least 5 mL sterile water to provide solution containing not more than 100 mg/mL.
Dosage/Administration: 1 gram, intravenous
For a complete listing of drug interactions, contraindications, and adverse reactions please see: https://online.lexi.com/lco/action/doc/retrieve/docid/uofwisconsin_f/3680280

Acetazolamide or the brand name Diamox is an FDA-approved medication with labeled indications including glaucoma, edema, altitude sickness, and epilepsy. Our protocol will utilize intravenous formulation only. Prior studies in the literature assessing cerebrovascular reserve used rapid 1 g intravenous injection over less than 1 minute[11]. Doses of 500 mg were reported to be insufficient for adequate carbonic anhydrase inhibition[12]. Acetazolamide is

contraindicated in patients with marked renal impairment, cirrhosis or liver disease, sulfonamide allergy, adrenocortical insufficiency, or hyperchloremic acidosis.

Risks:

This feasibility study presents minimal risks to participants. Subjects entering this study will not have the timing of their therapy, whether that be endovascular or open surgery, altered in any way that would differ from the standard of care offered at our institution. The potential risks from participating in this study include contrast and radiation exposure, side effects or adverse reactions to acetazolamide and the risk of breach of confidentiality.

Contrast exposure:

The main risks are allergic reaction and contrast-induced nephropathy (CIN). Prior to receiving the additional contrast media required by our study scan subjects will have already been given a prior dose of the same contrast medium for their standard of care conventional CTA. It will thus be clear to researchers whether the subjects are able to tolerate the agent. If any patient is experiencing any sign of contrast reaction at the conclusion of the clinical CTA, they will be withdrawn from this research study.

As it pertains to CIN, the standard maximum dose for a given study is 250 mL and the total dose for subjects participating in our research scans will be less than this. In a study of 11,588 patients undergoing CT scans with or without administration of contrast medium, Bruce and colleagues at UW-Madison concluded: “We identified a high incidence of acute kidney injury among control subjects undergoing *unenhanced* CT. The incidence of creatinine elevation in this group was statistically similar to that in the iso-osmolar contrast medium group for all baseline creatinine values and all stages of chronic kidney disease. These findings suggest that the additional risk of acute kidney injury accompanying administration of contrast medium (contrast-induced nephrotoxicity) may be overstated and that much of the creatinine elevation in these patients is attributable to background fluctuation, underlying disease, or treatment.”. In another study of 1,075 patients receiving routine CT angiography and CT perfusion, Josephson and colleagues 52 patients had a creatinine rise of > or = to 0.5 mg/dL. In 4 (0.37%) the administration of IV contrast medium possibly contributed to renal failure. They concluded that “The incidence of contrast nephropathy in neurovascular patients is low”. Thus, both our experience and additional literature support our belief that this small amount of added contrast dose poses virtually no added risk to these subjects when used as described in this protocol[21,22]. Additionally, in the 2017 American College of Radiology Manual on Contrast Media they report that there is not sufficient evidence to specifically endorse the decision to withhold a repeat contrast medium injection until more than 24 hours have passed nor to recommend a specific threshold of contrast medium volume beyond which additional contrast media should not be given within at 24-hour period.

Radiation exposure:

The American Association of Physicists in Medicine (AAPM) is the professional society most involved in work to reduce radiation exposure from medical and other sources and to evaluate the potential risks of radiation exposure. Their current position statement regarding the risks from medical imaging procedures states: "Risks of medical imaging at effective doses below 50 mSv for single procedures or 100 mSv for multiple procedures over short time periods are too low to be detectable and may be nonexistent. Predictions of hypothetical cancer incidence and deaths in patient populations exposed to such low doses are highly speculative and should be discouraged". http://www.fda.gov/RadiationEmittingProducts/RadiationEmittingProductsandProcedures/MedicalImaging/MedicalX-Rays/ucm115329.htm.

The radiation exposure received by subjects who are enrolled in our research is 8.8 mSv, which is far below the doses described above (100 mSv for multiple procedures). Additionally, this effective dose of the research imaging is only 1/3 that of the standard of care CT dose and, furthermore, this dose is equivalent to just over 1 year of natural background radiation. It would thus seem that this dose, equivalent to that received from background radiation would fall within the acceptable risks for "Minimal Risk". In other words, the added exposure received by the subjects participating in our research is equivalent to that they would receive from background radiation in their daily life.

Acetazolamide risks:

Acetazolamide is already an FDA-approved medication. Sullivan et al tested cerebrovascular reactivity in normal subjects in response to acetazolamide challenge and found the most common adverse reaction to be numbness and tingling which was transient over the course of several hours. Approximately half of subjects experienced headache and generalized fatigue. However, there were no serious or life-threatening reactions in any of the subjects[10]. Holl et al demonstrated use of intravenous acetazolamide in both normal subjects and subjects with major cerebral occlusion had no serious complications. They do report that there was a consistently produced rise in intracranial pressures (ICP) in patients with already disturbed cerebral spinal fluid (CSF) circulation, but this increase was transient and in their cohort it was symptomatic in only one patient who experienced a headache[15,20]. In our population if there is concern for increased ICP there would be an intracranial pressure monitor that would be providing CSF diversion to reduce ICP as a standard of care placed prior to administration of the drug. Therefore, this causes essential no clinical risk to this patient population.

Privacy/Confidentiality protections and sharing of data:

Data gathered from this study will be post-processed and evaluated by the study neuroendovascular physician in accordance with the protocol outlined above. Imaging data will be stripped of all direct patient identifiers and stored on a dedicated PACS system controlled by UWHC. Dr. Strother, will maintain the master list linking coded data to medical record numbers. The research workstation that will be used by analysis is password protected and uses departmental servers that are backed up by the UWHC firewall. Coded data, including images,

collected from this research will be shared with manufacturer of C-arm CBCT, Siemens Medical Solutions for further refinements in hardware and prototype software to improve imaging. No directly identifiable images or data will be disclosed outside of UWHC. All data obtained from the medical record will be stored in a HIPAA compliant manner.

Patient Follow Up:

Patients will receive follow up care by the primary treating neurosurgeon or neuroendovascular surgeon in a manner that is consistent with standard clinical care. Subjects will be inpatients and their recovery followed primarily by either the neurosurgery or neuroendovascular teams during their acute hospitalization.

Information Collected from Medical Records

Data collected from medical records will include:

1. Age, sex, medical history, physical exam, laboratory and imaging studies
2. Hunt and Hess Grade
3. Fisher Grade
4. Intracranial pressure
5. Location of aneurysm responsible for bleeding
6. Treatment modality for aneurysm (embolization versus clipping)
7. Anesthesia record
8. Presence of vasospasm or delayed cerebral ischemia
    a. Clinical: deterioration when other causes have been ruled out including hydrocephalus, re-bleed, or metabolic abnormalities
    b. Radiographic: detection of new infarct on imaging not visible on the admission or immediate post-treatment scan or both

FDA Considerations:

C-arm CBCTP: Siemens C-arm CBCT software currently has 510(k) (September 2004) clearance. The innovative C-arm CBCTP software is used to consecutively perform 10 CT sweeps with one single intravenous contrast injection. We are requesting a, “non-significant risk” determination by the IRB for the use of this novel software. Note that C-arm CBCT acquisitions are routinely and frequently utilized in our clinical practice and we do not foresee any potential risks. The package of ten C-arm CBCT sweeps and the innovative data processing software SMART RECON, are not FDA approved since they are in experimental validation research stage approved by the NIH at UW. The data obtained from this study may support the application and approval of the UW software in the future. However, the hardware (Siemens angiographic machine) to obtain the C-arm CBCT perfusion data does not introduce any new potential safety risks and is equivalent to and performs in the same fashion as standard C-arm CBCT.

Data and Safety Monitoring Plan

All researchers and research staff involved in this project have completed Human Subjects and HIPAA training and are familiar with all procedures. The PI and co-investigators will review the data collected after the initial patients have been treated and outcome data becomes available. Adverse events or problems will be reviewed by the PI and co-investigators as they occur and will be reported to the IRB by the PI in accordance with posted guidelines. The PI and the co-investigators will meet regularly to review the data, adherence to the protocol and IRB guidelines. Data and safety monitoring will occur on a continuous basis by the research staff. The study team will meet regularly to review study progress including recruitment, data collection, and they will address any concerns or challenges that may arise. If initial pilot data shows that this technique is validated a formal study will be proposed to the IRB.

Statistical Considerations

The initial pilot study was conducted as a feasibility study and no robust statistical evaluation is possible. Since we have determined that the research imaging can be achieved safely and data reproducibly collected, we now hope to amend the cohort to a total of 30 patients so that we can capture more patients with vasospasm in order to have a more robust analysis of the correlation between percent change in CBF to Diamox and the future development of cerebral vasospasm.

IRB Concerns

The gold standard for determining if a patient has vasospasm is the clinical neurological exam. There is no currently accepted radiographic method or procedure for predicting vasospasm. Therefore, when comparing this proposed CBCT approach to the competing method we would be comparing it to the clinical neurological exam. Additionally, comparisons are being made to current methods of predicting vasospasm including TCDs, multidetector CTA/CTP, and angiography.

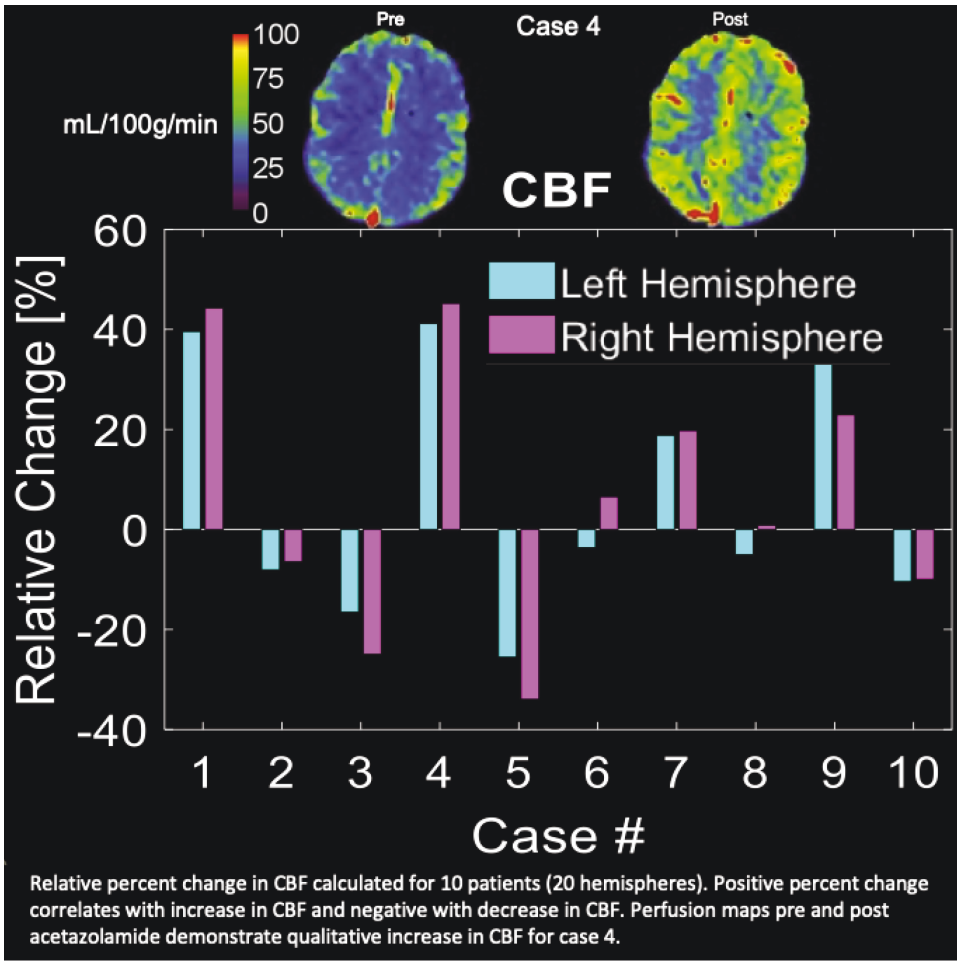
With our initial 10 patients we are able to report that in all 10 patients the images were successfully required. We then performed an analysis of the 20 total cerebral hemispheres (right and left). Nineteen of 20 hemispheres demonstrated a significant change in CBF perfusion in response to Diamox ($p<0.05$). Six hemispheres demonstrated a 30% change in CBF and 12 had a 15% change. In 9 hemispheres there was the expected increase in CBF in response to Diamox. In 10 hemispheres there was a decrease in CBF. There was no statistical difference in the percent change between left and right hemispheres which would correlate with the global vasodilatory effects of Diamox. Symptomatic vasospasm then only developed in 2 of our patients. In one of these patients there was a pathological decrease in CBF in response to Diamox while the other had an appropriate increase in CBF. The goal of the analysis in this extension of the study is to better understand the changes in CBF in patients that go on to develop symptomatic or clinical vasospasm based on a change in neurological exam. Unfortunately, in our first phase of the pilot study only 2 patients developed symptomatic vasospasm. The reason we are requesting an extension to 30 patients is so we can capture a

larger number of patients with symptomatic vasospasm. Then we can assess our statistical analysis to see if the we can consistently see a significant lack of response (either <30% increase in CBF or a decrease in CBF) to Diamox. With only 2 patients in our initial cohort developing symptomatic vasospasm it is impossible to make a more robust statistical proposal and that is why we are submitting a request to study more cases.

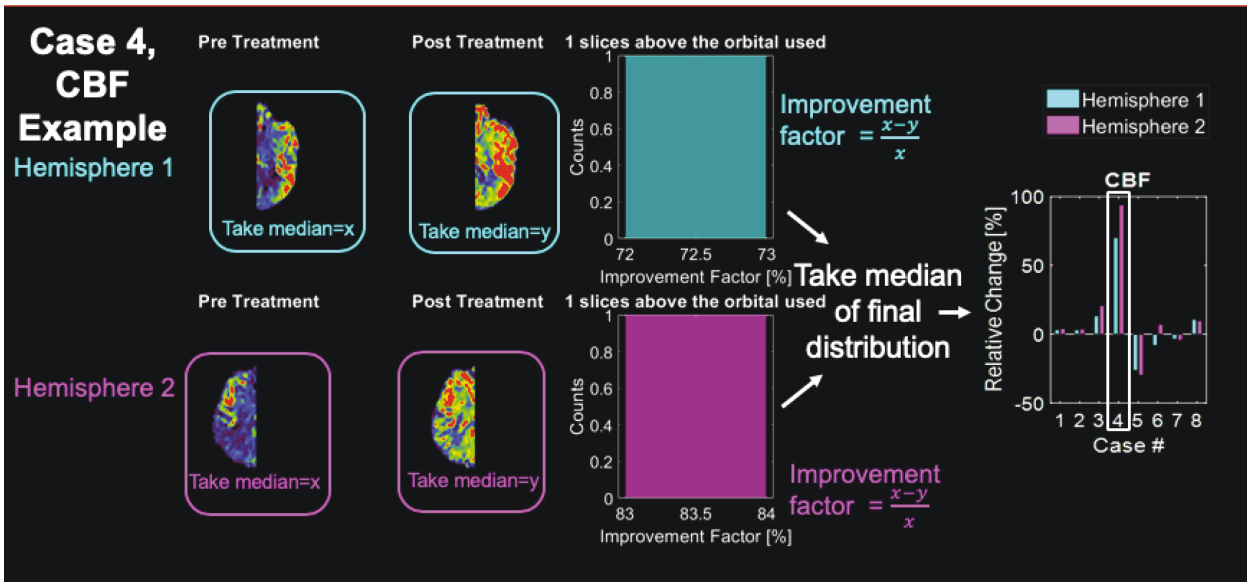
As discussed before, in this study design there is no need for a control group. We are comparing our CBCT information to the conventional method which is the clinical neurological exam change which indicates clinical or symptomatic vasospasm. The data that will be statistically compared is the pre-diamox perfusion in comparison to the post-diamox perfusion. A statistically significant change increase in CBF represents an appropriate response to Diamox. Lack of change in CBF or decrease in CBF could be suggestive of potential for developing vasospasm. More data with patients who develop clinical vasospasm is needed in order to correlate these changes with this subset of patients.

The statistics that will be performed on the data maps are outlined in the images below. Using the perfusion map values, we will calculate relative percent change or improvement factor which is detailed in the slides below. When we say the results were reproducible it means that we were able to detect a change in perfusion in response to Diamox and that the maps were of good enough quality to be diagnostic. I have included examples below.

The statistical analysis on the relative percent change in CBF was a standard basic paired t-test. This test was performed in an identical manner for each hemisphere for each perfusion parameter map. For a given hemisphere and map test here were 40 slices of the image above the orbital line, a mean measurement was made for each slice location of the hemisphere. Thus, for pre and post Diamox we obtained 40 paired samples. From these paired samples (paired meaning they shared the same slice location pre and post Diamox) the paired-test was performed by taking the difference between all of the pre and post paired samples to obtain a set of 40 differences. From these 40 difference values one can get a mean and standard deviation to obtain the T statistic where a corresponding p-value can then be calculated. For our data set, we are selecting p-value of <0.05 as significant. We do not plan to use this data for a power analysis. Reproducibility has been established, but we are now aiming to draw correlations between patients with vasospasm and their CBF response to Diamox and that is the main aim of this expanded portion of the study.



Relative percent change in CBF calculated for 10 patients (20 hemispheres). Positive percent change correlates with increase in CBF and negative with decrease in CBF. Perfusion maps pre and post acetazolamide demonstrate qualitative increase in CBF for case 4.



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Appendix A:

Diabetic

	Creatinine	eGFR
Iohexol	< 1.4	>45
Iodixanol	1.4 – 2.0	45 – 30
No IV Contrast	> 2.0	<30

Non-Diabetic

	Creatinine	eGFR
Iohexol	< 1.8	>30
Iodixanol	1.8 – 3.0	30 – 15
No IV Contrast	> 3.0	<15

Appendix B:

Hunt and Hess Grading Scale

- Grade 1: Asymptomatic or mild headache
- Grade 2: Cranial nerve palsy or moderate to severe headache/nuchal rigidity
- Grade 3: Mild focal deficit, lethargy, or confusion
- Grade 4: Stupor and/or hemiparesis
- Grade 5: Deep coma, decerebrate posturing, moribund appearance

Appendix C:

https://uconnect.wisc.edu/policies/clinical/uwhc-clinical/uwhc-wide/legal-affairs/417.policy

Appendix D: Consent Form Questions

Do you have to participate in this study?

_____

_____

What would you do if you decided that you no longer wanted to participate?

_____

_____

What are the risks to you if you participate?

Do you want to participate in the research study that has just been described to you?