Non-Invasive Measurement of Dynamic Autoregulation of Cerebral Blood Flow Using Diffuse Correlation Spectroscopy

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Biomedical Research **Section II**

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PROTOCOL TITLE

1. Full Title: Non-Invasive Measurement of Dynamic Autoregulation of Cerebral Blood Flow Using Diffuse Correlation Spectroscopy

2. Brief Title: Non-invasive Measurement of Cerebral Dynamic Autoregulation

STUDY SPONSORSHIP

1. Funding Sponsor: NIH R25 Research Grant

PROTOCOL ABSTRACT

List of Abbreviations

dCA	Dynamic Cerebral Autoregulation
CA	Cerebral Autoregulation
CPP	Cerebral perfusion pressure
CBF	Cerebral blood flow
oCBF	Optically measured Cerebral Blood Flow
MAP	Mean Arterial Pressure
TCD	Transcranial Doppler
DCS	Diffuse Correlation Spectroscopy
ICP	Intracranial Pressure
CVR	Cerebrovascular resistance
CT	Computed Tomography
PET	Positron emission tomography
MRI	Magnetic Resonance Imaging
DRS	Diffuse Reflective Spectroscopy
VRF	Vascular Risk Factors

OBJECTIVES

1. Overall Objectives

The overall objective of this study is to evaluate the use of diffuse correlation spectroscopy (DCS) to non-invasively measure dynamic cerebral autoregulation (dCA). Cerebral autoregulation (CA) refers to the process by which cerebral blood vessels change their caliber to ensure constant cerebral blood flow (CBF) in the face of changes in cerebral perfusion pressure (CPP). Optical cerebral blood flow (oCBF) measurements will be correlated with changes in arterial blood pressure (ABP) to assess how CBF is maintained in response to changes in ABP. CA measured by DCS will be compared with reference measurements using Transcranial Doppler (TCD).

2. Primary Objective

The primary objective of this study is to validate the use of DCS to quantify dCA in healthy controls. We will measure dCA with both TCD and DCS during acute changes in mean arterial pressure using thigh cuff deflation techniques in healthy subjects. Measurements will be compared between TCD and DCS in order to validate DCS as a tool to measure dCA. We hypothesize that DCS based measurements will be tightly correlated to TCD based measurements. We hypothesize that continuous oCBF measurements will allow calculation of an autoregulation index that will correlate well with established methods for measuring CA using TCD. The primary measured variable will be relative change in cerebral blood flow using DCS.

BACKGROUND

Cerebral Autoregulation

CA allows blood flow to remain nearly constant during beat-to-beat changes in blood pressure, matching perfusion to metabolic demand. CA can be subdivided into dCA and static CA (sCA). dCA is the transient response of cerebral blood vessels to changes in blood pressure through changes in vessel resistance and arteriolar diameter, and is the strictest definition of CA. sCA refers to the control of blood flow during steady state conditions. Static autoregulation methods measure cerebral blood flow at two different steady state blood pressures and then calculate a static rate of regulation by calculating the percent change in CBF (or cerebrovascular resistance) divided by the change in arterial pressure. While quantitative and relatively simple to interpret, static autoregulation measurements have multiple drawbacks. First, static measures provide a single snapshot and do not allow dynamic measurements of how autoregulation changes over time. In addition, these techniques require pharmacologic manipulations in blood pressure (such as infusion of a vasoconstricting agent to increase ABP), which may be contraindicated in critically ill patients and change other aspects of systemic physiology (such as vasomotor tone and cardiac output). Dynamic measures of autoregulation assess time varying changes in CBF and cerebrovascular resistance (CVR) in response to an abrupt change in blood pressure (Aaslid, Lindegaard et al. 1989) or in response to spontaneous fluctuations in ABP (Budohoski, Czosnyka et al. 2013). A standard method for calculating dynamic autoregulation is to measure the transient changes in cerebral blood flow that result from transient decreases in venous return and cardiac output following deflation of blood pressure cuffs applied to the thighs (Aaslid, Lindegaard et al. 1989).

Prior human studies have documented that CA tightly controls flow over a range of mean arterial pressure from 60-150mmHg (Paulson, Strandgaard et al. 1990). However, recent studies suggest that autoregulation may be impaired for up to 2 weeks following acute ischemic stroke (AIS), and that CA impairment may lead to poorer outcomes (Dawson, Blake et al. 2000, Dawson, Panerai et al. 2003, Reinhard, Roth et al. 2005, Atkins, Brodie et al. 2010, Aoi, Hu et al. 2012, Reinhard, Rutsch et al. 2012). The extent of CA impairment in acute stroke is likely highly variable. Early human studies determined that CA is impacted by age-related diseases, including hypertension and diabetes (McHenry, West et al. 1974, Dawson, Blake et al. 2000, Aries, Elting et al. 2010). Animal models have also demonstrated impaired dCA in AIS and that the tissue becomes much more vulnerable to changes in blood pressure (Yang, Shah et al. , Smeda, VanVliet et al. 1999, Smeda 2003). Based on the principle that CA is impaired following an acute ischemic event, current treatment recommendations revolve around tactics that increase cerebral perfusion (Goldstein 2000, Dawson, Panerai et al. 2003). The American Heart Association/American Stroke Association guidelines recommend permissive hypertension to systolic of 220mmHg and diastolic to 120mmHg (Adams, del Zoppo et al. 2007). However, above the upper limit of CA blood vessels are

not able to adequately constrict to limit blood flow, which can lead to endothelial injury, breakdown of the blood-brain barrier, and potentially cerebral edema (Nazir, Overell et al. 2004, Nazir, Overell et al. 2005). Data derived from this project will provide the groundwork for future projects using the DCS technique which may be able to establish a new bedside mechanism for identifying patients in whom dCA is impaired, allowing for more individualized use of permissive hypertension, intravenous fluids, and vasopressors.

Limitations of existing autoregulation measurements

Existing methods of measuring CBF include oxygen-15 positron emission tomography (PET), single-photon emission computed tomography (SPECT), arterial spin labeled MRI, and Xenon CT scanning, but these are not suitable for continuous or bedside monitoring (Chalela, Alsop et al. 2000, Baron 2001, Mahagne, David et al. 2004, Wintermark, Sesay et al. 2005). While transcranial doppler (TCD) ultrasound may be performed readily at the bedside, it does not directly measure CBF, but rather blood flow velocity (Bishop, Powell et al. 1986). DCS is a novel method for non-invasively monitoring CBF developed at Penn by Yodh et al. and translated for bedside monitoring of acute stroke patients with support of an ongoing NINDS Bioengineering Research Partnership on this topic (Durduran, Zhou et al. 2009). In DCS, light scatter from flowing red blood cells in brain tissue is used to track rapid fluctuations and is used to derive the blood flow index (BFI), which has previously been shown to correlate with other blood flow measurements (Kim, Durduran et al. 2010, Mesquita, Schenkel et al. 2013). The BFI is derived from the DCS intensity auto-correlation function. Current instrumentation allows for CBF calculations roughly every second (Durduran, Zhou et al. 2009). The benefit of this system is that it allows continuous bedside measurement of CBF and can be used in a variety of patient positions, such as supine compared to altered head-of-bed angles, as previously studied at our facility in brain injury patients, and in aging patients (Langewouters, Settels et al. 1998, Reinhard, Roth et al. 2005, Edlow, Kim et al. 2010, Kim, Durduran et al. 2010, Kim, Edlow et al. 2013). Head of bed (HOB) manipulation has important limitations as a measure of cerebral autoregulation. HOB manipulation may alter intracranial pressure and vascular resistance in addition to blood pressure. Dynamic measures of autoregulation assess time varying changes in CBF and CVR in response to an abrupt change in blood pressure (Aaslid, Lindegaard et al. 1989) or in response to spontaneous fluctuations in ABP (Budohoski, Czosnyka et al. 2013). A standard method for calculating dynamic autoregulation is to measure the transient changes in cerebral blood flow that result from transient decreases in venous return and cardiac output following deflation of blood pressure cuffs applied to the thighs (Aaslid, Lindegaard et al. 1989, Newell, Aaslid et al. 1994, Tiecks, Lam et al. 1995). To date, no evaluation of dCA with respect to acute blood pressure changes have been published using direct measurement of CBF via the DCS technique.

Transcranial Doppler allows for the assessment of flow velocity in blood vessels. It is based on the Doppler Effect, which results in sound being reflected at a higher or lower frequency depending on the velocity and direction of the reflector. The shift in frequency is directly related to the velocity of blood flowing through an insonated vessel. Velocity is an indirect measure of cerebral blood flow (flow is equal to velocity times area). TCD estimates of CBF may not be accurate if the area of the insonated vessel is variable. A small study suggested that CBF, directly measured in the internal carotid artery during a surgical procedure, correlated with flow velocity measured by TCD (Newell, Aaslid et al. 1994). As such, TCD has the potential to function as a useful surrogate for CBF; however, it is important to note that CBF at the tissue level often depends on blood supply from multiple vessels, not a single large artery. Given that the ideal method for measuring autoregulation should assess CBF at the tissue level, TCD may not be a sufficiently accurate method to measure autoregulation. In addition, TCD accuracy is operator dependent and requires an experienced technician. Finally, while noninvasive, TCD measurements can be uncomfortable for patients since the ultrasound probe must be held in one position on the scalp with significant pressure.

Dynamic cerebral autoregulation measurement using optics

Under the direction of Dr. Arjun Yodh at the University of Pennsylvania Department of Physics and Astronomy, a versatile all-optical brain imaging probe has been constructed which has the ability to measure total hemoglobin concentration, blood oxygenation and blood flow non-invasively. This instrument combines two qualitatively different and complementary diffuse optical imaging modalities: (1) Diffuse Reflection Spectroscopy (DRS) for computation of blood oxygen saturation and total hemoglobin concentration, and (2) Diffuse Correlation Spectroscopy (DCS) for

measurement of blood flow. These two diffuse optical imaging schemes hold a unique potential for continuous non-invasive bedside imaging in humans (Hintz, Cheong et al. 1999, Benaron, Hintz et al. 2000). By allowing for accurate, real-time measurements of relative cerebral blood flow, non-invasive dynamic measures of cerebral autoregulation should be possible.

The DCS device employed in this study uses diffuse light to probe tissue properties. Dynamic optical properties are monitored using diffuse correlation spectroscopy at 785 nm. Changes in the blood flow are obtained from the correlation decay times. Measurements are made from both the right and left frontal regions, with one rectangular probe on each side of the head. Each probe has 1 source and 2 detector fibers. The light from these probes penetrates about 0.5 cm into the brain. Each probe is covered with black padding (skin-compatible materials) in order to isolate the laser light and ensure good contact with the head. The probes are held in place with medical adhesive tape and a padded Velcro band. The input average power is 15 mW. Measurements are taken every 0.5 seconds.

Prior work from our group has validated DCS against other measures of CBF including Xenon CT and fluorescent microsphere measurements (Zhou, Eucker et al. 2009, Kim, Durduran et al. 2010). DCS has also been used in the laboratory to monitor changes during focal cerebral ischemia of rat brain (Zhou, Shimazu et al. 2008). Finally, DCS has been successfully used in normal human subjects, and in patients with a variety of disease states including severe traumatic brain injury and ischemic (Durduran, Yu et al. 2004, Durduran, Zhou et al. 2009, Kim, Durduran et al. 2010).

Optical CBF monitoring using DCS presents an exciting alternative to existing methods of measuring cerebral hemodynamics. Compared to MRI, CT and PET, optical CBF monitoring is comparatively portable, inexpensive, non-invasive, and fast. These unique attributes can be leveraged to study cerebral autoregulation in patients with brain injury and evaluate the impact of interventions in real-time. Optical measurements of cerebral blood flow do not require significant special technical expertise. In addition, since the multiple optical probes can be placed in different locations on the head, spatial heterogeneities in cerebral autoregulation can be assessed. Our goal is to measure dynamic autoregulation non-invasively using DCS. We will induce a blood pressure change by rapidly deflating thigh blood pressure cuffs and measure changes in cerebral blood flow. This will allow us to calculate changes in cerebrovascular resistance and provide a measure of cerebral autoregulation.

Thigh Cuff Utilization

Prior research evaluating dynamic cerebral autoregulation used thigh cuffs on healthy controls to artificially, but noninvasively and non-pharmacologically, induce brief changes in blood pressure. This study performed 6 episodes of 2 minute inflation in bilateral thigh cuffs to a pressure above the maximum systolic blood pressure of the awake, non-anesthetized subjects (Aaslid, Lindegaard et al. 1989). Other more recent studies have continued to use the thigh cuff technique in both healthy subjects (Tzeng, MacRae et al. 2014, Subudhi, Grajzel et al. 2015), as well as those with traumatic brain injury and stroke patients respectively (Bailey, Jones et al. 2013, Saeed, Panerai et al. 2013). Of these studies using thigh cuff in healthy controls, traumatic brain injury, and stroke patients, only one subject (1.2%) out of) 83 total (49 healthy controls, 12 traumatic brain injury, 22 stroke) withdrew due to discomfort from the thigh cuffs. None of these studies reported neurologic deterioration or any other adverse events secondary to thigh cuff utilization (Aaslid, Lindegaard et al. 1989, Bailey, Jones et al. 2013, Saeed, Panerai et al. 2013, Tzeng, MacRae et al. 2014, Subudhi, Grajzel et al. 2015).

Surgical literature supports the safety of pneumatic tourniquet devices for bloodless field techniques. For upper limb bloodless field surgery using a tourniquet device, two hours of cuff inflation is considered safe (Noordin, McEwen et al. 2009). Although no prospective trials have been conducted to identify the maximum safe duration of lower leg ischemia using a pneumatic tourniquet device, trials have been done to evaluate the difference in recovery with and without tourniquet use. One randomized controlled study demonstrated that for routine anterior cruciate ligament repair these devices are routinely used for a mean of 87 minutes with the cuff insufflated to an average of 269mmHg. This study was powered to determine if tourniquet use during surgery is associated with increased neuromuscular injury, strength deficits, or any impaired return of function. The study showed that there was no evidence of injury

based on a wide range of tests (thigh girth, strength, functional testing, arthrometer evaluation, Lysholm knee scores and EMG) and 6-12 months (Arciero, Scoville et al. 1996). In previous experiments and in our proposed experiments, the thigh cuffs are inflated for only 2-3 minutes. This brief period of ischemia is nearly 30 times less than what has been previously studied in the surgical literature. Given the safety of prolonged thigh cuff inflation, the brief periods of arterial occlusion used in this study are expected to be safe and well tolerated.

The tourniquet system that will be used in this study has been approved by the FDA as a Class-I medical devices, indicating that they present minimal harm to the user and do not present a reasonable source of injury through normal use (Noordin, McEwen et al. 2009). Development in tourniquet systems over the past 30 years make use much safer, including increased cuff width, micro-computer monitoring systems, auto-shut off in event of power failure, battery backup, and audio-visual alarms. Increased cuff width results in lower required tourniquet pressure to stop blood flow (McEwen, Kelly et al. 2002) and should further improve tolerability of cuff inflation.

CHARACTERISTICS OF THE STUDY POPULATION

1. Target Population

Healthy adult volunteers with no history of prior brain ischemia.

2. Accrual

20 subjects provides 90% power to detect a moderate correlation (rho=0.6), with alpha=0.05, based on a single sided test of correlation using Pearson's correlation coefficient. Because of a combination of technical and individual factors, it may be that not all enrolled subjects provide analyzable data. The study will continue to enroll until we have complete, analyzable data on 20 subjects, or a maximum of 30 subjects will be enrolled. We will evaluate the quality of obtained data on a rolling basis and halt study enrollment as soon as we have met our goal of 20 subjects with data for analysis.

3. Key Inclusion Criteria

A. Healthy Subjects
   1. Age ≥ 18 years

4. Key Exclusion Criteria

A. Healthy Subjects
   1. Pregnant women are excluded
   2. Prisoners are excluded
   3. Prior history of vascular risk factors (hypertension, diabetes, hyperlipidemia, coronary artery disease, atrial fibrillation, prior myocardial infarct or stroke, transient ischemic attack, or history of smoking)
   4. Prior neurosurgical procedure or traumatic brain injury, including hemicraniectomy or other skull defect.
   5. Prior lower extremity amputation.

5. Vulnerable Populations

Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study.

6. Populations vulnerable to undue influence or coercion

Penn employees and Penn students:

Care will be taken during the consenting process to ensure that any Penn employee who meets the inclusion criteria for this study is not forced to participate on the basis of pay or the threat of loss of his or her position. Care will be taken during the consenting process to ensure that any Penn student who meets the inclusion criteria for this study is not forced to participate on the basis of a grade.

Educationally disadvantaged persons:

Care will be taken during the consenting process to fully explain the study in easily understood terms and to confirm the patient's comprehension of the information put forward. For specific information on how this will be accomplished, please see the "consent process" section.

Economically disadvantaged persons:
Subjects will not be paid in an amount that would encourage subjects to assume greater risks to participate in this study.

7. Subject Recruitment
Volunteers will be recruited from the University of Pennsylvania community. Advertisements will be placed across campus describing the research study and providing contact information. In addition, volunteers from the surrounding community who are not affiliated with the University of Pennsylvania will be allowed to participate if they meet the inclusion criteria. Subjects will not be excluded on the basis of gender, economic status, or race.

STUDY DESIGN

1. Phase
Not applicable

2. Design
Observational study

3. Study Duration
Based upon the study design, 30 subjects will be enrolled over approximately 18 months. Each subject will be tested for approximately 1.5 hours with approximately a half hour for proper setup and removal of measuring instruments.

DRUGS OR DEVICES

The optical device used in this study was developed at the University of Pennsylvania in the Department of Physics and Astronomy under the direction of Dr. Arjun Yodh. The instrument has been approved by the Environmental Health and Radiation Safety Department at the University of Pennsylvania for laser safety (B00050001). It will be stored securely in a locked room in the ninth floor of the Silverstein building at HUP. During monitoring sessions it will be brought to the Neurology clinic for healthy volunteers and to the patient's bedside for inpatient subjects. After the study session, it will be secured by study personnel.

The Transcranial Doppler is standard equipment used in the neurodiagnostics lab at the University of Pennsylvania. It will be stored securely in a locked room in the 2nd floor of the Ravdin building at HUP. During monitoring sessions it will be brought to the Neurology clinic for healthy volunteers and to the patient's bedside for inpatient subjects. Following the study session, it will be secured by study personnel.

The Finapres device allows for non-invasive continuous arterial blood pressure measurement. It will be stored securely in a locked room in the ninth floor of the Silverstein building at HUP. During monitoring sessions it will be brought to the Neurology clinic for healthy volunteers and to the patient's bedside for inpatient subjects. After the study session, it will be secured by study personnel.

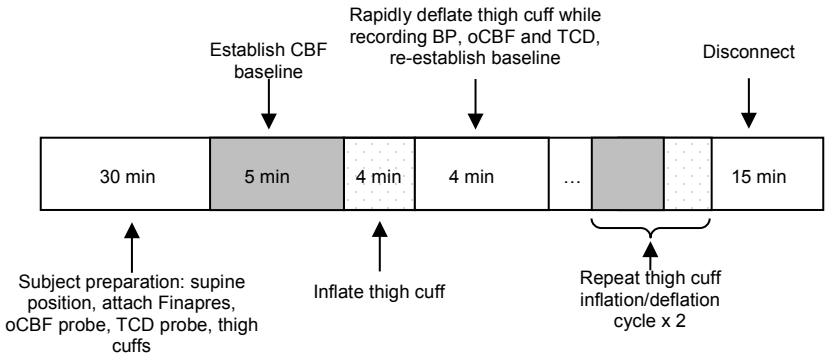
The Thigh Cuff device allows for artificial elevation of blood pressure and artificial abrupt drop in blood pressure. It will be stored securely in a locked room in the ninth floor of the Silverstein building at HUP. During monitoring sessions it will be brought to the Neurology clinic for healthy volunteers and to the patient's bedside for inpatient subjects. After the study session, it will be secured by study personnel.

STUDY PROCEDURES

1. Procedures

After obtaining informed consent, all subjects will be placed supine with the head of bed flat. A non-invasive Finapres blood pressure probe will be placed on a finger to continuously record arterial blood pressure. Heart rate will be calculated by analyzing the frequency of pulsatile blood flow. After the patient is comfortable optical probes will be attached to the patient's forehead. The probes are embedded in foam pads that will be secured to each side of the forehead using a combination of medical adhesive tape and a padded Velcro strap. The pads will be placed at the temporal margin of the forehead, superior to the frontal sinuses. A transcranial Doppler ultrasound probe will be placed on the scalp at the temporal bone to insonate the middle cerebral artery (MCA) and/or the anterior cerebral artery (ACA) bilaterally and secured in place using a commercial head frame The goal will be to insonate the MCA on one side and the ACA in the contralateral side. Due to limitations of TCD insonation and variability in temporal bone windows, this may not be possible in all subjects. In this way, optical blood flow from the right and left frontal cortex and blood flow velocity in the anterior cerebral circulation will be recorded simultaneously during the study session. A large blood pressure cuff will be placed around each thigh. Both cuffs will be connected together with a large bore Y-adapter that is connected to a bulb inflator.

Once the patient is comfortable, optical blood flow and TCD blood flow velocity will be measured for 5 minutes to establish a baseline. Both thigh cuffs will then be inflated to 20 mmHg above the patient's systolic blood pressure so that blood flow to the legs is occluded. Occlusion will be maintained for 4 minutes, followed by simultaneous deflation of bilateral cuffs and concurrent recording of blood pressure and CBF for an additional 4 minutes; 3 measures will be obtained per subject and averaged to establish a curve. The rapid deflation of the thigh cuffs will induce a 5-10% step decrease in blood pressure that is expected to last for about 10 seconds before cardiovascular reflexes restore MAP to baseline levels. During the thigh cuff deflation, changes in pulsatile blood pressure, and TCD blood flow velocity will be continuously recorded; oCBF will be recorded every 0.5 seconds. Intact autoregulation should cause a restoration of cerebral blood flow to pre-deflation values within 5-10 seconds in spite of the prolonged decrease in systemic blood pressure. We expect to see a sudden drop in optical cerebral blood flow and MCA velocity followed by a quick increase in both of these parameters. The change in cerebrovascular resistance (ΔCVR) can be calculated by dividing arterial blood pressure by cerebral blood flow. ΔCVR will be calculated using both optical CBF values and MCA velocity. The magnitude of ΔCVR over time gives a measure of dynamic cerebral autoregulation (see below for details regarding analysis). The thigh cuff occlusion will be repeated 4 times in each subject to establish a curve. A diagram of the study flow is shown below:



2. Data Collected

Information will be collected and stored securely from all study subjects. This information will include the following: age, sex, past medical history, current medications, non-prescription drug use.

3. Quantitative and Statistical Analysis

dCA will be calculated as change in blood pressure from baseline (ΔBP) divided by change in cerebral blood flow from baseline (ΔCBF) at each time point, thus dCA = ΔBP/ΔCBF(Aaslid, Lindegaard et al. 1989); this data will be plotted against time in seconds.

The data recorded from the TCD monitoring will be used to quantify the relation between changes in cerebrovascular resistance (ΔCVR) and blood pressure (ΔBP) as calculated by ROR = (ΔCVR/ΔT)/ΔBP and will be plotted along a curve for the first few seconds after cuff deflation (Aaslid, Lindegaard et al. 1989, Tiecks, Lam et al. 1995, Panerai, White et al. 1998, Lang, Mehdorn et al. 2002). The purpose of collecting TCD data is to show a correlation between the ROR calculated from TCD measures to that of dCA via DCS measurement, further validating our DCS measurements.

The optical CBF output is directly recorded as relative CBF. For blood flow velocity measured by TCD, relative CBF can be approximated by normalizing flow to baseline. This is an approximation of CBF that assumes that the vessel diameter does not change over time. Once the relative change in CVR over time is calculated, a dynamic rate of regulation index (dRoR) can be calculated by dividing the slope of the CVR over time curve by the maximum change in blood pressure (i.e. (ΔCVR/Δt)/ΔBP). Intuitively, if autoregulation is intact, there should be a steep decrease in cerebrovascular resistance with a drop in blood pressure. Perfect autoregulation would result in dRoR = 1.

Baseline heart rate, MAP, and MCA velocity will be recorded for each subject and descriptive statistics including mean and standard deviation will be reported for these values. For dRoR calculation, a mean dRoR will be calculated for each subject (from 5 trials) using both optical CBF and TCD. The optical dRoR and TCD dRoR will be compared for each subject and significant differences will be evaluated using Student's t-test or Wilcoxon rank-sum as appropriate. We will quantify the correlation between dRoR measured with TCD and DCS using Pearson or Spearman correlation coefficient as appropriate.

4. Confidentiality

How will confidentiality of data be maintained? Check all that apply.

- ☒ Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study.
- ☒ Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords.
- ☒ Prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information.
- ☒ Whenever feasible, identifiers will be removed from study-related information.

- ☐ A Certificate of Confidentiality will be obtained, because the research could place the subject at risk of criminal or civil liability or cause damage to the subject's financial standing, employability, or liability.
- ☐ A waiver of documentation of consent is being requested, because the only link between the subject and the study would be the consent document and the primary risk is a breach of confidentiality. (This is not an option for FDA-regulated research.)
- ☐ Precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys.
- ☐ Audio and/or video recordings will be transcribed and then destroyed to eliminate audible identification of subjects.
- ☐ Other *(specify):* _____

5. Privacy
Subject confidentiality will be maintained at all times and study information will be protected against release to unauthorized people. Subjects will be assigned study numbers for entry into the protocol; this number alone will identify them. Subjects are free to refuse participation in the study and can withdraw at anytime without compromising care.

All data obtained in this study will be entered into a secure password protected database and de-identified.

HIPAA
The following protected health information (PHI) will be collected:

- Name
- Date of birth
- Social Security Number

Collected PHI will be recorded on the case report form, which will be secured as detailed above. This data may be disclosed to the medical monitor in the event of a potential adverse event. It will otherwise not be disclosed to anyone not listed on Section I of this application.

The HIPPA authorization for this study will be incorporated into the informed consent form. In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization.

6. Tissue Specimens
Not applicable

7. Genetic Testing
Not applicable

RISK/BENEFIT ASSESSMENT
1. Potential Study Risks

Pregnancy risks
There is not enough information about the effect of infrared light to pregnant women, or their fetus. Female participants will be screened and excluded for pregnancy by clinical history. There is not a risk of pregnancy during the study as patients will be continuously monitored during the study period.

Risks of DCS/Optical Blood Flow Monitoring: There is a risk of damage to the eye if the eye is exposed directly to the infrared light coming from the DCS patches. Damage could include retinal (light sensitive tissue at the back of the eye) burn. In order to prevent such an injury we will put optical fibers in a foam pad where they will be away from the surface of the skin. Therefore the light will be concentrated on the top of the head. The probes will be secured by a lightly wrapped bandage which will ensure that the light pads remain secure, covered, and away from the eyes. In addition the patient can elect to wear safety goggles that will reduce the risk of retinal damage if probes and protective foam become dislodged.

A research staff member will be continuously monitoring the subject while on the study and will be able to cycle the light off in less than three seconds. The instrument has passed clinical engineering safety inspection.

A member of the study team will be present at all times and will assist in the placement of the probe(s) and the collection of the data. No discomfort should be associated with the procedure.

Risks of Transcranial Doppler Monitoring:

There is no known risk of the use of ultrasound equipment for transcranial doppler monitoring. It is non-ionizing radiation, and therefore does not have the same risk as x-rays or other types of radiation.

A member of the study team will be present at all times and will assist in the placement of the probe(s) and the collection of the data. At times the TCD probes can cause mild discomfort. If the subject feels uncomfortable study personnel will attempt to reposition the probes to maximize comfort. If at any point the discomfort becomes significant, the study will be terminated.

Risks of non-invasive blood pressure monitoring:

There is no known risk of the use of non-invasive blood pressure monitoring via the Finapress system.

A member of the study team will be present at all times and will assist in the placement of the probe and the collection of the data. No discomfort should be associated with the procedure.

Risks of Thigh Cuff Manipulation of Blood pressure

There is a risk of discomfort during the thigh cuff inflation. This discomfort will be related to the inflation of the cuff around the thigh and is expected to be the same amount of discomfort as experienced during routine brachial blood pressure measurement, only sustained for 3 minutes. A member of the study team will be present at all times. If the subject feels uncomfortable study personnel will attempt to reposition the cuffs around the thigh. If at any point the discomfort becomes significant, the study will be terminated.

2. Potential Study Benefits

There will be no direct benefit to subjects as a result of their participation in this study; however, information gained from this research will lead to a better understanding of cerebrovascular physiology.

3. Alternatives to Participation

Participation in this research study is voluntary. Subjects who do not wish to participate in the study will not be coerced into participating.

4. Data and Safety Monitoring

Who will monitor this study? Check all that apply.

☒ Principal Investigator
☒ Sponsor or contract research organization
☐ NCI sponsored cooperative group
☐ Cancer Center (if mandated by CTSMRC)
☐ Medical monitor
☐ Safety monitoring committee
☐ Data and safety monitoring board

5. Management of Information for Multi-center Research where a Penn Investigator is the Lead Investigator of a multi- center study, or Penn is the lead site in a multi-site study.

Not applicable

6. Risk/Benefit Assessment

Low Risk: This study represents a minor increase over minimal risk. There is a small risk in retinal damage from infrared laser radiation from the optical blood flow monitor; however, the exposure of infrared light to the patient's eye is minimal to zero. Information gained from this study may be foundational for future use of DCS technology and ultimately help take care of patients with many types of brain injury. In light of the anticipated benefits to others, the risks, which are quite modest, are reasonable.

SUBJECT COMPENSATION

Subjects will be compensated with $25.

INFORMED CONSENT

1. Consent Process

Informed consent is an ongoing process that takes place between the investigator/study staff and study participants. Informed consent for this research study will be obtained by the Principal Investigator or her designee (co-investigators or a research nurse/research coordinator from the Neurosurgery Clinical Research Division). It is the responsibility of the Principal Investigator (PI) to ensure that informed consent has been properly obtained.

During the consent process, the person obtaining consent will

1. Approach the prospective subject to introduce the research team and the project.
    - The discussions will take place in an area where privacy and confidentiality can be respected.
    - Subject must be given sufficient time to comprehend the research.
2. Review the research study and the informed consent form with the subject.
    - The researcher should clearly explain the background/purpose, voluntary nature, commitment, risks, benefits, alternatives, and other elements making sure to include all the necessary elements of informed consent.
3. Answer any preliminary questions.
4. Allow the subject time to review the informed consent form independently.
    - Provide the subject with a sample consent form to review prior to the consenting process and study appointment.
    - Subjects will be given time to discuss participation with family or friends if they so desire.
5. Evaluate the subject's understanding by asking open-ended questions about the study and addressing any misperceptions or unanswered questions. Possible questions include:
        - *Can you describe the study in your own words?*
        - *What more would you like to know?*
        - *Would you please explain to me what we are asking you to do?*
        - *What are your concerns?*
6. If willing, ask the subject to sign and date the consent document.
    - Subjects must sign and date the most recent IRB-approved version of the informed consent form.
    - The consent form must contain an approval stamp from the IRB.
    - The person obtaining consent should also sign and date the informed consent form.
7. Give the subject a copy of the signed and dated informed consent form.
8. Document the informed consent process. A note in the research records may include:
        - *Name of study and subject*
        - *Date and time of consent*
        - *Statement that the benefits, risks, commitment and alternatives were discussed*
        - *Presence of any family members, friends, or witnesses*
        - *Description of subject's level of understanding*
        - *Specific, relevant criteria not otherwise captured (e.g. time frames of screening tests that are not apparent in records)*

2. Waiver of Authorization

Not applicable

RESOURCES NECESSARY FOR HUMAN RESEARCH PROTECTION

All research staff have completed their Patient Oriented Research Training (POR) and/or Collaborative Institutional Training Initiative (CITI). There will be study-specific "Team Meetings" to train and review study processes ensuring compliance, patient safety and confidentiality. Study-specific monitoring will be conducted by the study sponsor as well UPHS regulatory committees responsible for review of patient oriented research.

Neither Dr. Detre nor Dr. Yodh will consent study subjects. Dr. Detre and Dr. Yodh will not personally acquire the primary data nor personally calculate the results of the primary data. In those cases where TCD data may be generated, to the extent (if any) Dr. Detre oversees analysis of any TCD data, he will do so without knowledge of the optical device findings.

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