Inter- and Intra-Observer Variability in Transcranial Doppler (TCD) Technique in Neurocritical Care Patients

Protocol No. 2019-0945

NCT 04583163

June 17, 2020

Hackensack Meridian *Health*

Protocol No. 2019-0945

Principal Investigator: **Stephen M. Cohn, MD, FACS**
Sub-Investigator: **Jyoti Sharma, MD, FACS, MPH**
Contact Information: **Department of Trauma and Surgical Critical Care**
Hackensack University Medical Center
30 Prospect Ave, Hackensack NJ 07601
551-996-2609

I. Summary

This study aims to determine the inter- and intra-variability of Transcranial Doppler (TCD) ultrasound in 12 neuro-critical care patients who are planned for daily TCD evaluation. Up to 12 subjects will be recruited over a 1 year period. Patients enrolled in the study are recruited from the pool of neuro-critical care patients admitted to the surgical intensive care unit (SICU) or surgical stepdown unit (3NTH). The duration of the study will be 3 days per study subject. The study aims to determine the inter- and intra-variability of TCD ultrasound in neuro critical care patients who are planned for daily TCD evaluation. This study will also describe the change in velocity that prompts clinical intervention in symptomatic and asymptomatic vasospasm.

II. Introduction and Background

Vasospasm after aneurysmal subarachnoid hemorrhage (aSAH) is a common serious complication estimated to affect 70-90% of patients, 30% of which are symptomatic.[1,2] Vasospasm leads to poor outcomes (disability, death) and delayed cerebral ischemia (DCI).[2] DCI is defined as focal neurological impairment, like hemiparesis, aphasia, hemianopia, or neglect or a global impairment, defined as a 2 point decrease on the Glascow Coma Scale (GCS).[3] DCI is a significant, often preventable outcome that can leave patients with permanent motor deficits, cognitive dysfunction, and reduced quality of life.[3] Currently, vasospasm has been cited to be the sole causal mechanism of DCI.[3]

The most common, least invasive modality to monitor vasospasm is transcranial Doppler (TCD) ultrasonography.[2] Multiple studies link increased TCD flow velocities to higher risk of DCI after aSAH, although the level and quality of evidence is weak.[4,5] There is a paucity of data describing the accuracy and precision of TCDs as a tool for monitoring symptomatic vasospasm as predictor of DCI in aSAH. Most studies calculating the reproducibility and validity of TCDs are from more than 20 years ago and therefore may not reflect advances in technology and experience.[6–8] Furthermore, this published data primarily uses the Pearson correlation coefficient (r) to describe inter- and intra-observer agreement. This statistic is inappropriate to measure the agreement between two variables which is better described using kappa or Bland-Altman analysis.[9]

This study aims to:

1. Determine the inter- and intra-variability of TCD ultrasound in neuro critical care patients who are planned for daily TCD evaluation.
2. Describe the change in velocity that prompts clinical intervention in symptomatic and asymptomatic vasospasm

III. Inclusion Criteria

1. Adults 18 years of age or older
2. Current hospitalization for a neurologic issue and admitted to the surgical intensive care unit or surgical stepdown unit
3. Undergoing daily transcranial Doppler imaging
4. English or Spanish speaking patients and/or legally authorized representative (LAR)

IV. Exclusion Criteria

1. Less than 18 years of age
2. Patient is unable to obtain consent and no LAR is identified to provide consent
3. Non-English or Non-Spanish speaking patients or LAR
4. Unable to perform the study due to lack of availability of TCD technologists.

V. Recruitment/Consent Procedures

Up to 12 subjects will be recruited over a 1 year period. Patients enrolled in the study are recruited from the pool of neurocritical care patients admitted to the surgical intensive care unit (SICU) or 3NTH. No monetary incentive is offered. When the patients are admitted in the surgical ICU, the study staff will determine eligibility based on the protocol inclusion criteria. Due to the nature of the disease, there is a high likelihood that patients are either unconscious, of limited mental capacity and/or have been intubated therefore when appropriate the legally authorized representative will be utilized to obtain research consent.

The research team will adhere to the guidelines pursuant to the HUMC policy 407-4: "Obtaining Informed Consent for a Research Study", HUMC policy 1834: "Next of Kin", HUMC IRB Policy SOP IC 704 "Consent Requirements for Inclusion of Decisionally Impaired Subjects in Research" as well as New Jersey Statute 26:14-5 "Access to Medical Research Act". No informed consent shall be obtained from a legally authorized representative if the participant is an otherwise competent person and will be able to provide adequate informed consent.

To meet study inclusion, transcranial Doppler (TCD) testing will be ordered as part of the standard of care for these patients. The test will not be ordered solely for research purposes. There are no known side effects from the non-invasive measurement of cerebral blood flow using ultrasound.

VI. Methodology

Three different TCD technicians will do triplicate readings on 3 consecutive days on up to 12 patients already undergoing TCD as ordered by their treating team. Standard of care on specific neuro critical care patients (such as cerebral aneurysms) is to undergo daily TCD monitoring to assess for possible vasospasm. Patients will be in the supine position while measurements are obtained. The probe will be placed in the preauricular region of the temporal window. Patients will not be billed for the additional two TCD technicians obtaining readings.

Day 1 (~ 15-30 minutes): TCD ultrasound will be performed at the bedside in the surgical ICU unit. The vascular technician will apply ultrasound gel to the transtemporal window. A bi-directional pulsed Doppler instrumentation

of 2MHz will be placed on the subject's head at the trans-temporal window (Figure 1). Once the window is identified, the middle cerebral artery will be assessed at a depth of 40-60 mm with flow direction towards the transducer and an anterior spatial relationship. The estimated time to measure the cerebral blood flow of the MCA is 5-10 minutes. A mean and peak MCA flow velocity will be measured. Designated research coordinator will be present to document the measurements

Day 2 (~ 15-30 minutes): TCD ultrasound will be performed at the bedside in the surgical ICU unit. The vascular technician will apply ultrasound gel to the transtemporal window. The TCD probe will be gently applied to measure the cerebral blood flow (CBF) of the middle cerebral artery (mean and peak). The estimated time to measure the cerebral blood flow of the MCA is 5-10 minutes. Designated research coordinator will be present to document the measurements

Day 3 (~ 15-30 minutes): TCD ultrasound will be performed at the bedside in the surgical ICU unit. The vascular technician will apply ultrasound gel to the transtemporal window. The TCD probe will be gently applied to measure the cerebral blood flow (CBF) of the middle cerebral artery. The estimated time to measure the cerebral blood flow of the MCA is 5-10 minutes. Designated research coordinator will be present to document the measurements

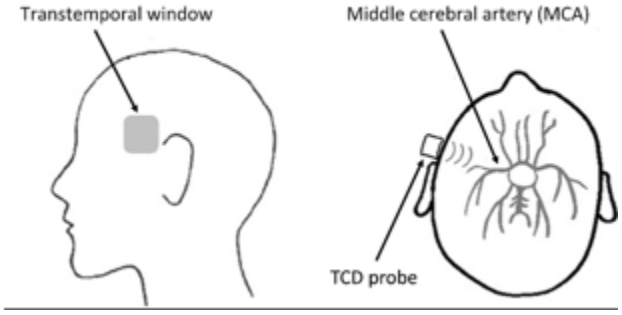

Figure 1.

It is anticipated that up to 20% of subjects may have an insufficient temporal bone window making TCD measurements difficult and/or inaccurate. This will be determined by the technician and these subjects will be considered as screen failures and excluded from further participation in the study.

VIII. Study Endpoints

Primary Endpoint:

- The peak and mean flow velocity of the middle cerebral artery (MCA)
- The peak and mean flow velocity of the posterior cerebral artery (PCA)
- The peak and mean flow velocity of the basilar arteries

IX. Statistical Analysis

The continuous variables (such as: flow velocity) will be summarized using mean, median, standard deviation, interquartile range, range, minimum and maximum. The categorical variables (such as: gender of participant) will be summarized using frequency and percentage. To measure the intra-variability (within each TCD technician), the intraclass correlation coefficient will be calculated.[10] To measure the inter-variability (between the TCD technicians), the Bland-Altman approach will be used.[11] The 95% confidence interval on the variables of interest will be calculated. When necessary, graphical techniques will be used to display the statistical results. Statistical analysis will be performed using the R language (R Core Team [2018]. R: A language and environment for statistical computing. R

Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.) or SAS software, Version 9.4 for Windows (SAS Institute Inc., Cary NC, USA. URL http://www.SAS.com).

X. Discomfort and Risks

There are no associated risks with TCD. The ultrasound measurements are completely noninvasive. The studies will be done expeditiously to avoid inconveniencing the subjects.

There is small risk of breach of confidentiality, however; once the subject completes the three visits, the data collected will be fully de-identified. Coded data will be kept indefinitely. The key linking the codes to the subjects' identities will be destroyed approximately 5 years after completion of data analysis.

XI. Benefits

There are no direct immediate benefits to patients. This study in the long-term may help elucidate the variability and accuracy of TCD ultrasound.

XII. Confidentiality

Data will be collected and coded on a paper form which will be stored and locked in a cabinet in the trauma office (St. John, G 834). The coded data will then be entered in REDCap, an on-line data entry and managing system. REDCap stands for Research Electronic Data Capture. Only designated research staff will enter the data and have access to the data.

There is small risk of breach of confidentiality, however; once the subject completes the three visits, the data collected will be fully de-identified. Coded data will be kept indefinitely. The key linking the codes to the subjects' identities will be destroyed approximately 5 years after completion of data analysis.

Any publication or presentation resulting from this study will not identify any individual whose data was included in the analysis.

XII. Bibliography

1. Oyama K, Criddle L. Vasospasm after aneurysmal subarachnoid hemorrhage. *Crit Care Nurse*. 2004;24(5):58-60, 62, 64-67. http://www.ncbi.nlm.nih.gov/pubmed/15526491. Accessed June 3, 2019.

2. Kumar G, Shahripour RB, Harrigan MR. Vasospasm on transcranial Doppler is predictive of delayed cerebral ischemia in aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis. *J Neurosurg*. 2015;124(5):1257-1264. doi:10.3171/2015.4.jns15428

3. Francoeus CL, Mayer SA. Management of delayed cerebral ischemia after subarachnoid hemorrhage. *Crit Care*. 2016;20(1):277. doi:10.1212/01.CON.0000415429.99394.e8

4. Carrera E, Schmidt JM, Oddo M, et al. Transcranial Doppler for predicting delayed cerebral ischemia after subarachnoid hemorrhage. *Neurosurgery*. 2009;65(2):316-323; discussion 323-4. doi:10.1227/01.NEU.0000349209.69973.88

5. Rigamonti A, Ackery A, Baker AJ. Transcranial Doppler monitoring in subarachnoid hemorrhage: a critical tool in critical care. *Can J Anesth Can d'anesthésie*. 2008;55(2):112-123. doi:10.1007/BF03016323

6. Maeda H, Etani H, Handa N, et al. A validation study on the reproducibility of transcranial Doppler velocimetry. *Ultrasound Med Biol*. 1990;16(1):9-14. http://www.ncbi.nlm.nih.gov/pubmed/2181766. Accessed June 3, 2019.

7. Baumgartner RW, Mathis J, Sturzenegger M, Mattle HP. A validation study on the intraobserver reproducibility of transcranial color-coded duplex sonography velocity measurements. *Ultrasound Med Biol*. 1994;20(3):233-237. http://www.ncbi.nlm.nih.gov/pubmed/7914715. Accessed June 3, 2019.

8. Totaro R, Marini C, Cannarsa C, Prencipe M. Reproducibility of transcranial Dopplersonography: a validation study. *Ultrasound Med Biol*. 1992;18(2):173-177. http://www.ncbi.nlm.nih.gov/pubmed/1580013. Accessed June 3, 2019.

9. Shen Q, Stuart J, Venkatesh B, Wallace J, Lipman J. Inter observer variability of the transcranial Doppler ultrasound technique: impact of lack of practice on the accuracy of measurement. *J Clin Monit Comput*. 1999;15(3-4):179-184. http://www.ncbi.nlm.nih.gov/pubmed/12568169. Accessed June 6, 2019.

10. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. *Psychol Bull*. 1979;86(2):420-428. http://www.ncbi.nlm.nih.gov/pubmed/18839484. Accessed June 7, 2019.

11. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet (London, England)*. 1986;1(8476):307-310. http://www.ncbi.nlm.nih.gov/pubmed/2868172. Accessed June 7, 2019.