DETERMINANTS OF EARLY STROKE RECOVERY: UNDERSTANDING HYDRATION AND STROKE OUTCOME

by

Mona N. Bahouth

A dissertation submitted to Johns Hopkins University School of Nursing in conformity with the requirements for the degree of Doctor of Philosophy

Baltimore, Maryland

July 2019

© 2019 Mona Bahouth

All rights reserved

Abstract:

Stroke is a leading cause of adult disability with only a few therapies (e.g. intravenous tissue plasminogen activator) proven to impact functional outcomes. An estimated 36-56% of patients presenting to the hospital with acute ischemic may be dehydrated, volume depleted, or both, as estimated by serological and clinical markers. Hydration status at the time of stroke appears to be an important determinant of worsened stroke outcomes. No mechanism has been firmly identified for this relationship, nor is it clear whether these alterations might particularly impact efficacy of acute stroke treatments, leading to variability in its benefit. This dissertation comprises parallel studies intended to explore the relationship between hydration status at the time of stroke and the degree of benefit from hyperacute stroke therapies. This work will inform future intervention studies focused on the potential benefit of early rehydration after stroke. The development of an inexpensive and globally available treatment, like targeted rehydration therapy, has the potential to reduce disability and improve quality of life for patients with stroke.

In the first two aims, we sought to understand the relationship between baseline hydration status and stroke outcomes after two approved hyperacute stroke treatments: tissue plasminogen activator (medication) and mechanical thrombectomy (surgery). Aim three focuses on the feasibility and acceptability of using a non-invasive cardiac output monitor to evaluate hydration status using a marker of potential fluid responsiveness. To achieve these aims, we evaluated outcomes from three separate cohorts of stroke patients: (1) a retrospective group of patients treated with tissue plasminogen activator; (2) a retrospective group of patients treated with mechanical thrombectomy; and (3) a prospective group of patients evaluated with a noninvasive cardiac output monitor. Together, these data broaden the understanding of the relationship between hydration status at the time of stroke and stroke recovery. These data will inform the development of a potential intervention to modify that relationship in future studies.

Primary reader/advisor:
Sarah L. Szanton, PhD, RN, FAAN

Secondary readers/committee members:
Martha M. Abshire, PhD, RN
Patricia M. Davidson, PhD, Med, RN, FAAN
Rebecca F. Gottesman, MD, PhD
Jose I. Suarez, MD

Alternates committee members:

Nancy Perrin, PhD

Daniel F. Hanley, MD

Funding:

Funding for this study was made possible by the Johns Hopkins School of Nursing Caylor Scholarship. The work in aim 3 would not have been possible without the in-kind donation of the Non-invasive cardiac output monitor by Cheetah Medical Technologies.

Dedications

To Sarah Szanton, my advisor and mentor on this PhD journey. You inspire me with your passion, clear vision, and ability to see what is important and influential. Your laser sharp attention to detail while seeing the big picture is amazing. Thank you for all of your guidance. I feel so fortunate that this phase of my education has brought us together. I know that this is only the beginning…

To Rebecca Gottesman: Since the moment of my first interview at Johns Hopkins, I knew that I wanted to work with you and learn from you. You have taught me so much and cheered me on through every phase of my training and education. Words are not enough to thank you for all of your guidance over the years. You are such a role model to so many.

To my committee: How could I be so lucky to learn from you? Each of you are wonderful examples of leadership, professionalism, and grace. I emulate pieces of each of you and look forward to working with you for many years to come. We have a lot to accomplish together and I cannot wait.

To Marian LaMonte: You have always inspired me to challenge the norm and find a way to do better for stroke patients. You have been a tremendous role model and impact on my life since I landed in Maryland. Thank you!

To my husband Andy: I am not sure how you tolerated all of the crazy twists and turns in our schedules over the last few years. Thanks for all of your support. I love you and look forward to watching the lightning bugs on the deck with you for years to come.

To my parents: You taught us to be kind and productive contributors to society. Your unconditional love made me the person that I am today. I can reach for the stars, knowing that you have built the best safety net for me when I fall. Thank you! I love you more than words can ever describe.

To the rest of my terrific family: brothers, sisters, nieces and nephews. Love you guys. Thanks for being the best family a person can have. I love watching each of you shine!

A special note of thanks to my patients and co-workers. Stroke is a condition that attacks within minutes. Your strength and resilience to persevere through this transition are an inspiration and provide me with the fuel to change systems of care for the better. Together we will wipe out the mark of this disease.

Dissertation Organization

This dissertation contains six chapters. The first chapter provides background, conceptual framework for this work, summary of study aims. Chapter 2 (Manuscript 1) is a review of the current state of the science in the area of dehydration and ischemic stroke outcome. It is published in the Journal of Neurology. Chapters 3-5 are (Manuscripts 2, 3, 4) are data based manuscripts that provide results for aims 1,2 and 3. They are pending submission. Chapter 6 summarizes findings, discusses implications for nursing, policy, and future research.

Table of Contents

Glossary of commonly used terms

Term	Definition
Blood urea/Creatinine ratio (BUN/creat)	Surrogate blood markers suggesting an alteration in hydration status; BUN/Creatinine ratio 15 may suggest at least mild dehydration (a volume contracted state). These are commonly collected at the time of hospitalization for most patients.
Mechanical thrombectomy	Surgical endovascular procedure to withdraw an obstructive blood clot from a large vessel that is causing a stroke in the brain.
Modified Rankin Scale **(mRS)**	Scale commonly used to rate functional outcome after stroke
National Institutes of Health Stroke Scale Score **(NIHSSS)**	Quantification of the neurological examination to communicate stroke severity
Neglect syndrome	Neurologic deficit common in large artery occlusion that places the patient at high risk for falls and poor functional recovery due to interference with the patient's ability to participate in rehab therapy
Noninvasive cardiac monitor **(NICOM)**	An external device used to measure intravascular volume status. This technology will be tested for feasibility of use in the stroke population.
Stroke	Clinical syndrome consistent with sudden death of brain cells due to lack of oxygen caused by disrupted blood flow to that region of the brain; diagnosis suspected by vascular specialist at the time of hospital presentation
Treatment in Cerebral Infarction **(TICI)**	Grading system used to determine response to stroke treatment based on angiographic appearance of the previously occluded blood vessel.
Tissue Plasminogen Activator **(tPA)**	The only FDA approved medical therapy for acute ischemic stroke. This intravenous drug must be administered within 4.5 hours from the time of stroke onset and the main side effect in intracranial hemorrhage.
Volume contracted state **(VCS)**	Descriptor used to describe the hydration variable of interest. This is a more precise term than dehydration.

Chapter 1. Introduction

Stroke is common and a leading worldwide cause of adult disability, with few therapies proven to impact functional outcome.[1] To date intravenous tissue plasminogen activator (tPA) is the only FDA approved medication for the treatment of acute ischemic stroke and mechanical embolectomy is the only approved surgical intervention, though benefit of these treatments has been variable.[2] Increasing evidence suggests that dehydration, or more accurately, a **volume contracted state (VCS)** is common at the time of **acute ischemic stroke** and contributes to a worsened functional outcome.[3-6] An estimated 36-56% of patients presenting to the hospital with acute ischemic may be dehydrated, volume depleted, or both, as estimated by serological and clinical markers. Furthermore, volume contraction may be a risk factor for early clinical worsening. A VCS likely impacts a stroke patient in a variety of ways including alterations in medication pharmacodynamics, disrupted cerebral perfusion, and altered distribution of inflammatory markers. No mechanism has been firmly identified for this relationship, nor is it clear whether these alterations might particularly impact efficacy of acute stroke treatments, leading to variability in its benefit.

Diagnosing a VCS remains highly subjective. **Noninvasive cardiac output monitors (NICOM)** are used in the management of patients with acute hydration issues (e.g. sepsis) to provide objective, real-time data about intravascular volume status. In early stroke care, surrogate serum chemistries are most often used to evaluate for the presence of a VCS. In our pilot studies, acute ischemic stroke patients in VCS, defined by serologic patterns, had a worse short-term clinical outcome measured at the time of hospital discharge than euvolemic patients.[7] In clinical practice, however, hydration practices in after acute stroke are often conservative due to concerns of precipitating heart failure or cerebral edema. Using a serum levels to measure hydration more precisely is invasive, painful, with time-delayed results. Guidance for more precise rehydration interventions are limited partly by uncertainty surrounding measures for clinical volume status and lack of a mechanistic rationale for the relationship between VCS and worsened stroke outcome. This knowledge gap offers an important opportunity for further study.

The overarching goal of this research was to examine the potential for early and expedited rehydration to improve functional outcome after stroke. Specifically, we evaluated if hydration status 1) modifies the tPA treatment effect, thus explaining some of the variability in its benefit;

2) interferes with revascularization during mechanical embolectomy; 3) can be measured objectively and noninvasively, using noninvasive cardiac output monitoring (NICOM).

The proposed study evaluates an important relationship between hydration status and outcomes and will inform the development of a future technology-supported clinical trial of intervention strategies aimed at improving stroke outcomes. To accomplish these objectives, we had the following aims:

Specific Aim 1. To determine whether the benefit of tPA differs in volume contracted versus euvolemic acute ischemic stroke patients.
A retrospective analysis of a prospective cohort of consecutive ischemic stroke patients presenting to the Johns Hopkins comprehensive stroke centers within 4.5 hours over 5 years.
Hypothesis 1.1: VCS patients treated with tPA will have less benefit (less likely to achieve a modified Rankin Scale (mRS) 0-2) than euvolemic patients treated with tPA, each compared to non-tPA receiving counterparts after controlling for demographic and disease specific covariates.
*Hypothesis 1.*2: VCS patients treated with tPA will have more clinical complications including fluctuation in neurological examination defined as increase in NIHSS >3 and intracerebral hemorrhage than will euvolemic tPA-treated patients.

Specific Aim 2. To compare rates of successful revascularization for acute ischemic stroke in volume contracted and euvolemic patients.
A retrospective analysis of a prospective cohort of consecutive ischemic stroke patients presenting to the Johns Hopkins comprehensive stroke centers within 6 hours over 5 years.
Hypothesis 2.1: Acute ischemic stroke patients in a VCS at the time of mechanical embolectomy will have lower rates of successful revascularization (> TICI2a) compared to euvolemic patients undergoing embolectomy.
Exploratory hypothesis: Among ischemic stroke patients undergoing mechanical embolectomy, those patients in a VCS at the time of the procedure will more early neurological worsening and intracerebral hemorrhage than similar patients who are euvolemic at the time of the procedure.

Specific Aim 3. To test the feasibility of noninvasive cardiac output monitoring to measure the frequency of VCS among hospitalized patients with acute ischemic stroke.
A prospective feasibility study of 30 consecutive, hospitalized acute ischemic stroke patients.

Hypothesis 3.1: Measuring hydration status with NICOM will be feasible and acceptable to hospitalized stroke patients
Hypothesis 3.2: Fluid responsiveness will be detected by NICOM at a similar frequency as lab-measured VCS (BUN/creatinine ratio > 15).

Understanding the relationship between baseline hydration status, functional outcome and the potential mechanism for this relationship will elucidate more precise treatments. This work will validate objective, continuous markers that could be used to quantify hydration status for use in future clinical trials. The results of this and future related studies have the potential to greatly impact stroke care by providing data about best fluid management. If beneficial to the acute stroke patient, rehydration may offer an inexpensive and globally available adjunct therapy to improve functional outcomes and reduce stroke related disability.

Background and importance of this research

Stroke remains a leading cause of adult disability worldwide.[1] Yet, there are very few treatments with proven impact on clinical outcome, and those therapies are underutilized, often due to limited access and lack of a uniform benefit.[2] While treatments like tPA and mechanical thrombectomy have proven benefit, it is likely that a host of variables contribute to worsened stroke severity and recovery despite these treatments. The brain of the stroke patient likely requires a finely-tuned physiologic environment to minimize neurologic injury and promote neural repair. Dehydration, or more accurately a **volume contracted state (VCS)** may worsen outcomes via alterations in cerebral blood flow, oxygen delivery, or distribution of inflammation. This proposal evaluates VCS as an important contributor to early stroke progression and clinical outcome.

Dehydration is common at the time of stroke, may increase risk for poor outcome, and is modifiable. There is mounting evidence that 36-56% of patients presenting to the hospital with **acute ischemic stroke** have an alteration in volume status as estimated by crude laboratory markers.[3-7] Furthermore, dehydration, which may actually reflect a VCS, has been hypothesized to be an important variable in stroke progression or stroke-in-evolution,[4-6,8] with stroke progression leading to higher mortality.[4,8] Clinicians may be reluctant to aggressively hydrate these patients with isotonic intravenous fluids citing risk for worsening hypertension, decompensated heart failure, or cerebral edema. Current practice guidelines acknowledge the importance of intravenous fluids for hypovolemic stroke patients based on expert opinion rather

than clinical trial data, but make no recommendation about the diagnostic criteria for hypovolemia, nor the timing or duration of treatment.[9] Although saline has not been formally studied as an active intervention in clinical trials, important observations from the study of other interventions provide data on the potential utility of saline. Hemodilution studies such as the ALIAS trial, using albumin after acute ischemic stroke, yielded equivocal results,[10-13] but importantly, this may have been because the control group was given saline, which may actually have led to better outcomes in this control group than would have been found were there a control group without any fluid therapy. Furthermore, no studies to date have sought to investigate dosing or duration of fluid therapy. ***If demonstrated to have a positive effect on stroke outcome, fluid replacement would be a low-cost, readily available treatment.***

Hydration status may be especially important during hyperacute therapies. The benefit of acute stroke treatments (tissue plasminogen activator tPA and mechanical embolectomy) have been variable, with an estimated 33% of recipients achieving good functional outcome (measured by modified Rankin Scale (mRS) of 0-1 at 3 months).[14,15] The benefit of tPA is likely modified by a variety of physiological parameters including baseline platelet activity, renal, and hepatic function.[16] Hydration status may be another important variable. Hydration could impact the effect of these acute therapies via changes in both drug delivery, support of collateral circulation to the penumbra, and reduction of drug related side effects. Additionally, hydration could play a role in the pharmacodynamics of tPA (e.g. medication's volume of distribution) and clearance, therefore altering the medication's ability to facilitate revascularization, and may even increase side effects. Finally, acute stroke patients who are dehydrated may develop earlier ischemic changes on CT scan or other exclusions to tPA therapy, thus contributing to a difference in rates of tPA administration. A recent study suggested that dehydration may be an important prognostic factor among patients receiving tPA.[17] To our knowledge no studies have evaluated if dehydration modifies tPA's ability to improve outcomes among all ischemic stroke patients who are within the 4.5 hour treatment window. There have been no studies to date exploring the association of dehydration and results of mechanical embolectomy.

Objective markers of clinical hydration status are neither easily available nor validated. Thus, the diagnosis of dehydration or a VCS is often inaccurate, subjective, leading to variability in clinical practice.[18-21] Further there is no validated method to monitor hydration status in real time in order to determine endpoints for rehydration therapy on an individualized basis. Acute ischemic stroke guidelines do not provide objective definitions of the target population or hydration endpoints.[9] Since the diagnosis of VCS has been largely based on

bedside observation, precise hydration strategies have been challenging to design or study. A quantitative surrogate marker of hydration status is useful in the evaluation of a patient's overall volume status.[22] In stroke patients, observational studies including our own (see *Preliminary Studies*) using surrogate lab markers suggest that elevated serum BUN, serum osmolarity, urine specific gravity, and/or plasma brain natriuretic peptide predict worsened outcomes.[3-7,23-27] These lab measures are commonly utilized in general medical care,[28] but require painful blood draw and a time lag to receive the results in order to determine the need to change therapy. A noninvasive cardiac monitor designed to trend intravascular volume may be one solution.

A noninvasive cardiac output monitor may more accurately measure volume status, but has not been tested in stroke patients. Traditional means of assessing intravascular volume has relied on invasive technologies (pulmonary artery (PA) catheter that requires right heart catheterization or measuring cardiac stroke volume variation via continuous cardiac output (PiCCO™) requiring central venous catheter placement for transpulmonary thermodilution).[29] More recently, a non-invasive cardiac output monitoring system based on chest bioreactance has been developed and validated against these invasive technologies.[30-34] In a prospective observational study validating the **noninvasive cardiac output monitor (NICOM)** against PA catheter, correlation between NICOM and PA catheter was strong (r=0.82), and sensitivity for detecting directional changes in intravascular volume was 93% with specificity 93% after 65,888 measurements,[35] suggesting that NICOM may indeed serve as a valid method for quantifying hydration status continuously and in real time. The NICOM device has not been validated in a population of patients with high likelihood of atherosclerosis and autoregulatory issues common in the stroke population. Such a measure of hydration that avoided painful blood draws and provided real-time data to the clinician could be a benefit to the patient in the form of more precise rehydration when needed.

A focus on such physiological disturbances could have an impact on patient outcomes. Though yet unproven, there are several mechanistic hypotheses to explain the relationship

between volume status and poor neurological function after stroke. These include changes in endothelial function, platelet activity, and perfusion with an impact on eventual prognosis.[36-41] In the setting of acute ischemic stroke, cerebral perfusion and autoregulation of perfusion are disrupted, thus leaving the brain vulnerable to ongoing ischemia. [42-43] When perfusion mechanisms fail, neuronal death progresses, and infarct expansion becomes inevitable.[43] VCS may reduce cerebral perfusion and hasten the progression from penumbra to infarcted tissue during acute ischemic stroke.[42-44] Success during the transition period after acute stroke is likely multifactorial and affected by physiological, environmental, and psychosocial conditions. We adapt Meleis' transition theory to conceptualize the process and guide our research agenda.[45] See **Figure 1**.

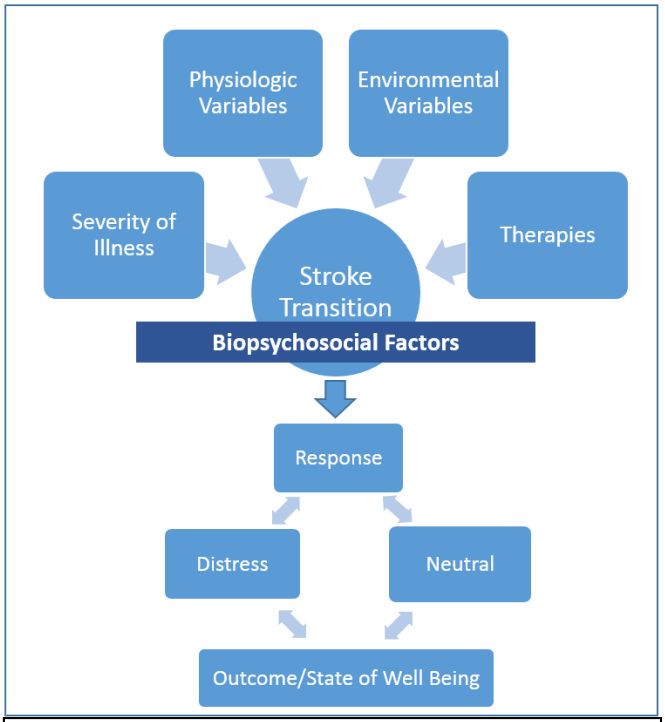


Figure 1. Adaptation of Meleis' theory of experiencing transition after stroke

Conceptualizing the relationship between hydration status and functional outcome. The diagnosis of VCS is a clinical one that is based predominantly on bedside observations. We suspect that hydration could contribute to both a change in acute treatment benefit and participation in rehabilitation (e.g. due to fatigue). Thus, hydration could have an effect on functional outcome through both direct physiological mechanisms (change in

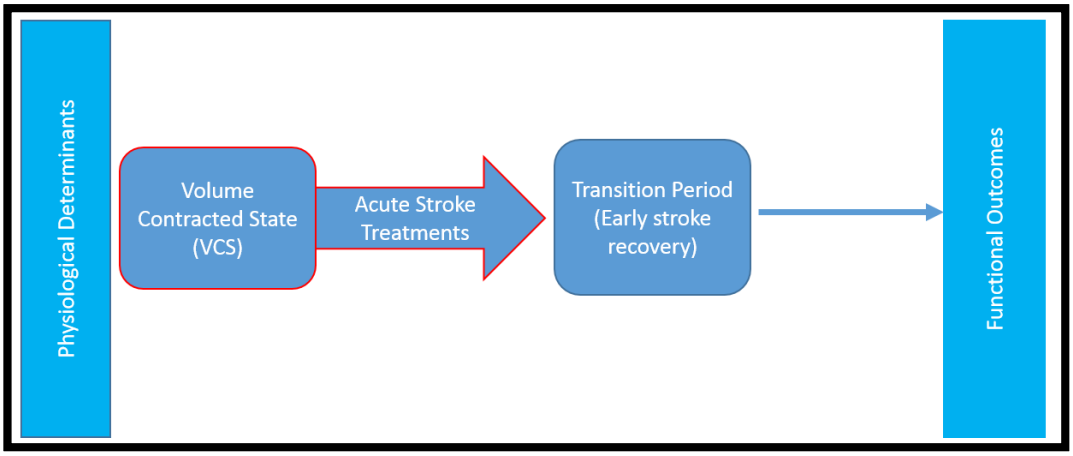


Figure 2. Conceptualizing hydration as a contributing factor within the stroke transition period

brain perfusion) and indirect mechanisms within the transition period after stroke (fatigue and decreased engagement with rehabilitation). See **Figure 2** for conceptual framework.

To date, stroke studies have focused on measuring functional outcomes using the modified Rankin scale. The modified Rankin scale is a 6 point ordinal scale that describes the functional outcome of a patient.[48] The scale has been used in the majority of therapeutic stroke studies to quantify potential functional benefit. The scale is easy to use by a variety of providers, can be administered over the phone, and has been well validated in stroke patients.

There is a clinical need driving the aims that are proposed in this study. Specifically, we: 1) investigated mechanisms underlying the relationship between VCS and outcomes after acute stroke treatments; and 2) identified the feasibility of a readily available yet precise method for identification of altered volume status in the stroke patient. See **Figure 3.** Two mechanisms by which dehydration impacts outcome were explored: 1) dehydration (a VCS) modifies the potential benefit from tPA (Aim 1), and/or may be associated with the success of mechanical thrombectomy (Aim 2). We measured the feasibility of measuring dehydration (VCS) using noninvasive cardiac output monitoring at the bedside of hospitalized stroke patients (Aim 3).

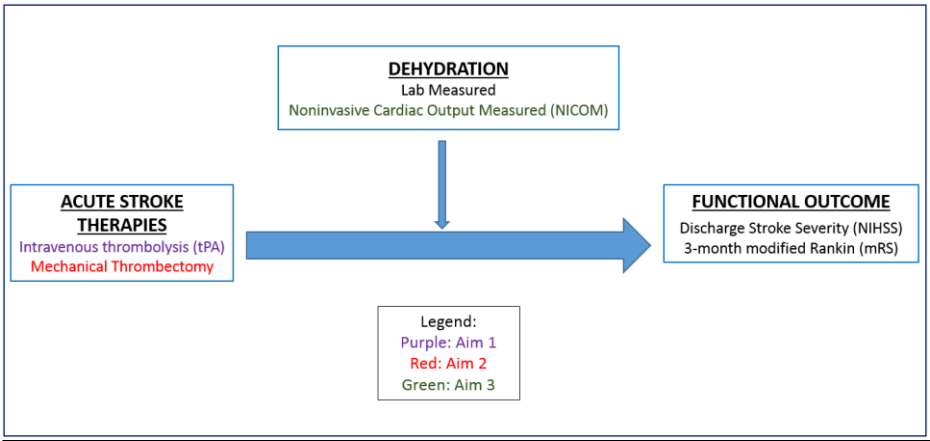


Figure 3. Identifying a potential relationship between hydration status and success of acute stroke therapy requires measuring hydration & examining outcomes after treatment in volume contracted & euvolemic conditions.

Summary: Overarching issues:

1) Dehydration or a volume contracted state (VCS) at the time of stroke is common and is independently associated with worsened severity and functional outcome.

2) The mechanism behind the relationship between dehydration and poor stroke outcome is unknown. Further, hydration status may modulate the effect of acute stroke therapies.

3) Current rehydration practices after stroke are variable, in part related to the subjective method for diagnosing dehydration; benefit of formal rehydration therapies are surprisingly understudied.

4) Development of appropriate rehydration strategies would benefit from knowing the hydration status of a patient in real time and without invasive and painful procedures (blood draws etc.).
5) In order to prescribe rehydration therapies accurately we must better understand the population at risk.

Combining fundamental knowledge of cerebral blood flow after acute ischemic stroke with observations of hydration practices in the clinical setting provides the platform for this study. The studies proposed in this application will allow for the development of a pragmatic clinical trial of rehydration after acute ischemic stroke with the long-term goal of developing a feasible intervention that would improve functional outcomes.

INNOVATION:

The only interventions for acute ischemic stroke that have been shown to improve outcome (IV tPA and mechanical thrombectomy) are not available to a large percentage of the world's population, either due to expense of the treatment or inaccessibility to the necessary technology (including imaging). Even in the US, still only an estimated 2-8% of ischemic stroke patients receive these interventions due to delay in arrival to a treating center after onset of symptoms.[49-52] Furthermore, outcome after these interventions is still variable, with many individuals not having the anticipated benefit despite receiving these therapies. Rehydration with intravenous saline (0.9% sodium chloride) is ubiquitously available and inexpensive; the proposed study could lay important groundwork for a clinical trial directly testing the utility of IV saline in a large population of acute ischemic stroke patients. **If fluid replacement in volume contracted patients improves outcome without increasing adverse events, it would provide the first effective stroke treatment that is globally available, widely accessible, and cost effective.** However, this simple intervention has not been sufficiently studied to guide specific recommendations of when and how to rehydrate stroke patients.[22]

The overall goal of this study is to determine the potential causes of poor functional outcome in patients with a VCS, and to test a continuous quantitative method for evaluating VCS for potential use in future clinical trials. To evaluate the causes of poor outcome, we will 1) test the relationship between VCS and efficacy of tPA in a retrospective observational study, 2) compare the percentage of patents who achieve successful revascularization after mechanical thrombectomy based on hydration status; and 3)

prospectively measure hydration status using a noninvasive cardiac output monitor. This hypothesis will be tested in a consecutive series of acute ischemic stroke patients admitted to a single comprehensive stroke center.

PRELIMINARY STUDIES

We have completed several foundational studies to support the hypothesis that volume contraction is frequent in acute ischemic stroke patients using indirect laboratory markers and may directly relate to worse clinical outcome after stroke.

1. ***VCS and hemispatial neglect in stroke***:[53] A retrospective review of 201 patients with non-dominant hemispheric ischemic stroke demonstrated that 65% of patients had elevated serum BUN/creatinine ratio > 15, the presence of which was associated with a 4-fold higher odds of severe neglect syndromes (OR 4.1, 95% CI 1.2, 14.4), independent of infarct size. Using a composite definition for VCS of elevated BUN/creatinine > 15 and urine specific gravity > 1.010, 57% of patients were volume contracted at the time of hospital admission for acute ischemic stroke. Further, ***all*** patients with elevated urine specific gravity had severe neglect syndromes (p=0.06) (**Figure 4**), defined by Z scores of -2 or less on at least two of three neglect tests, compared to normal controls. **These data support our hypothesis that many acute stroke patients are volume contracted at the time of stroke and that clinical severity may be directly influenced by volume status.**

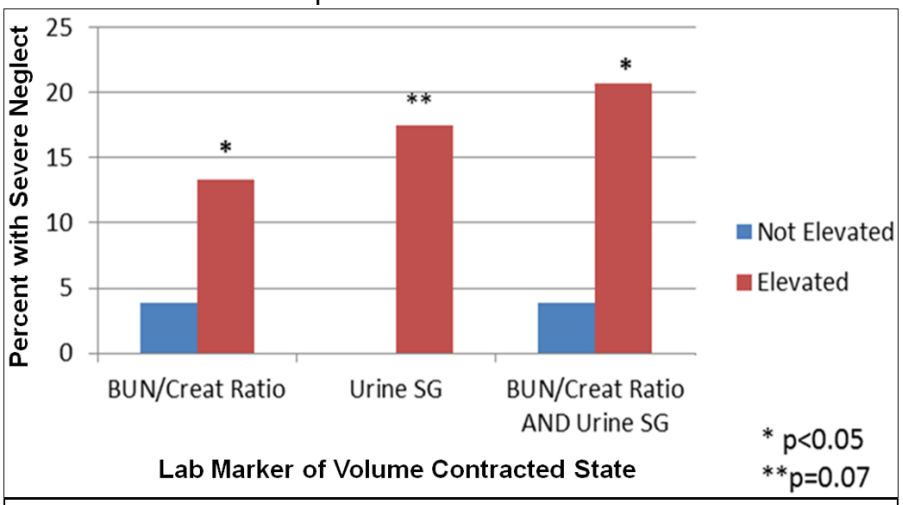


Figure 4: Graph demonstrates that patients in a VCS per combined surrogate lab markers of BUN/creatinine ratio and urine specific gravity demonstrated statistically significant increase in severe neglect.

2. ***VCS and short term outcomes:***[7] We examined the relationship between VCS and short term outcome at the time of hospital discharge in an observational study of 126 acute ischemic stroke patients. VCS was evaluated at the time of presentation for acute ischemic stroke, defined as BUN/creatinine ratio>15 and urine specific gravity>1.010 (found in 44% of patients), and NIHSS was documented at time of admission and discharge; the difference was calculated. Of the patients in a VCS, 42% were in the worst quartile as compared with 17% of the euvolemic group (p=0.02; **Figure 5**). Relative volume depletion remained a significant predictor of having the worst NIHSS change after adjustment for age, admission glucose, and baseline MRI lesion volume (OR=4.34, 95% CI 1.75-10.76). **These data support the hypothesis that VCS may affect longer term outcomes and could provide a potential biomarker to track response to rehydration therapy.**

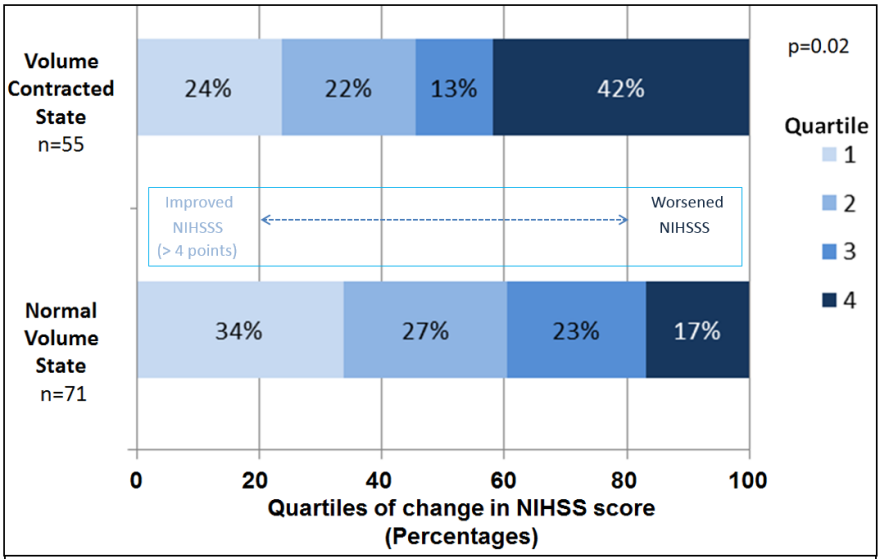


Figure 5: Distribution of quartiles of change in NIHSS between hospital admission and discharge for volume contracted versus normal volume states. Percentages shown are out of each total volume status group (e.g., 24% of patients in VCS were in quartile 1, suggesting most improved NIHSS).

Summary of preliminary results: Preliminary data show that a lab defined volume contracted state (BUN/creatinine ratio > 15) is common at the time of stroke, and patients with a VCS at the time of stroke may have worse outcomes. The issue is that current methods of detecting a VCS are invasive, potentially painful, and results are not available to providers in real-time in order to efficiently treat the condition. Additionally, there may be an interaction between VCS and acute stroke treatments making more precise and efficient diagnosis of VCS more of a clinical priority. Taken together, we will evaluate the relationship between VCS and outcomes after acute stroke treatments. Additionally, we will test the feasibility of NICOM measurement of VCS in a series of hospitalized stroke patients and correlate results with indirect markers of VCS (BUN/creatinine ratio). Should VCS be associated with worse outcome after treatment of acute stroke, these data could suggest the possibility that VCS is a modifiable risk factor, amenable to low cost and broadly available intervention. The data derived from this proposal will provide foundational data for future studies of such.

References: Chapter 1

1. Mozaffarian, D, Benjamin, EJ, Go, AS, Amett, DK, Blaha, MJ, Cushman, M, de Ferranti, S, Després, J, Fullerton, HJ, Howard, VJ, Huffman, MD, Judd, SE, Kissela, BM, Lackland, DT, Lichtman, JH, Lisabeth, LD, Liu, S, Mackey, RH, Matchar, DB, McGuire, DK, Mohler, ER, Moy, CS, Muntner, P, Mussolino, ME, Nasir, K, Neumar, RW, Nichol, G, Palaniappan, L, Pandey, DK, Reeves, MJ, Rodriguez, CJ, Sorlie, PD, Stein, J, Towfighi, A, Turan, TN, Virani, SS, Willey, JZ, Woo, D, Yeh, RW, Turner, MB; on behalf of the American Heart Association Statistics Committee. Heart Disease and Stroke Statistics – 2016 Update. A Report from the American Heart Association. Circulation. 2015; 132:e1-324.
2. Powers, WJ, Derdeyn, CP, Biller, J, Coffey, CS, Hoh, BL, Jauch, EC, Johnston, JC, Johnston, SC, Khalessi, AA, Kidwell, CS, Meschia, JF, Ovbiagele, B, Yavagal, DR. 2015 AHA/ASA Association focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment. Stroke. 2015; 46: 3024-3039.
3. Rowat, A, Graham, C, Dennis, M. Dehydration in hospital admitted stroke patients: detection, frequency and association. Stroke. 2012; 43:857-859.
4. Lin, LC, Fann, WC, Chou, MH, Chen, HW, Su, YC, Chen, JC. Urine specific gravity as a predictor of early neurological deterioration in acute ischemic stroke. Medical Hypotheses. 2011; 77:11-14.
5. Lin, LC, Yang, JT, Weng, HH, Hsiao, CT, Lai, SL, Fann, WC. Predictors of early clinical deterioration after acute ischemic stroke. American J Emerg Med. 2011; 29(6):577-581.
6. Lin, LC, Lee, JD, Hung, YC, Chang, CH, Yang, JT. BUN/creatinine ratio-based hydration for preventing stroke-in-evolution after acute ischemic stroke. American Journal of Emergency Medicine. 2014; 32:709-712.
7. Bahouth, MN, Gaddis A, Hillis AE, Gottesman, RF. A pilot study of volume contracted state and hospital outcome after stroke. *Neurol Clin Pract*. 2018; 8:1-6.
8. Sumer, M, Ozdemir, I, Erturk, O. Progression in acute ischemic stroke: frequency, risk factors, and prognosis. J Clin Neurosci. 2003; 10(2):177-180.
9. Jauch EC, Saver JL, Adams, Bruno, A, Connors, JJ, Demaerschalk, BM, Khatri, P, McMullan, PM, Qureshi, AI, Rosenfield, K, Scott, PA, Summers, DR, Wang, DZ, Wintermark, M, Yonas, H, on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Peripheral Vascular Disease, and Council on Clinical Cardiology. Guidelines for the early management of patients with acute ischemic stroke: a guideline for

healthcare professionals from the American Heart Association/American Stroke Association. 2013; 44:870-947.

10. Ginsberg, MD, Palesch, YY, Martin, RH, Hill, MD, Moy, CS. The albumin in acute stroke (ALIAS) multicenter clinical trial: safety analysis of part 1 and rationale and design of part 2. Stroke. 2011; 42:119-127.
11. Ginsberg, MD, Palesch, YY, Hill, MD, Martin, RH, Moy, CS, Barsan, WG, Waldman, BD, Tamariz, D, Ryckborst, KJ; ALIAS and Neurological Emergencies Treatment Trials (NETT) Investigators. High-dose albumin treatment for acute ischemic stroke (ALIAS) part 2: a randomized, double-blind, phase 3, placebo-controlled trial. Lancet Neurology. 2013; 12:1049-1058.
12. Bayer, AJ, Pathy, MS, Newcombe, R. Double-blind randomized trial of intravenous glycerol in acute stroke. Lancet. 1987; 1(8530):405-408.
13. Rudolf, J, HES in Acute Stroke Study Group. Hydroxyethyl starch for hypervolemic hemodilution in patients with acute ischemic stroke: a randomized, placebo-controlled phase II safety study. Cerebrovascular Dis. 2002; 14(10):33-41.
14. National Institute of Neurological Disorders (**NINDS**) and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *NEJM.* 1995;333(24): 1581-1587.
15. Hacke, W, Kaste, M, Bluhmki, E, Brozman, M, Davalos, A, Guidetti, D, Larrue, V, Lees, KR, Medeghri, Z, Machnig, T, Schneider, D, vonKummer, R, Wahlgren, N, Toni, D. Thrombolysis with alteplase 3-4.5 hours after acute ischemic stroke. N Engl J Med. 2008; 359:1317-1329.
16. Demchuk, AM, Tanne, D, Hill, MD, Kasner, SE, Hanson, S, Grond, M, Levine, SR. Predictors of good outcome after intravenous tPA for acute ischemic stroke. Neurology. 2001; 57(3): 474-480.
17. Wu, FF, Hung, YC, Tsai, YH, Yang, JT, Lee, TH, Liow, CW, Lee, JD, Lin, CJ, Peng, TI, Llin, LC. The influence of dehydration on the prognosis of acute ischemic stroke for patients treated with tissue plasminogen activator. BMC Cardiovasc Disord. 2017;17:154
18. Mange, K, Matsuura, D, Cizman, B, Soto, H, Ziyadeh, FN, Goldfarb, S, Neilson, EG. Language guiding therapy: the case for dehydration versus volume depletion. Annals of Internal Medicine. 1997; 127(9):848-853.
19. Bhave, G and Neilson. Volume depletion versus dehydration: how understanding the difference can guide therapy. Am J Kidney Dis. 2011; 58(2):302-309.

20. Armstrong, LE, Johnson, EC, McKenzie, AAL, Munoz, CX. Interpreting common hydration biomarkers on the basis of solute and water excretion. European Journal of Clinical Nutrition. 2013; 67:249-253.
21. Armstrong, LE. Assessing hydration status: the elusive gold standard. Journal of the American College of Nutrition. 2007; 26:575S-584S.
22. Visvanathan, A, Dennis, M, Whiteley, W. Parenteral fluid regiments for improving functional outcome in people with acute stroke. Stroke. 2016; 47:e6-e7.
23. Schrock, JW, Glasenapp, M, Drogell, K. Elevated blood urea nitrogen/creatinine ratio is associated with poor outcome in patients with ischemic stroke. Clinical Neurology and Neurosurgery. 2012; 114:881-884.
24. Bhalla, A, Sankaralingam, S, Dundas, R, Swaminathan, R, Wolfe, CD, Rudd, AG. Influence of raised plasma osmolality on clinical outcome after acute stroke. Stroke. 2000; 31:2043-2048.
25. Rodriguez, GJ, Cordina, SM, Vazquez, G, Suri, MF, Kirmani, JF, Qureshi, AI. The hydration influence on the risk of stroke (THIRST) study. Neurocritical Care. 2009; 10:187-194.
26. Shibazaki, K, Kimura, K, Okada, Y, Iguchi, Y, Uemura, J, Terasawa, Y, Aoki, J. Plasma brain natriuretic peptide as an independent predictor of in-hospital mortality after acute ischemic stroke. Internal Medicine. 2009; 48:1601-1606.
27. Beier, K, Eppanapally, S, Bazick, HS, Chang, D, Mahadevappa, K, Gibbons, FK, Christopher, KB. Elevation of blood urea nitrogen is predictive of long-term mortality in critically ill patients independent of 'normal' creatinine. Crit Care Med. 2011; 39:305-313.
28. Hollenberg, SM, Ahrens, TS, Annane, D, Astiz, ME, Chalfin, DB, Dasta, JF, Heard, SO, Martin, C, Napolitano, LM, Susla, GM, Totaro, R, Vincent, JL, Zanotti-Cavazzoni, S. Practice parameters for hemodynamic support of sepsis in adult patients. Critical Care Medicine. 2004; 32(9):1928-1948.
29. Harvey, S, Harrison, DA, Singer, M, Ashcroft, J, Jones, CM, Elbourne, D, Brampton, W, Williams, D, Young, D, Rowan, K. Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomized controlled trial. Lancet. 2005; 366:472-477.
30. Thiele, RH, Bartels, K, Gan, TJ. Cardiac output monitoring: a contemporary assessment and review. Critical Care Medicine. 2015; 43:177-185.
31. Kalantari, K, Chang, JN, Ronco, C, Rosner, MH. Assessment of intravascular volume status and volume responsiveness in critically ill patients. Kidney International. 2013; 83:1017-1028.

32. Squara, P, Cecconi, M, Rhodes, A, Singer, M, Chiche, JD. Tracking changes in cardiac output: methodological considerations for the validation of monitoring devices. Intensive Care Medicine. 2009; 35:1801-1808.
33. Marik, PE. Noninvasive cardiac output monitors: a state of the art review. Journal of Cardiothoracic and Vascular Anesthesia. 2013; 27(1):121-134.
34. Keren, H, Burkhoff, D, Squara, P. Evaluation of a noninvasive continuous cardiac output monitoring system based on thoracic bioreactance. American Journal Physiol Heart Circ Physiology. 2007; 293:H583-589.
35. Squara, P, Denjean, D, Estagnasie, P, Brusset, A, Dib, JC, Dubois, C. Noninvasive cardiac output monitoring (NICOM): a clinical validation. Intensive Care Med. 2007; 22:1191-1194.
36. Baskurt, O and Meiselman, HJ. Iatrogenic hyperviscosity and thrombosis. Seminars in Thrombosis and Hemostasis. 2012; 38; 8:854-864.
37. Lip, GYH, Blan, AD, Farooqi, IS, Zarifis, J, Sagar, G, Beevers, DG. Sequential alterations in haemorheology, endothelial dysfunction, platelet activation and thrombogenesis in relation to prognosis following acute stroke: the West Birmingham stroke project Blood Coagulation and Fibrinolysis. 2002; 13:339-347.
38. Wiseman, S, Marlborough, F, Doubal, F, & Webb, DJ. Blood markers of coagulation, fibrinolysis, endothelial dysfunction and inflammation in lacunar stroke versus non-lacunar stroke and non-stroke: systemic review and meta-analysis. Cerebrovascular Diseases. 2014; 37:64-75.
39. Widlansky, ME, Gokce, N, Kennedy, JF, Vita, JA. The clinical implications of endothelial dysfunction. J Am Coll Cardiol. 2003; 42:1149-1160.
40. Lu, D and Kassab, GS. Role of shear stress and stretch in vascular mechanobiology. J. R. Soc. Interface. 2011; 8:1379-1385.
41. Gonzalez-Alonso, J, Mora-Rodriguez, R, Below, PR, Coyle, EF. Dehydration reduced cardiac output and increases systemic and cutaneous vascular resistance during exercise. Journal of Applied Physiology. 1995; 79:1487-1496.
42. Stevenson, SF, Doubal, FN, Shuler, K, & Wardlaw, JM. A systematic review of dynamic cerebral and peripheral endothelial function in lacunar stroke versus control. Stroke. 2010; 41:e434-3442.
43. Astrup J, Seisjo BK, Symon L. Thresholds in cerebral ischemia – the ischemic penumbra. Stroke. 1981; 12:723-725.

44. Anderson, TJ, Uehata, A, Gerhard, MD, Meredith, IT, Knab, S, Delagrange, D, Lieberman, EH, Ganz, P, Creager, MA, Yeung, AC, Selwyn, AP. Close relation of endothelial function in human coronary and peripheral circulations. J Am Coll Cardiol. 1995; 26:1235-1241.
45. Meleis, A.I. Transitions Theory. Springer; New York 2010
46. Katzan, IL and Lapin, B. PROMIS GH (Patient-reported outcomes measurement information system global health) scale in stroke. Stroke. 2018; 49: 147-154
47. Katzan, IL, Thompson, N, Uchino, K. Innovations in stroke: the use of PROMIS and NeurQOL scales in clinical stroke trials. Stroke. 2016; 47(2):e27-30.
48. Fearon, P, McArthur, KS, Garrity, K, et al. Prestroke modified Rankin stroke scale has moderate interobserver reliability and validity in an acute stroke setting. Stroke; 2012: 43(12): 3184-3188.
49. Kleindorfer, D, Lindsell, CJ, Brass, L, Koroshetz, W, Broderick, JP. National US estimates of recombinant tissue plasminogen activator use: ICD9 codes substantially underestimate. Stroke. 2008; 39(3): 924-928
50. Kleindorfer, D, Xu, Y, Moomaw, CJ, Khatri, P, Adeoye, O, Hornung, R. US geographic distribution of rt-PA utilization by hospital for acute ischemic stroke. 2009; 40(11):3580-3584.
51. Moradiya, Y, Crystal, H, Valsamis, H, Levine, SR. Thrombolytic utilization for ischemic stroke in US Hospitals with neurology residency programs. Neurology. 2013; 81(23):1986-1995.
52. Opeolu, A, Hornung, R, Khatri, P, & Kleindorfer, D. Recombinant tissue-type plasminogen activator use for ischemic stroke in the United States: A doubling of treatment rates over the course of 5 years. Stroke. 2011; 42(7):1952-1955.
53. Bahouth, MN, Bahrainwala Z, Hillis AE, Gottesman RF. Dehydration status is associated with more severe hemispatal neglect after stroke. *Neurologist.* 2016; 21(6):101-105.

Chapter 2. Review of research*

*This chapter has been published:

Bahouth, MN, Gottesman, RF, Szanton, SL. Primary 'dehydration' and acute stroke: a systematic research review. Journal of Neurology. 2018; https://doi.org/10.1007/s00415-018-8799-6

Background and Purpose: Hydration status at the time of stroke has been acknowledged as an important determinant in early stroke recovery. However, the diagnosis of dehydration, or more accurately, a volume contracted state, at the time of stroke is challenging since there are currently no consensus diagnostic criteria. In this systematic review, we gather the available evidence about diagnosis and treatment of dehydration after stroke.

Methods: Studies of hospitalized ischemic stroke patients that reported rates of dehydration from January 1997 to March 2017 were screened for inclusion via a systematic search of PubMed, CINAHL, Cochrane and Scopus using keywords hydration, dehydration, hemodilution, viscosity, volume status and thirst.

Results: Twenty-five studies of 8699 acute stroke patients were included. Nineteen studies reported on the diagnostic approach to dehydration. Findings are synthesized into the three main categories of available research including studies that specify: 1) biological mechanisms using animal models to investigate the relationship between dehydration and stroke; 2) measures of dehydration in the acute human stroke population; 3) rehydration therapies after stroke; and 4) outcomes after stroke in dehydrated patients.

Conclusions: We found considerable variation in terminology specific to hydration status, diagnostic approach to dehydration, and few prospective studies of treatment strategies with varying results. This review supports the need for consensus development of operational diagnostic criteria, standardization of language, and the opportunity for prospective study of rehydration strategies to impact outcome after stroke.

Introduction: Dehydration is a major contributor to morbidity and mortality in the elderly.[1] Thirst drive decreases with age, leaving the older population vulnerable to high rates of dehydration.[2] A large percentage of stroke patients are dehydrated at the time of stroke and appear to have worsened functional outcomes.[1-3] Current acute stroke guidelines recommend, rehydration for patients who are dehydrated.[4] However, implementation of those guidelines have been challenging because definitions of dehydration are subjective, and rehydration recommendations are imprecise.[5] Additionally, the variety of terms used to describe alterations in hydration status in the clinical arena, further complicates and impedes research in the area of dehydration and stroke.[6]

Dehydration is both common at the time of stroke and a frequent complication of stroke due to swallowing dysfunction.[3] Although clinical diagnostic approaches involving bedside assessment of hydration status are available, identifying dehydration in stroke patients remains particularly challenging for several reasons. The clinical presentation of dehydration in patients with stroke may be nonspecific, not perceived as a priority by the clinical team, or reliant on invasive techniques for objective measurement of dehydration. Further, identification of thirst in the stroke patient may be masked by altered mental status, alteration in language function, or diminished thirst mechanisms common in the elderly or patients with hypothalamic circuit disruption. Under-treatment of altered hydration status may have negative consequences on the patient's recovery. Therefore, it is especially important for stroke providers to have clear and evidence-based parameters to guide patient care in this area.

Dehydration might adversely affect the acute stroke patient in several ways: 1) reduced brain perfusion,[7] 2) increased fatigue;[8] 3) impaired neuroplasticity.[9] During the early stroke recovery period, autoregulatory systems are impaired, leaving the brain vulnerable to blood viscosity and pressure changes that could further injure the area already compromised by decreased oxygen and nutrients. Next, the functional consequences of dehydration during the early stroke recovery period could include: increased rates of delirium, poor concentration, increased fatigue, or positional hypotension. These early functional consequences may be crucial since neuroplasticity is thought to peak in the first several weeks after stroke so engagement in physical therapy during this limited period is critical.[10]

Our research team sought to understand the state of the science in the area of dehydration and stroke to standardize terminology, summarize diagnostic approaches to dehydration, identify

hydration treatments in hospitalized stroke patients, and identify gaps in the scientific literature. We present the synthesis of research findings of clinical studies that evaluate hydration measurement strategies, clinical studies of rehydration techniques, and animal research that underscore the biological rationale for hydration and stroke research.

Methods:

Search and data abstraction methods**:** Literature for this research summary was systematically identified via *Pubmed, CINAHL, Cochrane, and Scopus* using the following search terms: "dehydration," "dehyd," "hydration," "blood viscosity," "volume contraction," "hypertonicity," "thirst," "hemodilution," "haemodilution," "stroke" [Mesh] from January 1997- March 2017. We selected 1997 as the start year to reflect a major change in acute stroke care with the advent and approval of thrombolytic therapy for acute stroke.[11] Additional literature was identified by reviewing bibliographies of each publication identified through the initial search. Classic research studies prior to the twenty year date range were reviewed with the purpose for developing knowledge about physiological mechanisms behind dehydration and stroke. Only research published in English was reviewable by the study team. Studies were included if they were specific to hydration status in hospitalized patients with first time ischemic stroke. We excluded research about dehydration due to swallowing difficulties, as well as dehydration occurring in the chronic (late) phase of stroke in order to maintain focus on the time period of interest (the immediate post-stroke period).

Quality assessment was performed using the Quality Assessment tool for quantitative studies.[12] Using this pre-specified tool, the reviewer (MB) abstracted and scored data from eligible studies including assessment of study design, and potential bias. An overall score was assigned to each individual study resulting in ratings of (1) strong, (2) moderate, or (3) weak.

Results:

Study selection and rationale: Using our above search strategy and manual searches of bibliographies, we identified 3665 potential publications for inclusion. Once narrowed based on removal of duplications, our language and exclusion criteria, 190 publications were screened eventually yielding 29 original research studies for inclusion (25 human,[3,13-36] and 4 animal[37-40]) plus 2 relevant Cochrane reviews.[41, 42] **See Figure 1**. Of note, there were no qualitative research publications in the area of hydration status and stroke. Both human and animal research is included in this review to give a comprehensive picture of the state of the science. We narrowed the clinical research to studies focused on patients with primary dehydration and hospitalized

stroke patients in order to target a more homogenous population. Ischemic and hemorrhagic strokes were included though patients with subarachnoid hemorrhage were excluded based on the unique aspects of post-aneurysm fluid management.

Study characteristics: Twenty-five studies of 8699 acute stroke patients were included.[3,13-36] Nineteen of those studies focused on diagnostic approaches to dehydration in this population[3,13-29,36] and five researched potential treatments of the condition.[30-34] The majority (90%) of included studies were conducted in Asia, Europe, and the Middle East.[13-27, 29-36] The remaining three studies were completed in the United States.[27,35,36] In general, patients included in these studies were older (mean age > 60 in all but one study). Women were well represented in all studies. Two studies reported race characteristics.[27,36]

Stroke confirmation for inclusion in studies: Radiologic confirmation of stroke with MRI (gold standard) was reported in 2/25 (8%) studies.[16, 28] Severity of the stroke using standard measure of the NIH stroke scale score was reported in 16/25 (64%) of studies. Stroke severity was mild to moderate with average baseline NIH stroke scale scores, among those studies where it was provided, ranging from 4-13.[15, 16, 19, 27, 30-33, 35,36] The study by Dharmasaroja and colleagues was the exception since that study was designed to include only patients with severe stroke (mean NIH stroke scale score was 20).[30] Several clinical outcome measures were used in the 13 studies reporting clinical outcomes. Modified Rankin scores, a score of functional outcome that is used in most stroke clinical trials,[43] was reported in four studies. Barthel Index, a well-validated score of level of independence in activities of daily living,[44, 45] was used in 3 studies. Final outcome assessment times ranged from three days to three months post-stroke.

Studies measuring dehydration: In the 24 human studies, a variety of terms were used to describe hydration status. Abnormality in hydration was called “dehydration” in most cases, though other authors used volume depleted, volume contracted, fluid imbalance, or increased urea to creatinine ratio. **Table 1** summarizes the nineteen studies (79%) that specifically addressed diagnostic approaches to dehydration in this population.[3,13-36] The majority used objective indirect diagnostic criteria: 18/20 (90%) used laboratory values,[13-16,18-30, 35,36] one study used weight,[24] and one used nursing clinical assessment.[25] Overall, rates of dehydration in the acute stroke population ranged from 29-70% using a variety of measurement techniques.[13, 16, 19, 20, 21, 24-27, 35,36] The substantial heterogeneity observed was not explained by comparing equivalent groups in multiple studies. The most common lab markers used in these studies was

blood urea nitrogen to creatinine ratio (BUN/Cr) which was used in 12 studies, though three different thresholds to define 'dehydration' were used (BUN/Cr ratios of > 15, > 20, > 25). Serum osmolality, a more direct marker of hydration status, was used in five studies. Of the twelve studies reporting patient outcomes, ten (83%) reported worse clinical outcomes in dehydrated stroke patients.[3, 14, 15, 17, 19-24, 26-28] A notable gap is that none of the studies of dehydration in the post-stroke patient measured the patient experience of thirst and only one used change in weight to measure hydration status.[24] One technology-based assessment of bioimpedence to measure hydration yielded negative results when trying to validate the tool against standard measures of dehydration.[29]

Studies evaluating treatments of dehydration: Two relevant comprehensive Cochrane reviews of therapeutic approaches to rehydration using parenteral fluids (12 studies, 2351 participants) and hemodilution (21 studies, 4174 participants) in the acute stroke population were published in 2015 and 2014 respectively. Since that time, five studies of rehydration in stroke have been published: 2 quasi-experimental, two historical case control, and one cohort study. **See Table 2**. Of those, 4/5 (80%) suggest improvement in function and lower death rates with rehydration.[31-34] One study suggested increased cerebral edema in patients with large stroke who receive higher volumes of rehydration.[31] Though only a single study, with moderate biases due to the retrospective study design, this potential complication is of substantial clinical relevance as cerebral edema is a primary concern after stroke and contributes to stroke mortality.

Biological Models: When considering the biological rationale for a potential relationship between hydration status and stroke outcome, one classic human study[46] and four studies using animal models were identified during our systematic literature search.[37-40] A classic paper published in 1974 by Ott and colleagues investigated the trends in hydration using blood viscosity.[46] They studied 50 patients with cerebral angiogram to assess atherosclerosis near the time of stroke and found that acute stroke patients with higher burden of atherosclerotic disease demonstrated high blood viscosity. Researchers surmised that hydration status in this cohort of patients with mean age of 70 may be contributing to stroke.[46] On this platform, animal studies have been conducted to investigate this phenomenon.[37-40] These are well designed studies using a variety of animal models of induced stroke. In all four studies, hydration status has been associated with worse outcome.[37-38] Most compelling is the finding that supported access to food and water was independently associated with decreased mortality regardless of infarct size in a series of mice with induced infarction.[37]

Summary of study outcomes: Taken together, this systematic review suggests that there appears to be a relationship between hydration status and poor outcome after stroke in both animal and human studies. The language used to describe hydration status within this body of research was imprecise but taken together underscore an important clinical issue for which best practice is still largely unknown. The studies provide critical information, though the majority have weak to moderate designs with limitations in the ability to generalize findings due to lack of diversity among included participants. Thus far, Asian populations and Caucasians appear to demonstrate the same relationship between hydration status and functional outcome after stroke, but extending the diversity of the study populations is very important especially when using lab based definitions to describe hydration status.

All clinical studies of dehydration measures at the time of stroke reported worse clinical outcomes in volume contracted patients. Studies of interventions or comparisons of rehydration approaches yielded varying results. One study identified increased rates of cerebral edema in patients with large stroke who received > 1.6L of fluids per day after stroke. Though a very concerning and clinically relevant concern, small sample size and retrospective design limit generalizability of these findings. Thus, further work will be needed to better understand this potential hazard as formalized therapies are being created. Studies by Lin and colleagues used a more formalized strategy to rehydrate stroke patients with isotonic saline at specified rates and demonstrated lower rates of stroke in evolution ($p=0.026$),[32] lower rates of infection ($p=0.018$),[33] and shorter lengths of hospital stay ($p=0.001$).[33] Thus, there is an opportunity to further investigate treatment strategies specific to rehydration and the impact on patient level outcomes. Future studies will require careful monitoring of patients with large territory stroke for complications related to cerebral edema as an important endpoint of measure.

Discussion: Although these studies have laid the biological foundations and groundwork, further work is needed in the area in order to determine the relationship between hydration status and functional outcome after stroke. We provide recommendations for future investigation based on both the knowledge and limitations of these research studies.

Recommendation 1 – a single, objective measure of dehydration should be validated and used in future studies.

The diagnosis of dehydration remains mostly subjective leaving a relative lack of a gold standard for objective clinical diagnosis of dehydration. Validation of such markers are ongoing. To date, BUN/Creatinine ratio has been used in stroke hydration studies and yielded the most consistent result in terms of stroke outcome. Elevation of this biomarker (suggesting abnormality in hydration status) is common, appears to correlate with worse functional outcome, and appears modifiable with intravenous fluids. The most common threshold for abnormality is BUN/creatinine ratio > 15. When using BUN/creatinine ratio as an indirect biomarker, we choose terminology specific to alteration in volume status (or a volume contracted state when the BUN creatinine ratio is > 15). BUN/creatinine likely reflects intravascular volume depletion and not true dehydration (no alteration in serum sodium). It is a broadly available lab test worldwide and obtained commonly at the time of stroke care. One weakness in selecting the BUN/ratio as a biomarker is that it requires painful blood draw which should be considered when performing serial assessment. Additionally, the time lag between lab draw and receipt of an actionable result leaves room for additional novel technologies to guide rehydration therapy more precisely. Despite these potential limitations, BUN/creatinine ratio > 15 has been used most commonly in stroke hydration research and appears to be a reasonable choice for use in future research specific to hydration and stroke outcome.

Recommendation 2 – research studies including more racially diverse populations are needed.

Because muscle mass and therefore creatinine may differ across gender and ethnic groups, it is important to include studies from diverse cohorts. In addition, stroke rates are higher in African American and Hispanic populations than caucaisans[46] and therefore the effect of race is a notable gap in the current literature when considering hydration status and stroke outcome. Prospective studies in the United States would be helpful in this area to allow recruitment of underrepresented populations. Study of the relationship between race, hydration status and stroke outcome is severely lacking and will be critical to individualizing care to the stroke population.

Recommendation 3. Exploration of the mechanistic link between hydration status and stroke outcome* should *be pursued

The majority of the studies reviewed did not include MRI confirmed stroke thus leaving some question of the homogeneity of the study sample. It will be important to include only those patients with known stroke in future studies to truly understand the physiological impact of

hydration status on outcome. To the recovering stroke patient, detrimental effects of altered hydration status may come in a variety of forms: reduction of cerebral perfusion, exposure to secondary complications such as delirium and positional orthostasis, alteration in medication metabolism, and lethargy contributing to decreased engagement in rehabilitative therapies. Additionally, homeostasis specific to volume status may benefit subjective states of well-being that could be measures with patient reported outcomes. A better understanding of the mechanistic link between hydration and stroke outcome will help to identify improved outcome measures as well as potential interventions for this population who remain at high risk for disability.

Recommendation 4. Prospective studies should standardize an approach to measuring hydration status, and to choosing relevant functional outcomes

This research synthesis underscores the need to include functional outcome measures such as quantitative measures of function, activities of daily living, and mortality. Stroke studies should include baseline objective markers of severity in order to adjust for this variable and create more robust statistical models as outcomes are interpreted. Complications such as cerebral edema and collateral vessel development will be equally important measures to better understand the impact of dehydration on neuroplasticity. The majority of studies included information about functional outcome at the time of hospital discharge and at the three month follow-up time point and future studies should attempt to standardize these time points for evaluation for better comparison. Lacking in the current body of literature are measures of patient experience, such as dehydration-induced fatigue. These markers of patient engagement in restorative therapies may inevitably play a role in patient outcome and stroke related disability.

Conclusions: Dehydration is generally considered a sign of illness with severity ranging from mild to severe. While there has been substantial research in the area of dehydration and stroke recovery, there is much work to be done specific to quantifying dehydration and providing treatment to resolve dehydration. This work can be rapidly translated into clinical practice to impact patient care and stroke related disability. Rehydration therapy would be a low cost and broadly available therapy for stroke patients if proven to benefit outcomes. It is a therapy that could be applied world-wide, perhaps with greatest impact on low resource countries.

References: Chapter 2

1. Stookey, JD, Purser, JL, Pieper, CF, Cohen, HJ. (2004) Plasma hypertonicity: another marker of frailty? *J Am Geriatr Soc 52(8):1313-1320.*
2. Kenney WL, Chiu P. (2001) Influence of age on thirst and fluid intake. *Med Sci Sports Exerc* 33:1524–1532.
3. Rodriguez, G.J, Cordina, SM, Vazquez, G, et al. (2009) The hydration influence on the risk of stroke (THIRST) study. *Neurocritical Care* 10(2):187-194.
4. Jauch, EC, Saver JL, Adams HP, et al. (2013) Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 44:870-947.
5. Armstrong, LE. (2007) Assessing hydration status: the elusive gold standard. *Journal of the American College of Nutrition* 26:575S-584S.
6. Mange, K, Matsuura, D, Cizman, B, et al. (1997) Language guiding therapy: the case of dehydration versus volume repletion. *Annals of Internal Medicine* 127(9):848-853.
7. Hillis, AE, Ulatowski, JA, Barker, PB, et al. (2003) A pilot randomized trial of induced blood pressure elevation: effects on function and focal perfusion in acute and subacute stroke. *Cerebrovascular Diseases* 16:236-246.
8. Acciarresi, M, Bogousslavsky, J, Paciaroni, M. (2014) Post-stroke fatigue: epidemiology, clinical characteristics and treatment. *European Neurology* 72:255-261.
9. Font, MA, Arboix, A, Krupinski, J. (2010) Angiogenesis, neurogenesis, and neuroplasticity in ischemic stroke. *Current Cardiology Review* 6(3):238-244.
10. Nudo, RJ. (2013) Recovery after brain injury: mechanisms and principles. *Frontiers in Human Neuroscience* 7, 887:1-14.
11. The National Institute of Neurological Disorders and Stroke tPA Stroke Study Group. (1995) Tissue plasminogen activator for acute ischemic stroke. *New England Journal of Medicine* 333:1581-1587.
12. National Collaborating Centre for Methods and Tools (2008) *Quality Assessment Tool for Quantitative Studies*. Hamilton, ON: McMaster University. (Updated 13 April, 2010) Retrieved from http://www.nccmt.ca/resources/search/14.
13. Akimoto, T, Ito, C, Ogura, M, Muto, S, Kusano, E. (2011) Reduced hydration status characterized by disproportionate elevation of blood urea nitrogen to serum creatinine among the patients with cerebral infarction. Medical Hypotheses, 77:601-604.

14. Bhalla, A, Sankaralingam, S, Dundas, R, et al. (2000) Influence of raised plasma osmolality on clinical outcome after acute stroke. *Stroke 31*:2043.
15. Bhatia, K, Mohanty, S, Tripathi, B.K, Gupta, B, & Mittal, MK. (2015) Predictors of early neurological deterioration in patients with acute ischaemic stroke with special reference to blood urea nitrogen (BUN)/creatinine ratio & urine specific gravity. *The Indian Journal of Medical Research 141*(3):299-307.
16. Chang, SW, Huang, YC, Lin, LC, et al. (2016) Effect of dehydration on the development of collaterals in acute middle cerebral artery occlusion. *European Journal of Neurology 23*(3):494-500.
17. Dehghani-Firoozabadi, M, Kazemi, T, Mehrpour, O. (2014) Association between blood urea nitrogen/creatinine ratio and mortality in patients with stroke. Journal of Research in Medical Sciences 91:97-98.
18. Furukawa, K, Abumiya, T, Sakai, K, et al. (2016) Increased blood viscosity in ischemic stroke patients with small artery occlusion measured by an electromagnetic spinning sphere viscometer. *Journal of Stroke and Cerebrovascular Diseases* 25(11):2762-2769.
19. Lin, LC, Yang, JT, Weng, HH, et al. (2011) Predictors of early clinical deterioration after ischemic stroke. *Am J Emerg Med 29:*577-581.
20. Lin, LC, Fann, WC, Chou, MH, et al. (2011) Urine specific gravity as a predictor of early neurological deterioration in acute ischemic stroke. *Medical Hypotheses 77*(1):11-14.
21. Lip, GY, Blann, AD, Farooqi, IS, Zarifis, J, Sagar, G, Beevers, DG. (2002) Sequential alterations in haemorheology, endothelial dysfunction, platelet activation and thrombogenesis in relation to prognosis following acute stroke: the West Birmingham Stroke Project. *Blood Coagulation and Fibrinolysis* 13:339-347.
22. Liu, CH, Lin, SC, Lin, JR, et al. (2014) Dehydration is an independent predictor of discharge outcome and admission cost in acute ischaemic stroke. *European Journal of Neurology 21*(9):1184-1191.
23. Murray, J, Doeltgen, S, Miller, M, Scholten, I. (2015) A descriptive study of the fluid intake, hydration, and health status of rehabilitation inpatients without dysphagia following stroke. *Journal of Nutrition in Gerontology and Geriatrics* 34(3):292-304.
24. O'Neil, PA, Davies, I, Fullerton, KJ, Bennett, D. (1992) Fluid balances in elderly patients following acute stroke. *Age and Ageing* 21:280-285.
25. Rowat, A, Graham, C, & Dennis, M. (2012) Dehydration in hospital-admitted stroke patients: Detection, frequency, and association. *Stroke 43*(3):857-859.

26. Rowat, A, Smith, L, Graham, C, Lyle, D, Horsburgh, D, & Dennis, M. (2011) A pilot study to assess if urine specific gravity and urine colour charts are useful indicators of dehydration in acute stroke patients. *Journal of Advanced Nursing 67*(9):1976-1983.
27. Schrock, JW, Glasenapp, M, & Drogell, K. (2012) Elevated blood urea nitrogen/creatinine ratio is associated with poor outcome in patients with ischemic stroke. *Clinical Neurology and Neurosurgery 114*(7):881-884.
28. Song, SH, Kim, JH, Lee, JH, Yun, YM, Choi, DH, Kim, HY. (2017) Elevated blood viscosity is associated with cerebral small vessel disease in patients with acute ischemic stroke. *BMC Neurology* 17:1-10.
29. Kafri, MW, Myint, PK, Doherty, D, Wilson, AH, Potter, JF, Hooper, L. (2013) The diagnostic accuracy of multi-frequency bioelectrical impedence analysis in diagnosing dehydration after stroke. *Medical Science Monitor* 19:548-570.
30. Dharmasaroja, PA. (2016) Fluid intake related to brain edema in acute middle cerebral artery infarction. *Translational Stroke Research* 7:49-53.
31. Lin, CJ, Yang, JT, Huang, YC, et al. (2016) Favorable outcome of blood urea nitrogen/creatinine-based hydration therapy 3 months after acute ischemic stroke. *The American Journal of Emergency Medicine 34*(12):2414-2418.
32. Lin, LC, Lee, JD, Hung, YC, Chang, CH, & Yang, JT. (2014) BUN/creatinine ratio-based hydration for preventing stroke-in-evolution after acute ischemic stroke. *The American Journal of Emergency Medicine 32*(7):709-712.
33. Lin, WC, Shih, HM, & Lin, LC. (2015) Preliminary prospective study to assess the effect of early blood urea Nitrogen/Creatinine ratio-based hydration therapy on post-stroke infection rate and length of stay in acute ischemic stroke. *Journal of Stroke and Cerebrovascular Diseases: The Official Journal of National Stroke Association 24*(12):2720-2727.
34. Mucke, S, Grotemeyer, KH, Stahlhut, L, et al. (2012) The influence of fluid intake on stroke recurrence – a prospective study. *Journal of the Neurological Sciences* 315:82-85.
35. Bahouth, MN, Bahrainwala, Z, Hillis, AE, Gottesman, RF. (2016) Dehydration status is associated with more severe hemispatial neglect after stroke. *Neurologist* 21(6):101-105.
36. Crary, MA, Humphrey, JL, Carnaby-Mann, G, Sambandam, R, Miller, L, Sillman, S. (2013) Dysphagia, nutrition, and hydration in ischemic stroke patients at admission and discharge from acute care. *Dysphagia* 28(1):69-76.
37. Lourbopoulos, A, Mamrak, U, Roth, S, et al. (2016) Inadequate food and water intake determine mortality following stroke in mice. *Journal of Cerebral Blood Flow & Metabolism* 37(6):2084-2097.

38. Morris, M, Li, P, Callahan, MF, et al. (1999) Neuroendocrine effects of dehydration in mice lacking angiotensin AT1a receptors. *Hypertension* 33:482-486.
39. Gross, PM, Kadekaro, M, Sokoloff, L, et al. (2005) Alterations of local cerebral glucose utilization during chronic dehydration in rats. *Brain Research* 330:329-336.
40. Hyodo, A, Heros, RC, Tu, YK, et al. (1999) Acute effects of isovolemic hemodilution with crystalloids in a canine model of focal cerebral ischemic. *Stroke* 20:534-540.
41. Visvanathan, A, Dennis, M, Whiteley, W. (2015) Parenteral fluid regimens for improving functional outcome in people with acute stroke. *The Cochrane Collaboration* 9:1-56.
42. Chang, TS and Jensen, MB. (2014) Haemodilution for acute ischaemic stroke. *The Cochrane Collaboration* 8:1-81.
43. vanSwieten, JC, Koudstaal, PJ, Visser, MC, Schouten, HJ, vanGijn, J. (1988) Interobserver agreement for the assessment o handicap in stroke patients. *Stroke* 19:604-607.
44. Granger, CV, Devis, LS, Peters, MC, Sherwood, CC, Barrett, JE. (1979) Stroke rehabilitation: analysis of repeated Barthel Index measures. *Arch Phys Med Rehabil* 60:14-17.
45. Sulter, G, Steen, C, DeKeyser, J. (1999) Use of the Barthel Index and modified Rankin scale in acute stroke trials. *Stroke* 30:1538-1541.
46. Ott, EO, Lechner, H, Aranibar. (1974) High blood viscosity syndrome in cerebral infarction. *Stroke* 5:330-333.
47. Sacco, RL, Boden-Albala, B, Abel, G, et al. (2001). Race-ethnic disparities in the impact of stroke risk factors: the Northern Manhattan Stroke Study. *Stroke* 32:1725-1731.
48. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. *PloS Med* 6(7): e1000097.
49. Nacu, A, Bringeland, GH, Khanevski, A, Thomassen, L, Waje-Andreassen, U, Naess, H. (2016). Early neurological worsening in acute ischaemic stroke patients. *Acta Neurol Scand* 133:25-29.

Table 1: Studies measuring dehydration in acute stroke

Lead author (year) Country	Years of recruitment	Number participants	Age	MRI verified stroke	Mean NIHSS; Type of stroke	Time from stroke enrollment	Hydration definition	Percent dehydrated	Outcome of interest	Selected result	Functional Outcome	Risk of bias	Observations
Akimoto, T (2011) Japan	2008-2009	97	76 (43%)	N	NR Ischemic	Not specified	BUN/Cr > 25 Plasma osmolality	28/97 (29%)	Quantifying percent dehydrated	More dehydration in subjects > 80 yo (p=0.02)	NR	3	High BUN/creat = more common cardioembolic stroke (p=0.02) Limitations: small sample; retrospective; ICD9 diagnoses; generalizability (Japanese with more intracranial atherosclerosis)
Bahouth, MN (2016) United States	2010-2013	201	65 (47%)	Y	6 Ischemic	48h	BUN/Cr > 15 and Urine SG > 1.010	114/201 (57%)	Hemispatial neglect	More elevated BUN/creatinine ratio in subjects with severe neglect compared to those without severe n neglect (23 vs 17 respectively; p=0.0003)	NR	3	All MRI confirmed ischemic stroke Retrospective design
Bhalla, A (2000) UK	1998-1999	167	73 (52%)	N	NR	24h	Plasma osmolality	NR	Survival 3 mo	Mean admission pOsm higher in patients w (300 v 293; p < 0.0001)	BI	3	70% hydrated orally; 30% hydrated intravenously Higher plasma osmolality and worse outcomes
Bhatia, K (2015) India	2012	114	57 (36%)	N	10 Ischemic	24 h	BUN/Cr > 15; Urine SG > 1.010	45/114 (39%)	Early neurological deterioration (END)	BUN/Creat >15 and Urine SG > 1.010 independent risk for neurological worsening	NR	2	(END ≥ 3 pt change NIHSS; 3d) – All with END were MCA territory strokes 645 with END had edema
Chang, SW (2016)	2012-2014	87	74 (47%)	Y	13 Ischemic	3d	BUN/Cr > 15	70%	Collateral development	Dehydration had a negative impact on collateral development within 3 days from stroke (p=0.001) Mean time stroke onset to MRI 23h	mRS	3	ICC 0.924 – high interrater reliability assessing collaterals No significant difference in functional outcome at 3 mo by hydration status

Crary, MA (2013) United States	NR	67	66 (57%)	N	9 Ischemic	Not specified	BUN/Cr > 15	(36/67) 53%	Change in BUN/Cr at discharge	Percent of patients who were dehydrated worsened at hospital discharge (55% v 66% respectively)	mRS	3	54% of cohort African American Time from stroke onset to hospitalization was not reported; likely secondary dehydration due to swallowing issues
Dehghani-Firoozabadi, M (2013) Iran	2009-2011	586	69 (49%)	N	NR Both	Not specified	Not specified	NR	Death (hospitalization and 3 months)	BUN/Creat 20.8 v 12.7 (died v survived hospitalization, $p < 0.001$) BUN/Creat 17.4 v 12.5 (died vs survived 3 mo, p= 0.007)	NR	3	Retrospective design; diagnosis unclear – selection bias
Furukawa, K (2016) Japan	2014-2015	92	74 (41%)	N	NR Ischemic	2 weeks	Viscosity	NR	Trend in viscosity stroke v control	Baseline viscosity in small vessel stroke: 5.4 v 4.7 ($p < 0.01$) Viscosity decreased at 1 week (IVF); Viscosity increased at 2 weeks (no IVF) BUN/Creat ratio did not change over the course of lab draws	NR	3	Trend in viscosity; no report of how much intravenous fluid administered though statement made that viscosity trends are related to rehydration
Lin, LC (2011) Taiwan	2007-2008	196	70.6 (33%)	N	8 Ischemic	12h	BUN/Cr > 15	30/196 (15%)	Stroke in evolution (SIE) (≥ 3 pt change NIHSS; 3d)	Stroke severity: NIHSS (SIE = 9.6; No SIE = 7.3) Dehydration -> 3x more likely to have SIE (95% CI, 1.36-7.62, p=0.008) 30/194(15%) had SIE	NR	3	Subjective judgment of SIE – no adjudication
Lin, LC (2011) Taiwan	2007-2010	317**	70 (43%)	N	Ischemic		Urine specific gravity > 1.010	177/317 (56%)	Stroke in evolution (SIE) (≥ 3 pt change NIHSS; 3d)	Dehydrated group = 2.78 times more likely to develop SIE (95% CI, 1.1-6.96, p=0.030)	NR	3	**NOTE THAT 196 of the cohort were from the prior study

Liu, CH (2014) Taiwan	2009-2011	3143	60 (41%)	N	NR Both (2570 (I); 573 (H)	NR	BUN/Cr ≥ 15	48%	Discharge outcome Infection rates	Dehydrated group: worse median NIHSS (5 v 4; p< 0.001); higher infection (p=0.006) longer LOS; worse discharge mRS 3.6 v 3.1 (0.002)	D/C mRS BI	2	Large sample size based on ICD9 codes – both stroke types Difference in outcome not clinically meaningful; Broad definition of infection Excluded "high admission costs" patients Long length of stay (18 days)
Lip, GY (2002) UK	NR	59	64 (39%)	N	NR Both (59 (I); 15 (H); 12 (TIA)	12h	Viscosity vonWillebrand factor Fibrinogen	NR	Mortality	High ddimer in patients who died though not significant (p=0.08)	6mo	2	Multiple hematological measures evaluated and trended Restricted to subjects < 75 years old Outcomes of death only
O'Neill, PA (1992) UK	NR	15	79 NR	N	NR; NR	8h (4-21h) (Median)	Osmolality; arginine vasopressin (AVP)	NR	BI; Good versus Bad outcome	Patients with high AVP had poor outcomes (p=0.02)	BI	3	Greater reduction in s osm in patients with IVF; high morbidity & death rate (10/15)
Murray, J (2015) Australia	2009-2011	86	65 (36%)	N	NR Ischemic		BUN/Cr > 20 Daily weight	34/85 (40%) 44% at day 7	Fluid intake Adverse health outcomes	Average 1.5L consumed per day after stroke Subjects consumed 67% of required fluid intake by weight Mobility issues correlated with poor intake (R2=0.064) and elevated BUN/Cr ratio (p=0.018)	NR	2	Adverse events very subjective: constipation, urinary tract infection, dehydration Bias – participants were aware of study and therefore may a heightened awareness for dehydration

Rowat, A (2011) Scotland	2007-2008	20	79 (56%)	N	NR; NR	NR	Clinical assessment Urea: creat > 60 8 point colour chart	9/20 (45%)	Nursing assessment SG: urine test strips versus refractometer	Nursing assessment: 11/20 (55%) of subjects were dehydrated compared with 45% by urine SG 70/174 urine samples (40%) agreement strips with refractometer	NR	3	The only study to include clinical assessment of any kind Pilot study results do not support use of urine test strips to detect dehydration
Rowat, A (2012) Scotland	2005-2008	2591	76 (46%)	N	NR Both	14d	Urea/Creatinine ratio > 80	927 (36%)	Mortality	687/1580 (43%) dehydrated patients died in hospital v. 177/969 (18%) without dehydration (p< 0.0001) Odds of good outcome if dehydrated 0.17, 95% CI 0.13, 0.23)	NR	3	Outcome measure not well defined Major limitation is lack of a gold standard measure for dehydration
Schrock, JW (2012) United States	2007-2009	324	NR (50%)	N	4 Ischemic	24h	BUN/Creatinine > 15	138/324 (43%)	Death or nursing home	2.2 increased odds worse 30 day outcome if dehydrated despite more being treated with tPA (22 v 11%, p=0.04)	30d	3	ONLY STUDY REPORTING RACE: 31% African American, 6% Hispanic Less than 20% of African Americans were dehydrated using this lab indicator
Song (2017) Korea	2013-2014	63	65 (34%)	Y	NR Ischemic	< 3 days	Whole blood viscosity	NR	Stroke type v viscosity	DBV 274.7 small artery stroke v 215 large artery stroke (o 0.003)	NR	3	No comparison to non-stroke; no functional outcomes; 16 stroke mimics

Table1 Legend: NR= not reported; Dehyd = dehydrated; Stroke type: I=ischemic; H= hemorrhagic; 3=both; BUN/Cr = blood urea nitrogen to creatinine ratio; Urine SG = specific gravity; s osm = serum osmolarity; SIE = stroke in evolution (neurological worsening); mRS=modified Rankin score; TIA = transient ischemic attack; Risk of bias assessment: (1)=strong; (2)=moderate; (3)=weak design.

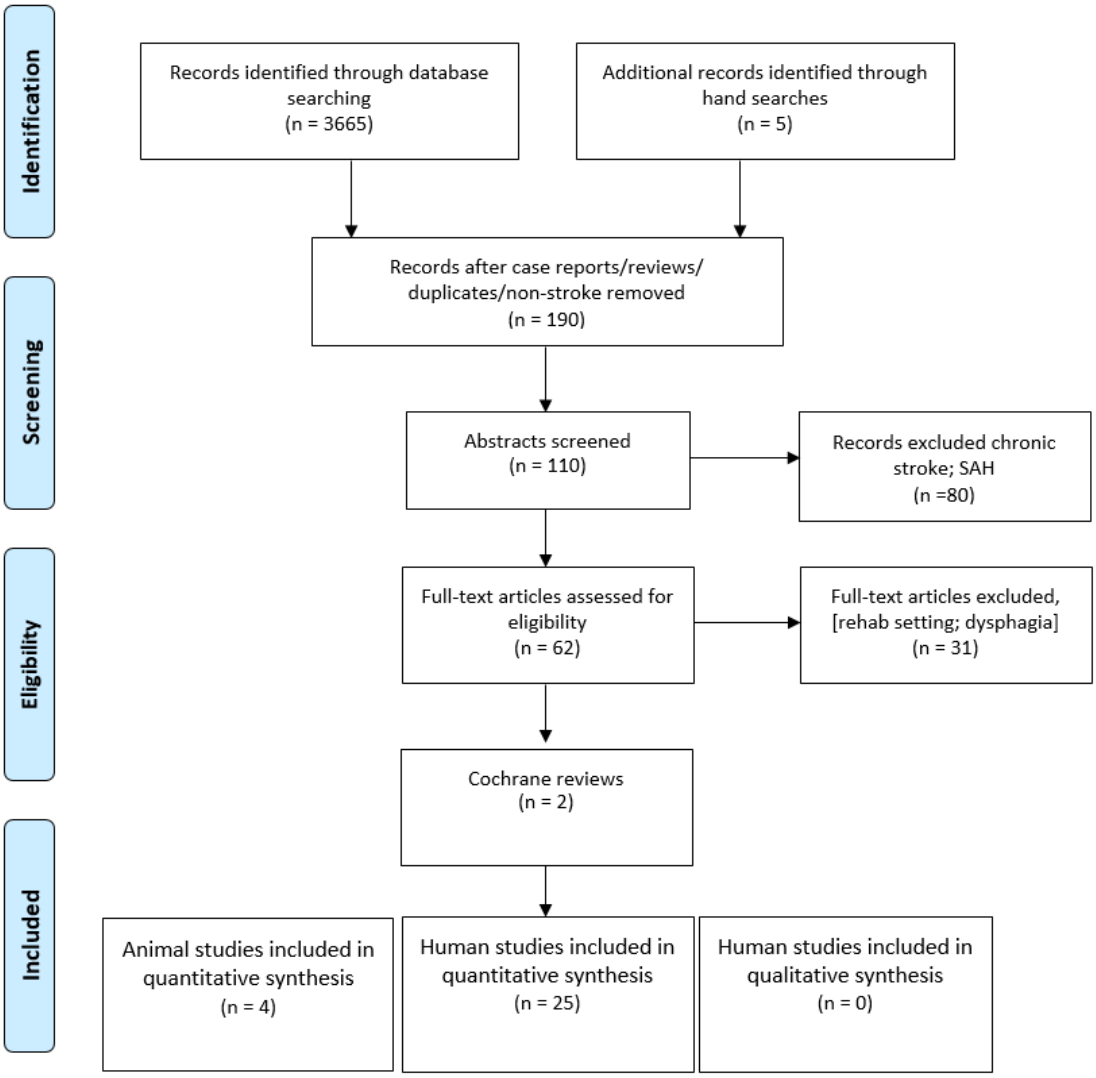
Table 2: Studies including recommended hydration therapies for acute stroke patients

Lead author (year)	Dates of enrollment	Design	Intervention N	Control N	Age (years)	MRI verified stroke?	Type of stroke ; Mean NIHSS	Time from stroke to enrollment	Period of surveillance	Hydration definition and Intervention	Percent dehydrated	Primary outcome	Outcome	Risk of bias	Reviewer observations
Dharmasaroja, P (2016) Thailand	2011-2014	Q	193	N/A	67 (49%)	No	Ischemic 20	24h	12mo	Not specified	Not specified	Cerebral edema Mortality	ROC analysis: 1654 mL predicted malignant brain edema with 84% sensitivity and 68% specificity 43% died in 12 month follow-up period	3	Retrospective design; Inclusion criteria for large ischemic stroke; tPA to 24%; Decompressive surgery 18% Fluid type not specified (isotonic, hypertonic) which can effect edema
Lin, LC (2014) Taiwan	2010-2012	E	92	97	70 (49%)	No	Ischemic 6 v 6	12h	3d	BUN/Cr > 15	All had elevated BUN/Cr to be enrolled	SIE (change in NIHSS $\geq$ 4 points)	Less experienced SIE in rehydration group (9 v 21; p=0.026)	2	Change in definition of SIE from prior studies
Lin, LC (2016) Taiwan	2011-2013 (control 2007-2010)	E	134	103	73 (49%)	No	Ischemic 6 v 7 (control v intervention)	12h	3mo	BUN/Cr > 15	Only dehydrated patients recruited	mRS $\leq$ 2 at 3 months	Hydration group with better 3 mo outcome 65/134 (p=0.016); lacunar group better with hydration	2	tPA patients excluded mean volume IVF infused 3.9L v 2.8L over 72 h
Lin, WC (2015)	2011-2013	E	134	103	74 v 70	No	Ischemic	12h	3d	BUN/Cr > 15	All had elevated	Length of stay	Intervention group: 4.2L and control 2.4 L	3	Unblinded, single arm, phase II

Taiwan	(control 2007-2010)				(50 v 47%)		6 v 4				BUN/Cr to be enrolled	Infection rates	Infection lower in rehydration group (7.5% v 17.5% (p=0.018) LOS shorter in rehydration group (10 v 16 days P = 0.001)		Intervention: (fluid bolus plus 40-80 mL/hour IVF x 3d) Control: (IVF 40-60 mL/hr x 24 h) Selection bias – controls prior to intervention group Infection defined as the need for antibiotics Adverse events cerebral edema equal in both groups
Mucke, S (2012) Germany	NR	Q	248	208	59 (30%)	No	Ischemic NR	24h	24mo	Serum osmolarity	Not specified	Stroke recurrence	Recurrent stroke event: 16.8% low fluid intake v 12.3% high fluid intake (p=0.013)	3	Controls drank < 2L/day compared to intervention > 2L intake per day Add on to a drug RCT – did not report baseline stroke severity

Table 2 legend: NIHSS = NIH stroke scale score; tPA = tissue plasminogen activator; BUN/Cr = blood urea nitrogen to creatinine ration; IVF = intravenous fluid; L=liters; Q= Quasi-experimental design; E = Experimental design; RCT = randomized controlled trial

Figure 1. PRISMA flow diagram of included studies



Chapter 3. Association between volume contracted state and outcome in acute ischemic stroke patients who present to hospital within 4.5 hours from symptom onset

Abstract: Elevated BUN/creatinine ratio suggestive of a **volume contracted state (VCS)** is common after acute ischemic stroke and associated with early neurological worsening and worse clinical outcome. Whether VCS influences the effect of medical reperfusion treatment is unknown. We assessed whether increased BUN/creatinine ratio influences the administration of **tissue plasminogen activator (tPA)** or modifies the effect of tPA benefit in patients with acute ischemic stroke.

Methods: We collected data for all patients admitted to the Johns Hopkins Comprehensive Stroke center within 4.5 hours of symptom onset for acute ischemic stroke. VCS was defined as BUN/creatinine ratio > 15. The primary outcome measures, in separate logistic regression models, were administration of tPA and the adjusted odds ratio for good functional outcome defined as the achievement of modified Rankin score 0-2, at 90 days post-stroke. Secondary outcome variables included early neurological worsening and the development of intracranial hemorrhage after tPA.

Results: Of the 382 patients identified, 326 were eligible for inclusion. Patients in a VCS demonstrated reduced odds of achieving a good functional outcome defined as modified Rankin score 0-2 (bivariate OR 0.56, 95% CI 0.33, 0.95; p=0.030). Of the total cohort, 181 were treated with tPA; there was no difference in tPA administration by hydration status (56% were in a VCS and 55% were not) nor was there evidence for effect modification of tPA by hydration status (OR 0.49 95% CI 0.17, 1.43; p=0.193). We found an important qualitative difference in good 3 month outcomes for tPA treated patients who were and who were not in a VCS at the time of hospitalization (OR 0.81 CI 0.37, 1.76, p=0.60 versus OR 1.66 0.79, 3.49; p=0.182, respectively. There was no relationship to the development of post-tPA intracerebral hemorrhage between VCS and non-VCS patients (8% versus 14% respectively, p=0.215).

Conclusions: We found no difference in tPA administration based on baseline BUN/creatinine ratio. Benefit from tPA may be reduced in patients who have an elevated BUN/creatinine ratio at the time of hospital presentation. Further investigation is needed to determine if this is a modifiable relationship.

Background: Tissue plasminogen activator (tPA) is the only FDA approved medical treatment for acute ischemic stroke and improves functional outcome in the percentage of patients eligible to receive the time sensitive medication.[1] Selection of patients appropriate for this treatment is made based on multiple factors including presentation to a tPA-capable hospital within 4.5 hours from stroke symptom onset.[2-3] Despite compelling data emphasizing the positive benefit from tPA, many patients do not achieve the expected result, and have significant disability despite having received tPA.[3] Understanding who is at high risk for bad outcome despite tPA, and whether there are modifiable factors impacting this outcome is a critical area for further study. Hydration status at the time of tPA administration may be one such variable.

Recent studies have suggested that more than half of acute ischemic stroke patients present to the hospital in a dehydrated or volume contracted state (using an indirect lab measurement of elevated blood urea nitrogen (BUN) to creatinine ratio) and that these patients have worse outcome.[4-6] Serum BUN/creatinine is an indirect marker for intravascular volume status, and the treatment of elevated BUN/creatinine ratio typically includes the administration of isotonic fluids to correct this physiological abnormality. A volume contracted state has been associated with more severe hemispatial neglect, more frequent early neurological worsening, and poor 3 month functional outcomes.[7,8] Possible underlying mechanisms of the association between a VCS and poor outcome in stroke patients include hemodynamic changes that decrease cerebral perfusion in the setting of disrupted cerebral autoregulation, and increased blood viscosity via alterations in coagulation activity.[9] More recently, observational studies describe an association between dehydration and poor outcome in tPA treated patients,[10,11] but these studies do not include a comparison group of non-tPA treated patients in a similar time window, so it is unknown if dehydration status modifies the expected good outcome resulting from tPA administration. To our knowledge, no animal models nor human clinical trials have reported whether VCS alters the treatment effect of tPA on functional outcome.

We hypothesize that patients in VCS may also have a unique panel of comorbid conditions influencing the likelihood of receiving tPA (both due to physician decision and due to contraindication due to comorbidity) and, given the above described mechanisms for an effect of VCS on poor outcome, hypothesized that a VCS might reduce efficacy of tPA effect. In this single-center study, we tested the relationship between VCS and tPA administration, and whether VCS is associated with reduced odds of a good 3-month functional outcome after tPA.

Methods: This is a retrospective observational study of acute ischemic stroke patients admitted to an urban, comprehensive stroke center between 2011 and 2016. The study site is a comprehensive stroke center certified by the Joint Commission. tPA is administered by stroke specialists according to American Heart Association guidelines.[12] Patients were included if they were diagnosed with ischemic stroke within 4.5 hours from symptom onset. Patients were excluded if they had history of kidney disease, baseline serum creatinine > 2 or underwent mechanical thrombectomy. Clinicians making decisions at the time of tPA administration were blinded to the hypothesis of this study. This study was approved by the institutional review board of the Johns Hopkins University School of Medicine.

Measures: Baseline demographic, relevant comorbid conditions and home medication use, hemodynamic measurements, and stroke severity indicators were compared between the group of patients receiving tPA. The assessed clinical parameters were from the medical record and included age, gender, common vascular risk factors such as hypertension, atrial fibrillation, and diabetes, baseline mean arterial pressure, markers of stroke severity, and serum markers relevant to hydration status including serum sodium and glucose.[13] Labs are measured upon arrival for evaluation of acute stroke in anticipation of potential tPA administration.

Exposure: Bloodwork to measure BUN/creatinine ratio is collected as routine standard of care at the time of acute stroke evaluation. Volume contracted state defined as BUN/creatinine ratio >15 during emergency evaluation was the independent variable when investigating whether tPA administration was modified by hydration status.

Outcomes: Primary outcomes were 1) administration of tPA and 2) achievement of good functional outcome defined as a 3-month modified Rankin score 0-2 measured by the stroke center nursing staff who were blinded to the hypotheses of this study, as a part of routine stroke care. Secondary outcomes included evidence of 1) early neurological worsening defined as increase in NIHSS >3 points or death, 2) development of intracerebral hemorrhage defined as any symptomatic or asymptomatic hemorrhage after tPA as documented by the stroke neurologists caring for the patient at the time of stroke admission.

Statistical analysis: Characteristics were compared between the group who received tPA and those who did not using t-tests (continuous variables) and chi-squared tests (categorical variables). The binary outcome measures were analyzed using multivariable logistic regression.

Adjustments were made for known covariates that influence functional outcome after stroke including age, initial NIHSS score, initial mean arterial pressure, and history of atrial fibrillation.[14] VCS was the moderator variable of interest when investigating the relationship between tPA and functional outcome.

TPA treatment effect modification by admission BUN/creatinine ratio or VCS was assessed by including interaction of these variables after binarizing tPA treated patients with good functional outcome (mRS 0-2) and poor outcome (mRS >2). We additionally performed a subgroup analysis of functional outcome defined as modified Rankin score 0-2 after excluding patients with mild stroke defined as NIHSS 1 or who were rapidly improving as the reason for tPA exclusion since these patients would likely have a good outcome despite the intervention. Finally, we explored functional outcome under the assumption that all missing modified Rankin scores were in the worst possible outcome category (mRS >2). Significance was considered $p< 0.05$. Statistical analysis was performed using Stata version 15 (Stata Statistical Software: Release 15, College Station, Texas).

Results: Admission BUN/creatinine ratios were available for all 382 patients who presented with ischemic stroke within 4.5 hours. Of those, 56 were excluded for the following reasons: additional treatment with mechanical thrombectomy (12), history of kidney disease (23), serum creatinine >2 (21) leaving 326 subjects available for analysis. Forty seven percent (154 of 326) of the sample were in a volume contracted state at the time of admission. Average BUN/creatinine ratio was 16. In 240/326 subjects with 3 month modified Rankin scores available, odds of achieving a good functional outcome defined as modified Rankin score 0-2 differed for those who were in a VCS (bivariate OR 0.56, 95% CI 0.33, 0.95; p=0.030).

Thrombolysis (TPA): Intravenous thrombolysis was administered to 181/326 (56%) of patients admitted within 4.5 hours from stroke symptom onset. tPA-treated patients were younger, had higher average NIHSS scores, had elevated mean arterial pressures, higher heart rates, and higher serum hemoglobin/hematocrits. **See Table 1**. The reasons that tPA was not administered to the 145/326 (44%) were documented for 121 (83%) patients. Most common reasons that tPA was not administered to this group included: symptoms too mild or rapidly improving (48%); taking anticoagulation or elevated INR (12%); bleeding risks (12%); or changes on CT scan (12%). Other exclusions like recent stroke, blood pressure issues, or patient refusal were less frequent. There was no difference in tPA administration in the 87/181 (56%) patients in a VCS compared with

94/181 (55%) who were not in a VCS (p=0.738). Time from symptom onset to tPA administration did not differ between groups in a VCS and those who were not (157 versus 154 minutes; p=0.784).

Functional outcome: Three-month modified Rankin scores were available for 240/326 (74%) patients. In the entire cohort, 150/240 (63%) achieved a good outcome predefined as mRS 0-2. In the total cohort, tPA use was not associated with good outcome, but when removed mild stroke from non-tPA group 1.65 increased odds of good outcome (95% CI 0.91, 3.01; p=0.101). In the entire cohort, there was a significantly reduced odds of good outcome for every unit increase in BUN/creatinine ratio (OR 0.94, 95% CI 0.90, 0.99; p=0.012) compared to those who were not in a VCS. This relationship persisted in multivariable analysis adjusted for age, initial NIHSS, tPA administration, initial mean arterial pressure, and history of atrial fibrillation (OR 0.95; CI 0.91, 0.99; p=0.046). **See table 2.**

Tissue Plasminogen Activator group: In the tPA treated group, 88/138 (64%) achieved a good outcome. There is no evidence for moderation of tPA benefit by VCS (p=0.193). While not statistically significant, we see an important qualitative difference in good 3 month outcomes associated with tPA use in patients who were and who were not in a VCS at the time of hospitalization (OR 0.81 CI 0.37, 1.76, p=0.60 versus OR 1.66 0.79, 3.49; p=0.182, respectively). If analyzed with missing mRS scored as the worst possible outcome, we see a narrowing in this difference (VCS OR 0.88 (95% CI 0.46, 1.70; p=0.713) versus no-VCS 0.70 (95% CI 0.39, 1.28; p=0.243).

Sensitivity analysis: In order to compare functional outcomes of those who had not received tPA because of mild symptoms, we performed a sensitivity analysis by removing the group of patients who were rapidly improving or had a mild stroke. In this subgroup of 106 patients, the odds of achieving a good outcome associated with tPA was 2.48 (95% CI 1.06, 5.82, p=0.037) in patients who were euvolemic compared with a 1.13 increased odds of good outcome in the group who were in a VCS at the time of presentation (CI 0.48, 2.68, p=0.783) (p interaction =0.204).

Early Complications: Among tPA treated patients, 8/9 (89%) of people who demonstrated early worsening or death were in a VCS compared with 77/170 (45%) who did not worsen. Odds of early neurological worsening was increased in tPA treated patients who were in a VCS compared with those who were not (p=0.016). There were six symptomatic intracerebral hemorrhage events

(3.3%) and 20 (11%) total ICH (symptomatic and asymptomatic ICH combined). We did not observe a difference in post-tPA hemorrhage based on BUN/creatinine ratio at the time of tPA treatment adjusted OR 0.61 (95% CI 0.21, 1.76; p=0.361). **See Table 3.**

Discussion: In this single-center study, we found that patients presenting within 4.5 hours after stroke who were dehydrated were not differentially treated with regards to tPA administration, but we found some evidence that 3-month benefit from tPA was reduced in individuals with a volume contracted state. This relationship was particularly clear when we excluded those individuals who did not receive tPA because of rapidly resolving or mild strokes (and thus their inclusion might dilute the benefit from tPA.

To our knowledge, no other studies have investigated possibility of modification of tPA effect by VCS. Other studies reported an association between dehydration and poor functional outcome after tPA, but did not consider individuals who did not receive tPA.[10,11] This study demonstrates similar rates of VCS as cited in prior studies.[15-18] While there was no statistically significant tPA effect modification on functional outcome by VCS in the overall sample, qualitative comparison suggests that odds of achieving a good functional outcome are notably different between groups who were and were not in a VCS at the time of tPA. This is an important clinical finding, especially in the context of recent studies of intravenous fluid after ischemic stroke.[19,20] Furthermore, we find stronger evidence of differences between these groups when we eliminate individuals who would not be considered eligible for tPA even within this time window (the rapidly resolving, or minor stroke group), allowing us to consider tPA's benefit more fairly. The fact that the overall benefit of tPA, regardless of hydration status, is not seen until we conducted this sensitivity analysis, is evidence of the importance of considering VCS as we consider the potential to improve outcomes for stroke patients.

The potential to modify the association between VCS and outcome hasn't been studied for stroke patients receiving tPA, but has been studied more broadly. In a recently completed randomized trial, Suwanwela and colleagues demonstrated that administration of normal saline at 100mL/hour for 72 hours after arrival to the hospital with ischemic stroke was safe and associated with decreased early neurological worsening.[19] This was consistent with a prior, unblinded, Phase II single site study of saline bolus followed by 40-80mL/hour of saline administered for 72 hours.[20] These studies excluded patients who received thrombolytic therapy and enrolled patients up to 72 hours after stroke, but the rationale driving those studies can be applied to the current study

of patients who are within 4.5 hours from stroke symptoms onset. Specifically, disrupted cerebral autoregulation makes the patient more vulnerable to changes in intravascular volume and thus cerebral perfusion. A VCS may contribute to the distribution of tPA and medication pharmacokinetics as seen in other studies of medications in animal models.[21]

In addition to the retrospective study design, this study has several limitations to consider. First, BUN/creatinine ratio is an indirect marker of VCS and can be affected by other conditions.[22-26] While we attempted to reduce the risk of these events with our exclusion criteria and analysis of relevant co-variates, elevated BUN/creatinine ratio may simply reflect a yet unmeasurable "sicker" population of stroke patients.[27] Second, low initial NIHSS in the non-treated group created a floor effect impacting secondary analysis looking for change in NIHSS. Next, we do not have information about amount of intravenous fluid administered to this population in order to measure treatment differences and how these might impact outcome. Future prospective studies will include this important variable. There are likely additional unmeasured confounders contributing to the outcomes that aren't well captured and wouldn't be adjustable but might relate to VCS and thus lead to differences that we can't account for.[28] Early neurological worsening was notable more often in patients in a VCS however the low number of patients who worsened make this difficult to interpret and will need to be explored in future studies. Finally, missingness of the 3 month modified Rankin score must be considered. It is possible that those patients with missing mRS may reflect patients with the worse functional outcomes. Thus we undertook an analysis that scored any missing mRS as the worse outcome which showed a narrowing in that difference. Considering these results together, it is likely that the truth lies somewhere between these two extremes and will need consideration in future prospective trials. Strengths of our study are that this is a cohort of all ischemic stroke patients who present with stroke symptoms within 4.5 hours from symptom onset. It is a real-world data sample managed by a consistent team of vascular neurologists who administer tPA based on American Heart Association guidelines.[12]

Conclusion: We demonstrated that VCS was not associated with a difference in tPA administration rates but may decrease the odds of achieving a good 3 month functional outcome. Future studies are needed to explore this relationship and consider whether early correction of a VCS would have an effect on clinical outcome.

References: Chapter 3

1. National Institute of Neurological Disorders (**NINDS**) and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *NEJM.* 1995;333(24): 1581-1587.
2. Hacke, W, Kaste, M, Bluhmki, E, Brozman, M, Davalos, A, Guidetti, D, Larrue, V, Lees, KR, Medeghri, Z, Machnig, T, Schneider, D, vonKummer, R, Wahlgren, N, Toni, D. Thrombolysis with alteplase 3-4.5 hours after acute ischemic stroke. N Engl J Med. 2008; 359:1317-1329.
3. Demchuk, AM, Tanne, D, Hill, MD, Kasner, SE, Hanson, S, Grond, M, Levine, SR. Predictors of good outcome after intravenous tPA for acute ischemic stroke. Neurology. 2001; 57(3): 474-480.
4. Rowat, A, Graham, C, Dennis, M. Dehydration in hospital admitted stroke patients: detection, frequency and association. Stroke. 2012; 43:857-859.
5. Lin, LC, Fann, WC, Chou, MH, Chen, HW, Su, YC, Chen, JC. Urine specific gravity as a predictor of early neurological deterioration in acute ischemic stroke. Medical Hypotheses. 2011; 77:11-14.
6. Lin, LC, Yang, JT, Weng, HH, Hsiao, CT, Lai, SL, Fann, WC. Predictors of early clinical deterioration after acute ischemic stroke. American J Emerg Med. 2011; 29(6):577-581.
7. Lin, LC, Lee, JD, Hung, YC, Chang, CH, Yang, JT. BUN/creatinine ratio-based hydration for preventing stroke-in-evolution after acute ischemic stroke. American Journal of Emergency Medicine. 2014; 32:709-712.
8. Bahouth, MN, Gaddis A, Hillis AE, Gottesman, RF. A pilot study of volume contracted state and hospital outcome after stroke. *Neurol Clin Pract*. 2018; 8:1-6.
9. Shi, Z, Zheng, WC, Yang, H, Fu, XL, Cheng, WY, Yuan, WJ. Contribution of dehydration to END in acute ischemic stroke not mediated via coagulation activation. Brain and Behavior. 2019; 9:e01301.
10. Wu, FF, Hung, YC, Tsai, YH, Yang, JT, Lee, TH, Liow, CW, Lee, JD, Lin, CJ, Peng, TI, Lin, LC. The influence of dehydration on the prognosis of acute ischemic stroke for patients treated with tissue plasminogen activator. BMC Cardiovasc Disord. 2017;17:154
11. Li, SS, Yin, MM, Zhou, ZH, Chen, HS. Dehydration is a strong predictor of long-term prognosis of thrombolysed patients with acute ischemic stroke. Brain and Behavior. 2017; 7: e00849.
12. Jauch EC, Saver JL, Adams, Bruno, A, Connors, JJ, Demaerschalk, BM, Khatri, P, McMullan, PM, Qureshi, AI, Rosenfield, K, Scott, PA, Summers, DR, Wang, DZ, Wintermark, M, Yonas, H, on behalf of the American Heart Association Stroke Council, Council on Cardiovascular

Nursing, Council on Peripheral Vascular Disease, and Council on Clinical Cardiology. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. 2013; 44:870-947.

13. Sumer, M, Ozdemir, I, Erturk, O. Progression in acute ischemic stroke: frequency, risk factors, and prognosis. J Clin Neurosci. 2003; 10(2):177-180.
14. Sadeghi-Hokmabadi, E, Yazdchi, M, Farhoui, M, Sadeghi, H, et al. Prognostic factors in patients with acute ischemic stroke treatment with intravenous tissue plasminogen activator. Iran J Neurol. 2018; 17(1): 31-37.
15. Schrock, JW, Glasenapp, M, Drogell, K. Elevated blood urea nitrogen/creatinine ratio is associated with poor outcome in patients with ischemic stroke. Clinical Neurology and Neurosurgery. 2012; 114:881-884.
16. Bhalla, A, Sankaralingam, S, Dundas, R, Swaminathan, R, Wolfe, CD, Rudd, AG. Influence of raised plasma osmolality on clinical outcome after acute stroke. Stroke. 2000; 31:2043-2048.
17. Rodriguez, GJ, Cordina, SM, Vazquez, G, Suri, MF, Kirmani, JF, Qureshi, AI. The hydration influence on the risk of stroke (THIRST) study. Neurocritical Care. 2009; 10:187-194.
18. Bahouth, MN, Gottesman, RF, Szanton, SL. Primary 'dehydration' and acute stroke: a systematic research review. J Neurol. 2018; 265(10): 2167-2181.
19. Suwanwela, NC, Chutinet, A, Mayotarn, S, Thanapiyachaikul, R, Chaisinanunkul, N, Asawavichienjinda, T, Watcharasaksilp, K, Tiamkao, S, Vongvasinkul, P, Charnwut, S, Saver, JL. A randomized controlled study of intravenous fluid in acute ischemic stroke. Clinical Neurology and Neurosurgery. 2017; 161: 98-103.
20. Lin, CJ, Yang, JT, Huang, YC, Tsai, YH, Lee, MH, Lee, M, Shiao, CT, Hsiao, KY, Lin, LC. Favorable outcome of blood urea nitrogen/creatinine-based hydration therapy 3 months after acute ischemic stroke. American Journal of Emergency Medicine. 2016: 34: 2414-2418.
21. Elsheikh, HA, Intisar, AM, Eltayeb, IB, Abdullah, AS. Effect of dehydration on the pharmacokinetics of oxtetracycline hydrochloride administered intravenously in goats. Gen Pharmac. 1998; 31(3):455-458.
22. Mange, K, Matsuura, D, Cizman, B, Soto, H, Ziyadeh, FN, Goldfarb, S, Neilson, EG. Language guiding therapy: the case for dehydration versus volume depletion. Annals of Internal Medicine. 1997; 127(9):848-853.

23. Bhave, G and Neilson. Volume depletion versus dehydration: how understanding the difference can guide therapy. Am J Kidney Dis. 2011; 58(2):302-309.
24. Armstrong, LE, Johnson, EC, McKenzie, AAL, Munoz, CX. Interpreting common hydration biomarkers on the basis of solute and water excretion. European Journal of Clinical Nutrition. 2013; 67:249-253.
25. Armstrong, LE. Assessing hydration status: the elusive gold standard. Journal of the American College of Nutrition. 2007; 26:575S-584S.
26. Visvanathan, A, Dennis, M, Whiteley, W. Parenteral fluid regiments for improving functional outcome in people with acute stroke. Stroke. 2016; 47:e6-e7.
27. Beier, K, Eppanapally, S, Bazick, HS, Chang, D, Mahadevappa, K, Gibbons, FK, Christopher, KB. Elevation of blood urea nitrogen is predictive of long-term mortality in critically ill patients independent of 'normal' creatinine. Crit Care Med. 2011; 39:305-313.
28. Shibazaki, K, Kimura, K, Okada, Y, Iguchi, Y, Uemura, J, Terasawa, Y, Aoki, J. Plasma brain natriuretic peptide as an independent predictor of in-hospital mortality after acute ischemic stroke. Internal Medicine. 2009; 48:1601-1606.

Table 1. Demographics for TPA versus non-TPA treated patients presenting to Johns Hopkins Hospital in 4.5 hours

	Overall (N=326)	**TPA Treated (N=181)**	**No TPA (N=145)**	**p**
Age	62 (15)	60 (15)	63 (14)	0.058
Sex (women) N (%)	154 (47%)	88 (49%)	66 (46%)	0.577
Hypertension N (%)	261 (80%)	143 (79%)	118 (81%)	0.663
Atrial fibrillation N (%)	64 (20%)	33 (18%)	31 (21%)	0.492
Diabetes N (%)	94 (29%)	54 (30%)	40 (28%)	0.633
Smoker N (%)	100 (31%)	58 (32%)	42 (29%)	0.549
Initial NIHSS score	6.9 (6.3)	**7.9 (5.9)**	**5.6 (6.5)**	**0.001**
Ejection fraction <50% N (%)	61 (19%)	33 (19%)	28 (20%)	0.970
BUN/creatinine ratio	16 (6)	15 (5)	16 (8)	0.241
Initial Mean Arterial Pressure (mmHg)	112 (20)	**114 (20)**	**109 (20)**	**0.031**
Systolic blood pressure (mmHg)	160 (32)	162 (33)	157 (30)	0.164
Diastolic blood pressure (mmHg)	88 (17)	**90 (16)**	**85 (18)**	**0.012**
Heart rate (bpm)	85 (20)	**87 (23)**	**82 (17)**	**0.035**
Serum Sodium mEq/L	140 (4)	140 (3)	140 (4)	0.475
Serum glucose (mg/dL)	133 (66)	133 (69)	133 (62)	0.997
Serum Hemoglobin (mg/dL)	13 (2)	**14 (2)**	**13(2)**	**0.005**
Serum Hematocrit (%)	40 (5)	**40 (5)**	**39 (6)**	**0.012**
Serum platelets	241 (130)	245 (152)	235 (97)	0.491
Urine specific gravity	1.017 (0.011)	1.017 (0.010)	1.018 (0.011)	0.592
Length of stay (days)	5.8 (7.4)	6 (9)	5 (5)	0.127

*Mean (SD) unless otherwise specified; Chi-square for dichotomous variables N(%); t-test for continuous variables displayed as mean (SD); BUN=blood urea nitrogen (BUN/creatinine ratio is the indirect marker for volume contracted state); NIHSS = National Institutes of Health Stroke Scale; mmHg= millimeters of mercury

Table 2. Logistic regression prediction of good 3 month functional outcome defined as modified Rankin score of 0-2 (N=234)

	Adjusted Odds Ratio	**p**
BUN/creatinine ratio (continuous)	0.95 (0.91, 1.00)	0.046
Age	0.97 (0.94, 0.99)	0.003
Initial NIHSS score	0.90 (0.86, 0.95)	<0.001
Initial Mean arterial pressure (MAP)	0.99 (0.98, 1.01)	0.618
Atrial fibrillation	1.18 (0.57, 2.47)	0.654
TPA	1.25 (0.68, 2.30)	0.465

*Logistic regression with adjustment for all variables in the model listed in the above table

Table 3. Odds of hemorrhagic complication after tPA administration for ischemic stroke (N=179)

	Odds Ratio	**p**
BUN/creatinine ratio (continuous)	0.89 (0.79, 1.01)	0.061
Age	1.01 (0.97, 1.05)	0.696
Initial NIHSS	1.04 (0.96, 1.13)	0.315
Initial Mean arterial pressure	1.02 (0.99, 1.04)	0.142
Baseline Hemoglobin	1.14 (0.85, 1.54)	0.382
Atrial fibrillation	2.20 (0.64, 7.53)	0.211

*Logistic regression with adjustment for all variables in the model listed in the above table

Chapter 4: Volume contracted state and outcomes in patients with acute ischemic stroke patients undergoing mechanical thrombectomy

Abstract: Impaired hydration measured by elevated blood urea nitrogen (BUN) to creatinine ratio has been associated with worsened outcome after acute ischemic stroke. Whether hydration status is relevant for patients with acute ischemic stroke treated with mechanical thrombectomy remains unknown.

Materials and Methods: We conducted a retrospective review of consecutive acute ischemic stroke patients who underwent endovascular procedures for anterior circulation large artery occlusion at Johns Hopkins Comprehensive Stroke Centers between 2012 and 2017. A volume contracted state (VCS), was determined based on surrogate lab markers and defined as blood urea nitrogen (BUN) to creatinine ratio greater than 15. Endpoints were achievement of successful revascularization (TICI 2b or 3), early re-occlusion, and short term clinical outcomes including development of early neurological worsening and functional outcome at 3 months.

Results: Of the 158 patients who underwent an endovascular procedure, 102 patients had a final diagnosis of anterior circulation large vessel occlusion and met the inclusion criteria for analysis. Volume contracted state was present in 62/102 (61%) of patients. Successful revascularization was achieved in 75/102 (74%) of the cohort. There was no relationship between VCS and successful revascularization, but there was a 1.13 increased adjusted odds (95% CI 1.01, 1.27) of re-occlusion within 24 hours for every point higher BUN/creatinine ratio in the subset of patients who underwent radiological testing for pre-procedure planning (n=57). There was no relationship between VCS and clinical outcomes including early neurological worsening and 3 month outcome.

Conclusions: Patients with VCS and large vessel anterior circulation stroke may have a higher odds of early re-occlusion after mechanical thrombectomy than their non-VCS counterparts, but no differences in successful revascularization nor clinical outcomes were present in this cohort. These results may suggest an opportunity for the exploration of pre-procedure hydration to improve outcomes.

Background: Ischemic stroke is a common and disabling condition.[1] Patients presenting with stroke and a volume contracted state (measured through elevated blood urea nitrogen (BUN) to creatinine ratio) may have poor clinical outcomes compared to patients who are not in a volume contracted state regardless of age or relevant comorbid conditions.[2-5] No direct mechanism yet explains this relationship but may include alteration in blood viscosity and alteration of cerebral perfusion. Acute stroke guidelines recommend that intravenous fluids be administered for those in a volume contracted state, but diagnosis of a VCS is subjective and therefore implementation of these recommendations, especially during time sensitive stroke treatments is variable.[6] Very few therapies to reverse the consequences of ischemic stroke are available.

Mechanical thrombectomy is one such procedure and clinical success for this procedure is determined based on successful revascularization, avoidance of large artery re-occlusion, avoidance of early neurological deterioration, and achievement of good functional outcome often defined as modified Rankin scale score between 0-2.[7] Selection of patients who may benefit the most from this procedure is made based on characteristics including age, stroke severity, and presence of collateral circulation.[8] The aim of this paper was to evaluate the association between admission VCS status and clinical outcomes in patients with acute, large artery ischemic stroke who were eligible for mechanical thrombectomy. We hypothesized that, among individuals undergoing mechanical thrombectomy for acute ischemic stroke, hydration status at the time of stroke may relate to the success of revascularization procedure and early clinical outcomes defined as change in neurological status or development of post-procedure hemorrhage. We additionally suspected that a VCS at the time of acute stroke would associate with poor functional outcomes defined by 3 month modified Rankin scale score.

Methods: This is a retrospective observational study of patients with acute ischemic stroke who were admitted to the Johns Hopkins Comprehensive Stroke center with angiogram-confirmed large artery stroke in the anterior circulation between 2012 and 2017. Data were included if the patient was suspected to have large artery, acute ischemic stroke eligible for mechanical thrombectomy, within 6 hours from stroke onset which was customary for treatment during this time.[9] Patients were further excluded from this study if they had kidney disease reported in the medical history or if serum creatinine was > 2 on arrival, had evidence of active GI bleeding that could have elevated BUN, or if stroke was due to occlusion in the posterior circulation. Additionally, patients without BUN/creatinine measurement on presentation to the hospital were

excluded. This study was approved by the Johns Hopkins Medical Institutions IRB and this report is generated using STROBE guidelines.[10]

Definitions:

Setting and Measures: Patients are evaluated for eligibility for mechanical thrombectomy by a single stroke team at the Johns Hopkins Comprehensive Stroke center.[7] Cerebral angiograms and mechanical thrombectomy were and are performed by a single stroke team that serves two campuses separated by less than 10 miles in distance; therefore, no technical differences existed between the two groups. Medical histories included report of hypertension, heart failure, atrial fibrillation, and any cancer. Kidney disease was defined as patient reported chronic kidney disease or serum creatinine > 2. Physiological variables collected were mean arterial pressure measured upon arrival to the emergency department. Intravascular volume status was measured indirectly using the surrogate marker of elevated blood urea nitrogen to creatinine ration (BUN/creatinine ratio). Stroke severity was measured using NIH stroke scale score by the treating team at baseline and 24 hours after the procedure. Alberta Stroke Program Early CT scores (ASPECTS) were calculated using standard approaches by a stroke neurologist blinded to the hydration status of the patient.[11]

Angiographic procedure and grading of collateral circulation:

Baseline leptomeningeal collaterals were assessed on CT angiograms that were obtained during standard of care operations. Two independent, blinded experienced readers (vascular neurology; vascular neuroradiology) scored collateral patterns as favorable or unfavorable using the Metiff scoring system commonly used in stroke populations.[12,13] A third rater adjudicated discrepancies. Contrast filling greater or equal to 50% on the side of infarct was considered good collateral flow, and contrast filling less than 50% was considered as poor collateral flow. The primary collateral scale was then binarized as favorable or unfavorable collateral patterns using predefined definitions.[13] Successful revascularization was assessed using the thrombolysis in ischemic cerebral infarction (TICI) scale and measured immediately after the completion of each attempted intervention by specialists who were blinded to the hypothesis of this study.[8] Post procedure TICI scores of 2b or 3 were considered a good revascularization outcome.[8,14] Re-occlusion after 24 hours was assessed for any patient who required repeat vascular imaging (CT or MR) as a part of routine care.

Clinical outcomes: The NIHSS was measured and recorded by the primary clinical team, as per standard practice, at baseline and at 24 hours post-procedure. Early neurological worsening was defined as an increase in NIHSS > 3 points in the first 24 hours after attempted mechanical thrombectomy.[17] Functional outcomes were measured by stroke center nurses per clinical routine 3 month months after stroke using the modified Rankin score. Poor outcome was predefined as modified Rankin score >2. Symptomatic and asymptomatic intracerebral hemorrhage were analyzed as per standard acute stroke treatment definitions. All clinical scores were generated by stroke team providers who were blinded to the hypotheses of this study.

Statistical plan: The primary outcome of interest was successful revascularization. Independent variable was volume contracted state both as a continuous variable (BUN/creatinine ratio) and dichotomous value (VCS yes or no). Secondary outcomes included large vessel reocclusion after 24 hours, early neurological worsening defined as increase in NIHSS score > 3 points in the first 24 hours, and odds of poor functional outcome defined as mRS 0-2 after 3 months.[16-18]

Bivariate comparisons of relevant medical and hemodynamic factors between the groups of patients in VCS and non-VCS states were made using independent t-tests or chi-squared tests of association. In multivariable analyses, potential confounding variables were identified by physiological plausibility and included in the models.[18] Statistical analysis was completed using Stata/IC 15.0.

Power analysis: Prior data indicate that approximately 50% of the cohort would be in a volume contracted state and that 60% of the group would achieve the primary endpoint of good revascularization.[18-23] Therefore we anticipated needing 94 total cases (47 in each hydration group) to test our hypothesis with power 0.8. Statistical significance for all analyses was evaluated at $p< 0.05$.

Results: Of the 158 patients eligible for participation, 56 were excluded for the following reasons: history of renal failure (16), creatinine >2 (18), posterior circulation occlusion (14), cervical common carotid artery occlusion without intracranial lesion (8). The average age was 65 years; 32% of patients were African American, 58% white. Strokes were moderately large (with average initial NIHSS was 15 ($\pm$7)), and more than half (62/102, or 61%) were categorized in a VCS. Although by definition all patients underwent mechanical thrombectomy, in 53/102 (53%) this was preceded by intravenous thrombolysis. Of the cohort, 58% underwent pre-procedure CT

angiogram with unfavorable collateral pattern observed in 16 (27%). There was no difference in unfavorable collateral pattern for patients in a VCS and those who were not (p=0.11). Subjects in a VCS were older (p=0.001) and more often had history of hypertension (p=0.01). See **Table 1** for additional detail.

Successful revascularization: Of the 102 subjects, 75 (74%) achieved successful revascularization defined as TICI 2b/3. Current smoking was the only characteristic associated with reduced chance for successful revascularization (adjusted OR 0.30; 95% CI 0.09, 0.96). See **Table 2**. Patients in a volume contracted state had similar odds of good revascularization with mechanical thrombectomy as did those with euvolemia; unadjusted OR 1.01 (95% CI; 0.95; 1.08; p=0.78). There was no significant relationship between VCS and achievement of successful revascularization (unadjusted OR 1.01; 95% CI 0.94, 1.08; p=0.86).

Large vessel re-occlusion at 24 hours: There were 67 patients with repeat CT or MRI scan and sufficient radiographic data to evaluate the development of re-occlusion within 24 hours after mechanical thrombectomy. Of those, 14/67 (21%) demonstrated re-occlusion. There was an increased odds of re-occlusion for every point increase in BUN/creatinine ratio and this association persisted after adjusting for age, history of hypertension, current smoking, serum glucose, and administration of thrombolytic medication (OR 1.13; 95% CI 1.01, 1.27). See **Table 3.**

Clinical outcomes: In this cohort, 19/102 (19%) patients demonstrated early neurological worsening by pre-specified NIHSS score criteria. For every 1 point increase in BUN/creatinine ratio there was 1.04-times increased odds of early neurological worsening (95% CI 1.00, 1.15; p=0.05) but this relationship did not persist in multivariable regression analysis (p=0.22). There was no relationship between VCS and 3 month modified Rankin score (p=0.98). Age and unfavorable collateral circulations were strong predictors of early neurological worsening in the subset of 57 patients with baseline vessel imaging prior to mechanical thrombectomy. See **Table 5**. There was no relationship between VCS and hemorrhagic transformation in the 16 patients with intracerebral hemorrhage.

Discussions:

This retrospective observational study assessed the association between VCS, as measured by an indirect blood marker, and relevant procedural and clinical outcomes of attempted mechanical thrombectomy. In this cohort, there is no relationship between VCS and procedural or clinical outcomes in a group of patients with acute ischemic stroke who were eligible for mechanical thrombectomy. We found that smoking was strongly associated with reduced likelihood of successful revascularization. This differs from studies of the effect of thrombolysis in patients who smoke where the "smokers paradox" of good outcome after thrombolysis after MI and stroke has been reported.[24] It additionally differs from the observational cohort reported where report of smoking was reported to be associated with higher rates of arterial recanalization in smokers versus nonsmokers (86% versus 79%; p= 0.048). There may be pathophysiological rationale for this association in that smoking may lead to greater thrombus burden and/or accelerated atherosclerosis raising the complexity of the access to the thrombus via angiographic techniques.[24-26]

We also observed an association between VCS and vessel re-occlusion within 24 hours of thrombectomy even after adjustment for clinically relevant factors. Increased odds of vessel re-occlusion within 24 hours after thrombectomy in patients with VCS is a significant and clinically meaningful association that deserves further exploration.[27] This finding follows the physiological hypotheses driving this study. In a volume contracted state, patients are suspected to be in a relatively hyperviscous/pro-thrombotic state which may accelerate re-occlusion in endothelium that was recently disrupted by catheter angiography and device deployment for clot extraction. We report this relationship with caution as this may represent bias; this subgroup had a clinical change warranting this repeated radiographic assessment via CT or MR in order to demonstrate re-occlusion. This relationship will need replication using a single radiographic technique in future prospective studies. These results suggest that VCS could be a modifiable factor in the durable success of mechanical thrombectomy.

Overall, our rates of VCS remain consistent with prior reports.[5, 28-29] Differing from the literature, we did not observe a difference in collateral circulation based on hydration status as previously reported by Chang and colleagues.[30] In their series, elevated BUN/Creatinine ratio was related to poor collateral circulation based on magnetic resonance imaging in 87 subjects (p=0.001). The differences between our results and those reported by Chang et al could be explained in several ways including the differences in the subjects included (tPA patients were excluded in the Chang study) and timing delays between arrival and acquisition of MRI in that cohort.[30] Future

assessment of the relationship between hydration status and collateral circulation in larger cohorts would be valuable.

Aside from age, collateral circulation was the only variable strongly associated with clinical outcomes in our cohort. Regardless of hydration status, collateral status is again demonstrated to be an important determinant of final infarct size. Collateral circulation in the brain generally refers to subsidiary vascular networks that provide redundant blood supply to cells and help stabilize cerebral blood flow whenever primary channels are impaired. In the event of ischemic stroke, collaterals serve to provide a temporary blood supply to hypoperfused tissue at risk of infarction. As such, good collateral circulation has been identified as an independent determinant of favorable stroke outcome, regardless of treatment. It also has been associated with slower infarct growth, lower volume of hypoperfusion, lessened stroke severity, greater penumbra/core mismatch (greater penumbra, smaller core), and faster, more effective revascularization results after mechanical thrombectomy. Furthermore, one study has found that patients with good to intermediate collaterals benefitted the most from mechanical thrombectomy even after the typical 6-hour therapeutic window, while patients with poor collaterals tended not to benefit at all from mechanical thrombectomy more than 5 hours after onset.[31] Another study suggested that collateral status may be dynamic on a very short time scale, and may change quickly enough in response to hemodynamic fluctuations during stroke to not be categorized based on one testing.[32] Contrary to the original assumption that the severity of the baseline perfusion lesion linearly predicts infarct growth, rapid changes in collateral circulation may vary considerably and, in fact, potentially cause a worsening of infarct growth.[33-35] Therefore we considered that it would be biologically plausible that VCS would be relevant to the collateral blood supply in patients with stroke. Future studies exploring the relationship between hydration status and outcomes after mechanical thrombectomy in an extended time window are needed.

Multiple other limitations common to retrospective design and small sample size are notable. Though we only included those who presented to the angiogram suite within 6 hours from stroke onset, time of vessel revascularization was not typically recorded at our stroke center during this study period and therefore this data is unavailable for analysis. We were not able to include the total amount of fluid (intravenous and oral) administration after the procedure in our analysis due to inconsistent documentation of these volumes. Post procedure fluid intake may be an important modifier of outcomes, particularly for individuals in a VCS. Finally, several clinical variables of interest such as history of atrial fibrillation and heart failure could not be considered for inclusion

in the regression analysis since inclusion of additional variables would have led to overfitting of the logistical regression models given the small sample size, or were not available.

It is important to note that this series of mechanical thrombectomy patients was collected prior to the release of practice guidelines that standardized stroke center approaches to this therapeutic intervention.[7] Therefore, the criteria used to select patients based on more favorable imaging profiles and standardized selection of clot retrieval devices differed from current practices, and might underestimate the good outcomes of the group overall. That said, several important observations are notable. First, the average age for those in a VCS is significantly higher than among individuals undergoing thrombectomy but not in a VCS, supporting prior reports that dehydration is more common in older subjects who may lose their thirst drive or who have impaired mobility. In this group, subjects with a history of hypertension were more likely to be in a VCS than their counterparts without. This might be related to differences in medications, specifically use of diuretics for blood pressure control, though data about baseline medications were not available for comparison.

Conclusions: In this cohort, there was no relationship between technically successful revascularization and baseline hydration status nor statistically meaningful differences in collateral circulation patterns by hydration status. The significant association between volume contracted state and higher odds of re-occlusion, amongst patients presenting to the hospital in a volume contracted state warrants additional study in a larger cohort. Should this relationship persist, early rehydration may be a low cost and broadly available treatment to consider.

References: Chapter 4

1. Mozaffarian, D, Benjamin, EJ, Go, AS, Amett, DK, Blaha, MJ, Cushman, M, de Ferranti, S, Després, J, Fullerton, HJ, Howard, VJ, Huffman, MD, Judd, SE, Kissela, BM, Lackland, DT, Lichtman, JH, Lisabeth, LD, Liu, S, Mackey, RH, Matchar, DB, McGuire, DK, Mohler, ER, Moy, CS, Muntner, P, Mussolino, ME, Nasir, K, Neumar, RW, Nichol, G, Palaniappan, L, Pandey, DK, Reeves, MJ, Rodriguez, CJ, Sorlie, PD, Stein, J, Towfighi, A, Turan, TN, Virani, SS, Willey, JZ, Woo, D, Yeh, RW, Turner, MB; on behalf of the American Heart Association Statistics Committee. Heart Disease and Stroke Statistics – 2016 Update. A Report from the American Heart Association. Circulation. 2015; 132:e1-324.
2. Schrock, JW, Glasenapp, M, Drogell, K. Elevated blood urea nitrogen/creatinine ratio is associated with poor outcome in patients with ischemic stroke. Clinical Neurology and Neurosurgery. 2012; 114:881-884.
3. Bhalla, A, Sankaralingam, S, Dundas, R, Swaminathan, R, Wolfe, CD, Rudd, AG. Influence of raised plasma osmolality on clinical outcome after acute stroke. Stroke. 2000; 31:2043-2048.
4. Rowat, A, Graham, C, Dennis, M. Dehydration in hospital admitted stroke patients: detection, frequency and association. Stroke. 2012; 43:857-859.
5. Bahouth, MN, Gottesman, RF, Szanton, SL. Primary ‘dehydration’ and acute stroke: a systematic research review. J Neurol. 2018; 265(10): 2167-2181.
6. Jauch EC, Saver JL, Adams, Bruno, A, Connors, JJ, Demaerschalk, BM, Khatri, P, McMullan, PM, Qureshi, AI, Rosenfield, K, Scott, PA, Summers, DR, Wang, DZ, Wintermark, M, Yonas, H, on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Peripheral Vascular Disease, and Council on Clinical Cardiology. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. 2013; 44:870-947.
7. Powers, WJ, Derdeyn, CP, Biller, J, Coffey, CS, Hoh, BL, Jauch, EC, Johnston, JC, Johnston, SC, Khalessi, AA, Kidwell, CS, Meschia, JF, Ovbiagele, B, Yavagal, DR. 2015 AHA/ASA Association focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment. Stroke. 2015; 46: 3024-3039.
8. Higashida, RT, Furlan, AJ, Roberts, H, et al. Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke. Stroke. 2003; 34e:109-137 [TICI]

9. Adams, HP, del Zoppo, G, Alberts, MJ, Bhatt, DL, Brass, L, Furlan, A, Grubb, RL, Higashida, RT, Jauch, EC, Kidwell, C, Lyden, PD, Morganstern, LB, Qureshi, AI, Rosenwasser, RH, Scott, PA, Wijdicks, EF. Guideliens for the early management of acults with ischemic stroke. Stroke. 2007; 38: 1655-1711.
10. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, et al. (2007) The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting Observational Studies. PLoS Med 4(10): e296
11. Barber, PA, Demchuk, AM, Zhang, J, et al. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy: ASPECTS Study group. Lancet. 2000; 355:1670-1674.
12. Liebeskind DS. Collateral Circulation. *Stroke*. 2003; 34:2279-2284.
13. McVerry, F, Liebeskind, DS, Muir, KW. Systematic review of methods for assessing leptomeningeal collateral flow. American Journal Neuroradiology. 2012; 33: 576-582.
14. Fugate, JE, Klunder, AM, Kallmes, DF. What is meant by TICI? American Journal Neuroradiol. 2013; 34: 1792-1797.
15. National Institute of Neurological Disorders (**NINDS**) and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *NEJM.* 1995;333(24): 1581-1587.
16. Sumer, M, Ozdemir, I, Erturk, O. Progression in acute ischemic stroke: frequency, risk factors, and prognosis. J Clin Neurosci. 2003; 10(2):177-180.
17. Seners P, Turc G, Maïer B, Mas JL, Oppenheim C, Baron JC. Incidence and predictors of early recanalization after intravenous thrombolysis: a systematic review and meta-analysis. *Stroke*. 2016;47:2409–2412
18. Berkhemer, OA, Fransen, PS, Beumer, D, vanDen, LA, Lingsma, HF, Yoo, AJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. NEJM. 2015; 372: 11-20.
19. Schrock, JW, Glasenapp, M, Drogell, K. Elevated blood urea nitrogen/creatinine ratio is associated with poor outcome in patients with ischemic stroke. Clinical Neurology and Neurosurgery. 2012; 114:881-884.
20. Bhalla, A, Sankaralingam, S, Dundas, R, Swaminathan, R, Wolfe, CD, Rudd, AG. Influence of raised plasma osmolality on clinical outcome after acute stroke. Stroke. 2000; 31:2043-2048.
21. Rowat, A, Graham, C, Dennis, M. Dehydration in hospital admitted stroke patients: detection, frequency and association. Stroke. 2012; 43:857-859.

22. Lin, LC, Lee, JD, Hung, YC, Chang, CH, Yang, JT. BUN/creatinine ratio-based hydration for preventing stroke-in-evolution after acute ischemic stroke. American Journal of Emergency Medicine. 2014; 32:709-712.
23. Bahouth, MN, Gaddis A, Hillis AE, Gottesman, RF. A pilot study of volume contracted state and hospital outcome after stroke. *Neurol Clin Pract*. 2018; 8:1-6.
24. Kurmann, R; Engelter, ST; Michel, P, et al. Impact of smoking on clinical outcome and recanalization after intravenous thrombolysis for storke: multicenter cohort study. Stroke. 2018; 49: 1170-1175.
25. Zahger D, Cercek B, Cannon CP, Jordan M, Davis V, Braunwald E, Shah PK. How do smokers differ from nonsmokers in their response to thrombolysis? (the TIMI-4 trial). **Am J Cardiol**. 1995; 75:232
26. de Chillou C, Riff P, Sadoul N, Ethevenot G, Feldmann L, Isaaz K, Simon JP, Boursier M, Khalife K, Thisse JY, Aliot E. Influence of cigarette smoking on rate of reopening of the infarct-related coronary artery after myocardial infarction: a multivariate analysis. **J Am Coll Cardiol**. 1996; 27:1662
27. Campbell BC, Christensen S, Tress BM, Churilov L, Desmond PM, Parsons MW, et al. Failure of collateral blood flow is associated with infarct growth in ischemic stroke. *J Cereb Blood Flow Metab*. 2013;33:1168-1172.
28. Lin, LC, Yang, JT, Weng, HH, Hsiao, CT, Lai, SL, Fann, WC. Predictors of early clinical deterioration after acute ischemic stroke. American J Emerg Med. 2011; 29(6):577-581.
29. Lin, LC, Lee, JD, Hung, YC, Chang, CH, Yang, JT. BUN/creatinine ratio-based hydration for preventing stroke-in-evolution after acute ischemic stroke. American Journal of Emergency Medicine. 2014; 32:709-712.
30. Chang, SW, Huang, YC, Lin, LC, Weng, HH, Tsai, YH, Lee, TH. Effect of dehydration on the development of collaterals in acute middle cerebral artery occlusion. European Journal of Neurology. 2016; 23: 494-500.
31. Rha, JH, Saver, JL. The impact of recanalization on ischemic stroke outcome: a meta-analysis. Stroke. 2007; 38:967-973.
32. Seners, P, Roca, P, Legrand, L, Turc, G, Cottier, JP, Cho, TH, Arquizan, C, Bracard, S, Ozsancak, C, Hassen, WB, Naggara, O, Lion, S, Debiais, S, Berthezene, Y, Costalat, V, Richard, S, Magni, C, Mas, JL, Baron, JC, Oppenheim, C. Better collaterals are independently associated with post-thrombolysis recanalization before thrombectomy. Stroke; 2019; 50:867-872

33. Marks MP, Lansberg MG, Mlynash M, et al. Effect of collateral blood flow on patients undergoing endovascular therapy for acute ischemic stroke. *Stroke*. 2014;45:1035-1039.
34. Raymond SB and Schaefer PW. Imaging Brain Collaterals: Quantification, Scoring, and Potential Significance. *Topics in Magnetic Resonance Imaging*. 2017;26:67-75.
35. Zaidat OO, Yoo AJ, Khatri P, Tomsick TA, von Kummer R, Saver JL, et al; Cerebral Angiographic Revascularization Grading (CARG) Collaborators; STIR Revascularization Working Group; STIR Thrombolysis in Cerebral Infarction (TICI) Task Force. Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. *Stroke*. 2013; 44:2650–2663.

Table 1. Patient characteristics by hydration status at admission (BUN/creatinine ratio)*

		Total sample stratified by hydration status (N=102)		
	All (N=102)	**Normal BUN/creatinine (N=40)**	**Elevated BUN/Creatinine Ratio (VCS) (N=62)**	**P value**
Age (years) (Mean (SD))	65 (17)	**60 (17)**	**68 (16)**	**0.01**
Sex (Female)	54 (53)	18 (45%)	36 (58%)	0.20
Race (Black)	33 (32)	15 (38%)	18 (29%)	0.37
Smoker -Current -Past	 12 (16) 26(34)	 6 (19%) 10 (31%)	 6 (13%) 16 (36%)	0.80
Atrial fibrillation	36 (35)	14 (35%)	22 (36%)	0.96
Hypertension	74 (73)	**23 (58%)**	**51 (82%)**	**0.01**
Diabetes	23 (23)	6 (15%)	17 (27%)	0.14
Ejection Fraction below 50%^	23 (24)	12 (32%)	11 (19%)	0.16
Tissue plasminogen activator (tPA)	53 (52)	20 (50%)	33 (53%)	0.75
Baseline MAP (mmHg) (mean (SD))	106 (19)	111 (19)	103 (18)	0.05
Serum Sodium (mean (SD))	140 (4)	141 (4)	140 (5)	0.24
Serum Glucose (mean (SD))	146 (58)	136 (51)	152 (62)	0.18
Baseline Hemoglobin (man (SD))	12 (2)	12 (3)	12 (2)	0.82
Baseline Hematocrit (mean (SD))	38 (6)	38 (6)	37 (6)	0.60
Initial NIHSS (mean (SD))	15 (7)	16 (7)	15 (6)	0.39
Initial ASPECTS score (CT)	9 (2)	8.8 (1.3)	8.6 (1.9)	0.51
Unfavorable collateral pattern+	16 (27)	3 (14%)	13 (33%)	0.11

*Results reported as N(%) unless otherwise specified; Chi-square for dichotomous variables N(%); t-test for continuous variables displayed as mean (SD); ^Sample size for patients with available data about ejection fraction is N=96; +Unfavorable collateral circulation defined as Miteff score 0-1; Sample size for collateral grading with 60 available CTAs prior to the procedure;

Table 2: Association of VCS and other clinical variables with achievement of TICI 2b/3 revascularization (n= 102)

Predictor	Achievement of TICI2b/3			
	Bivariate		Multivariable*	
	Odds Ratio (CI, 95%)	**P**	**Odds Ratio (CI, 95%)**	**P**
BUN/Creatinine Ratio	1.01 (0.94, 1.08)	0.86	1.02 (0.94, 1.09)	0.68
Age	1.00 (0.97, 1.03)	0.95	1.01 (0.98, 1.04)	0.66
Hypertension	0.51 (0.17, 1.53)	0.23	0.45 (0.10, 2.01)	0.30
Current Smoking	**0.30 (0.10, 0.90)**	**0.03**	**0.30 (0.09, 0.96)**	**0.04**
Serum glucose	1.00 (0.99, 1.01)	0.99	1.00 (0.99, 1.01)	0.93
Thrombolysis	1.23 (0.51, 2.97)	0.64	1.22 (0.24, 21.3)	0.47

*Multivariable regression analysis with adjustment for all variables listed in this table

Table 3: Bi- and multivariable logistic regression demonstrating odds of vessel re-occlusion 24 hours after procedure in subgroup with repeat imaging (CT or MR) sufficient to score patency (N=67)

Predictor	24 hour re-occlusion			
	Bivariate		Multivariable*	
	Odds Ratio (CI, 95%)	**P**	**Odds Ratio (CI, 95%)**	**P**
BUN/Creatinine Ratio	**1.12 (1.02, 1.23)**	**0.02**	**1.13 (1.01, 1.27)**	**0.04**
Age	1.01 (0.97, 1.04)	0.62	0.97 (0.91, 1.04)	0.33
Hypertension	2.05 (0.51, 8.26)	0.31	2.21 (0.29, 17.1)	0.45
Current Smoking	2.27 (0.50, 10.3)	0.29	2.27 (0.36, 14.3)	0.38
Serum glucose	1.00 (0.99, 1.01)	0.99	1.00 (0.99, 1.02)	0.85
Thrombolysis	1.28 (0.39, 4.21)	0.68	2.00 (0.41, 9.83)	0.39

Table 4: Bivariable and multivariable logistical regression to describe: 1) odds of early neurological worsening and 2) odds of poor three month functional outcome (N=57)

Predictor	Early Neurological worsening (NIHSS)				Poor 3 month outcome (mRS)			
	Univariable		Multivariable*		Univariable		Multivariable*	
	Odds Ratio (CI, 95%)	**P**	**Odds Ratio (CI, 95%)**	**P**	**Odds Ratio (CI, 95%)**	**P**	**Odds Ratio (CI, 95%)**	**P**
BUN/Creatinine Ratio	1.08 (1.00, 1.15)	0.05	0.22 (0.96, 1.19)	0.22	1.05 (0.98, 1.11)	0.16	0.99 (0.89, 1.11)	0.98
Age	**1.04 (1.00, 1.07)**	**0.04**	**1.06 (0.99, 1.12)**	**0.08**	**1.05 (0.01, 0.37)**	**0.001**	**1.08 (1.01, 1.13)**	**0.01**
Initial NIHSS	1.02 (0.95, 1.10)	0.61	0.94 (0.81, 1.09)	0.38	**1.08 (1.01, 1.15)**	**0.02**	1.01 (0.90, 1.14)	0.86
Unfavorable collateral pattern	**5.6 (1.44, 21.8)**	**0.01**	**5.6 (1.09, 28.9)**	**0.04**	**6.2 (1.25, 30.9)**	**0.03**	**6.60 (1.04, 41.8)**	**0.04**
Thrombolysis	0.79 (0.29, 2.16)	0.65	1.01 (0.19, 5.36)	0.99	0.87 (0.40, 1.93)	0.74	0.71 (0.19, 2.78)	0.62
TICI 2b/3	0.85 (0.27, 2.69)	0.79	1.66 (0.15, 17.7)	0.68	0.52 (0.20, 1.30)	0.16	0.20 (0.03, 1.40)	0.11

Chapter 5: Noninvasive monitor to quantify hydration status in ischemic stroke patients: a feasibility study

Abstract: Individuals suffering an acute ischemic stroke are dehydrated, volume contracted or both at the time of hospitalization and have worse clinical outcomes. Currently, there is no gold standard method for measuring hydration status, except indirect markers of a **volume contracted state (VCS)** including elevated BUN/creatinine ratio, which may supplement a clinical diagnosis. Thus a noninvasive and real-time measure of hydration status may have benefit in the early phase of acute stroke care. This feasibility study was designed to assess the role of an innovative medical technology to measure volume status using non-invasive cardiac output monitoring before starting a larger clinical trial. We sought to 1) test the feasibility and acceptability of a non-invasive cardiac output monitor (NICOM) for the measurement of hydration status in a group of hospitalized ischemic stroke patients; 2) compare agreement between commonly used indirect lab indicators of VCS (BUN/creatinine ratio) and device-measured VCS (NICOM); and 3) explore level of agreement between laboratory and device measures of VCS in common co-morbid conditions such as diabetes and heart failure.

Methods: Thirty patients hospitalized with acute ischemic stroke were enrolled into this prospective observational feasibility study. Hemodynamic parameters were assessed via NICOM. Successful acquisition of relevant hemodynamic data was the primary objective of this study. Patients with increase in stroke volume index (SVI) of >10% after delivery of “autobolus” (defined by passive leg raise) were considered potentially fluid responsive and thus categorized in a VCS. Results of blood urea nitrogen (BUN) and creatinine within 8 hours from NICOM measurement were collected from the patient’s medical record and categorized as a VCS if BUN/creatinine ratio > 15. Cohen’s kappa statistic was used to evaluate level of agreement between these two potential markers of hydration status.

Results: In this group of hospitalized stroke patients, 29 out of 30 tolerated use of the NICOM well and hemodynamic data was collected in all 30 patients. Data capture took an average of 10 min and 15 seconds. Agreement between NICOM and BUN/creatinine ratio was 70%; (expected agreement 51%; kappa 0.38). Agreement was better in the cohort without history of diabetes (81% agreement; kappa 0.61)

Conclusions: NICOM is feasible in hospitalized stroke patients and well-tolerated by this group of patients with multiple hemodynamic and comorbid conditions. Agreement with commonly used lab markers was moderate, with particularly high agreement in non-diabetic patients. Future studies will evaluate device reliability based on the relationship with individual characteristics and clinical outcomes. The identification of an objective, real-time measure of hydration status would be clinically useful, and could allow delivery of more individualized and goal-directed care.

Background: Stroke is a common cause of death and disability and successful treatments such as thrombolysis and mechanical thrombectomy underscore the importance of early intervention to decrease the burden of disease.[1,2] Post-stroke treatment requires diligent clinical management to optimize homeostasis and decrease the risk of complications.[2] Stroke disrupts cerebral autoregulation leaving the brain reliant on blood pressure and intravascular volume to maintain adequate cerebral perfusion.[3] Because hydration supports intravascular volume, hydration status is a key physiological parameter in post-stroke treatment. Without a gold standard to objectively assess hydration status, diagnosis is often subjective and targeted rehydration treatment is challenging particularly in the context of concern of airway viability and also fluid overload in patients with co-existing cardia disease.[4-7] One parameter often incorporated into clinician assessment of volume status is elevated blood urea nitrogen (BUN) to creatinine ratio. There is accumulating evidence that increased BUN/creatinine ratio, for instance at a level >15 is associated with worse outcome after acute ischemic stroke.[8-10] This laboratory measurement, however, is somewhat invasive, requires blood draw, and has a long lag time for results in many hospitals, which can be a disincentive to repeat measurements. Therefore, there is a need in the early phase of stroke care for a noninvasive and real time monitor of hydration status.

The role of non-invasive cardiac output monitoring

In many areas of clinical care reliable and valid measures of assessment are sought after, particularly those that are non- invasive and minimize risks to the patient. Bioimpedance and bioreactance analysis systems have been widely investigated due to the non-invasive nature of the procedure, the low cost and the portability the devices that estimate body composition in a variety of clinical conditions such as chronic heart failure.[11-13] The non-invasive cardiac output monitor (NICOM) (Cheetah Medical Technology) is a hemodynamic monitor that uses bioreactance to measure biventricular volume reserve indicating intravascular volume status. This device has been tested against invasive hemodynamic measurement devices including pulmonary artery catheter and pulse contour cardiac output (PiCCO) catheters in a variety of patient populations with varying results.[11,14-16] Passive leg raise technique allows for objective determination of fluid responsiveness and therefore can be used to guide rehydration therapy in real time.

To date, a noninvasive device such as NICOM has not been tested in patients with stroke or other neurological injury, but this population represents a vulnerable group in whom validation may be particularly important in directing clinical management. Stroke patients have a combination of

comorbid conditions that make lying flat challenging including aspiration risks, increased chance of elevated intracranial pressure, and higher frequency of heart failure. Additionally, these patients commonly display hemodynamic instability due to dysautonomia from common conditions like diabetic autonomic neuropathy. Prior reports have demonstrated variability in other populations with dysautonomia. Thus, in this study we undertook a prospective assessment to determine: (1) if the application of device was technically feasible; (2) if the passive leg raise maneuver was tolerated by patients; (3) if use of the device was minimally burdensome in the context of clinical care; and (4) the level of agreement between diagnosis of VCS using NICOM (device) as compared with BUN/creatinine ratio (labs) to evaluate the potential future utility of the NICOM device in monitoring hydration status in studies of stroke- related outcome

Materials and Methods:

Subjects: Patients were eligible for this prospective, observational study if admitted to the Johns Hopkins Stroke Center with the diagnosis of ischemic stroke between 2017 and 2019, and if they had BUN/creatinine ratio measured (as is routine) during hospital stroke evaluation. Patients were not enrolled if baseline creatinine was > 2, if they had documented kidney disease history, or if there was concurrent gastrointestinal bleeding or infection noted by the clinical team at the time of enrollment. Relevant patient characteristics about comorbid conditions and stroke severity, as well as these exclusion criteria, were abstracted from the electronic medical record. We were specifically interested in conditions that could affect heart rate variability and autonomic function including medications, heart failure and diabetes. The study was approved by the Johns Hopkins Institutional Review Board.

Noninvasive cardiac output monitor: The noninvasive cardiac output monitor was used by study team members who completed standard device training. Technical details of the NICOM have been described previously.[17] After the consent process and written consent was signed by the patient or legal representative, patients were assisted into a semi-recumbent position and four dual NICOM sensors were placed on the chest wall then connected to the portable NICOM controller. After baseline readings were obtained, patients were transitioned to a flat position with legs elevated in order to deliver the estimated 300cc autobolus to the intravascular system through passive leg raise. Relevant hemodynamic parameters, including calculated repeat SVI and a patient's position on the Starling curve are displayed on the monitor **(See Figure 1)**. If

change in SVI was >10% then the patient was considered to be potentially volume responsive and labeled as being in a volume contracted state.

Lab defined volume contracted state: The electronic medical record was then abstracted for relevant data including lab results collected nearest to the time of the NICOM measurement and within 12 hours from the time of NICOM procedure. BUN/creatinine ratio > 15 was considered a volume contracted state as used in prior acute stroke studies.[18-21]

Statistical plan: The primary outcome was feasibility of successful NICOM hydration measurement defined as acquisition of sufficient hemodynamic data to measure change in stroke volume index. Bivariate comparisons of study variables including relevant medical history and characteristics of stroke severity between groups of patients in VCS and euvolemic states were made using independent t-tests and chi-squared tests of association.[22] Due to the anticipated small sample size in this feasibility study, no multivariable analysis was planned due to risks of overfitting models. Bivariate odds ratios and 95% confidence intervals were calculated using logistic regression to understand the characteristics of the subgroup in whom labs and device did not agree. Statistical significance for all analyses was pre-set at $p<0.05$. Tests of association between lab and device measured VCS was conducted using Cohen's kappa coefficient. Definitive criteria for the interpretation of kappa coefficients have been previously proposed.[23] Values between 0.4 and 0.75 represent moderate to good agreement, and values > 0.75 suggest excellent agreement. Statistical analysis was completed using Stata/IC 15.0.

Results:

This cohort was comprised of 30 patients who were an average of 62 (range 30-84) years of age, 13/30 (43%) of whom were female, and 5/30 (17%) who reported heart failure in their medical history. Average initial NIH Stroke scale score was 10 (range 0-28), reflective of moderate size strokes in this group. The average BUN/creatinine ratio was 17 ($\pm$ 7), and 63% of this group reported daily beta blocker use, with approximately 30% taking a diuretic as a standing medication at the time of admission. Though not meeting statistical significance, women appeared to be in a VCS more often than men according to the NICOM (59% versus 41%, respectively) but not by BUN/creatinine ratio (44% versus 56%, respectively). **See Table 1** for individual characteristics. The average time to complete hemodynamic assessment with passive leg raise was 10 minutes and 15 seconds from the time that the patient was connected to the monitor. Hemodynamic data

was collected in 30/30 patients and 29/30 tolerated without complaints. One patient who arrived to the hospital with atrial fibrillation and rapid ventricular rate reported shortness of breath while lying flat near the end of the passive leg raise maneuver for autobolus delivery. This resolved with return to a semi-recumbent position. The average time between lab collection and NICOM was 4 hours and 42 minutes.

A volume contracted state was detected by BUN/creatinine ratio (labs) in 17/30 (57%; mean BUN/creatinine ratio =21) compared with 18/30 (60%; mean BUN/creatinine ratio= 19) by NICOM (device). Overall, we found agreement between labs and NICOM in 21/30 (70%; k=0.38) measurements. See **Table 2**. Patients with history of diabetes had higher odds of disagreement between the device and lab tests (OR 5.31; 95% CI 0.96, 29.29; p=0.06) than patients without history of diabetes. In a group of patients who were not diabetic, agreement was 81% (k= 0.61)**.** In a subgroup of 5/30 patients, we observed an unexpected phenomenon of SVI *decrease* upon delivery of the autobolus with passive leg raise. There was no association of a SVI decrease with age or sex. However, there was increased odds of a *decrease* in SVI with passive leg raise for every 10 mg/dL increase in serum glucose (adjusted OR 1.37; 95%CI 0.99, 1.89; p=0.06).

Discussion:

In this study we found use of NICOM to categorize volume status is feasible and was acceptable to patients. We found that hospitalized ischemic stroke patients tolerated the positioning required for NICOM measurement of VCS with the exception of 1 patient who experienced transient shortness of breath during the passive leg raise maneuver. The device was otherwise easy to use and data was analyzable in all cases. The NICOM (device) demonstrated fair agreement with BUN/creatinine ratio (by labs), although interestingly, that agreement improved for the subset of patients without history of diabetes.

Multiple potential physiological rationale could be considered for this relationship and the stronger association between labs and NICOM in non-diabetic patients. First, diabetic patients commonly demonstrate cardiovascular autonomic neuropathies.[24] These types of dysautonomias can impact heart rate variability and could impact stroke volume index since heart rate contributes to the measurement of stroke volume index. Additionally, other medications commonly used to manage secondary complications of diabetes have heart rate effect and therefore may also interfere with heart rate response during the fluid challenge portion of NICOM testing. Finally,

many medications prescribed to manage comorbid conditions in diabetics are potentially dehydrating, or could directly alter the BUN/creatinine ratio, and thus the correlation with NICOM. The patients with disagreement between lab and NICOM, measured VCS were notably different when considering history of diabetes.

We explored characteristics of the nine subjects where labs and NICOM device disagreed. While this group was small, we found a trend toward sex-specific differences in those diagnosed with VCS using the NICOM device that were not present by lab definition; women were more often in a VCS according to the NICOM device only. See **Figure 3**. This has not been previously reported in prior studies of monitors using bioreactance and raises the possibility either of the need for sex-specific parameters in the NICOM algorithm, or in sex-specific parameters in lab-based definition of VCS.[25,26] This would require additional testing in a larger population, but would be important to consider before applying the NICOM device to a larger sample, as its utility might differ in distinct clinical populations.

Rates of VCS using either the lab or NICOM device definitions are consistent with the previously reported literature.[10] Early studies of the NICOM demonstrated high sensitivity and specificity against a 'gold standard' defined as pulmonary artery catheter.[27,28] The passive leg raise is a procedure to test fluid responsiveness with relatively high sensitivity and specificity, 86 and 79% respectively, when tested against central venous pressure in a population of patients with septic shock. Meta-analysis of the passive leg raise technique demonstrated sensitivity and specificity were previously reported as 89% and 91% respectively.[29] Bioreactance measurement of hydration status offers another potential method by which fluid responsiveness might be measured, but data have been mixed: while our level of agreement is lower than that reported by Jones and colleagues who used bioreactance methods to study hemodynamic changes in healthy subjects during exercise,[16] recent study of 19 subjects found that bioreactance *did not* agree with thermodilution (concordance 54.8%) suggesting that interpopulation characteristics may influence accuracy of hemodynamic measures using bioreactance methods.[14] Stroke patients have a different panel of highly comorbid conditions. Our study further differs from these described studies as elevated BUN/creatinine ratio is an indirect measure of potential volume contracted state; we thus chose not to consider the laboratory measures as a "gold standard", at least by classical definitions, and instead present percent agreement rather than sensitivity and specificity.[30,31]

This lack of a gold standard hydration measure for comparison in addition to small sample size are the major limitations of this study. The comparison between surrogate, indirect markers such as BUN/creatinine is an important limitation. For acute stroke patients, it is not feasible to use invasive monitors such as pulmonary artery catheters of PiCCO devices in order to measure stroke volume. Furthermore, our study was not sufficiently powered to investigate clinical outcomes based on NICOM-measured VCS, but there is compelling evidence emphasizing the importance of studying volume contraction status in understanding factors associated with stroke outcome. Future studies will need to be designed to include the common comorbid conditions in regression models investigating clinical outcomes by NICOM-measured hydration status.

Stroke patients with a suspected volume contracted state, measured with elevated BUN/creatinine at the time of hospital arrival have worse clinical outcomes including increased odds of early neurological worsening, the presence of more severe hemispatial neglect, and the potential for worsened functional status at 3 months, and future studies will need to consider if NICOM-measured volume status similarly related to meaningful outcome measures.[8, 32] Correction of the VCS may be a low cost solution and an objective, real-time monitor that could allow for more precise rehydration with isotonic fluid could yield a similar benefits to those reported for patients with sepsis.[26]

Measurement of intravascular volume in a critically ill population remains one of the more challenging clinical tasks and work in this area remains underpinned by limited or conflicting data and lack of a clinically feasible gold standard.[31] In order to deliver goal directed therapies to correct VCS and augment cerebral perfusion in a group of stroke patients, one must identify an objective marker on which to base the treatment algorithm.[33] Until recently this required the insertion of devices to measure cardiac output, central venous pressures and stroke volumes which is not warranted in stroke patients with mild-moderate level dehydration in most cases. The potential for a low cost, goal directed therapy to improve outcomes for stroke patients who are dehydrated necessitates the continued pursuit of identifying an objective, non-invasive measurement approach such as NICOM.

Conclusions: Hospitalized ischemic stroke patients tolerated the positional changes required to measure volume contracted state using the noninvasive cardiac output monitor. Agreement with a currently used lab parameter yielded fair agreement, with especially high agreement in non-diabetic patients. Further investigation of noninvasive monitoring is necessary before widespread recommendation and adoption.

References: Chapter 5

1. Mozaffarian, D, Benjamin, EJ, Go, AS, Amett, DK, Blaha, MJ, Cushman, M, de Ferranti, S, Després, J, Fullerton, HJ, Howard, VJ, Huffman, MD, Judd, SE, Kissela, BM, Lackland, DT, Lichtman, JH, Lisabeth, LD, Liu, S, Mackey, RH, Matchar, DB, McGuire, DK, Mohler, ER, Moy, CS, Muntner, P, Mussolino, ME, Nasir, K, Neumar, RW, Nichol, G, Palaniappan, L, Pandey, DK, Reeves, MJ, Rodriguez, CJ, Sorlie, PD, Stein, J, Towfighi, A, Turan, TN, Virani, SS, Willey, JZ, Woo, D, Yeh, RW, Turner, MB; on behalf of the American Heart Association Statistics Committee. Heart Disease and Stroke Statistics – 2016 Update. A Report from the American Heart Association. Circulation. 2015; 132:e1-324.
2. Jauch EC, Saver JL, Adams, Bruno, A, Connors, JJ, Demaerschalk, BM, Khatri, P, McMullan, PM, Qureshi, AI, Rosenfield, K, Scott, PA, Summers, DR, Wang, DZ, Wintermark, M, Yonas, H, on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Peripheral Vascular Disease, and Council on Clinical Cardiology. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. 2013; 44:870-947.
3. Castillo J, et al., Blood pressure decrease during the acute phase of ischemic stroke is associated with brain injury and poor stroke outcome. Stroke, 2004, 35(2): 520-526.
4. Armstrong, LE. Assessing hydration status: the elusive gold standard. J Am Coll Nutr. 2007; 26:575S-584S.
5. Armstrong, LE, et al., Interpreting common hydration biomarkers on the basis of solute and water excretion. European Journal of Clinical Nutrition, 2013, 67: 249-253.
6. Lacey, J, Corbett, J, Forni, L, et al. A multidisciplinary consensus on dehydration: definitions, diagnostic methods, and clinical implications. Annals of Medicine. 2019; 51: 232-251.
7. Visvanathan, A, Dennis, M, Whiteley, W. (2015) Parenteral fluid regimens for improving functional outcome in people with acute stroke. *The Cochrane Collaboration* 9:1-56.
8. Schrock, JW, Glasenapp, M, Drogell, K. Elevated blood urea nitrogen/creatinine ratio is associated with poor outcome in patients with ischemic stroke. Clinical Neurology and Neurosurgery. 2012; 114:881-884.
9. Rowat, A, Graham, C, Dennis, M. Dehydration in hospital admitted stroke patients: detection, frequency and association. Stroke. 2012; 43:857-859.

10. Bahouth, MN, Gottesman, RF, Szanton, SL. Primary 'dehydration' and acute stroke: a systematic research review. J Neurol. 2018; 265(10): 2167-2181.
11. Nguyen, LS and Squara, P. Noninvasive monitoring of cardiac output in critical care medicine. Front Med. 2017; 4: 200.
12. Khalil, SF, Mohktar, MS, Ibrahim, F. The theory and fundamentals of bioimpedance analysis in clinical status monitoring and diagnosis of diseases. Sensors. 2014; 14(6): 10895-10928.
13. Thiele, RH et al. Cardiac output monitoring: a contemporary assessment and review. Critical Care Medicine. 2015; 43: 177-185.
14. Han, S, Lee, JH, Kim, G, et al. Bioreactance is not interchangeable with thermodiltuoin for measuring cardiac output during adult liver transplantation. PLOS One. 2015; 10(5): e0127981
15. Kupersztych, E, Teboul, JL, Artigas, A, Talbot, A, Sabatier, C, Richard, C, Monnet, X. Bioreactance is not reliable for estimating cardiac output and the effects of passive leg raising in critically ill patients. British Journal of Anaesthesia. 2013; 111(6): 961-966.
16. Jones, TW, Houghton, D, Cassidy, S, MacGowan, GA, Trenell, MI, Jakovljevic, DG. Bioreactance is a reliable method for estimating cardiac output at rest and exercise. British Journal of Anaesthesia. 2015; 111 (3): 386-391.
17. Keren, H, et al. Evaluation of a non-invasive continuous cardiac output monitoring system based on thoracic bioreactance. Am J Physiol Heart Circ Physiol. 2007; 293: H583-H589.
18. Schrock, JW, Glasenapp, M, & Drogell, K. (2012) Elevated blood urea nitrogen/creatinine ratio is associated with poor outcome in patients with ischemic stroke. *Clinical Neurology and Neurosurgery 114*(7):881-884.
19. Lin, L.C., et al., Predictors of clinical deterioration during hospitalization following acute ischemic stroke. European Neurology, 2012, 67: 186-192.
20. Bhatia, K, Mohanty, S, Tripathi, B.K, Gupta, B, & Mittal, MK. (2015) Predictors of early neurological deterioration in patients with acute ischaemic stroke with special reference to blood urea nitrogen (BUN)/creatinine ratio & urine specific gravity. *The Indian Journal of Medical Research 141*(3):299-307.
21. Rowat, A, Graham, C, & Dennis, M. (2012) Dehydration in hospital-admitted stroke patients: Detection, frequency, and association. *Stroke 43*(3):857-859.
22. Sumer, M., et al., Progression in acute ischemic stroke: frequency, risk factors and prognosis. Journal of Clinical Neuroscience, 2003, 10(2): 177-180.

23. Jelles F, Van Bennekom CA, Lankhorst GJ et al (1995) Inter- and intra-rater agreement of the rehabilitation activities profile. J Clin Epidemiol 48(3):407–416
24. Verotti, A, Prezioso, G, Scattoni, R, Chiarelli, F. Autonomic neuropathy in diabetes mellitus. Frontiers in Endocrinology. 2014; 5: 1-7.
25. Marik, PE. Noninvasive cardiac output monitors: a state-of –the-art review. Journal of Cardiothoracic and Vascular Anesthesia. 2013; 27(1): 121-134.
26. Lathrum, HE, Bengtson, CD, Saterwhite, C, et al. Stroke volume guided resuscitation in severe sepsis and septic shock improves outcomes. J Critical Care. 2017; 42:42-46.
27. Squara, P, Denjean, D, Estagnasie, P, Brusset, A, Dib, JC, Dubois, C. Noninvasive cardiac output monitoring (NICOM): a clinical validation. Intensive Care Med. 2007; 22:1191-1194.
28. Squara, P, Rotcajg, D, Denjean, D, Estagnasie, P, Brusset, A. COMparison of monitoring performance of bioreactance versys pulse contour during lung recruitment maneuvers. Crit Care. 2009; 13(4): 1-6.
29. Cavallaro, F, Sandroni, C, Marano, C, LaTorre, G, Mannocci, A, DeWaure, C, Bello, G, Maviglia, R, Antonellil, M. Diagnostic accuracy of passive leg raising for prediction of fluid responsiveness in adults: systematic review and meta-analysis of clinical studies. Intensive Care Med. 2010; 36(9): 1475-1483.
30. Visvanathan, A, Dennis, M, Whiteley, W. (2015) Parenteral fluid regimens for improving functional outcome in people with acute stroke. *The Cochrane Collaboration* 9:1-56.
31. Armstrong, LE. Assessing hydration status: the elusive gold standard. Journal of the American College of Nutrition. 2007; 26:575S-584S.
32. Bahouth, MN, Gaddis A, Hillis AE, Gottesman, RF. A pilot study of volume contracted state and hospital outcome after stroke. *Neurol Clin Pract*. 2018; 8:1-6.
33. Lacey, J, Corbett, J, Forni, L, et al. A multidisciplinary consensus on dehydration: definitions, diagnostic methods, and clinical implications. Annals of Medicine. 2019; 51: 232-251.

Table 1. Patient characteristics by hydration measure and status

	Overall (N=30)	Lab (BUN/Creatinine> 15)			NICOM (SVI > 10%)		
		VCS (N=18)	Euvolemic (N=12)	p	VCS (N=17)	Euvolemic (N=13)	p
Age (years)	62 (15)	65 (14)	58 (16)	0.27	63 (16)	61 (15)	0.77
Sex (Female) N(%)	13 (43)	8 (44)	5 (42)	0.88	10 (59)	3 (23)	0.05
Race (Black) N(%)	17 (57)	10 (56)	7 (58)	0.88	9 (53)	8 (62)	0.64
Smoker* N(%)	19 (63)	13 (72)	6 (50)	0.22	12 (71)	7 (54)	0.35
Atrial fibrillation N(%)	4 (13)	3 (17)	1 (8)	0.51	3 (18)	1 (8)	0.43
Hypertension N(%)	26 (87)	16 (89)	10 (83)	0.66	14 (82)	12 (92)	0.43
Diabetes N(%)	9 (30)	7 (39)	2 (17)	0.19	4 (24)	5 (38)	0.38
Heart failure N(%)	5 (17)	3 (17)	2 (17)	0.68	3 (18)	2 (15)	0.87
Ejection Fraction below 50% N(%)	8 (30)	6 (38)	2 (18)	0.28	6 (43)	2 (15)	0.12
Revascularization (tPA or thrombectomy) N(%)	4 (13)	3 (17)	1 (8)	0.51	3 (18)	1 (8)	0.43
Home diuretic N(%)	10 (33)	7 (39)	3 (25)	0.43	2 (15)	8 (47)	0.07
Baseline heart rate	77 (18)	79 (22)	74 (10)	0.40	76 (22)	78 (13)	0.84
Baseline mean arterial pressure (mmHg)	96 (16)	94 (13)	99 (19)	0.37	92 (13)	100 (18)	0.18
Serum Sodium (dL)	142 (3)	141 (3)	142 (4)	0.64	142 (3)	141 (3)	0.64
Serum Glucose	125 (38)	134 (41)	118 (41)	0.32	120 (32)	138 (50)	0.24
Baseline Hemoglobin	13 (2)	13 (2)	14 (1)	0.28	14 (2)	13 (2)	0.27
Baseline Hematocrit	40 (5)	40 (6)	41 (4)	0.53	42 (5)	39 (5)	0.19
Mean Initial NIHSS	10 (9)	11 (9)	10 (10)	0.85	9 (9)	12 (9)	0.35

NICOM= noninvasive cardiac output monitor; Values are mean (SD) unless otherwise described; *Smoking=ever (current or past); NIHSS = NIH Stroke Scale Score; Continuous variables with ttest; Dichotomous chi squared analysis

Table 2. Comparing measures of hydration status: VCS by labs compared with noninvasive cardiac output monitor

		Lab-measured Hydration (BUN/creatinine ratio)		
		Dehydrated (VCS)	**No Dehydration**	**Total**
Device measured Hydration (NICOM)	**Dehydrated (Fluid responsive)**	13 (76%)	5 (38%)	18
	No dehydration (Not fluid responsive)	4 (24%)	8 (62%)	12
	Total	17	13	30

Figure 1: Display from two representative patients without and with evidence of fluid responsiveness during fluid challenge testing

NICOM suggests no evidence of fluid responsiveness. If clinician treated volume contracted state in this patient may be an increased risk for volume overload or complications.

NICOM suggests fluid responsiveness consistent with volume contracted state. If clinician treated volume contracted state, may have benefit to correct this condition and improve perfusion.

Chapter 6. Synthesis and Future Directions

Current stroke guidelines remind us that “there are no data to guide volume and duration of parenteral fluid delivery” after stroke.[1] Observational studies suggest an association between dehydration status and worsened functional outcome. The studies herein sought to fill this gap by examining the relationship between a volume contracted state and outcomes after ischemic stroke. We additionally tested a novel technology to objectively measure volume status since a major barrier to understanding this phenomenon and the safety of fluid replacement in a relatively frail population with multiple comorbid conditions including heart failure. Specifically, we observed the relationship between hydration status and benefit from the two currently available hyperacute treatments, intravenous thrombolysis and mechanical thrombectomy. Our findings underscore the importance of biological contributions to overall recovery during early stroke treatment. Additionally, we took a first step in evaluating the feasibility of a noninvasive monitor that could serve as a real time and objective measure of volume status that could guide more precise hydration therapies.

Summary of findings

In these studies, we will explored the relationship between a volume contracted state (VCS) defined by indirect surrogate lab markers and outcome after acute stroke treatment with intravascular tPA or mechanical thrombectomy. We then conducted a prospective feasibility study of objectively measuring hydration status in a non-invasive, and real-time way using a noninvasive cardiac output monitor (NICOM) and patient report of thirst. Subjects for all aims of this study were recruited from the Johns Hopkins Comprehensive stroke center. Johns Hopkins is an urban, tertiary care center. Patients are cared for by a multidisciplinary team of stroke

experts who are certified in the acute treatment of these patients. Together, these data provide results from “real-world” treatment experiences.

Results for Aims 1 and 2 suggest that a volume contracted state, defined by elevated baseline BUN/creatinine ratio at the time of hyperacute revascularization treatments and measured indirectly using BUN/creatinine ratio is associated with early neurological worsening. This is clinically important as patients with early neurological worsening have demonstrated worse functional outcomes and higher rates of death in prior studies.[2] This relationship to decreased tPA benefit was observed in aim 1. In aim 2 we demonstrated an important association between early vessel re-occlusion un dehydrated patients who underwent mechanical thrombectomy as compared to those who were not dehydrated. In aim 3, we determined that a noninvasive cardiac output monitor is feasible for use in a population of hospitalized stroke patients and that comorbid conditions such as diabetes may impact accuracy of this device. Together these findings augment the literature and help to advance this area of science toward a system of more precise patient management in the area of post-stroke fluid management.

Implications for Nursing

The primary purpose of nursing research is to provide evidence for patient care practices that promote health and quality outcomes for patients. In the early phase of stroke care, it is nursing assessment of neurological changes, and rapid response to clinical changes that are essential for best patient outcome. Hydration status is one of the body’s basic physiological needs. In the case of hydration status, we are limited by lack of a standard and objective measure of hydration status and thus research in this area has been relatively sparse. This research is a foundational step in both understanding the importance of the contributions of hydration to outcomes but in the measurement of that phenomenon. If we can identify a real-time, objective measure for hydration

status, then the management of a volume contracted state could be standardized and managed by the bedside nurse in order to provide more precise an responsive care to the patients. Next phases in this research will include evaluation of outcomes based on amount of intravenous fluid delivered to further confirm that this is a modifiable determinant of stroke outcome. Perhaps we will one day design and test the benefits of a fluid replacement sliding scale for use by the bedside nurse. With the right measure, this knowledge could be applied to other patient populations in which hydration status may be an important determinant of success.

Implications for Policy Changes

Over recent years, stroke guidelines have fluctuated in terms of language to guide hydration therapy after ischemic stroke in response to increasing observational data without clinical trial to guide official recommendations. Without objective measures, however, this condition is difficult to identify with consistency and challenging to determine the best timing and duration of treatment. Identification of it is difficult to implement treatments with high fidelity. Lacey and colleagues underscored the complexity of dehydration assessment without single objective measure in a recently published multidisciplinary consensus about terminology in this area. It will be critical that we create a precise algorithm that is guided by objective measures for stroke patients and is effective and easy to implement. If we can accomplish this, it would be the first acute stroke therapy available to patients world-wide.

Recommendations for Future Research

The primary focus of this dissertation was to understand the relationship between a volume contracted state and benefit of acute ischemic stroke therapies. Next phases of study will examine the potential for volume contracted state as a modifiable variable in early stroke recovery. We will need to test various dosages of intravenous or oral fluids in relation to safety and functional

outcomes. While it will be important to use standard functional measures after stroke like the modified Rankin scale, we will also expand exploration to include thirst as an important patient reported symptom. This may prove to be challenging in a population of patients with known cognitive and language disturbances, but will be an important direction of study.

Additionally, we sought to test the feasibility of a novel technology to assist with the diagnosis of a volume contracted state that was objective and acceptable to the patients. The next phases of this research will need to further validate this technology and the relationship between hydration status as measured by noninvasive cardiac monitor with clinical outcome.

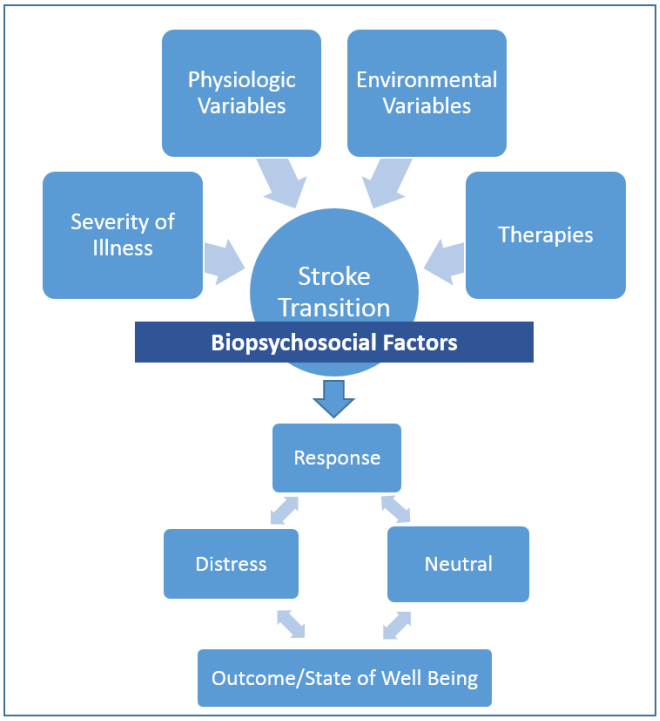


Figure. Adaptation of Meleis' transition theory to guide early stroke recovery research agenda

In parallel, my research will shift to examining the relationship with various dosages of intravenous fluids and clinical outcomes. Using comparative effectiveness methodologies, we will need to determine the potential to modify patient outcomes using the best dose and duration of intravenous fluid administration. It is only then that we can deliver the most precise patient care to deliver the right treatment to the right patient at the right time.

This research focus fits into a larger research agenda that will attempt to identify and modify determinants of early stroke recovery, using technology supported interventions that could allow for the delivery of more precise and effective care. The overarching goal is to reduce stroke-

related disabilities on the long term by implementing healing treatments in the early phase of a patient's care. Stroke remains a leading cause of adult disability and there is a sensitive window for brain recovery. Assuring that we deliver care that addresses all of the biological and environmental determinants of recovery during that time may have the potential to reduce stroke related disability. Using our conceptual framework as a guide, a holistic and comprehensive approach to early recovery research will uncover treatment approaches that accelerate or detract from patient recovery during this critical time. See **Figure**. Then once treatments are identified, we must combine cutting edge technologies to enrich the care process and concepts of implementation science to assure that those treatments are delivered with the highest fidelity. This foundation of clinical research is critical as we develop evidence and change the paradigm of early stroke care to promote successful recovery for stroke patients.

Summary: Stroke providers currently manage dehydration after stroke without adequate evidence for best practice. Taken together, this grant will provide direction for the development of future studies that will answer the important questions of if, *when* and *how* to rehydrate patients after stroke in order to improve patient outcome. This proposal is the starting point; it provides foundational data that will inform a future multicenter trial of early, efficient rehydration after stroke. This intervention is an example of a low cost and globally available stroke therapy with the potential to improve outcomes for a growing population of stroke patients.

References

1. Jauch EC, Saver JL, Adams, Bruno, A, Connors, JJ, Demaerschalk, BM, Khatri, P, McMullan, PM, Qureshi, AI, Rosenfield, K, Scott, PA, Summers, DR, Wang, DZ, Wintermark, M, Yonas, H, on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Peripheral Vascular Disease, and Council on Clinical Cardiology. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. 2013; 44:870-947.
2. National Institute of Neurological Disorders (**NINDS**) and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *NEJM.* 1995;333(24): 1581-1587.
3. Specogna, AV, Patten, SB, Turin, TC, Hill, MD. The reliability and sensitivity of the National Institutes of Health Stroke Scale for spontaneous intracerebral hemorrhage in an uncontrolled setting. PLOS One. 2013; 8(12): e84702.
4. Fearon, P, McArthur, KS, Garrity, K, et al. Prestroke modified ranking stroke scale has moderate interobserver reliability and validity in an acute stroke setting. Stroke; 2012: 43(12): 3184-3188.
5. Demchuk, AM, Tanne, D, Hill, MD, Kasner, SE, Hanson, S, Grond, M, Levine, SR. Predictors of good outcome after intravenous tPA for acute ischemic stroke. Neurology. 2001; 57(3): 474-480.
6. Beier, K, Eppanapally, S, Bazick, HS, Chang, D, Mahadevappa, K, Gibbons, FK, Christopher, KB. Elevation of blood urea nitrogen is predictive of long-term mortality in critically ill patients independent of 'normal' creatinine. Crit Care Med. 2011; 39:305-313.
7. Naylor, J, Churilov, L, Rane, N, Chen, Z, Campbell, BCV, Yan, B. Reliability and utility of the Alberta Stroke Program Early Computed Tomography Score in hyperacute stroke. J Stroke Cerebrovasc Dis. 2017; 26(11):2547-2552.
8. Weir, NU, Pexman, JH, Hill, MD, Buchan, AM; CASES investigators. How well does ASPECTS predict the outcome of acute stroke treated with IV tPA? Neurology. 2006; 67(3): 516-518
9. Castillo J, Leira, R, Garcia, MM, Serena, J, Blanco, M, Davalos, A. Blood pressure decrease during the acute phase of ischemic stroke is associated with brain injury and poor stroke outcome. Stroke. 2004; 35(2):520-526.

10. Pa, YT, Lee, JD, Lin, YH, Huang, YC, Weng, HH, Lee, M, Wu, CY, Hsu, HL, Yang, HT, Hsu, CY, Lee, TH, Liu, SJ, Peng, TY, Liou, CW, Chang, KC, Huang, YC. Comparisons of outcomes in stroke subtypes after intravenous thrombolysis. Springerplus. 2016; 5: 47
11. Mori, M, Naganuma, M, Okada, Y, Hasegawa, Y, Shiokawa, Y, Nakagawara, J, Furui, E, Kimura, K, Yamagami, H, Kario, K, Okudo, S, Koga, M, Minematsu, K, Toyoda, K. Early neurological deterioration within 24 hours after intravenous rt-PA therapy for stroke patients: the stroke acute management with urgent risk factor assessment and improvement rt-PA registry. Cerebrovasc Dis. 2012; 34(2):140-146.
12. Zaidat, OO, Yoo, AJ, Khatri, P, Tomsick, TA, vonKummer, R, Saver, JL, marks, MP, et al. Recommendations on angiographic revascularization grading standards for acute ischemic stroke. Stroke. 2013; 44(9): 2650-2663.
13. Tung, EL, McTaggart, RA, Baird, GL, Yaghi, S, Hemendinger, M, Dibiasio, EL, Hidlay, DT, Tung, GA, Jayaraman, MV. Rethinking thrombolysis in cerebral infarctions 2b. Stroke. 2017; 48: 1-7.
14. Lansberg, MG, Straka, M, Kemp, S, Mlynash, M, Wechsler, LP, Jovin, TG, Wilder, MJ, Lutsep, HL, Czartoski, TJ, Bernstein, RA, Change, CW, Warach, S, Fazekas, F, Inoue, M, Tipirneni, A, Hamilton, SA, Zaharchuk, G, Marks, MP, Bammer, R, Albers, GW, DEFUSE 2 study investigators. MRI profile and response to endovascular reperfusion after stroke (DEFUSE 2): a prospective cohort study. Lancet Neurology. 2012; 11(10):860-867.
15. Squara, P, Denjean, D, Estagnasie, P, Brusset, A, Dib, JC, Dubois, C. Noninvasive cardiac output monitoring (NICOM): a clinical validation. Intensive Care Med. 2007; 22:1191-1194.
16. Churchill, M, Grimm, S, Reding, M. Risks of diuretic usage following stroke. Neurorehabilitation and Neural Repair. 2004; 18(3):161-165.
17. Ramos-Cabrer, P, Campos, F, Sobrino, T, Castillo, J. Targeting the ischemic penumbra. Stroke. 2011; 42: S7-S11.
18. Luby, M, Bykowski, JL, Schellinger, PD, Merino, JG, Warach, S. Intra-and Interrater reliability of ischemic lesion volume measurements on Diffusion-Weighted, Mean Transit Time and Fluid-Attenuated Inversion recovery MRI. Stroke. 2006; 37:2951-2956.
19. Gaudinski, MR, Henning, EC, Miracle, A, Luby, M, Warach, S, Latour, LL. Establishing final infarct volume: stroke lesion evolution past 30 days is insignificant. Stroke. 2008; 39(10):2765-2768.
20. Zaidi, SF, Aghaebrahim, A, Urra, X, Jumaa, MA, Jankowitz, B, Hammer, M, Nogueira, R, Horowitz, M, Reddy, V, Jovin, TG. Final infarct volume is stronger predictor of outcome than

recanalization in patients with proximal middle cerebral artery occlusion treated with endovascular therapy. Stroke, 2012; 43: 3238-324.

21. Krongold, M, Almekhlafi, MA, Demchuk, AM, Coutts, SB, Frayne, R, Eilaghi, A. Final infarct volume estimation on 1-week follow-up MR imaging is feasible and is dependent on recanalization status. Neuroimage. 2015; 7:1-6.

Mona N. Bahouth, MD, MSN

30 Northwood Drive
Lutherville, Maryland 21093
Cell: (443) 377-5876
mbahout1@jhmi.edu

Education

2016-present	PhD student, Johns Hopkins School of Nursing
2006-2010	MD, University of Maryland School of Medicine
1995-1997	MSN, Syracuse University-Nursing, Adult Nurse Practitioner
1989-1993	BSN, University at Buffalo - Nursing

Postgraduate Training:

2014-2016 **Cerebrovascular Fellow**, Department of Neurology
Johns Hopkins Hospital; Director: Argye E. Hillis, MD

- Science of Clinical Investigation Training Program;
  Johns Hopkins School of Public Health
- Armstrong Institute of Patient Safety & Quality Leadership scholar
- American Academy of Neurology; Emerging Leader Forum

2011-2014 **Resident,** Johns Hopkins Hospital; Department of Neurology
Johns Hopkins Hospital; Chair: Justin McArthur, MD

- Executive chief resident
- NINDS R25 grant recipient;
  Mentor Rebecca Gottesman, MD, PhD

2010-2011 **Intern, Department of Medicine**
University of Maryland Medical Center; Director: Susan Wolfsthal, MD

Professional Experience:

2016-present **Johns Hopkins School of Medicine, Baltimore, MD**
Assistant Professor of Neurology, Department of Neurology

2005-2009 **University of Maryland Medical Center, Baltimore, MD**
Project Manager for Advanced Practice Nursing

1998-2006 **University of Maryland Medical System, Baltimore, MD**
Director, Clinical Programs & Research, *Department of Neurology*

1997-1998 **VA Medical Center, Syracuse, NY**
Clinical educator, Department of Neurosurgery

1997-1998 **Syracuse University, Syracuse, NY**
Clinical Nursing Instructor

1995-1997 **University Hospital, Syracuse, NY**
Registered Nurse; Neurosurgical Intensive Care

1994-1995 **TravCorps, Boston, MA**
Registered Nurse
1993-1994 **SUNY Health Science Center, Syracuse, NY**
Registered Nurse; *General Surgery/ Renal Transplant*

Consulting:

July 2015-
June 2016 **St. Agnes Hospital**, Baltimore, Maryland
Neurologist, Neurohospitalist
Perform all in patient and emergency department consultations and manage patients on neurohospitalist service

September 2007
- 2008 **Western Maryland Health Center**, Cumberland, Maryland
Acute Stroke Consultant, Telemedicine
Assessment, diagnosis, management, and treatment of acute stroke patients via emergency telemedicine consultation.

September 2006 **NINDS; Stroke Progress Review Group II**: Health Services Implementation;http://www.ninds.nih.gov/find_people/groups/stroke_prg/09_2006_stroke_prg_report.htm

February 2001-
March 2002 **Texas Biotechnology Corporation**, Houston, Texas
Specialty Consultant - Acute Stroke Clinical Trial
Protocol and document development, trial implementation, and staff education related to a Phase II clinical trial for acute stroke

November 1998
-2004 **St. Mary's Hospital,** Leonardtown, MD
Nurse Practitioner-Acute Stroke Consultant
Assessment, diagnosis, management, and treatment of acute stroke patients via emergency telemedicine consultation.

Faculty Appointment:

2016-present Assistant Professor of Neurology
Johns Hopkins School of Medicine

2001-2010 Adjunct Faculty, Nursing
University of Maryland School of Nursing

1997-1998 Clinical Instructor of Medical/Surgical Nursing,
Syracuse University School of Nursing

Medical Licensure: Maryland (D78293)

Nursing Licensure: Maryland (NP142764)
New York (F302103-1)

Professional Board Certification:

December 2016	Vascular Neurology, American Board of Psychiatry and Neurology
September 2014	Neurology, American Board of Psychiatry and Neurology
April 1999	National Certification, Acute Care Nurse Practitioner
February 1998	National Certification, Adult Nurse Practitioner
March 1998	Certification, Neuroscience Registered Nurse
August 1996	Certification, Critical Care Registered Nurse

Awards and Honorary Societies:

2016	Caylor Scholar; Johns Hopkins School of Nursing
2015	National Institutes of Health Loan Repayment Program Award
2015	Emerging Leaders Forum; American Academy of Neurology
2015	Armstrong Institute Patient Safety and Quality Leadership Academy; Johns Hopkins Medicine
2014	Thomas Preziosi Clinical Excellence Award; Department of Neurology; Johns Hopkins Hospital
2014	Frank L Coulson, Jr Award for Clinical Excellence; Johns Hopkins Hospital
2010	Medical Student Prize for Excellence; American Academy of Neurology
2007	State Excellence Award; American Academy of Nurse Practitioners
2006	Unsung Hero Award, University of Maryland Medical Center
2002	Governors Health Council, State Advisory Council on Heart Disease and Stroke Prevention
1999	Dean's Young Careerist Award, Syracuse University School of Nursing
1997	Sigma Theta Tau, International Honor Society of Nursing

Memberships in Professional Societies:

American Stroke Association
American Academy of Neurology
American Association of Critical Care Nurses
American Association of Neuroscience Nurses
Registered Nurse Advisory Committee for Transplant Donor Services
Coalition of Nurse Practitioners
Nurse Practitioner Association of Maryland

Committees:

President's Business Innovation Task Force; American Academy of Neurology
Leadership Development Committee, American Academy of Neurology
Neurocritical Care Early Mobility Committee, Johns Hopkins Hospital
Founder, New NP Peer Group, University of Maryland Medical Center
Founder and Chair, APN Executive Council, University of Maryland Medical Center
Medical Care Policy Committee, University of Maryland Medical Center

Ethical Advisory Board, University of Maryland Medical Center
Joint National Committee for Nurse Practitioners, Maryland Board of Nursing
Magnet Committee, University of Maryland Medical Center
Patient Care Services Board, University of Maryland Medical Center
Quality Improvement Committee, University of Maryland Medical Center
Institutional Review Board, University of Maryland Medical Center
Founder, Advanced Practice Nurse Group, University of Maryland Medical Center
Chairperson, Community Outreach Subcommittee, American Heart Association,
Nursing Research Committee, VA Medical Center, Syracuse, New York
Chairperson, Clinical Practice Committee, VA Medical Center, Syracuse, New York

Community Service:

Make-A-Wish-Foundation of Maryland, Wish Granter, 1998-2002
Peace, Inc. Big Brother/Big Sister, Big Sister, 1997-1998

Teaching and Mentoring:

2017	Johns Hopkins School of Medicine; Clinical Reasoning and Case Based Localization Course MS III/IV.
2017	Johns Hopkins Hospital; Physical Medicine and Rehabilitation, Nicole Langton (dysphagia and stroke); Sowmya Kumble (early mobilization after stroke)
2016	Johns Hopkins University; Postbaccalaureate Medical Tutorial Program: Steven Thornton (dehydration & stroke), Mina Bakhtiar (hospital readmission after stroke), Amelia Kohn (early mobility)
2015	Johns Hopkins School of Medicine; PRECEDE; Pre-Clerkship Education; Stroke MS III and IV
2014	Johns Hopkins School of Medicine; Lumbar Puncture Simulation Lab; MS III and IV
2008	Mentor, University of Maryland School of Nursing; Nurse Practitioner student; Sun Ah Lee
2003-2004	Mentor, University of Maryland School of Nursing; Nurse Practitioner student
2003	Mentor, John's Hopkins School of Nursing: Samantha Sterling
2002, 2003	University of Maryland School of Medicine. Year II Therapeutics and Pathophysiology Course, Neuroscience
2002-2003	Facilitator, University of Maryland PhD/MD Program student Brain Attack Team rotation, Conrad Liang
2001	Facilitator for the Short Term Research Training Program USPHS Training Grant, HL 07612-14, Katherine Sabat, MSII
2000	Preceptor, University of Maryland School of Nursing: Nancy Bass-Eisenberg; Nurse Practitioner student
1999	Facilitator for the Short Term Research Training Program USPHS Training Grant, HL 07612-14, Eric Blum, MSII

Media Releases

NPR: Here and Now; March 5, 2019: https://www.wbur.org/hereandnow/2019/03/05/stroke-risks-luke-perry

The Daily Beast March 4, 2019: https://www.thedailybeast.com/luke-perry-star-of-90210-and-riverdale-wasnt-too-young-for-a-stroke

Neurology reviews: MDedge March 23, 2015: https://www.mdedge.com/neurology/article/97545/stroke/dehydration-may-contribute-clinical-deterioration-stroke-patients

MD Magazine February 13, 2015: https://www.mdmag.com/conference-coverage/asa-2015/dehydration-signals-worse-stroke-outcome

American Heart Association News Archive March 2015: https://newsarchive.heart.org/dehydration-linked-worsening-stroke-conditions/

Medscape February 19, 2015: Dehydration worsens stroke outcome: https://www.medscape.com/viewarticle/840062

NPR March 2015 Dehydration and stroke

Clinical Research:

Co-Investigator	"Randomized double-blind, Evaluation in secondary Stroke Prevention comparing the EfficaCy and safety of the oral Thrombin inhibitor dabigatran etexilate (110mg or 150mg, oral bid) versus acetylsalicylic acid (100 mg oral qd) in patients with Embolic Stroke of Undetermined source (RESPECT ESUS) Boerhringer Ingelheim, Johns Hopkins Hospital, 2016-2018
Co-Investigator	"TIA-Minor Stroke Outpatient Pathway Safety Implementation Study (TOP-SAILS) -2018.
Co-Investigator	"Platelet-Oriented Inhibition in New TIA and Minor Stroke (POINT) Trial" Neurological Emergencies Treatment Trials network (NETT) and the EMMES corporation. 2014-2016.
Co-Investigator:	"Rapid Assessment of Transient Ischemic Attack Etiology." National Emergency Medicine Association & Boehringer Ingelheim, University of Maryland Medical Center, May 2003 - 2005
Co-Investigator:	"Portable Non-Invasive Acoustic Identification of Stroke." Active Signals Technology, University of Maryland Medical Center, March 2003-2005.
Co-Investigator	"A Single Rising Dose Study of FK506 Lipid Complex (LCG) in Patients with Recent Ischemic Stroke." Fujisawa Inc., University of Maryland Medical System, 2002-2003.
Co-Investigator:	"A Randomized, Placebo-Controlled, Three-Treatment Arm Study to Determine the Safety and Efficacy of Argatroban Injection in Patients with Acute Ischemic Stroke (ARGIS-I)." Texas

	Biotechnology Corporation, University of Maryland Medical System. 2001- 2002.
Co-Investigator:	"Non-Invasive Acoustic Detection of Ischemic and Hemorrhagic Stroke." Active Signals Technology, Inc, University of Maryland Medical Center. 2001-2002.
Co-Investigator:	"Hemicraniectomy and Durotomy Upon Deterioration From Infarction Related Swelling: A Prospective, Randomized, Pilot Clinical Trial." NINDS, University of Maryland Medical System. 2000-2003.
Co-Investigator:	"Abciximab in Acute Ischemic Stroke: A Randomized, Double-blind, Placebo-controlled Trial." Centecor, Inc., Eli Lilly and Company, University of Maryland Medical System. 2000-2003.
Sub Investigator:	"A Double-Blind, Placebo Controlled, Multi-Center Study to Evaluate the Safety and Efficacy of a 72-hour Infusion of CP-101, 606 in Subjects with Acute Ischemic Stroke in the Forebrain." Pfizer Inc., University of Maryland Medical Center. 2000-2001.
Sub Investigator:	"A Double-Blind, Randomized, Placebo-Controlled Study of Atorvastatin as Prevention of Cerebrovascular Events in Patients With a Previous Transient Ischemic Attack (TIA) or Stroke (Protocol 981-124)." Parke-Davis, University of Maryland Medical System. 1998-2003.
Sub Investigator:	"Protocol AST02: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of HU23F2G (LeukArrest^{TM}) in Patients with Acute Ischemic Stroke." ICOS Corporation, University of Maryland Medical System. 1999-2000.
Sub Investigator:	"The Effects of 2000 mg Citicoline on Clinical Outcome and the Evolution of Lesion Volume in Human Stroke." Interneuron Pharmaceuticals, Inc., University of Maryland Medical System. 1998-1999.

Grants:

Bahouth, MN, Winslow, R, Miller, M, Suarez, J, Gottesman, RF. Hydration is vital: understanding the neuro-consequences of dehydration after stroke. American Heart Association Innovative Project Award (18IPA34170403). July 1, 2018- June 30, 2019. PI – Awarded $200,000

Bahouth, MN, Leigh, R, Grams, M, Suarez, J, Hillis, AH, Gottesman, RF. Dehydration and early stroke outcome. American Heart Association Career Development Award (18CDA34110126). July 1, 2018- June 30, 2021. PI – Awarded $231,000

Bahouth, MN. Pilot study of a novel, low cost, wearable sensor to measure dehydration after acute stroke. Discovery Fund Innovation Award. July 2017-June 2018. Principal Investigator – Awarded $50,000

Bahouth MN, Klein, L, Kumble, S, Steinhorn, G, Szanton, S. Physiological and Environmental Contributors to Delayed Mobilization Times for Hospitalized Stroke Patients: A Pilot Study. Johns Hopkins School of Nursing, Dorothy Evans Lyne Fund for Collaborative Nursing Research. April 2017-May 2018. Team Leader – Awarded $10,000 (to SZ).

Bahouth, MN, Hillis, A, Gottesman, R. Precise stroke care to decrease early stroke progression:

a case for hydration. Johns Hopkins School of Medicine, Richard Starr Ross Physician Scientist Award. July 2016-June 2017. PI – Awarded $80,000.

Bahouth, MN, Hillis, A, Gottesman, R. A prospective study of the effect of dehydration on stroke severity. July 2013-2016 (with extension awarded for 2015-2016). R25 funding from the NINDS Research Education Program for Residents and Fellows in Neurology (RFA-NS 09-001)

Bahouth, MN, Yarbrough, K, and Gunawardane, R, LaMonte, MP. Telemedicine for Regional Stroke Education: A Feasibility Study. Other Tobacco Related Disease Grant. June 2002. Co-Principal Investigator - Awarded $50,000.

Bahouth, MN, Yarbrough, K, Pathan, M, LaMonte, MP. Increasing Stroke Awareness through Education provided at the Office of the Primary Care Provider. The Maryland Statewide Health Network. May 2001. Co- Principal Investigator–Awarded $50,000.

Bahouth, MN, Yarbrough, K, Gunawardane, R, and Pathan, M, LaMonte, MP. Creating Stroke Education Modules for use Statewide. The Maryland Statewide Health Network. May 2001. Co- Principal Investigator - Awarded $19,000.

Books:

Bahouth, MN (Editor), Blum, K, Simone, S. Transitioning into hospital based practice: A guide for Nurse Practitioners and Administrators. Springer, 2013.

Book Chapters:

Gonzalez-Fernandez, M, Langton-Frost, N, Wright, AN, Karagiorgos, E, **Bahouth, MN.** Stroke Rehabilitation. Chapter 4: Swallowing disorders after stroke. Elsevier, (in press).

Bahouth, M. Critical Care Nursing: A Holistic Approach (tenth edition). Chapter 34: Neurologic Assessment. Lippincott Williams & Wilkins, Philadelphia; 2017.

Bahouth, MN. A practical approach to NP recruiting and onboarding. Transitioning into hospital based practice: A guide for Nurse Practitioners and Administrators. Springer, 2013.

Duke, CR, Simone, S, **Bahouth, MN**. Nurse Practitioner Orientation: The Transition. Transitioning into hospital based practice: A guide for Nurse Practitioners and Administrators. Springer, 2013.

Bahouth, M. and Yarbrough, K. Critical Care Nursing: A Holistic Approach (ninth edition). Chapter 34: Neurologic Assessment. Lippincott Williams & Wilkins, Philadelphia; 2007.

LaMonte, ML, **Bahouth, MN**, Hu, P, McKenzie, C. Telemedicine Applied to Stroke Care. Acute Stroke Bench to Bedside, Informa Healthcare, 2007, pages 415-419.

LaMonte, MP, **Bahouth, MN,** Hu, P, Xiao, Y**.** Acute Stroke: Bench to Bedside. Chapter 36: Telemedicine Applied to Stroke Care. 2006; pages 423-427.

Bahouth, MN (reviewer). Core Curriculum for Critical Care Nursing (sixth edition). Section 4. The Neurologic System. Saunders Elsevier; 2006. pages 381-524.

Bahouth, M. and Yarbrough, K. Critical Care Nursing: A Holistic Approach (eighth edition). Chapter 34: Neurologic Assessment. Lippincott Williams & Wilkins, Philadelphia; 2005.

Peer Reviewed Articles:

Waligora, KJ, **Bahouth, MN**, Han, HR. The self-care needs and behaviors of dementia informal caregivers: a systematic review. Gerontologist; June 2018; epub ahead of print (PMID 29931147)

Kaas, B, Zeiler, SR, **Bahouth, MN**, Llinas, RH, Probasco, JC. Autoimmune limbic encephalitis in association with acute stroke. Neurology Clinical Practice; August 2018; 8(4): 349-351. (PMID 30140588)

Urrutia, VC, Faigle, R, Zeiler, SR, Marsh, EB, **Bahouth, MN**, Trevino, MC, Dearborn, J, Leigh, R, Rice, S, Lane, K, Saheed, M, Hill, P, Llinas, RH. Safety of intravenous alteplase within 4.5 hours for patients awakening with stroke symptoms. PLoS ONE; 2018; 13(5):e0197714. (PMID 29787575)

Bahouth, MN, Power, MC, Zink, EK, Kozeniewski, K, Kumble, S, Deluzio, S, Urrutia, VC, Stevens, RD. Safety and feasibility of a neuroscience critical care program to mobilize patients with primary intracerebral hemorrhage. Archives of Physical Medicine and Rehabilitation. 2018; in press

Bahouth, MN, Gottesman, RF, Szanton, SL. Primary 'dehydration' and acute stroke: a systematic research review. Journal of Neurology; March 2018 epub ahead of print (PMID 29497817)

Sun, L, Pearl, M, **Bahouth, MN**, Schuette, J, Hoops, K, McCaul, MC, Felling, R. Mechanical thrombectomy in an infant with acute embolic stroke. Pediatric Neurology. 2018; in press.

Deluzio, S, Vora, I, Kumble, S, Zink, E, Stevens, R, **Bahouth, MN.** Feasibility of early, motor assisted upper extremity cycle ergometry in critically ill neurological patients with upper extremity weakness and variable cognitive status. American Journal of Physical Medicine and Rehabilitation; May 2018; 97(5):37-41 (PMID 29095167).

Bahouth, MN, Gaddis, A, Hillis, AE, Gottesman, RF. A pilot study of volume contracted state and hospital outcome after stroke. Neurology Clinical Practice; Jan 2018; 8(1):1-6 (PMID 29517060).

Barreras, P, Benavides, D, Barreras, JF, Pardo, CA, Jani, A, Faigle, R, **Bahouth, MN**. A dedicated lumbar puncture clinic; performance and short-term patient outcomes. Journal of Neurology; August 2017 (PMID 28836071)

Kumble, S, Zink, EK, Burch, M, Deluzio, S, Stevens, RD, **Bahouth, MN.** Physiologic effects of early incremental mobilization of a patient with acute intracerebral and intraventricular hemorrhage requiring dual external ventricular drainage. Neurocritical Care; February 2017; ePub (PMID 28243999)

Bahouth, MN, Bahrainwala, Z, Hillis, AE, Gottesman, RF. Dehydration is associated with more severe hemispatial neglect after stroke. The Neurologist; November 2016; 21(6):101-105. (PMID 27801770)

Faigle, R, **Bahouth, MN**, Urrutia, V, Gottesman, RF. Racial and socioeconomic disparities in gastrostomy tube placement after intracerebral hemorrhage in the US. Stroke. February 2016; 47(4):964-970. (PMID 26892281)

Brown, C, Faigle, R, Klinker L**, Bahouth, MN,** Max, L, LaFlam, A, Neufeld, KJ, Mandal K, Gottesman, RF, Hogue, C. The Association of Brain MRI Characteristics and Postoperative Delirium in Cardiac Surgery Patients. Clinical Therapeutics. December 2015; 37(12):2686-2699. (PMID 26621626)

Bahouth, MN, Ackerman, M, Ellis, EF, Fuchs, J, McComiskey, C, Stewart, ES, Thomson-Smith, C. Centralized resources for nurse practitioners: common early experiences among leaders of six large health systems. Journal of the American Academy of Nurse Practitioners. April 2013; 25(4):203-212. (PMID 24218238).

Bahouth, MN & Esposito-Herr, MB**.** An Orientation Program for Hospital-Based Nurse Practitioners. AACN Advanced Critical Care. 2009; 20(1):82-90. (PMID 19174640)

LaMonte, MP, **Bahouth, MN,** Magder, LS, Alcorta, RL, Brown, BJ, Floccare, DJ, Gaasch, WR. A Regional System of Stroke Care Provides Thrombolytic Outcomes Comparable with the NINDS Stroke Trial. Annals of Emergency Medicine. 2009; 54(3):319-27. (PMID 19101059)

Aldrich, EM, Lee, AW, Chen, CW, Gottesman, RF, **Bahouth, MN,** Gailloud, P, Murphy, K. Local intraarterial fibrinolysis administered in aliquots for the treatment of central retinal artery occlusion: The Johns Hopkins Hospital Experience. Stroke, June 2008; 39(6):1746-1750. (PMID 18420951)

LaMonte, MP, **Bahouth, MN,** Hu, P, Xiao, Y, Mackenzie, C, Baquet, C. Outcomes from a Comprehensive Stroke Telemedicine Program Support Expanding Stroke Services Using Telemedicine**.** Telemedicine and ehealth, May 2008; 14 (4): 351-356. (PMID 18570562)

Bahouth, MN, Esposito-Herr, MB, Babineau, TJ. The Expanding Role of the Nurse Practitioner in an Academic Medical Center and its impact on Graduate Medical Education. Journal of Surgical Education, September/October 2007; 64(5), 282-288. (PMID 17961886)

Bahouth, MN and LaMonte, MP**.** The Role of an Acute Stroke Nurse Practitioner: Practice Outcomes. (Abstract). Stroke. February 2006; 37(2): 746.

Bahouth, MN and LaMonte, MP. Acute Ischemic Stroke: Evaluation & Management Strategies, Topics in Advanced Practice Nursing on Medscape. Dec 2005; 5(4).

LaMonte, MP, Sewell, J, **Bahouth, MN,** and Sewell, C. A Noninvasive Portable Acoustic Diagnostic System to Differentiate Ischemic from Hemorrhagic Stroke. Journal of Neuroimaging, Jan 2005; 15(1): 57-63. (PMID 15574575)

LaMonte, MP, Xiao, Y, Hu, PF, Gagliano, DM, **Bahouth, MN**, Gunawardane, RD, Mackenzie, CF, Gaasch, WR, & Cullen, J. Shortening Time to Stroke Treatment using Ambulance Telemedicine: TeleBAT. Journal of Stroke and Cerebrovascular Diseases, Jul-Aug 2004; 13 (4): 148-154. (PMID 17903967)

LaMonte MP**,** Sewell J, **Bahouth MN**, Sewell C. Noninvasive Brain Assessment of Stroke Subtype Use of a Portable Acoustic Diagnostic System: A Pilot Study. Journal of Neuroimaging. 2003; 13(4).

LaMonte, M, **Bahouth, M**, Hu, P, Pathan, M, Yarbrough, K, Gunawardane, R, Crarey, P, & Page, W. Telemedicine for Acute Stroke: Triumphs and Pitfalls. Stroke. 2003; 34(3): 725-728. (PMID 12624298)

LaMonte, MP, Garber H, **Bahouth, MN**, Impacting Stroke in Maryland, Med Chi, August 2002; 4(1); 30,48. (PMID 12652860)

Bahouth, M. and LaMonte, MP. Update on Stroke Prevention and Acute Management. Primary Care Practice, November 2000; 4(6): 545-562. (PMID 11933370)

Presented Abstracts:

Bahouth, MN. Research in the area of quality and safety. *American Academy of Neurology Annual meeting*. Invited oral presentation. Los Angeles, April 2018

Bahouth, MN, Simpkins, AN, Ghotra, P, Hillis, AE, Gottesman, RF, Leigh, R. Normalization of BUN/creatinine ratio in acute ischemic stroke patients is associated with less infarct expansion. *American Neurological Association Annual Meeting*. Oral data blitz presentation, Baltimore, October 2016

Bahouth, MN. Utilization of a progressive mobility algorithm for intracerebral hemorrhage patients in the neuroscience critical care unit. *JHM Annual Safety Summit*. Podium Presentation, Baltimore, October 2016

Kumble, S, Burch, M, Zink, EK, Stevens, RD, **Bahouth, MN**. Physiologic effects of incremental, early mobilization of a patient with acute intracerebral and intraventricular hemorrhage with dual external ventricular drainage devices. *Neurocritical Care Society 14th Annual Meeting*. Poster, National Harbor, September 2016

Barrera, P, Benavides, D, Faigle, R, **Bahouth, MN.** Outcomes from a formal lumbar puncture clinic. *American Academy of Neurology International Conference*. Poster, April 2016.

Bahouth, MN, Hillis, AE, Gottesman, R. Worse functional outcome in stroke patients with elevated urine specific gravity. *International Stroke Conference*; Moderated Poster Session, February 2016

Bahouth, MN, Hillis, AE, Gottesman, R. A prospective study of the effect of dehydration on stroke severity and short term outcome. *International Stroke Conference*; Moderated Poster Session, February 2015

Bahouth, MN, Hillis, AE, Gottesman, R. Hydration Practices for the Acute Stroke Patient in an Academic, Certified Stroke Center. *American Academy of Neurology Annual Meeting; Philadelphia, Pennsylvania*, March 2014.

Bahouth, MN, Johnston, M, Pardo, C. The need for repeat diagnostic testing for the identification of ovarian pathology in a patient with anti-NMDA receptor limbic encephalitis. *American Academy of Neurology Annual Meeting; Philadelphia, Pennsylvania*, March 2014.

Bahouth, MN, Bahrainwala, Z, Hillis, A, and Gottesman, R. Dehydration is Associated with More Severe Hemispatial Neglect in Patients with Right Hemispheric Stroke. *American Academy of Neurology Annual Meeting; San Diego, California*, March 2013

Bahouth, MN, Mohassel, P, and Pardo, C. Reversible third nerve paralysis and blast-like cells in cerebrospinal fluid as unusual presentation of neuroborreliosis. *American Academy of Neurology Annual Meeting;* New Orleans, Louisiana, March 2012.

Lee, SA, **Bahouth, MN**, and Xiao, Y. Acute Care Nurse Practitioners as Key Agents in Continuity of Care through Communication. *National Conference for Nurse Practitioners and Advanced Practice Clinicians;* Philadelphia, Pennsylvania, May 7-10, 2008.

LaMonte, MP, and **Bahouth, MN**. A Comprehensive Telemedicine Program for Stroke: The University of Maryland Experience. American Telemedicine Association Annual Meeting; Oral presentation, San Diego, California, May 2006

Hu, P, Xiao, Y, Hu, P, Mackenzie, C, LaMonte, M, **Bahouth, MN**, Gagliano, D, Defouw, G, Davies, P, Macanna, T, Reifman, J. Lesson Learned: Design and Deploy the Mobile Video and Patient Vital Signs Transfer System for Pre-Hospital Care. America Telemedicine Association Annual Meeting; Oral presentation, San Diego, California, May 2006

Bahouth, MN, LaMonte, MP, Zink, EK, Yarbrough, KY, and Seipp, MJ. The Role of an Acute Stroke Nurse Practitioner: Practice Outcomes. American Heart Association, 31st International Stroke Conference; Oral presentation, Orlando, Florida, February 2006

Aldrich, EM, **Bahouth, MN**, Wityk, R, Gailloud, P, Murphy, K and Miller, N. Intra-arterial Fibrinolysis for Central Retinal Artery Occlusion Using Small Aliquots Rather than Continuous Infusion. American Heart Association, 31st International Stroke Conference; Poster presentation, Orlando, Florida, February 2006.

Bahouth, MN and LaMonte, MP. Development and Use of a Stroke Risk Assessment Tool. 16th International Nursing Research Congress; Oral Presentation, Hawaii, July 2005.

Bahouth, MN and LaMonte, MP. Telemedicine for Regional Stroke Education. 16th International Nursing Research Congress; Oral Presentation, Hawaii, July 2005.

LaMonte, MP and **Bahouth, MN.** Developing a Comprehensive Telemedicine Program for

Acute Stroke. American Academy of Neurology International Meeting; Oral presentation, Miami, FL, April 2005.

Bahouth, MN, LaMonte, MP, Seipp, MJ, Yarbrough, K, Zink, E. Defining the Role of an Acute Stroke Nurse Practitioner: The University of Maryland Eight-Year Experience. American Heart Association, 30th International Stroke Conference. Oral presentation, New Orleans, LA, February 2005.

LaMonte, MP; Sewell, J; **Bahouth, MN**; Sewell, C; Marriott, MA; Bridger, K; Embert, C; Zink, EK; Mitrou, M, Spanfelner, J; Mathews, K; Webb, R; Kufera, JA. A Phase II study of a portable, non-invasive acoustic diagnostic system to differentiate ischemic and hemorrhagic stroke. American Heart Association, 30th International Stroke Conference. Oral presentation, New Orleans, LA, February 2005.

LaMonte MP, Zink, EK, Gaasch WR, Pathan, MY, **Bahouth MN**, Bloom, RL, Pohl, M, Sims, KP. Dispatcher Recognition of Acute Stroke: A Pilot Study. American Heart Association, 30th International Stroke Conference. Poster presentation, New Orleans, LA, February 2005.

LaMonte MP and **Bahouth MN**. Telemedicine Stroke Education for Medically Underserved Communities. American Telemedicine Association, Oral presentation, Orlando, Florida, May 2004.

LaMonte MP, Zink EK, Kuo D, DeFilipi C, **Bahouth MN**, Gunawardane RD, Wozniak MA. Rapid Assessment and Treatment of TIA Etiology. American Academy of Neurology. Poster presentation, San Francisco, California, April 2004

LaMonte, MP, Zink, EK, Kuo, D, **Bahouth, MN** et al. Rapid Assessment and Treatment of Transient Ischemic Attack Etiology (RATE). Neurology, 62 (7), supp 5, pp. A244

LaMonte MP and **Bahouth MN**. Telemedicine Stroke Education for Medically Underserved Communities. American Heart Association 29th International Conference. Poster presentation, San Diego, California, February 2004.

LaMonte MP**,** Sewell J, **Bahouth MN**, Sewell C. Noninvasive Brain Assessment of Stroke Subtype Use of a Portable Acoustic Diagnostic System: A Pilot Study. American Society of Neuroimaging. Oral Presentation; Phoenix, Arizona, January 2004.

Bahouth, MN and LaMonte, MP. Measuring the impact of a Stroke Educational Poster used in the Office of a Primary Care Provider. 14th International Nursing Research Congress; Evidence-based practice: Strategies and Successes in Clinical Implementation. Poster presentation, St. Thomas, Virgin Islands, July 2003.

LaMonte, M, Yarbrough, K, **Bahouth, M**, Pathan, M, Asad, S, Gunawardane, R, Floccare, D, Bass, R. Air and Ground Interfacility Transport to a Stroke Treatment Center: Thrombolytic Administration and 3-Month Outcome. Society of Critical Care Medicine International Congress. Oral presentation, San Antonio, Texas, February 2003.

Sewell, J, LaMonte, M, **Bahouth, M**, Sewell, C, Marriott, M, Zink, E, Gunawardane, R, Yarbrough, K, and Kufera, J. A Non-Invasive, Portable Brain Assessment Monitor for Acute Stroke Subtyping. American Heart Association, 28th International Stroke Conference. Poster presentation; Phoenix, Arizona, February 2003.

Bahouth, MN, LaMonte, MP, Yarbrough, KL. Stroke Risk Assessment Tool. Neurology, 58:3, 2002

LaMonte, M, Bates, V, **Bahouth, M**, Gunawardane, R, Yarbrough, K, Pathan, M, Page, W, Mehlman, I, and Crarey, P. Safe rt-PA Administration for Ischemic Stroke during Telemedicine Consultation. American Heart Association, 26th International Conference on Stroke and Cerebral Circulation. Oral presentation; Fort Lauderdale, Florida, February 2001.

LaMonte, MP, Bates, V, **Bahouth, MN**, Gunawardane RD, Yarbrough, KL, Pathan, MY, Page, CW, Melman, I. Safe rt-PA Administration for Ischemic Stroke During Telemedicine Consultation. Stroke, 32(1); 374; January 2001.

LaMonte, MP**,** Blum E, **Bahouth M**, Hebel R, Gunawardane R, David E: Medical Efficacy and Medical and Economic Efficiency of a Stroke Treatment Center. Stroke, 31(1), 2000.

Bahouth, M, Yarbrough, K, & LaMonte, MP. Design & Pilot of a Stroke Risk Assessment Tool. American Academy of Neurology Annual Meeting, Poster presentation; San Diego, CA, April 2000.

LaMonte, MP, Blum E, **Bahouth, M**, Hebel, R., Gunawardane, R, & David, E. Medical Efficacy and Medical and Economic Efficiency of a Stroke Treatment Center. American Stroke Association, 25th International Conference on Stroke and Cerebral Circulation. Oral presentation; New Orleans, LA, February 2000.

Invited Oral Presentations:

Women in Leadership. American Academy of Neurology. Los Angeles, California. April 2018

Transdisciplinary approach to mobilizing acute stroke patients in the Neurocritical Care Unit. Evidence Based Practice Research Conference. New Orleans, Louisiana. September 2017

Early Stroke Recovery. Mater Misericordiae University Hospital; UCD School of Medicine. Dublin, Ireland. August 2017

Clinical Research in the Area of Practice, Quality and Patient Safety. Navigating your Career; American Academy of Neurology International Conference. Vancouver, Canada. April 2017

Normalization of BUN/creatinine ratio in acute ischemic stroke patients is associated with less infarct expansion. American Neurological Association National Meeting (ANA). Data blitz, Baltimore, Maryland. October 2016

Advancing your leadership skill: The successful Chief Resident. Navigating your Career; American Academy of Neurology International Conference. Vancouver Canada. April 2016

Volume status & short term outcomes after stroke. American Heart Association Northeast Cerebrovascular Consortium (NECC) Annual Summit; Newport Rhode Island. October 2015

Developing Systems for Hospital Wide Nurse Practitioner Orientation. Society of Critical Care Medicine Annual Congress; Miami, Florida; January 2010

Transition into Nurse Practitioner Practice into the Acute Care Setting. American Academy of Nurse Practitioners Annual Congress. Nashville, Tennessee; May 2009.

Transition into Nurse Practitioner Practice into the Acute Care Setting. National Trauma Institute; New Orleans, Louisiana; April 2009

Transition into Hospital Based Practice: Establishing a System for NP Orientation. First National Summit on NP Practice in Acute Care. Rochester, New York; November 2008.

Update on Stroke Management for the Nurse Practitioner. Nurse Practitioner Association of Maryland; Baltimore, Maryland; June 2006.

24 Hours/Day: Creative Solutions to Providing Acute Stroke Care. Stroke Centers of Excellence Conference; A World Research Group Healthcare Management Series Conference; Las Vegas, Nevada; May 2006

Creating a Focus Plan: Practical Strategies to Translate Concept into Action (featured panelist). Stroke Centers of Excellence Conference; A World Research Group Healthcare Management Series Conference; Las Vegas, Nevada; May 2006

Acute Stroke Management: Approaches to Care and Future Trends. Acute and Critical Care Trends in Nursing Practice. The University of Maryland Medical Center; Baltimore, Maryland; May 2006.

The Biology of the Stroke Patient. Johns Hopkins University; Baltimore, Maryland; April 2006.

Management of the Acute Stroke Patient. Nurse Practitioner Association of Long Island. November 2005.

Update on Acute Stroke. Mid-Atlantic Regional Conference for Nurse Practitioners. Nurse Practitioner Association of Maryland. April 2005.

Stroke Care: Current Guidelines and Future trends. Johns Hopkins University; Acute Care Nurse Practitioner Program; Baltimore, Maryland; April 2005.

Update on Acute Stroke Management for the Nurse Practitioner. Mid-Atlantic Regional Conference for Nurse Practitioners. Nurse Practitioner Association of Maryland. April 2004

The Role of the Acute Care Nurse Practitioner: Strategies for Success. Futures Conference. Association of Critical Care Nursing. Baltimore, Maryland. March 2004

Keynote Address: Stroke: Current Strategies & Future Directions. Human Anatomy & Physiology, Northeast Regional Conference; College of Southern Maryland; Oct 2003.

Update on Stroke Management for ED providers. ED Consortium. Upper Chesapeake Hospital. Bel Air, Maryland. July 2003

Brain Attack Management. 3rd Annual Update on Internal Medicine. Harbor Court Hotel. Baltimore, Maryland. May 2003

Telemedicine for Regional Stroke Education. Inaugural Scientific Forum on Cancer and Other Tobacco-Related Diseases. Marriott Hotel. Baltimore, Maryland April 2003.

Dispatcher Recognition of Acute Stroke. Inaugural Scientific Forum on Cancer and Other Tobacco-Related Diseases. Marriott Hotel. Baltimore, Maryland April 2003.

Use of a stroke Educational Poster in the office of a primary care provider. Inaugural Scientific Forum on Cancer and Other Tobacco-Related Diseases. Marriott Hotel. Baltimore, Maryland April 2003.

Ask the Expert. Television interactive stroke education session, WMAR–Channel 2, October 2002

Brain Attack for Pre-hospital providers: EMS refresher. Norrisville, Maryland, October 2002.

Stroke Education: Train the Trainer. Satellite Telemedicine Symposium, Western Maryland Community Nursing Association, October 2002.

Diagnosis, Management, and Treatment of Acute Brain Attack. University of Maryland Graduate School of Nursing, September 2002.

Emergency Stroke Update. Maryland State Firemen's Association, Maryland Fire and Rescue Institute. Ocean City, Maryland. June 2002.

Emergent Treatment of Acute Ischemic Stroke, Including the Intravenous Administration of Thrombolytic Therapy. American Academy of Neurology. Washington D.C., June 2002.

Stroke Certification Course. Western Maryland Health Department. Deep Creek, Maryland. June 2002

Update on Stroke Management: Pre-hospital Provider. Washington County Hospital Annual Refresher Course. Hagerstown, Maryland May 2002

Stroke Prevention: Know Your Risk. Maryland Statewide Stroke Awareness Day, American Stroke Association. Baltimore, Maryland, May 2001.

Acute Stroke Clinical Trials: Ethical Issues & Common Pitfalls. ARGIS-I Principal Investigator Meeting. Texas Biotechnology Corporation. San Diego, California, February 2001.

Interfacility Transport of the Brain Attack Patient. Maryland ExpressCare Paramedic Annual Program. Baltimore, Maryland, January 2001.

Update on Acute Stroke Management and Stroke Clinical Trials. Emergency Department Educational Update, North Arundal Hospital, Maryland, September 2000.

Management of Stroke and Transient Ischemic Attack. Acute Care Nurse Practitioner Diagnosis and Management Course, University of Maryland School of Nursing, September 2000.

Neurological Assessment. Critical Care Nurse Practitioner Program. University of Maryland School of Nursing, September 2000

Stroke: Defining the Therapeutic Window. Trends in Critical Care Concepts. University of Maryland Medical System, September 2000.

Learning the Warning Signs of Stroke. Maryland Backyard Bash 2000. The American Heart Association, Maryland Council, September 2000.

Health Promotion: Acute Care Nurse Practitioner Review Course. Health Leadership Associates, Washington D.C., May 22, 2000.

Brain Attack: Stroke Recognition and Treatment. Maryland State Firemen's Association Conference, Ocean City, Maryland, June 18-21, 2000.

Management of the Acute Stroke Patient. 20th Annual National Nurse Practitioner Symposium. Baltimore, Maryland, April 2000.

Management of Acute Stroke. Critical Care Nursing Annual Symposium, American Association of Critical-Care Nurses, Columbia, MD, March 2000.

Primary and Secondary Stroke Prevention. Medicare Excellence Conference, HCFA, Baltimore, MD, January 2000.

Role of the Acute Care Nurse Practitioner in an Academic Setting. American Academy of Neurology: Annual Meeting, Seattle, WA, October 1999.

Brain Attack: Risk Reduction and Symptom Recognition. May is Stroke Awareness Month Talk Series, American Heart Association, May 1999.

Brain Attack for Pre-Hospital Providers. Montgomery County Paramedics, May 1999.

Update on Brain Attack: Considerations during Air Transport. Maryland Institute for Emergency Medical Services Systems (MIEMSS), April 1999.

Diagnosis, Management, and Treatment of Acute Brain Attack. University of Maryland Graduate School of Nursing, October 1998.

Concepts of Intracranial Pressure. Albany Medical Center, March 1998.

Post-Operative Management after Brain Tumor Resection. Grand Rounds, Buffalo VA Medical Center, January 1998.

Caring for the Patient undergoing Anterior Cervical Discectomy. Syracuse VA Medical Center, November 1997.

Basic Concepts of Neurological Assessments. Grand Rounds, Syracuse VA Medical Center, October 1997.

Nurses Making a Difference. National Nurses Week Celebration, University Hospital Syracuse, NY, May 1997.

_____

Mona N. Bahouth, MD, MSN