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Cerebral blood flow change with fluid resuscitation in acute ischemic stroke

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Abstract:

BACKGROUND: In acute ischemic stroke (AIS), cerebral autoregulation becomes dysfunctional, impacting the brain's ability to maintain cerebral blood flow (CBF) at adequate levels. Reperfusion of affected and nearby brain tissue in AIS is currently the aim of treatment in AIS, but the effectiveness of fluid resuscitation on increasing the CBF is debated.

OBJECTIVE: We investigated the hypothesis that early fluid resuscitation with normal saline bolus would improve CBF velocity in the initial resuscitation of patients with AIS.

METHODS: We conducted a prospective, quasi-experimental study on 30 patients in the early stages of AIS management. Patients had a National Institutes of Health Stroke Scale (NIHSS) score of 3 or higher. Patients met inclusion criteria if they were 18–90 years old and had time of stroke onset within 12 h. Patients with a severe underlying disability, hemorrhagic stroke, advanced directives for comfort care/hospice, as well as pregnant patients were excluded. Noninvasive hemodynamic monitoring was performed. We performed transcranial Doppler (TCD) insonation of the middle cerebral arteries (MCAs) to measure CBF velocity. Each patient received a 500-ml normal saline crystalloid bolus as a standardized intervention, then had hemodynamic and TCD measurements repeated. Analysis was limited to patients with stroke confirmed with neuroimaging. Mean flow velocity (MFV) was compared before and postreceiving the bolus in the MCA ipsilateral to the ischemic location.

RESULTS: Thirty patients were analyzed who had confirmed AIS. The mean age was 53 ± 13 years, 50% were female, and the median NIHSS was 6 (interquartile range: 4–7). Outcomes measured included various cerebrovascular and cardiovascular parameters. Infusion of 500-mL normal saline bolus produced increases in systolic blood pressure (+7 mmHg, 95% confidence interval [CI] 0.6–13 mmHg) and stroke volume (SV) index (+2.2 ml/m^2, 95% CI 0.3–4.1 ml/m^2). The mean change in MFV was not statistically significant (+0.3 cm/s, 95% CI-3.7–4.3 cm/s). An adjusted model showed higher age and lower baseline SV index were not associated with improved MFV following administration of the fluid bolus.

CONCLUSION: Our prospective study of AIS patients revealed that a fluid bolus improves hemodynamic parameters, but did not significantly increase CBF velocity.

TRIAL REGISTRATION: clinicaltrials.gov (identifier: NCT02056821).

Keywords:

Acute ischemic stroke, cerebral blood flow, fluid resuscitation, Transcranial Doppler

Introduction

In acute ischemic stroke (AIS), cerebral autoregulation has the potential to become dysfunctional. Cerebral autoregulation is the ability of the cerebrovascular system to maintain cerebral blood flow (CBF) at specific flow rates. This allows the brain to receive adequate nutrients and oxygen, despite external fluctuations in mean arterial pressure (MAP). When MAP is outside of normal limits (60–150 mmHg), cerebral autoregulation becomes dysfunctional and can potentially cause intracerebral hemorrhage or cerebral ischemia.[1,2] The

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mainstay of AIS management is reperfusion therapy, which aims to rescue the penumbra (the functioning tissue surrounding the infarct) from further tissue ischemia and irreversible infarction.[3,4]

The American Heart Association's (AHA) and American Stroke Association's current guidelines regarding AIS advise correcting existing hypotension and hypovolemia to sustain systemic perfusion levels essential for supporting physiological organ function.[3] In practice, the understanding of this recommendation is that patients who are euvolemic should receive maintenance fluids while those who are hypovolemic should receive a fluid bolus to maintain adequate MAP. Multiple prior observational studies have shown an association between lower blood pressures (BPs) and worse outcomes, while other studies did not.[5-12] Regardless, there is limited data to guide the volume or duration of parenteral fluid resuscitation during AIS episodes.[13]

With this in mind, the context of delivering a fluid bolus during AIS episodes becomes clearer. Some studies suggest that the benefit of a fluid bolus is due to AIS patients being dehydrated upon presentation, and thus an increase in their effective circulating volume would augment their ability to perfuse the body's vital organs.[14] Nevertheless, whether fluid resuscitation can increase CBF early in AIS management is not well studied. Here, we examined the effect of a crystalloid bolus on cardiac hemodynamic variables and CBF velocities as measured by transcranial Doppler (TCD).

Methods

This study was a prospective, quasi-experimental study at a busy urban emergency department (ED) that is in a comprehensive stroke care hospital from July 2014 to September 2016. Approval for the study was granted by the hospital's IRB, with either the patient or a legally authorized representative providing informed consent. We enrolled adult patients (aged 18–90) with suspected AIS presenting within 12 h of symptom onset and a National Institutes of Health Stroke Scale (NIHSS) of at least 3. Patients with AIS were enrolled in this study regardless of the involved segment (i.e., M1, M3) or large vessel occlusion (LVO) versus small vessel disease. We excluded patients with severe underlying disability (prestroke modified Rankin Scale over 3), pregnancy, intracranial hemorrhage on computed tomography imaging, treatment with thrombolysis or mechanical thrombectomy, or advanced directive for comfort care/hospice. Thrombolytic and mechanical thrombectomy patients were excluded due to concern that treatment-related reperfusion might confound TCD measurements of CBF velocity. We also excluded patients for analysis if their neurological imaging evaluation revealed that AIS was not present. Table 1 describes the clinical characteristics of patients who were enrolled.

Trained investigators obtained informed consent from the patient or representative and recorded baseline demographic and clinical characteristics. Neuroimaging studies were reviewed for stroke location. A trained clinician documented each patient's NIHSS upon arrival to the ED and on day 1 of hospitalization. An investigator used a clinically validated, noninvasive device for cardiac hemodynamic measurements (Nexfin device, Edwards Lifesciences, Irvine, CA).[15,16] This device uses pulse contour analysis to calculate patient cardiac hemodynamic data, including cardiac output (CO), cardiac stroke volume (SV), and indexed values. After initiating continuous hemodynamic measurements, a trained investigator also performed TCD imaging to measure the mean flow velocity (MFV) of the bilateral middle cerebral arteries (MCAs). The MFV measurements confirmed to be on the ipsilateral side to the acute stroke were used for analysis.

For analysis, we recorded the average of all TCD and hemodynamic measurements over 5-min periods,

Table 1: Clinical characteristics of the study participants

Characteristic	*n* (%)
Sex	
Male	15 (50)
Female	15 (50)
Age (years), mean±SD	62.5±13.1
Race	
Black	23 (77)
Hispanic	1 (3)
Other	1 (3)
White	5 (16)
Comorbid conditions	
Atrial fibrillation	4 (13)
Coronary artery disease	5 (17)
Cancer	7 (23
Congestive heart failure	2 (7)
Diabetes mellitus	12 (40)
Stroke or transient ischemic attack	11 (37)
Myocardial infarction	1 (3)
Hyperlipidemia	8 (27)
Hypertension	25 (83)
Pulmonary veno-occlusive disease	1 (3)
Chronic kidney disease	4 (13)
Tobacco use	10 (33)
Localization of stroke	
Cortical	10 (33)
Lacunar	14 (47)
Posterior	6 (20)
NIHSS, mean±SD	5.96±3.3
BUN/creatinine ratio, mean±SD	15.4±6.95

SD: Standard deviation, NIHSS: National Institutes of Health Stroke Scale, BUN: Blood urea nitrogen

regardless of localization of stroke or segment involvement. We reported continuous variables as median with interquartile range (IQR) or mean with standard deviation as suitable. We compared means using a paired Student's *t*-test. We used a multivariable linear regression model to test the modifying effect of baseline SV index and age on MFV change. Results were reported with 95% confidence intervals (CIs). A 2-sided $P < 0.05$ was considered statistically significant. Analysis was completed with SAS 9.4 (Cary, NC).

Results

We enrolled 38 patients, 30 of whom had confirmed acute, ischemic stroke. The mean age was 62 years (±13). Fifty percent of enrolled patients were female. The median NIHSS score was 6 (IQR 4, 7) and the initial systolic BP was 159 (±26) mmHg. Table 1 shows the clinical characteristics of enrolled patients. Table 1 also shows the distribution of regions affected by strokes.

Following infusion of a crystalloid bolus statistically significant increases in systolic BP (+7, 95% CI 0.6–13 mmHg) and SV index (+2.2, 95% CI 0.3–4.1 ml/m^2) were each appreciated [Table 2]. The mean difference in MFV, however, was not found to be significant (0.3, 95% CI-3.7–4.3 cm/s). Figure 1 shows the individual patient pre-and postfluid bolus change in MCA MFV.

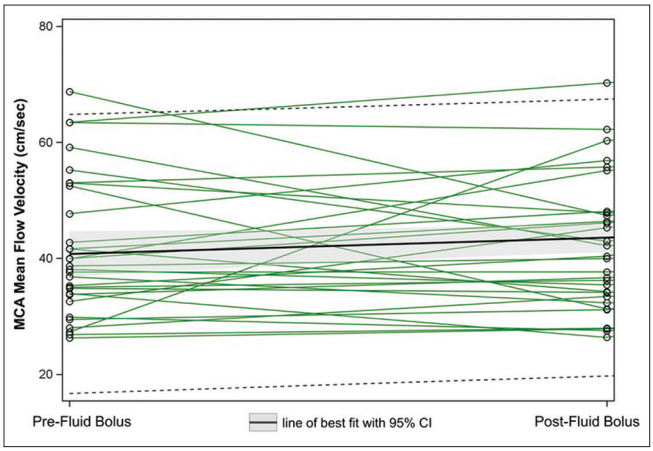

Figure 1: Mean Flow Velocity Before and After Fluid Bolus

In an exploratory linear regression model adjusting for age, baseline SV index, and systolic BP, we found no significant factors associated with change in MFV following a fluid bolus (adjusted $R^2 = 0.012$).

Discussion

In this small exploratory study, we found that a 500-ml crystalloid bolus produced a modest change in cardiac hemodynamic parameters but did not produce a significant change in cerebral MFV. These findings may reflect a cohort with overall intact cerebral autoregulation, or the change in cardiac hemodynamics was too modest to impact CBF.

Cerebral autoregulation is a complex, nonlinear system regulated by many factors, including but not restricted to myogenic, neurogenic, metabolic, and endothelial mechanisms.[22] Autoregulation maintains brain perfusion such that CBF is maintained during episodes of physiological strain. Because of acute stroke, autoregulation has the potential to fail and contribute to acute ischemia. Poor cardiovascular reserve, as may be seen if CO or SV is impaired, could compound the failure of cerebral autoregulatory mechanisms.

Current AHA guidelines for support of AIS patients include maintenance fluids for euvolemic patients and rapid fluid replacement in hypovolemic patients.[3] It is reasonable to administer intravenous fluids to AIS patients, particularly those at risk of dehydration.[14,23] Due to the limitations noted below, our study was limited to determine whether these guidelines translate to improvements in CBF. An analysis adjusting for baseline cardiac SV index, which if low could indicate hypovolemia, did not show an association with a significant effect from bolus intravenous fluids.

Another potential strategy to ensure adequate CBF is adjusting the patient's head position. Decreasing the angle of the head, so the circulation is no longer going against gravity,[24] is a potentially simple solution to improving CBF in the setting of altered autoregulation. Multiple studies have investigated what angle is best, with a meta-analysis by Olavarría *et al*. finding a significant MFV increase in only the affected hemisphere when the head position was

Table 2: Hemodynamic measurements before and after crystalloid fluid bolus[17-21]

Measurement	Prebolus	Postbolus	Change (95% CI)	Reference range
SBP (mmHg) (SD)	155 (33)	162 (35)	+7 (0.6–13)	<120
MAP (mmHg) (SD)	108 (22)	112 (22)	+3.6 (−1.0–8.1)	>60
CI (L/min/m^2)	2.9 (0.7)	3.1 (0.8)	+0.2 (−0.02–0.33)	2.5–4
SVI (ml/m^2) (SD)	40 (10)	42 (11)	+2.2 (0.3–4.1)	>35
MFV (cm/s) (SD)	42 (12)	42 (11)	+0.3 (−3.7–4.3)	<120

SBP: Systolic blood pressure, SVI: Stroke volume index, MFV: Mean flow velocity, CI: Cardiac index, SD: Standard deviation, CI: Confidence interval, MAP: Mean arterial pressure

0°–15° compared to at 30°.[24] A further multinational study (HeadPoST) assessed 90-day disability or serious adverse events in patients who were assigned to either 0° or 30° and found no significant difference between either angle.[25] Whether intravascular volume status and head position interact in acute stroke care remains unknown.

In this exploratory study assessing the efficacy of a 500 ml 0.9% normal saline bolus in AIS patients, we found infusion of the bolus failed to cause a significant increase in CBF velocity. We did find that the bolus led to an expected increase in cardiac hemodynamic parameters. The design of future research on fluid administration may take a more pragmatic approach in evaluating the effects of volume resuscitation. Notably, a similar study by Mullen *et al*. has also noted relative increases in CBF in response to administration of crystalloid bolus, although likewise failed to establish clinical relevance with their findings.[26]

Our study had significant limitations. One such weakness is the small sample size; our sample was 38 patients and had a small overall range of measured hemodynamic parameters, with average mild-to-moderate stroke severity. We sought to enroll patients early in their stroke presentation, however, considering the difficulties of confirming a diagnosis of AIS and the requirements for obtaining informed consent, the study cohort was smaller than originally planned and included only mild-to-moderate severity strokes. Moreover, the only criteria measured were immediate hemodynamic parameter improvement; long-term clinical outcomes, while relevant, were not assessed in this study. In addition, our hemodynamic measurements only utilized noninvasive monitoring, without echocardiographic or invasive confirmation; still, the Nexfin device has shown in previous studies to provide reliable measurements of hemodynamic change and is more feasible in this research setting than invasive measures.[15,16] As modern AIS treatment increasingly involves thrombolysis and thrombectomy, excluding patients who underwent these interventions may limit the generalizability and applicability of our findings in current clinical practice.[4] Finally, given the overall low stroke severity of included patients, it is possible cerebral autoregulation was not significantly dysregulated in this cohort. As this study assessed for individual patients' response to an intervention, it did not include a control group, who did not receive the fluid bolus, controlling for confounding variables between participants is difficult. The lack of data on the etiology of the AIS and LVO also holds potential implications for the generalizability of the results of this study.

Conclusion

In this sample of AIS patients, a crystalloid bolus overall did not increase CBF velocity, despite an improvement in cardiac parameters. While reperfusion therapy remains the mainstay of treatment, the role of fluid resuscitation in supporting CBF is not fully understood. Our findings suggest that a crystalloid bolus may produce modest changes in cardiac hemodynamic markers without significant impact on CBF velocity. Our study also faced substantial limitations including a limited sample size and ultimately the exclusion of patients with strokes of greater severity, which may have an impact on the transferability of our findings. Future research on fluid administration, including a more pragmatic approach to measuring its effects on CBF is warranted.

Author contributions

Joseph Miller: Conceptualisation, methodology, supervision; J Aidan Moloney: Writing- original draft preparation; Noah Elagamy: Writing- Reviewing and editing; Jacob Tuttle: review/editing; Sam Tirgari: review/editing; Sean Calo: data curation; Richard Thompson: data curation; Bashar Nahab: data curation; Christopher Lewandowski: conceptualization; Phillip Levy: conceptualization.

Ethical policy and institutional review board statement

The study was approved by the Henry Ford Health IRB (#12079, approved in March, 2014). The study was conducted in accordance with the Declaration of Helsinki.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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JM discloses that Edwards Lifesciences provided the Nexfin device at no cost but provided no other financial support.

Conflicts of interest

The Henry Ford Health System funded the study through an investigator-initiated grant. PL discloses the receipt of unrelated research funding from Edwards Lifesciences. The remaining authors declare that they have no conflicts of interest.

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