

Cerebral Blood Flow Response During Bolus Normal Saline Infusion After Ischemic Stroke

Michael T. Mullen, MD, MS,*† Ashwin B. Parthasarathy, PhD,‡ Ali Zandieh, MD,*
Wesley B. Baker, PhD,§¶ Rickson C. Mesquita, PhD,¶ Caitlin Loomis, MD,#
Jose Torres, MD,** Wensheng Guo, PhD,†† Christopher G. Favilla, MD,*
Steven R. Messé, MD,* Arjun G. Yodh, PhD,§ John A. Detre, MD,* and
Scott E. Kasner, MD*

Goals: We quantified cerebral blood flow response to a 500 cc bolus of 0.9% normal saline (NS) within 96 hours of acute ischemic stroke (AIS) using diffuse correlation spectroscopy (DCS). **Materials and Methods:** Subjects with AIS in the anterior, middle, or posterior cerebral artery territory were enrolled within 96 hours of symptom onset. DCS measured relative cerebral blood flow (rCBF) in the bilateral frontal lobes for 15 minutes at rest (baseline), during a 30-minute infusion of 500 cc NS (bolus), and for 15 minutes after completion (post-bolus). Mean rCBF for each time period was calculated for individual subjects and median rCBF for the population was compared between time periods. Linear regression was used to evaluate for associations between rCBF and clinical features. **Results:** Among 57 subjects, median rCBF (IQR) increased relative to baseline in the ipsilesional hemisphere by 17% (−2.0%, 43.1%), $P < 0.001$, and in the contralesional hemisphere by 13.3% (−4.3%, 36.0%), $P < .004$. No significant associations were found between ipsilesional changes in rCBF and age, race, infarct size, infarct location, presence of large vessel stenosis, NIH stroke scale, or symptom duration. **Conclusion:** A 500 cc bolus of .9% NS produced a measurable increase in rCBF in both the affected and nonaffected hemispheres. Clinical features did not predict rCBF response.

Key Words: Cerebral blood flow—diffuse correlation spectroscopy—stroke, intravenous fluids—saline

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Introduction

In the normal brain, cerebral autoregulation maintains cerebral blood flow (CBF) at a constant level despite

variations in mean arterial pressure (MAP).¹⁻⁴ In patients with acute ischemic stroke, autoregulation is thought to be impaired and CBF may vary with changes in MAP.⁵⁻⁷ In acute stroke, clinical symptoms represent permanent

From the *Department of Neurology, University of Pennsylvania, Philadelphia, Pennsylvania; †Leondard David Institute for Health Economics, University of Pennsylvania, Philadelphia, Pennsylvania; ‡Department of Electrical Engineering, University of South Florida; §Department of Physics and Astronomy, University of Pennsylvania, Philadelphia, Pennsylvania; ¶Department of Neurology, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; ¶Institute of Physics, University of Campinas, Campinas, Brazil; #Department of Neurology, Yale University, New Haven, Connecticut; **Department of Neurology, New York University, New York City, New York; and ††Department of Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, Pennsylvania.

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Address correspondence to Michael Mullen, MD, MS, Department of Neurology, Hospital of the University of Pennsylvania, 3400 Spruce St, 3 West Gates, Philadelphia, PA 19104. E-mail: mmullen@pennmedicine.upenn.edu.

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damage to the infarct core, and reversible damage to surrounding tissue, the ischemic penumbra. Acute stroke therapies are intended to increase blood flow to the penumbra.

Simple approaches to increase CBF, such as lowering head of bed position and administration of intravenous .9% normal saline (NS) are used commonly in clinical practice, although their clinical utility is uncertain. Prior studies have shown that lowering head of bed has a small but measurable impact on CBF; although, a large cluster-randomized trial showed no difference in clinical outcomes between head of bed flat (0°) and elevated ($\geq 30^\circ$).⁸⁻¹¹ Similarly, volume expansion and hemodilution have been shown to increase CBF, but not to improve clinical outcomes.^{12,13} Limited data suggest that bolus NS increases regional CBF in patients with subarachnoid hemorrhage.¹⁴ Data on the CBF response to NS after ischemic stroke is limited.^{15,16}

We aimed to quantify the CBF response to a 500 cc bolus of NS administered within 96 hours of acute ischemic stroke. We employed diffuse correlation spectroscopy (DCS) to monitor changes in CBF. DCS is a transcranial noninvasive optical technique that uses near infrared light. DCS provides a real-time, continuous bedside measure of changes in CBF (ie, relative CBF, rCBF). Unlike near-infrared spectroscopy or diffuse optical spectroscopy, which measures oxy- and deoxy-hemoglobin tissue concentration and uses blood volume as a surrogate for changes in blood flow, DCS, a newer technique, directly quantifies microvascular CBF. Relative CBF measured with DCS has been validated against other blood flow imaging/monitoring technologies, and DCS has been used to measure changes in CBF in both healthy and stroke subjects.^{8,11,17-25} The significance of this work is two-fold. First, by quantifying the rCBF response to bolus NS, this study provides information about the physiologic response to an intervention that is frequently used in clinical practice. Second, this study demonstrates the potential for DCS, a real-time continuous monitor of rCBF, to quantify individual response to an intervention over an extended period of time. With continued technical refinement, this technology holds the potential to enable clinicians to individualize care and optimize CBF.

Materials and Methods

Population

A single center, nonrandomized, pilot, single arm time-series clinical trial was conducted at a single comprehensive stroke center and was approved by the University of Pennsylvania institutional review board. Inclusion criteria included: age ≥ 18 years, acute ischemic stroke in the territory of the anterior, middle, or posterior cerebral artery territory, and enrollment within 96 hours of symptom onset. Exclusion criteria included: infarct limited to the brainstem and/or cerebellum, bi-hemispheric infarcts or infarct in the contralesional hemisphere within the past 30 days, symptoms

of active congestive heart failure (dyspnea, orthopnea, increased oxygen requirement), exacerbation of congestive heart failure requiring hospitalization within the past 30 days or severe systolic dysfunction with ejection fraction $<20\%$, end-stage renal disease requiring hemodialysis or creatinine clearance <20 mL/min/1.7m², hemicraniectomy or other skull defect, pregnant women, current enrollment in another clinical trial, and any other illness or condition that the enrolling investigator felt would pose a hazard to the subject from participating in the study.

Study Measurements and Intervention

After informed consent was obtained, demographic and clinical variables were recorded, including past medical history, infarct location, size, vascular imaging results, and the National Institute of Health stroke scale (NIHSS). The DCS probe was placed on the patient at the temporal margin of the forehead bilaterally (supplemental Fig 1).

The custom DCS instrument used in this study measures relative cortical CBF using near-infrared light. The details of this device have been described previously.²³ The instrument uses a laser (785 nm, 80 mW, CrystaLaser Inc., Reno NV) of constant intensity and custom fiber-optic detectors (Fiberoptic Systems, CA) integrated onto a 2 cm x 5 cm rubber probe. Light transmitted through tissue was detected at 1.0 cm and 2.5 cm source-detector separations. Unlike near-infrared spectroscopy/diffuse optical spectroscopy, which indirectly estimates changes in CBF based on measured changes in oxy- and deoxy-hemoglobin, DCS provides a direct measure of microvascular CBF by quantifying temporal fluctuations of the intensity of light scattered by moving red blood cells. Temporal fluctuations in the detected light intensity are quantified using an intensity temporal autocorrelation function computed with custom software. An index of CBF is derived by fitting the measured light intensity temporal autocorrelation functions to a solution of a 2-layer light diffusion model through tissue.^{26,27}

After the DCS probes were placed and secured with a cloth headband, the patient was asked to remain in bed and to be still for the duration of the monitoring session. For the first 15 minutes of the 60-minute monitoring session there was no NS infusion (baseline), then 500 cc of .9% NS was infused over 30 minutes (bolus). Monitoring continued for 15 minutes after the completion of the bolus (postbolus). During the monitoring session, heart rate and blood pressure were recorded every 15 minutes. The patient was assessed for adverse events during the monitoring session and 24 hours after the monitoring session.

Relative changes in CBF were estimated for each subject. Details of this analysis methodology are presented in the online supplement. DCS intensity autocorrelation functions were preprocessed to remove and correct for motion artifacts. Intensity autocorrelation functions at 1.0 and 2.5 cm source detector separations were processed together to estimate changes in CBF. We employed the

modified Beer Lambert law for flow, adapted for a 2-layer tissue photon diffusion model to account for the influence of blood flow changes in the scalp.^{26,27} As a final post processing step, rCBF measurements that were less than -100% or greater than 250% were considered nonphysiologic, and were removed to reduce bias from measurement error. This correction affected only 1% of the measured CBF values.

Analysis

We hypothesized that bolus administration of NS would increase CBF in the ipsilesional hemisphere, and that there would be no change in CBF in the contralesional hemisphere. Baseline demographics and clinical information were summarized using descriptive statistics. The NIHSS stroke scale was categorized as mild (0-4), moderate⁵⁻⁹ and severe (10+). Infarct location was categorized as: anterior cerebral artery (ACA), posterior cerebral artery, anterior middle cerebral artery (MCA) with cortical involvement, posterior MCA with cortical involvement, and deep MCA territory without cortical involvement (subjects could be in multiple categories). Infarct volume was estimated using the ABC/2 method and categorized as <15 cc, 15-30 cc, and >30 cc.^{28,29} Infarct etiology was classified as cardioembolism, large vessel atherosclerosis, small vessel, cryptogenic, and other/multiple. Ipsilesional large vessel stenosis was categorized as <50%, 50%-95%, and near occlusion/occlusion. Baseline MAP was the mean of the MAP recorded at the start of monitoring (time 0 minutes) and immediately before initiation of NS bolus (time 15 minutes); postbolus MAP was the mean of MAP recorded immediately after completion of the NS bolus (time 45 minutes) and at the end of monitoring (time 60 minutes).

The mean rCBF values in each time period (baseline, bolus, and postbolus) were calculated for each subject. The median values for the entire population were summarized and signed rank test was used to compare rCBF at baseline and bolus as well as rCBF at baseline and postbolus. Postbolus rCBF was summarized across key clinical subgroups, including infarct size (<15 cc and \geq 15 cc), ipsilesional large vessel stenosis (<50%, and 50%-100%), infarct location (ACA and/or anterior MCA territory versus all others), and NIHSS (0-4 versus 5+). Categories were dichotomized given the relatively small number of subjects. Finally, the change in mean rCBF from baseline to postbolus was calculated for each subject. Univariate linear regression was used to quantify the relationship between clinical features and change in rCBF, with the plan to create a multivariable model including any variables associated at $P < .05$ in the univariate analysis. We hypothesized that larger infarcts, ipsilesional large vessel stenosis, ACA and/or anterior MCA location, and higher NIHSS would be associated with a greater increase in rCBF. In an exploratory analysis we used linear regression to quantify the association between the change in rCBF and

the change in MAP from baseline to postbolus. Finally, mixed effects regression was used to estimate the relationship between rCBF and time as a linear relationship in the baseline and bolus time periods. This model used restricted maximum likelihood estimation, unstructured covariance, and included an interaction term to estimate the change in slope after the start of the NS bolus (time \times NS bolus), which represents the relative increase in rCBF attributable to the saline infusion. All analyses were conducted separately in the ipsilesional and contralesional hemisphere using Stata version 15 (StataCorp LLC, College Station, TX). A priori power calculations, which assumed rCBF would be normally distributed, correlation between baseline and postbolus rCBF of .6-.8 and a standard deviation of 10%-15%, suggested that 57 subjects would provide 80% power to detect a 5% increase in rCBF.

Results

A total of 81 subjects were enrolled. A technical advancement in DCS fiber optic probe design which increased signal-to-noise ratio occurred after the first 8 subjects; these subjects were excluded because their data were not comparable to later subjects. There were 5 subjects who failed to complete the monitoring session and 11 subjects were excluded due to poor data quality (details in supplemental Table 1). The remaining 57 subjects were analyzed. Baseline characteristics of these subjects are summarized in Table 1.

MAP increased from median (IQR) of 100.1 mmHg (93.2-110.0 mmHg) at baseline to 104.8 (96.7-113.9) postbolus period ($P < .001$). Median rCBF (% change) across all subjects and its IQR is shown in Figure 1 for both the ipsilesional and contralesional hemispheres. All data points from all subjects are shown in supplemental Figure 2. Median rCBF by hemisphere and time period is shown in Table 2. The difference in rCBF between baseline and bolus, and between baseline and postbolus was significant in both hemispheres ($P < .05$ for all comparisons using Wilcoxon signed rank test). The median rCBF was numerically greater in the ipsilesional hemisphere, although there was not a statistically significant difference between the hemispheres in the bolus (rCBF ipsilesional = 13.8%, rCBF contralesional = 8.0%, $P = .39$) or postbolus time periods (rCBF ipsilesional = 17.0%, rCBF contralesional = 13.3%, $P = .64$).

Postbolus rCBF across clinical subgroups is summarized in Table 3. Univariate regression results, evaluating the association between clinical factors and the change in rCBF from baseline to postbolus, is presented in Table 4. There were no statistically significant associations in the ipsilesional hemisphere. In the contralesional hemisphere, there was a smaller change in rCBF among subjects with an ACA and/or anterior MCA infarction compared to other locations. The data did not support our pre-existing hypotheses that larger infarcts, greater NIHSS, anterior MCA location, and ipsilesional large vessel stenosis

Table 1. Study population

Variable	N	
Age, median (IQR)	57	61 (53-72)
Female	26	46%
Race		
White	30	53%
Black	26	46%
Other	1	2%
Past medical history		
Hypertension	41	72%
Diabetes	10	18%
Hyperlipidemia	28	49%
Atrial fibrillation	6	11%
Congestive heart failure	2	4%
CAD/Prior MI	8	14%
Chronic kidney disease	2	4%
Peripheral artery disease	4	7%
Prior stroke	11	19%
Smoking status		
Current	12	21%
Former	20	35%
Time from onset, median (IQR)	66 (49-83)	
<48 h	14	25%
48+ h	43	75%
NIHSS at monitoring, median (IQR)	2 (1-7)	
NIHSS 0-4	39	68%
NIHSS 5-9	8	14%
NIHSS 10+	10	18%
Infarct Location		
ACA	2	4%
Anterior MCA, cortical involvement	24	42%
Posterior MCA, cortical involvement	14	25%
MCA, deep penetrator only	20	35%
PCA	4	7%
Infarct Volume, median (IQR)	2 (1-9)	
<15 cc	47	84%
15-30 cc	5	9%
>30 cc	4	7%
Infarct etiology		
Cardioembolism	12	22%
Large vessel atherosclerosis	10	18%
Small vessel lacune	9	16%
Cryptogenic	18	32%
Other/multiple	8	14%
Ipsilesional large vessel stenosis		
<50%	43	75%
50%-95%	5	9%
Near occlusion/occlusion	9	16%

would be associated with a greater increase in rCBF. Graphs of rCBF over time by clinical subgroup are presented in supplemental Figures 3-7. Multivariable regression was not performed due to lack of associations in the univariate analysis. We did not detect a significant association between the change in rCBF and the change in MAP from baseline to postbolus (Figure 2A, ipsilesional hemisphere: $\beta = .1$, 95% CI: $-.8$ to 1.1 , $P = .80$; Figure 2B: contralesional hemisphere: $\beta = -.5$, 95% CI: -1.5 to $.5$, $P = .35$).

In the mixed effects regression, the interaction term for time \times NS bolus was significant in both the ipsilesional ($\beta = .05$, 95% CI: $.03$ -. 07 , $P < .001$) and contralesional hemispheres ($\beta = .08$, 95% CI: $.05$ -. 11 , $P < .001$), representing a significant change in slope after the start of the NS bolus. Over the 30-minute bolus time period this equates to a 6.0% increase in rCBF in the ipsilesional hemisphere (95% CI: 3.2-8.8) and a 9.4% increase in rCBF in the contralesional hemisphere (95% CI: 6.3-12.6). Estimates from the mixed effects regression differ from the primary analysis because the model attempts to account for changes in rCBF over time in the baseline period.

The study intervention was well tolerated; no serious adverse events occurred. There were 3 adverse events which were possibly related to the study intervention: an IV infiltrated in 1 patient, monitoring stopped due to a systolic blood pressure >220 mm Hg in 1 patient, and 1 patient, who was in atrial fibrillation at the start of the monitoring session, had tachycardia during the monitoring session which was asymptomatic.

Discussion

In patients with acute ischemic stroke, 500 cc of .9% NS administered over 30 minutes was associated with a measurable increase in rCBF in both the ipsilesional and contralesional hemispheres. There was not a statistically significant difference between hemispheres.

Fluid resuscitation is a common treatment strategy in acute ischemic stroke. American Heart Association guidelines recommend correction of hypovolemia, but note "there are no data to guide volume and duration of parenteral fluid delivery."^{30,31} Our study provides evidence that a 500 cc bolus of NS results in increased CBF. This builds on prior reports showing increased cerebral perfusion measured using MRI during induced hypertension from isotonic fluids and confirms a physiologic rationale for the use of bolus isotonic fluids in the early management of ischemic stroke and/or in patients with fluctuating symptoms.³²⁻³⁴

Our results raise several important questions. First, it is uncertain whether the measured changes in rCBF could have a meaningful clinical impact. Prior studies of hemodilution and/or volume expansion have failed to demonstrate an improvement in clinical outcomes, and overly aggressive fluid resuscitation has the potential to be harmful.^{13,35} Second, there was wide variability in rCBF response to bolus NS across subjects, as illustrated by the wide IQR for rCBF. This may be due in part to the heterogeneous patient population. Also, studies have questioned the extent of autoregulation impairment after stroke, suggested that the range of autoregulation is narrower than classical models, and suggested that autoregulation curves may vary across subjects; all of which may also be contributing to the observed variability.^{2,36-42} Finally, although we expected the contralesional hemisphere to serve as a control, with no change in CBF during saline infusion, we

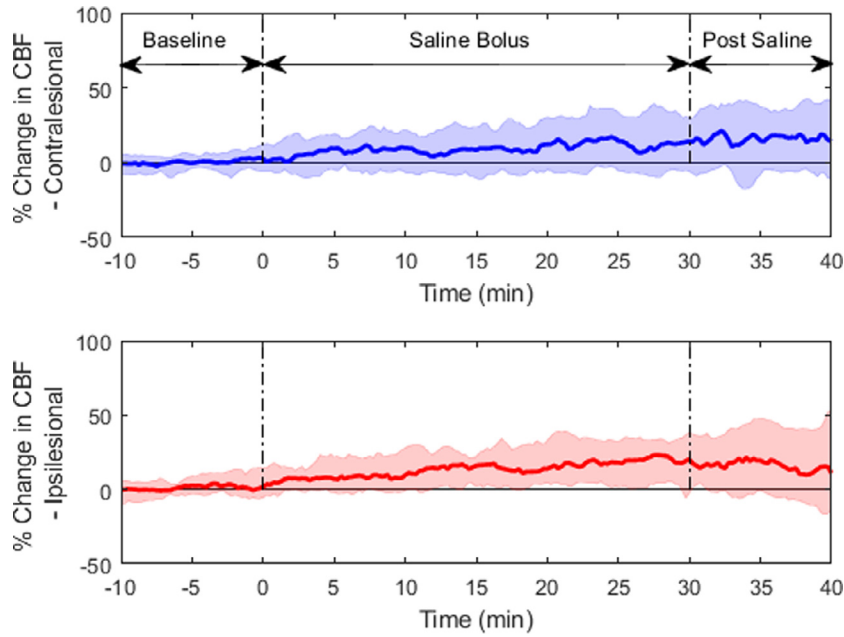


Figure 1. Time course of percent change in CBF; solid lines are median responses averaged across all subjects, shaded regions are IQRs. Abbreviation: CBF, cerebral blood flow.

observed increased CBF bilaterally. This change in CBF was not associated with changes in MAP. There is limited evidence from studies in healthy subjects that changes in cardiac output can lead to changes in CBF that is independent of changes in MAP.^{43,44} Unfortunately, we did not directly measure cardiac output or cerebral autoregulation in this study. Further study is necessary to address all of these important questions in order to better understand the CBF response to NS infusion, and to determine if there is any potential therapeutic benefit.

Still, our study highlights the potential utility of a real-time continuous CBF monitor, such as DCS, to inform and individualize stroke care. If individual CBF response to interventions cannot be inferred by clinical factors or measurement of MAP, then direct measurement of CBF is required to maximize therapeutic benefit. This logic applies to a range of possible therapeutic approaches beyond NS, including head of bed position, volume expansion, cerebral vasodilators, or induced hypertension.

This study has limitations. Although the measured changes in rCBF were modest overall, some individual measurements were larger than would be expected given the intervention. DCS is a direct measure of microvascular CBF, which is more sensitive to arterial than venous

contributions.^{45,46} DCS CBF measurements have been validated against MRI techniques, Xenon CT, TCD, and fluorescent microspheres in both healthy controls and neurologically injured populations.^{17-19,21} Still, in the setting of extended monitoring across a wide range of subjects, measurement error could conceivably be biasing the results. DCS is an evolving technology and advancements in the field of optical imaging should help to improve its accuracy and utility in future studies. Key recent advancements include the ability to use a real-time software correlator to improve the temporal resolution of DCS measurements and the use of a pressure modulation algorithm to more accurately separate cerebral from extracerebral signals.²⁵ Additionally, with the use of indocyanine green as a dynamic contrast agent, DCS can be calibrated to generate absolute, rather than relative, estimates of CBF.^{47,48} The current study predates some of these advances. Additionally, the DCS probes used in this study measure rCBF in the frontal poles, and may not be sampling penumbra in many cases. Ongoing work is aimed at monitoring other cortical territories (ie through hair).

The monitoring session was not sufficiently long to know the duration of rCBF elevation after NS bolus. It

Table 2. Percentage change in CBF, relative to baseline, by time period

	Bolus		Postbolus	
	Median	IQR	Median	IQR
Ipsilesional Hemisphere	13.8%	(5.3, 23.5)	17.0%	(−2.0, 43.1)
Contralesional Hemisphere	8.0%	(−2.1, 21.0)	13.3%	(−4.3, 36.0)

IQR=interquartile range

Table 3. Percentage change in CBF, relative to baseline, in the postbolus time period, by clinical subgroup

Subgroup	N	Ipsilesional		Contralesional	
		Median (IQR)	P value	Median (IQR)	P value
Infarct size					
<15 cc	47	20.5% (-0.6, 43.6)	.06	13.3% (-4.3, 37.5)	.89
15 cc+	9	-2.0% (-15.1, 15.3)		21.3% (5.9, 28.4)	
Stenosis					
<50%	43	13.5% (3.4, 23.3)	.99	9.7% (-6.0, 22.5)	.54
50%-100%	14	17.9% (10.0, 28.1)		6.3% (1.3, 20.0)	
Location					
Anterior Cortical MCA	24	17.7% (-8.2, 36.1)	.69	3.0% (-22.4, 26.2)	.02
All others	33	17.0% (-.6, 43.4)		23.1% (5.9, 43.2)	
NIHSS					
NIHSS 0-4	39	18.8% (-10.6, 43.4)	.93	21.3% (-4.3, 37.5)	.24
NIHSS 5+	18	16.1% (1.1, 36.6)		5.4% (-15.6, 32.6)	
Time from onset					
<48 h	14	8.2% (-24.3, 29.1)	.19	3.0% (-15.6, 32.6)	.28
48+ h	43	18.8% (-.6, 43.6)		21.3% (1.8, 36.3)	

IQR, interquartile range

is also possible that response to bolus NS depends on intravascular volume status, which was not objectively measured. Because most patients were enrolled more than 24 hours after admission, it is likely that they had received some fluid resuscitation prior to enrollment. Given our relatively small sample size and the heterogeneous study population, there was limited power to detect significant differences across clinical subgroups. In particular, we had very few subjects with large infarcts and/or an ipsilesional large vessel occlusion.

Our comparison of change in rCBF to change in MAP is limited by the fact that blood pressure was measured only twice in the baseline and postbolus time periods. Continuous blood pressure monitoring would allow for a more rigorous analysis of the relationship between rCBF and MAP. Despite these limitations, it is notable that we were able to measure a significant change in rCBF in a population that was predominately comprised of minor strokes. These results highlight the power of DCS to detect small changes in CBF.

Table 4. Univariate linear regression

	Ipsilesional				Contralesional			
	β	Std Error	95% CI	P value	β	Std Error	95% CI	P value
Age (per year)	1.0	.3	(-.7, .7)	.98	-.2	.4	(-.9, .6)	.66
Race								
White	Ref				Ref			
Black/other	6.0	8.5	(-11.1, 23.1)	.49	8.3	9.2	(-10.2, 26.8)	.37
Volume								
<15 cc	Ref				Ref			
15 cc+	-19.6	11.5	(-42.7, 3.5)	.10	.1	12.4	(-24.8, 24.9)	1.00
NIHSS								
0-4	Ref				Ref			
5+	4.3	9.2	(-14.1, 22.6)	.65	-11.7	9.8	(-31.4, 8.0)	.24
Location								
ACA or Anterior MCA	-5.9	8.6	(-23.1, 11.4)	.50	-19.7	9.0	(-37.7, -1.7)	.03
Other	Ref				Ref			
Stenosis								
<50%	Ref				Ref			
50%-100%	-1.1	9.9	(-21.0, 18.8)	.91	13.1	10.6	(-8.2, 34.3)	.22
Time from onset								
<48 h	Ref				Ref			
48+ h	17.8	8.6	(-1.5, 37.1)	.07	11.2	10.7	(-10.2, 32.5)	.30

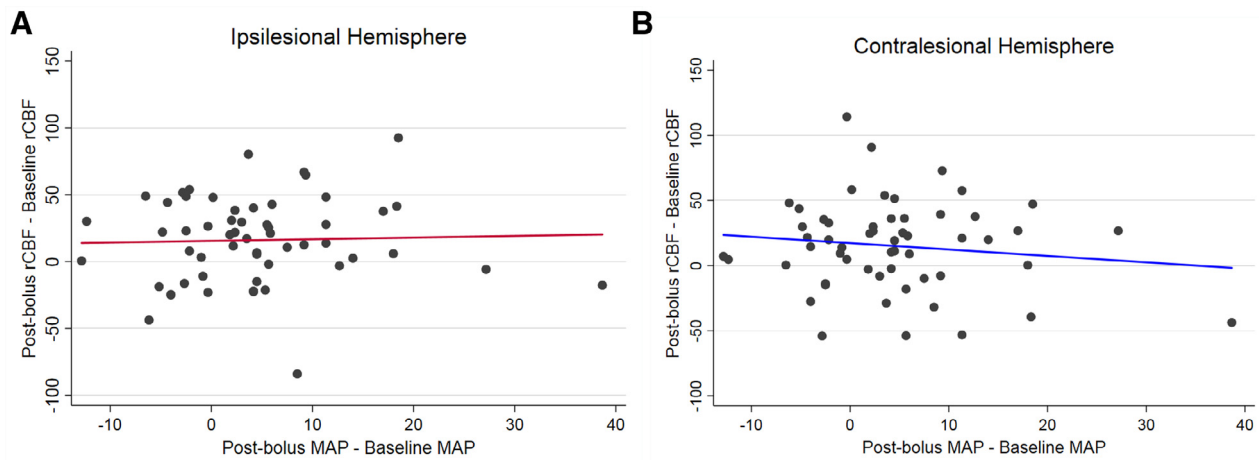


Figure 2. Change in rCBF (postbolus mean rCBF—baseline mean rCBF) and change MAP (postbolus MAP—baseline MAP) are graphed by subject. Linear regression showed no significant relationship in the ipsilesional hemisphere (A, $\beta = .1$, 95% CI: $-.8$ to 1.1 , $P = .80$) or the contralesional hemisphere (B, $\beta = -.5$, 95% CI: -1.5 to $.5$, $P = .35$). Abbreviation: rCBF, relative cerebral blood flow.

Conclusions

A 500 cc bolus of .9% NS, administered over 30 minutes, resulted in a measurable increase in rCBF in subjects with acute ischemic stroke. There was significant interindividual variability in rCBF response, which was not associated with measured clinical factors or with change in MAP. This study highlights a potential physiologic rationale for the use of isotonic fluid resuscitation in acute ischemic stroke, although more study is needed to better understand the physiologic response to saline infusion and to determine whether observed changes in rCBF are clinically meaningful.

Declaration of Competing Interest

Arjun Yodh and John Detre are inventors on patents submitted on behalf of the Trustees of the University of Pennsylvania that have at least some overlap with this research: US10,064,554, US8,082,015, and provisional patent 2016036101717 (A.Y. and J.D.) and US6,076,010 (A.Y.). The study was conducted in accordance with the University of Pennsylvania conflict of interest policy. This conflict of interest was disclosed on the informed consent document. Neither Dr. Detre nor Dr. Yodh consented any study subjects involved in this study. They did not personally acquire the primary data nor did they calculate the results of the primary data.

Author Contribution Statement

Michael T. Mullen—study design, subject enrollment, data collection, data analysis, data interpretation, manuscript preparation; Ashwin B. Parthasarathy—data collection, data analysis, data interpretation, manuscript preparation; Ali Zandieh—subject enrollment, data collection; Wesley B. Baker, PhD - data collection, data analysis, data interpretation, manuscript preparation; Rickson C. Mesquita—study design, data interpretation, manuscript

preparation; Caitlin Loomis—subject enrollment, data collection, manuscript preparation; Jose Torres - subject enrollment, data collection, manuscript preparation; Wensheng Guo—statistical approach, data analysis, data interpretation, manuscript preparation; Christopher G. Favilla—data collection, manuscript preparation; Steven R. Messé—study design, data interpretation, manuscript preparation; Arjun G. Yodh—study design, data interpretation, manuscript preparation; John A. Detre—study design, data interpretation, manuscript preparation; and Scott E. Kasner—study design, data interpretation, manuscript preparation.

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Supplementary Materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2019.07.010.

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