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Vasopressor Infusion after Subarachnoid Hemorrhage Does Not Increase Regional Cerebral Tissue Oxygenation

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Abstract

Introduction—Vasopressors are commonly used after aneurysmal subarachnoid hemorrhage (aSAH) to sustain cerebral pressure gradients. Yet, the relationship between vasopressors and the degree of cerebral microcirculatory support achieved remains unclear. This study aimed to explore the changes in regional cerebral and peripheral tissue oxygen saturation (rSO₂) as well as blood pressure (BP) before and after vasopressor infusion in aSAH patients.

Methods—Continuous non-invasive cerebral and peripheral rSO₂ was obtained using near-infrared spectroscopy for up to 14 days after aSAH. Within-subjects differences in rSO₂ before and after the commencement of vasopressor infusion were analyzed controlling for Hunt and Hess grade and vasospasm.

Results—Of 45 patients with continuous rSO₂ monitoring, 19 (42%) received vasopressor infusion (all 19 on norepinephrine, plus epinephrine in 2, phenylephrine in 4, and vasopressin in 2). In these 19, their vasopressor infusion times were associated with higher BP (systolic [b=15.1], diastolic [b=7.3] and mean [b=10.1], $p=0.001$), but lower cerebral rSO₂ (left cerebral rSO₂ decreased by 4.4% [b=-4.4, $p<0.0001$]; right cerebral rSO₂ decreased by 5.5% [b=-5.5, $p=0.0002$]).

Conclusions—Despite elevation in systemic BP during vasopressor infusion times, cerebral rSO₂ was concurrently diminished. These findings warrant further investigation for the effect of induced hypertension on cerebral microcirculation.

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Keywords

cerebral oxygen; norepinephrine; cerebral blood flow; subarachnoid hemorrhage

INTRODUCTION

Aneurysmal subarachnoid hemorrhage (aSAH) is often associated with poor functional and cognitive outcomes,¹ which are attributed to the initial hemorrhage as well as secondary complications such as cerebral vasospasm, delayed cerebral ischemia, or myocardial injury.^{2–4} These complications can result in lower levels of cerebral blood flow and oxygenation.^{5,6} Vasoactive drugs may be utilized to improve cerebral blood flow, particularly when cerebral vasospasm is suspected, to maintain a pressure gradient sufficient to perfuse the brain.^{1,2,7} Although the effect of vasopressors on improving mean arterial pressure and thereby cerebral macrovascular perfusion pressure is well established,⁸ their simultaneous impact on the cerebral tissue oxygenation is not well studied.

Near-infrared spectroscopy (NIRS) assesses the concentration differences between oxygenated and deoxygenated hemoglobin,⁹ by deriving the ratio of oxy-hemoglobin concentration to the total hemoglobin concentration, thus reflecting the proportion between cerebral oxygen extraction and supply.¹⁰ A decrease in NIRS values indicates an increase in oxygen extraction or insufficient delivery, leading to cerebral ischemia. NIRS has been utilized in patients with intracranial injuries including aSAH to measure regional cerebral tissue oxygen saturation (rSO₂) as well as in healthy subjects to assess the effect of vasopressors on cerebral oxygenation.^{11–13} However, there is conflicting evidence regarding the effect of vasopressor administration on rSO₂ measured by NIRS among different patients/subjects populations. In healthy volunteers, a norepinephrine infusion of 0.1 mcg/kg/min was associated with decreased frontal lobe oxygenation and internal jugular venous oxygen saturation.¹⁴ While others have reported that norepinephrine infusion improved cerebral rSO₂ in aSAH patients with impaired cerebral autoregulation.⁷ Yet, the effectiveness of vasopressor infusion on improving cerebral microcirculation as assessed by cerebral tissue oxygen in the general population of aSAH remains understudied. The aim of this study was to explore the effect of vasopressor infusion on regional and peripheral rSO₂ as well as systemic blood pressure (BP) for patients diagnosed with aSAH.

MATERIAL AND METHODS

This was a prospective longitudinal study (R01NR014221) approved by the local institutional review board, and all patients (or surrogates) provided consent prior to enrollment.

Patients and Setting

This study was conducted at a Comprehensive Stroke and Level I Regional Resource Trauma Center in Western Pennsylvania. Inclusion criteria were: aSAH within five days prior to admission, ages 21–75 years, and Fisher grade >1. Exclusion criteria were: mycotic aneurysm, recurrent aSAH, or chronic debilitating neurological deficit. Patients were

recruited between 10/18/2014 and 11/02/2016. The diagnoses of subarachnoid hemorrhage and aneurysm rupture were confirmed by computerized tomography (CT) scan and digital subtraction angiography. After eligibility criteria were confirmed, patients or their legal representatives were approached by the research team. The study procedures were explained in detail and patients/legal representatives were given the choice to voluntarily participate in the study. Data collection started immediately after patient's approval.

This study was conducted in a high volume medical center where treatment of aneurysms included either endovascular or surgical aneurysm obliteration. Patients were monitored in the neurovascular intensive care unit (NVICU) for up to 14 days per institutional aSAH protocol. An external ventricular drain was used for cerebrospinal fluid diversion and to intermittently monitor intracranial pressure in patients with Hunt and Hess grades 3–5 and /or in the presence of hydrocephalus. Oral Nimodipine was used in the standard of dose 60 mg every 4 hours but if hypotensive then 30 mg every 2 hours. Vital signs were assessed continuously via bedside monitoring and charted bi-hourly unless patients exhibited signs of clinical deterioration, in which case more frequent assessments were obtained.

Blood Pressure Management and Monitoring

Blood pressure monitoring commenced at the time of NVICU admission. In the acute phase of care and during vasopressor infusion, BP was continuously monitored primarily via arterial catheter. Once patients stabilized, arterial catheters were discontinued and blood pressure was monitored using a non-invasive blood pressure cuff. All recorded BP values (invasive and noninvasive) were downloaded from the electronic medical record and utilized.

Per institutional aSAH care protocol, initial target systolic BP was <120–140 mmHg before securing the aneurysm, and liberalized following aneurysm repair. In patients with neurological deterioration and/or cerebral vasospasm after aneurysm repair, systolic BP was targeted at >160 mmHg or minimum of 20 mmHg above average for stay. To achieve this goal, systolic BP below threshold was first treated with fluid optimization, and then supported with vasopressor infusion to maintain systolic BP above the target range. The vasopressor of choice was norepinephrine, with the addition of epinephrine, phenylephrine or vasopressin as needed to achieve the goal.

Cerebral and Peripheral Regional Tissue Oxygen Saturation

Continuous non-invasive cerebral and peripheral rSO₂ commenced immediately following study enrollment using NIRS (INVOS Cerebral Oximeter, Somanetics, Troy, MI, USA). Cerebral rSO₂ was acquired utilizing two separate sensors affixed to the left and right forehead, while peripheral rSO₂ was obtained utilizing a single sensor attached to either the left or right hand thenar eminence. Sensors remained in place until patients were discharged from the NVICU, or earlier if they requested sensor removal. Continuous cerebral and peripheral rSO₂ values were recorded every 5 milliseconds and then averaged on 5-minute intervals for statistical analyses.

Vasopressors

Vasopressor infusion was used for BP support as described. Vasopressors were analyzed as a time-varying variable, and each patient in the sample, all of whom received pressors at some point, had their BP and cerebral and peripheral regional tissue oxygen saturation data tagged as receiving or not receiving vasopressors at each rSO₂ or BP time point. The main vasopressor used was norepinephrine with a starting dose was 0.04 mcg/kg/min and titration was based on targeted systolic BP. Other vasopressors infused, additive to norepinephrine, were epinephrine, phenylephrine, and vasopressin.

Cerebral Vasospasm

Neurological examinations were performed bi-hourly or more frequently if clinical deterioration was noted. Cerebral vasospasm was assessed by digital subtraction angiography which was performed on day 7 post bleeding or whenever patients exhibited neurological deterioration that couldn't be explained by CT scan, EEG, or other assessment tools. Cerebral angiography was performed and scored by an independent neurosurgeon with a narrowing of <25% indicating no spasm, 25–75% indicating moderate spasm, and >75% indicating severe spasm. Severe vasospasm was controlled for in the statistical analyses.

Statistical Analyses

Descriptive statistics and frequency distributions using IBM SPSS 24 were utilized to describe the sample. The sample was restricted to only patients receiving vasopressor, to serve as their own controls (data during times vasopressor not infusing) and cases (data during times when vasopressor was infusing). This within-subject case and control design was done to achieve better control over extraneous variables. Comparisons of rSO₂ and BP at the times of presence or absence of vasopressor infusion were performed using means and standard deviations. To take into account for the repeated measures within each subject, we used mixed model linear regression (SAS 9.3) to test if cerebral rSO₂, peripheral rSO₂, and BP (systolic, diastolic, and mean) were statistically different between vasopressor infusion time, and times off pressors. Vasopressors group assignment (on or off) was treated as a time-varying variable. All multivariate analyses were conducted while controlling for Hunt and Hess grade. Importantly, severe angiographic vasospasm was also controlled for in the analyses.

RESULTS

Out of 45 patients with continuous rSO₂ data, 19 (42%) received vasopressors. The mean age for those patients (n=19) was 56.7±10.5 years, 84% were female, and 79% were Caucasian. Approximately, 26% of patients had HH grade 2, 48% had HH grade 3, 21% had HH grade 4, and 5% had HH grade 5. BP monitoring commenced upon admission to the NVICU, while rSO₂ monitoring was started after aneurysm securement in all patients. The mean time from injury to starting monitoring was 10.2±11.6 hours for BP, and 64.7±33.1 hours for continuous rSO₂ monitoring. The mean monitoring duration was 322.6±30.5 hours (13.4±1.3 days) for BP and 242.8±68.4 hours (10.1±2.8 days) for rSO₂. All 19 patients who received vasopressors received norepinephrine infusion (100%), of whom 2 (11%) also received epinephrine, 4 (21%) also received phenylephrine, and 6 (32%) also received

vasopressin. Six of the 19 patients (32%) had severe angiographic vasospasm, while 5 (26%) had moderate vasospasm. The remaining 8 patients with vasopressors had no evidence of severe or moderate angiographic vasospasm.

Descriptively, the cerebral rSO₂ mean values for the total sample were greater when vasopressors were not infusing (left = 64.4±9.2; right = 67.2±9.2) than during vasopressor infusion (left = 59.7±7.2; right = 60.6±8.2). However, the peripheral rSO₂ mean values for the total sample were slightly greater during vasopressor infusion times (60.4±11.0) compared to times with no vasopressor infusion (58.7±11.6) [Table 1]. To test if these observed within-subjects differences were statistically significant, mixed model linear regression analysis was conducted and revealed that during vasopressor infusion times there was significantly lower bilateral cerebral rSO₂ even after controlling for Hunt and Hess grade and severe angiographic vasospasm. During vasopressor infusion times, left cerebral rSO₂ was decreased by 4.4% (b= -4.4, *p* < .0001) and right cerebral rSO₂ decreased by 5.5% (b= -5.5, *p* = .0002), while there was a nonsignificant increase in peripheral rSO₂ by 1.5% (b= 1.5, *p* = .457) [Table 2].

Mean values for systolic, diastolic and mean arterial BP were greater during vasopressor infusion times (160.6±25.8, 79.1±16.2, and 106.3±18.6, respectively) than for times when no vasopressors were infusing (142.7±29.7, 70.2±16.7, and 93.7±19.3 respectively) [Table 1]. The analysis of mixed model linear regression showed that systolic BP was increased by 15 mmHg [b=15.1], diastolic BP was increased by 7.3 mmHg [b=7.3] and mean BP was increased by 10 mmHg [b=10.1] during vasopressor infusion times, also while controlling for HH grade and severe angiographic vasospasm (*p* = .0001) [Table 2].

DISCUSSION

With patients serving as their own cases (times with vasopressors infusing) and controls (times when vasopressors not infusing), although BP significantly increased during times of vasopressor infusion, cerebral rSO₂ significantly decreased during infusion times, even after controlling for severe vasospasm and Hunt and Hess grade.

It is unclear whether vasopressors contributed to further drop in cerebral rSO₂, or whether the drop in cerebral rSO₂ was due to dynamic nature of vasospasm, but the vasopressors blunted a further decrease (i.e. cerebral rSO₂ may have been worse without vasopressors). Importantly, in 8 patients with vasopressors but no evidence of cerebral vasospasm, a decrease in cerebral rSO₂ was observed during vasopressor infusion. This finding suggests that the noted depression of cerebral rSO₂ is not due exclusively to vasospasm, but perhaps a direct result of global microcirculatory vasoconstriction induced by vasopressors. In contrast, there was an improvement in the peripheral saturation during the same times of vasopressor infusion, although not statistically significant.

A negative relationship between vasopressor infusion and cerebral oxygenation has been reported in the literature. In a case report by Zeiler et al.,¹⁵ two patients with aSAH demonstrated worsening neurological exam after norepinephrine was initiated to treat delayed cerebral ischemia, and then neurologic improvement as soon as norepinephrine was

discontinued. In patients undergoing carotid endarterectomy, Sato et al.,¹⁶ reported that despite the positive effect of norepinephrine on blood pressure, it was associated with decreased left and right frontal cerebral oxygen saturation. Important to the current study, healthy subjects who received a norepinephrine dose of 0.1 mcg/kg/min or higher had a decrease in cerebral oxygenation as well as decreased internal jugular venous oxygen saturation.¹⁴ In a study by Gaither et al.,¹⁷ patients with delayed cerebral ischemia were randomized to induced hypertension with norepinephrine or not, and those with norepinephrine did not display an overall improvement in cerebral blood flow by computed tomographic perfusion during infusion.

In animal experiments, norepinephrine infusion has been shown to cause vasoconstriction and consequent decrease in oxygen saturation in the cerebral microvasculature.¹⁸ Meybohm et al.,¹⁹ conducted an experiment in which they induced hypotension in seven piglets by withdrawing blood, after which norepinephrine infusion was initiated. The applied norepinephrine infusion did not result in a significant increase in brain tissue oxygen. In a study of sheep, norepinephrine infused at doses of up to 60 mcg/min did not change cerebral oxygen consumption.²⁰ Likewise, epinephrine administration to patients during cardiopulmonary resuscitation did not result in significant improvement in cerebral rSO₂.²¹

Although norepinephrine has been demonstrated in some studies to result in short-term neurologic improvement, long-term outcome improvement has yet to be demonstrated.^{22,23} Findings from the current study as well as those from others suggest that further study with larger samples into these seemingly disparate effects of vasopressors on cerebral and peripheral microcirculation is warranted, as well as examination of a mechanistic explanation, including the role of intact or impaired autoregulation, the ability of vasopressors to cross the blood brain barrier, and the integrity of this barrier after aSAH.^{7,12,24} Possibly, further study regarding vasodilatory and other inotropic agents should also be further explored,¹⁵ to determine if they might result in greater short term benefit as demonstrated by cerebral microcirculation, and the long term benefit as demonstrated by mortality, functional, and cognitive outcomes. It is also possible that both the complex mechanisms thought to be causative for vasospasm as well as genetic predisposition may warrant variable treatments across the population as well.^{22,23,25}

This study has a number of limitations. The sample size was small, albeit greater than other studies examining this question.^{11,26,27} The small sample also lends to limited variation in demographic, aneurysm treatment and bleed severity, leading to limited generalizability. We did not formally assess cerebral autoregulation, vasopressor dose effect, intravascular volume, or the amount of administered intravenous fluid. These variables could be examined in a larger sample to provide more insight to our findings. Also, there are several variables that we did not control for and might have affected rSO₂ levels such as body and head position, hemoglobin levels, temperature, and mechanical ventilation. Lastly, rSO₂ measured by NIRS may be sensitive to changes in cerebral blood flow, but this is a limitation for the NIRS technology itself. Future studies will be needed to assess the effect of these potentially impactful variables.

CONCLUSIONS

In summary, patients with aSAH who were on vasopressors demonstrated increased blood pressure, but decreased cerebral tissue oxygen saturation as measured by near-infrared spectroscopy during pressor infusion times, even while controlling for injury severity (Hunt and Hess) and severe angiographic vasospasm. The degree to which vasopressors are helpful or harmful to cerebral microcirculatory support, and the dysynchrony between cerebral and peripheral microcirculatory impact require further study.

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TABLE 1

Total sample (n=19), univariate descriptive statistics for blood pressure and regional oxygen saturation while on or off vasopressors.

Variables	While Off Vasopressors		While On Vasopressors	
	Mean	SD	Mean	SD
SBP (mmHg)	142.7	29.7	160.6	25.8
DBP (mmHg)	70.2	16.7	79.1	16.2
MAP (mmHg)	93.7	19.3	106.3	18.6
Left cerebral rSO ₂ (%)	64.4	9.2	59.7	7.2
Right cerebral rSO ₂ (%)	67.2	9.2	60.6	8.2
Peripheral rSO ₂ (%)	58.7	11.6	60.4	11.0

Key: SBP = systolic blood pressure, DBP = diastolic blood pressure, MAP = mean arterial blood pressure
rSO₂ = regional tissue oxygen saturation

TABLE 2

Mixed model linear regression models (n=19) with norepinephrine infusion on as the independent variable (with Hunt and Hess grade and severe vasospasm as the covariates)

Pressure	Estimate	SE	p-value
SBP	15.1	4.4	.001
DBP	7.3	2.2	.001
MAP	10.1	2.9	.001
Left cerebral rSO ₂	-4.4	1.05	<.0001
Right cerebral rSO ₂	-5.5	1.5	.0002
Peripheral rSO ₂	1.5	2.0	.457

Key: SBP = systolic blood pressure, DBP = diastolic blood pressure, MAP = mean arterial blood pressure, rSO₂ = regional tissue oxygen saturation

* each row represents a separate model.