ANESTHESIOLOGY

Ephedrine *versus* Phenylephrine Effect on Cerebral Blood Flow and Oxygen Consumption in Anesthetized Brain Tumor Patients

A Randomized Clinical Trial

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ABSTRACT

Background: Studies in anesthetized patients suggest that phenylephrine reduces regional cerebral oxygen saturation compared with ephedrine. The present study aimed to quantify the effects of phenylephrine and ephedrine on cerebral blood flow and cerebral metabolic rate of oxygen in brain tumor patients. The authors hypothesized that phenylephrine reduces cerebral metabolic rate of oxygen in selected brain regions compared with ephedrine.

Methods: In this double-blinded, randomized clinical trial, 24 anesthetized patients with brain tumors were randomly assigned to ephedrine or phenylephrine treatment. Positron emission tomography measurements of cerebral blood flow and cerebral metabolic rate of oxygen in peritumoral and normal contralateral regions were performed before and during vasopressor infusion. The primary endpoint was between-group difference in cerebral metabolic rate of oxygen. Secondary endpoints included changes in cerebral blood flow, oxygen extraction fraction, and regional cerebral oxygen saturation.

Results: Peritumoral mean ± SD cerebral metabolic rate of oxygen values before and after vasopressor (ephedrine, 67.0 ± 11.3 and 67.8 ± 25.7 μmol · 100 g^{-1} · min^{-1}; phenylephrine, 68.2 ± 15.2 and 67.6 ± 18.0 μmol · 100 g^{-1} · min^{-1}) showed no intergroup difference (difference [95% CI], 1.5 [–13.3 to 16.3] μmol · 100 g^{-1} · min^{-1} [$P = 0.839$]). Corresponding contralateral hemisphere cerebral metabolic rate of oxygen values (ephedrine, 90.8 ± 15.9 and 94.6 ± 16.9 μmol · 100 g^{-1} · min^{-1}; phenylephrine, 100.8 ± 20.7 and 96.4 ± 17.7 μmol · 100 g^{-1} · min^{-1}) showed no intergroup difference (difference [95% CI], 8.2 [–2.0 to 18.5] μmol · 100 g^{-1} · min^{-1} [$P = 0.118$]). Ephedrine significantly increased cerebral blood flow (difference [95% CI], 3.9 [0.7 to 7.0] ml · 100 g^{-1} · min^{-1} [$P = 0.019$]) and regional cerebral oxygen saturation (difference [95% CI], 4 [1 to 8]% [$P = 0.024$]) in the contralateral hemisphere compared to phenylephrine. The change in oxygen extraction fraction in both regions (peritumoral difference [95% CI], –0.6 [–14.7 to 13.6]% [$P = 0.934$]; contralateral hemisphere difference [95% CI], –0.1 [– 12.1 to 12.0]% [$P = 0.989$]) were comparable between groups.

Conclusions: The cerebral metabolic rate of oxygen changes in peritumoral and normal contralateral regions were similar between ephedrine- and phenylephrine-treated patients. In the normal contralateral region, ephedrine was associated with an increase in cerebral blood flow and regional cerebral oxygen saturation compared with phenylephrine.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Phenylepherine may reduce regional cerebral oxygen saturation in anesthetized patients without cerebral pathology when compared with ephedrine

What This Article Tells Us That Is New

- In adult patients with brain tumors, there were no differences in cerebral metabolic rate of oxygen in peritumoral regions or in the contralateral cerebral hemisphere after administration of ephedrine or phenylepherine

Patients with cerebral tumors often develop elevated intracranial pressure (ICP) and impaired autoregulation, which has the potential to cause cerebral ischemia.[1,2] During brain tumor surgery, one task for the anesthesiologist is therefore to maintain adequate cerebral perfusion pressure to ensure sufficient cerebral blood flow to meet metabolic demands. Induction of general anesthesia is often associated with a reduction in the mean arterial blood pressure (MAP) and cerebral perfusion pressure attributable to a decrease

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in cardiac output (CO) and systemic vascular resistance (SVR). Phenylephrine, a pure α-adrenergic agonist, and ephedrine, an indirectly acting α and β adrenergic agonist, are commonly administered during neurosurgical procedures to counteract cardiovascular depression and treat anesthesia-related hypotension.[3,4] However, near-infrared spectroscopy studies in anesthetized patients without cerebral pathology suggest that phenylephrine reduces regional cerebral oxygen saturation compared with ephedrine, despite a marked increase in the MAP.[4–8] It remains unclear whether these changes in brain oxygenation reflect significant regional changes in the cerebral metabolic rate of oxygen, cerebral blood flow, or both, specifically in response to phenylephrine and ephedrine administration.

Vasopressors increase vascular resistance and cerebral perfusion pressure, but in addition to improving the blood supply they may inadvertently impair the extraction of oxygen from blood by disturbing capillary flow patterns, despite achieving the target cerebral perfusion pressure.[9–11] The brain microcirculation is the primary site of oxygen exchange, and the effective capillary surface area available for oxygen extraction depends on the homogeneity of capillary flows.[12] Thus, although vasopressors modulate vascular smooth muscle cell tone mainly *via* α-adrenergic receptors, these receptors are also expressed on contractile pericytes downstream, and therefore vasopressor effects on brain oxygenation may not be derived from their effects on cerebral blood flow alone.[13]

In patients with cerebral pathology, elevated ICP and regional edema may compress individual capillaries, reducing tissue oxygenation by causing the shunting of oxygenated blood through the capillary bed.[14,15] In the context of brain tumor surgery, vasopressors are therefore administered under conditions in which affected brain tissue, paradoxically, may be susceptible to hypoxic injury despite the maintenance of normal cerebral perfusion pressure and cerebral blood flow.[12,15–17]

Using positron emission tomography, this randomized study aimed to quantify the effects of phenylephrine and ephedrine on the cerebral metabolic rate of oxygen in brain tumor patients. The cerebral metabolic rate of oxygen was determined in peritumoral tissue, which may be particularly sensitive to changes in oxygen delivery, and in contralateral brain tissue as a proxy for the value in normal brain tissue. As a secondary aim, we assessed the effects of phenylephrine and ephedrine on cerebral blood flow, the oxygen extraction fraction, and regional cerebral oxygen saturation. We hypothesize that phenylephrine reduces the cerebral metabolic rate of oxygen in both peritumoral and contralateral brain tissue compared with ephedrine. It is further hypothesized that a potential phenylephrine-induced decrease in the cerebral metabolic rate of oxygen in the selected brain regions is the result of the differential effects of the two vasopressors on the cerebral metabolic rate of oxygen, cerebral blood flow, and/or oxygen extraction fraction.

Materials and Methods

Trial Design

This study was a prospective, single-center, parallel-group, double-blinded, randomized and controlled trial that enrolled patients from November 1, 2016 to November 29, 2017. The trial protocol has been published previously.[18] Written informed consent was obtained from all participants. The trial was approved by the Central Denmark Region Committee on Health Research Ethics and registered at clinicaltrials.gov (NCT02713087) on February 10, 2016 by Dr. Koch (principal investigator). The trial was conducted in accordance with the Note for Guidance on Good Clinical Practice. Monitoring of the study was performed by the Good Clinical Practice Unit, Aarhus University Hospital, Aarhus, Denmark.

Patients and Randomization

We screened all patients aged 18 to 75 yr who were scheduled for elective craniotomy for supratentorial tumors with a minimum size of 3 cm (measured as the largest diameter in any plane on magnetic resonance imaging). Participants were approached and recruited by study staff, who evaluated patient eligibility, obtained informed consent, and enrolled the participants. Exclusion criteria were a history of allergy or intolerance to one of the study medications, an American Society of Anesthesiologists (ASA) Physical Status IV–VI, pregnancy (positive pregnancy urine test) or breastfeeding, renal failure (estimated glomerular filtration ratio less than 60 $ml \cdot min^{-1}$ per 1.73m^2), or the inability to give written informed consent.

Patients were randomized to receive the infusion of either ephedrine (2 $mg \cdot ml^{-1}$) or phenylephrine (0.1 $mg \cdot ml^{-1}$) in a 1:1 fashion. The doses for ephedrine and phenylephrine infusion were selected according to dosage and infusion schemes applied in previous studies and clinical recommendations.[19,20] In general anesthesia practice ephedrine is most commonly administered as a bolus injection. However, in contrast to the previous studies, in which ephedrine and phenylephrine were administered as bolus injections, an infusion regime was selected because of the necessity of maintaining a stable blood pressure throughout the positron emission tomography examination (lasting approximately 45 min).[4] The treatment allocation sequence was generated using permuted block randomization with a block size of 4 and was concealed with sequentially numbered sealed envelopes. Allocation and concealment were performed by a third-party colleague. On the day of surgery, a third-party nurse opened the envelope and prepared the study medication in 50-ml syringes, which were indistinguishable from each other and marked with a randomization code known only to the study nurses. The treating physicians, nurses, and patients were all blinded to the study group allocation. The capillary transit time heterogeneity,

a magnetic resonance imaging parameter, was initially and incorrectly defined as the primary outcome variable.[18] This was detected after the end of patient enrollment but before the unblinding and data analysis. Capillary transit time heterogeneity cannot be determined with positron emission tomography, and therefore the cerebral metabolic rate of oxygen was defined as the primary outcome variable.

Anesthesia, Monitoring, and ICP Measurement

On the day of surgery, patients were anesthetized in a room adjacent to the positron emission tomography scanner. All patients received anesthesia according to institutional guidelines. Accordingly, anesthesia was induced with propofol and remifentanil. A low dose of suxamethonium was administered to facilitate intubation. Anesthesia was maintained with a continuous infusion of propofol (4.8 to 12 mg · kg^{-1} · h^{-1}) and remifentanil (15 to 30 μg · kg^{-1} · h^{-1}).[18] The bispectral index (BIS) was continuously monitored. To ensure adequate and equal anesthetic depth in the two groups, the infusion rates of propofol and remifentanil were adjusted to maintain a BIS value between 40 and 60.[21] Controlled ventilation with 50% oxygen in air was applied and adjusted to achieve a pretreatment arterial carbon dioxide tension ($Paco_2$) between 35 and 45 mmHg (*i.e.*, normoventilation) and arterial oxygen tension (Pao_2) greater than 100 mmHg. After normoventilation was obtained, the ventilator settings were maintained throughout the positron emission tomography examination. Isotonic saline was infused at a rate of 3 ml · kg^{-1} · h^{-1}, and the patients were kept warm during the positron emission tomography examination. The oxygen saturation and heart rate were monitored. An intra-arterial catheter was inserted to obtain continuous blood pressure measurements and arterial blood gas samples. Cerebral oxygenation was monitored with near-infrared spectroscopy (INVOS cerebral oximeter, Covidien, USA) and continuously recorded during the positron emission tomography examinations.[22] The near-infrared spectroscopy sensor was placed on the forehead over the hemisphere contralateral to the tumor. This placement of the near-infrared spectroscopy sensor was selected for several reasons. First, we aimed to repeat the procedure used for previous cerebral oxygenation measurements performed in anesthetized subjects without cerebral pathology.[4,8,23] Second, bilateral near-infrared spectroscopy measurements were not possible because of the simultaneous placement of the frontal BIS electrode. Furthermore, the differences in tumor locations and sizes of the peritumoral area did not consistently allow for near-infrared spectroscopy measurements of cerebral oxygenation. The near-infrared spectroscopy electrode emits near-infrared light that passes through skin, bone, and other tissues at wavelengths that are differently absorbed by oxygenated and deoxygenated hemoglobin across the light spectrum (730 and 810 nm). The detector is sensitive to light absorption to a depth of approximately 3 cm. The near-infrared spectroscopy technology considers contributions from venous and arterial vessels at a 3:1 ratio, yielding the venous-weighted percentage of saturation.[22] Because ICP may influence cerebral blood flow and the cerebral metabolic rate of oxygen, particularly in the peritumoral area, the subdural ICP was measured after removal of the bone flap and before the opening of the dura mater as previously described.[24,25]

Experimental Protocol

The experimental protocol has previously been described.[18] Pretreatment positron emission tomography examinations, including cerebral blood flow and cerebral metabolic rate of oxygen measurements, were performed in the anesthetized patient before the administration of the study medication (fig. 1). The pretreatment MAP was defined as the first MAP measured at the time of the initial positron emission tomography transmission scan sequence. The study medication was initially infused with a dedicated venous line at 30 ml/hr and titrated to increase the MAP to at least 60 mmHg or by 20% relative to the pretreatment MAP.[4] Positron emission tomography measurements were repeated when the vasopressor treatment had raised the MAP to reach the desired plateau with stable values for 5 min (fig. 1). Infusion of the study medication was carefully titrated to avoid hypertension. Hypotensive episodes before the commencement of the study medication were treated with a temporary reduction in the dosage of the anesthetics and/or an additional bolus of 0.9% saline solution and atropine. Blood samples for the pre- and posttreatment gas analyses of Pao_2 and $Paco_2$ were drawn from the arterial catheter at the initiation of each positron emission tomography scan. After the positron emission tomography examinations, the anesthetized patient, with ongoing infusion of study medication was transported to the neurosurgical suite, where surgery was initiated and the ICP and cerebral perfusion pressure were measured.

Neuroimaging

Each patient was examined with a series of positron emission tomography sequences on a Siemens High-Resolution Research Tomography scanner to map the cerebral blood flow and cerebral metabolic rate of oxygen. A transmission scan of the head for attenuation correction purposes preceded the mapping of cerebral blood flow, which was measured with 500 millibeqeurel of intravenously injected [^{15}O]H_2O, and the cerebral metabolic rate of oxygen was measured with 1,000 millibeqeurel of [^{15}O]O_2 that was inhaled and then immediately exhaled. After the injection of [^{15}O]H_2O and the inhalation of [^{15}O]O_2, a five-minute or three-minute positron emission tomography image acquisition of the brain, respectively, was initiated together with arterial blood sampling *via* the radial artery catheter at a rate of 7 ml of blood per minute. The oxygen saturation and hemoglobin concentration were measured at four predefined time points

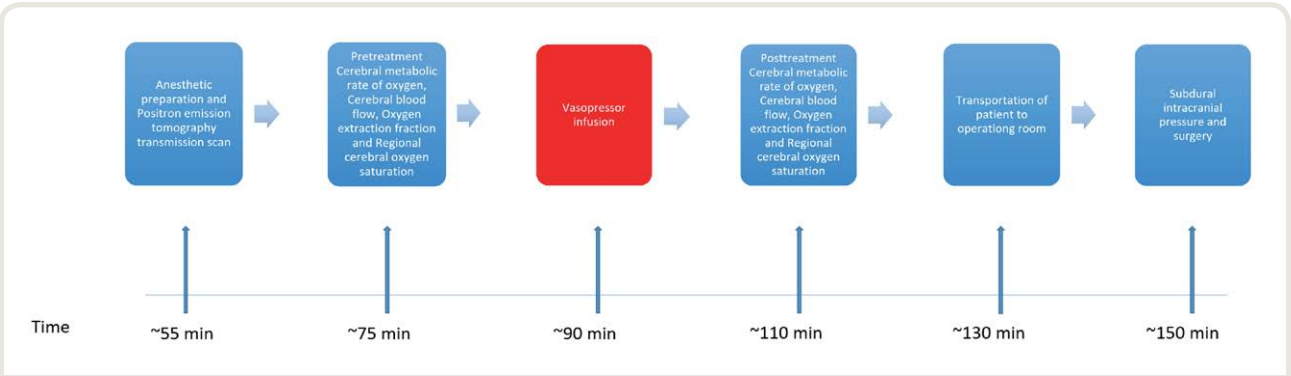

Fig. 1. The initial transmission scan sequence lasted 5 to 10 min, and then a paired session of $[^{15}O]H_2O$ and $[^{15}O]O_2$ administration was conducted that lasted 20 min. Infusion of the study medication and the steady-state period lasted until the desired effect on blood pressure was achieved (15 min). Finally, another 20-min paired session of $[^{15}O]H_2O$ and $[^{15}O]O_2$ administration ended the positron emission tomography examinations. Because it required approximately 65 min to complete the protocol, 45 min to anesthetize and prepare the patient, and 20 min to transport the patient, a total of approximately 130 min passed before the patient was ready for surgery. Another 20 min elapsed before the subdural intracranial pressure measurement.

during the scan procedure. All patients underwent magnetic resonance imaging of the brain as a consequence of clinical investigations performed during their preparations for surgery; T1-weighted magnetic resonance imaging was coregistered with positron emission tomography for each patient. Voxel wise estimation of the cerebral blood flow and cerebral metabolic rate of oxygen was performed using the arterial blood radioactivity as the input function and a one-tissue compartment model based on previous works.[26–28] The oxygen extraction fraction was calculated from the cerebral blood flow and cerebral metabolic rate of oxygen according to the following formula:

$$\text{Oxygen extraction fraction} = \frac{\text{Cerebral metabolic rate of oxygen}}{\text{Cerebral blood flow } CaO_2}$$

where CaO_2 is the arterial content of oxygen calculated as (hemoglobin concentration · oxygen saturation).[29]

The regions of interest were defined as the contralateral hemisphere gray matter and the peritumoral area, which is typically a mixture of gray and white matter. The contralateral hemisphere region of interest was defined according to the T1-weighted magnetic resonance images. The contralateral hemisphere region of interest was automatically calculated by the Perfusion Graphical User Interface, an in-house-developed software program. A minor manual correction was applied for midline herniation caused by the tumor in the opposite hemisphere. Both the tumor and surrounding peritumoral area were manually outlined for each patient on the T1- and T2-weighted images. Subtraction of the tumor from the combined tumor and the peritumoral outline finally defined the peritumoral area. The regions of interest outlined on the magnetic resonance images were subsequently coregistered to the positron emission tomography images (fig. 2).

The dynamic positron emission tomography images were coregistered according to the International Consortium for Brain Mapping ICBM152 space by using a stepwise process with an average of 152 T1-weighted magnetic resonance imaging scans.[30,31]

The individual magnetic resonance images in native space were coregistered to an in-house atlas magnetic resonance imaging brain in ICBM152 space by using a two-step process. First, a linear transformation of the individual magnetic resonance images was performed. Second, the linearly transformed magnetic resonance images were nonlinearly transformed to maximize the fit with the atlas brain.[32,33]

The individual positron emission tomography images were coregistered to the individual magnetic resonance images in native space, and then the positron emission tomography-to-magnetic resonance imaging and magnetic resonance imaging-to-ICBM152 transformation coordinates were combined to transform the positron emission tomography images to ICBM152 space, which was used to calculate all of the cerebral blood flow and cerebral metabolic rate of oxygen data. All transformation processes were done with the in-house software (Study Fit). Parametric maps were then calculated from the dynamic positron emission tomography images and time–activity curves obtained from the arterial sampling according to the methods of Ohta and Blomqvist.[26–28] In short, the model relies on Fick's principle and assumes 100% absorption of $[^{15}O]H_2O$ during the first pass.

Endpoints

The primary endpoint was the between-group difference in the cerebral metabolic rate of oxygen measured in the peritumoral surroundings and contralateral gray matter brain tissue. The secondary endpoints were the between-group

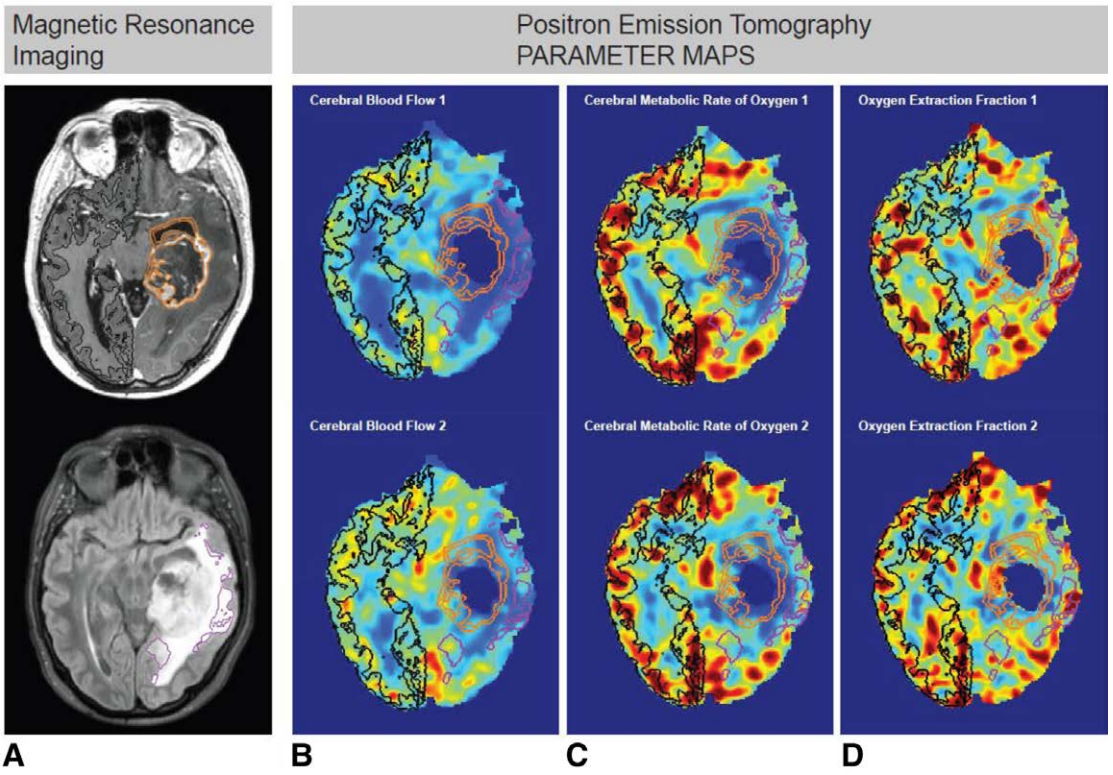

Fig. 2. Magnetic resonance and positron emission tomography images of a patient with a tumor in the left hemisphere. (*A*) The contralateral hemisphere region of interest, tumor region of interest, and peritumoral region of interest were outlined on magnetic resonance images. (*B–D*) Subsequently, the positron emission tomography parameter maps were coregistered to the magnetic resonance images (color maps of cerebral blood flow, cerebral metabolic rate of oxygen, and oxygen extraction fraction). The contralateral hemisphere is in *black*, the tumor is in *orange*, and the peritumoral area is in *pink*. Cerebral blood flow 1, cerebral metabolic rate of oxygen 1 and oxygen extraction fraction 1 denote the pretreatment conditions, and cerebral blood flow 2, cerebral metabolic rate of oxygen 2 and oxygen extraction fraction 2 denote the posttreatment conditions.

differences in cerebral blood flow, oxygen extraction fraction, and regional cerebral oxygen saturation.

Statistics

The study was designed as a superiority trial. No formal sample size analysis was performed, because no relevant references exist for the estimation of the magnitude of the difference between the effects of phenylephrine and ephedrine on the cerebral metabolic rate of oxygen in anesthetized patients. Accordingly, the sample size was based on two pieces of evidence. First, a study by Meng *et al.*,[4] which reported a 10% difference in the regional cerebral oxygen saturation between anesthetized patients treated with ephedrine and phenylephrine to be clinically significant. Second, a sample size calculation used in a magnetic resonance imaging study protocol, which has previously been described.[4,18] Here, the sample size calculation was based on an expected 10% difference in the capillary transit time heterogeneity between the phenylephrine and ephedrine groups.[18] The capillary transit time heterogeneity is a flow parameter measured by magnetic resonance imaging.[17,18]

The expected 10% difference in the capillary transit time heterogeneity was translated into an estimated prevasopressor magnetic resonance imaging − capillary transit time heterogeneity value of 3.216 s, and a 10% difference yielded a mean difference of 0.3216 s (difference of phenylephrine − difference of ephedrine ≥ 10%). Considering a significance level of 0.05 and a power of 0.9 ($\beta = 0.1$), a sample size of nine patients was required in each randomization arm of the study. To compensate for missing data and dropouts, the sample size was increased to a total of 12 patients in each arm of the study.

The ephedrine and phenylephrine groups were compared to determine the balance in terms of demographics with an independent samples *t* test. Differences in physiologic variables, brain monitoring, anesthesia, and positron emission tomography–derived parameters were assessed by the calculation of within- and between-group differences. The within-group changes over time were assessed

by using a paired Student *t* test. The between-group differences, including the primary and secondary outcomes, were assessed by using an independent-samples Student *t* test of the delta values. Quantile–quantile plots were constructed to confirm that each variable followed a normal distribution. All data are expressed and displayed as the mean ± SD unless the data did not follow a normal distribution. In this case, the data are represented as the median (25th percentile; 75th percentile), and the Wilcoxon rank sum test was applied to test whether there was any difference between groups.

All statistical hypothesis tests were two sided, with $P < 0.05$ considered statistically significant. The statistical analyses were performed with Stata V.14 (StataCorp, USA).

Results

Between November 1, 2016, and November 29, 2017, a total of 24 patients were enrolled, whereas 265 of the 289 screened patients did not enter the study (fig. 3). The most common reasons for study exclusion were a lack of scanner availability (102 of 289 [35%]), failure to conform to the inclusion criteria (94 of 289 [33%]), the unavailability of research staff (62 of 289 [21%]), or the patient declining to enter the study (7 of 289 [2.5%]). Among the 94 patients who failed to meet the inclusion criteria, the most common reasons were age and renal failure. The patient demographics in the two groups did not differ significantly (table 1). No adverse events were observed in the study, and there were no cases with unacceptable hypertension as a result of vasopressor infusion.

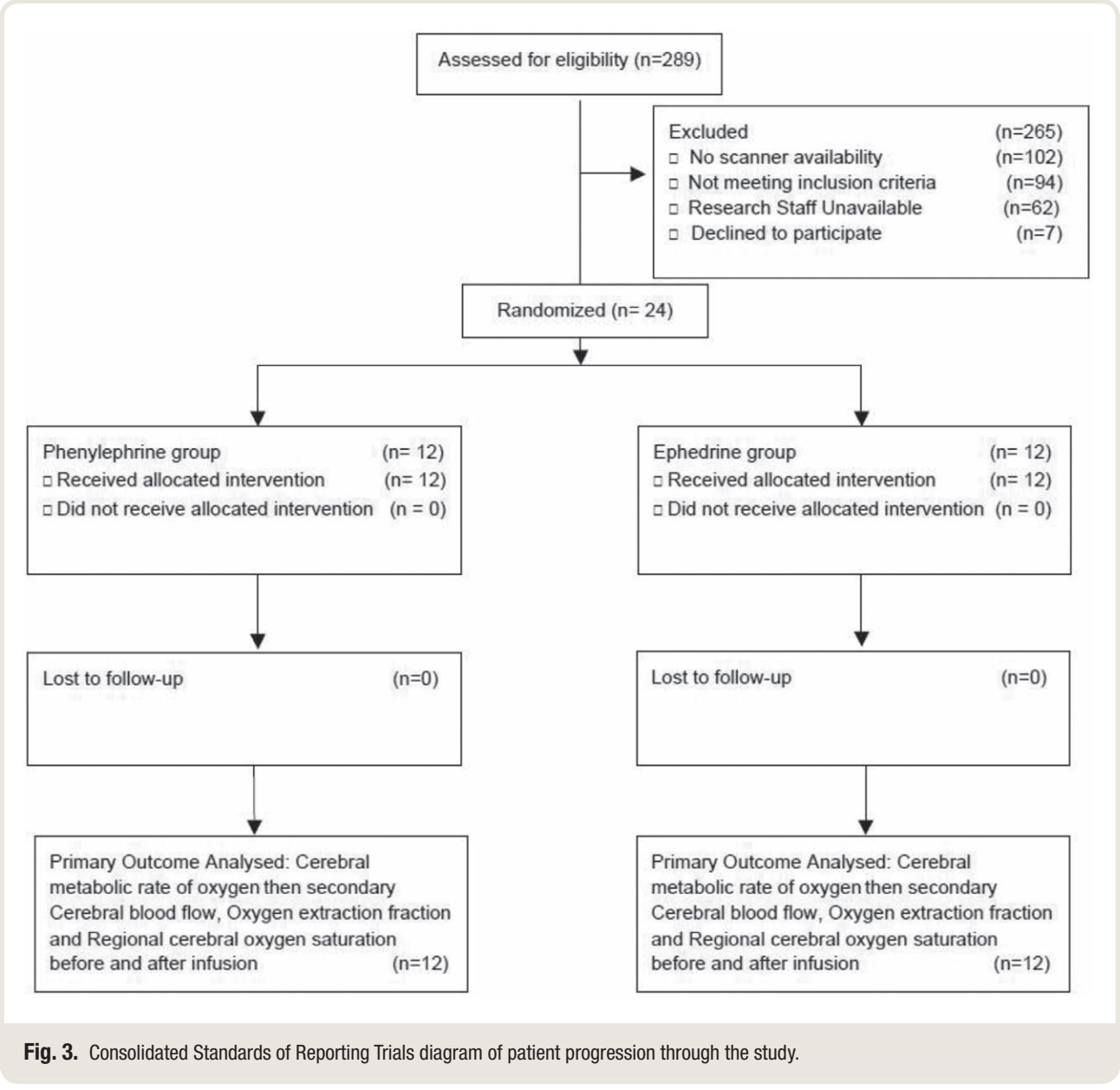

Fig. 3. Consolidated Standards of Reporting Trials diagram of patient progression through the study.

Table 1. Demographics

Demographics	Phenylephrine (n = 12)	Ephedrine (n = 12)	*P* Value
Age, yr	54 (36–66)	60 (43–74)	0.179
Gender, n (%)			
Male	6 (50)	5 (42)	
Female	6 (50)	7 (58)	
Weight, kg	83 ± 23	83 ± 18	0.977
Tumor pathology			
Meningeoma, n (%)	2 (8)	5 (21)	
Glioblastoma, n (%)	5 (21)	3 (12)	
Arteriovenous malformation, n (%)	1 (4)	0 (0)	
Cerebral metastasis, n (%)	3 (13)	4 (17)	
Astrocytom, n (%)	1 (4)	0 (0)	
Tumor size, cm^3	33.0 (19.8–54.8)	34.2 (23.3–56.2)	0.729

Data are presented as mean ± SD for continuous variables and frequency (%) for categorical variables. Tumor size did not follow the normal distribution, and thus data are given as median (25th percentile; 75th percentile) and the Wilcoxon rank-sum test was applied to test whether there was any group difference. The *P* value is the statistical difference between the phenylephrine and ephedrine group.

Comparison of Physiologic and Anesthetic Variables

The changes in physiologic and anesthetic variables are shown in tables 2 and 3 and figure 4. There was no significant intergroup difference between the pretreatment $Paco_2$ ($P = 0.145$), Pao_2 ($P = 0.759$), MAP ($P = 0.236$), heart rate ($P = 0.572$), regional cerebral oxygen saturation ($P = 0.139$), or BIS ($P = 0.777$).

Ephedrine was associated with a significant increase in $Paco_2$ compared with phenylephrine (difference [95% CI], 2.5 [1.2–3.9] mmHg [$P = 0.001$]). The difference of Pao_2 was higher in the phenylephrine group (difference [95% CI], −24.3[−38.6 to −10.1] mmHg [$P = 0.002$]). A comparable increase in MAP was observed in both groups ($P = 0.360$). A plot of the blood pressure *versus* time is shown for each patient in the Supplemental Digital Content (http://links.lww.com/ALN/C394). In addition, the heart rate decreased in the phenylephrine group and increased in the ephedrine group (difference [95% CI], 19 [13–25] beats per minute [$P < 0.0001$]).

Anesthetic Depth and Cerebral Oxygenation

Ephedrine induced a significant increase in regional cerebral oxygen saturation compared with phenylephrine (difference [95% CI], 4 [1–8] % [$P = 0.024$], table 3). The dosages of propofol and remifentanil were similar in the two groups ($P = 0.227$ and $P = 0.904$, respectively). However, there was a larger increase in the BIS during ephedrine treatment compared to that observed during treatment with phenylephrine (difference [95% CI], 5 [1–9] % [$P = 0.018$]), as shown in table 3 and figure 4. There was no difference in the subdural intracranial pressure and cerebral perfusion pressure between the two groups.

Cerebral Metabolic Rate of Oxygen, Cerebral Blood Flow, and Oxygen Extraction Fraction in Regions of Interest

In table 4, positron emission tomography–derived parameters are shown according to the region of interest (*i.e.*, the peritumoral area region of interest and the contralateral hemisphere region of interest).

Peritumoral Area

There was no intergroup difference in the pretreatment cerebral metabolic rate of oxygen ($P = 0.808$), cerebral blood flow ($P = 0.266$), or oxygen extraction fraction ($P = 0.326$). The posttreatment cerebral metabolic rate of oxygen showed no intergroup difference ($P = 0.839$). There was a similar small increase in the cerebral blood flow in both groups, and there was no statistically significant difference between the groups difference [95% CI], (3.4 [−0.7 to 7.6] ml · 100 g^{-1} · min^{-1} [$P = 0.101$]). The oxygen extraction fraction decreased

Table 2. Physiologic Variables

Physiologic Variables	Phenylephrine (n = 12)			Ephedrine (n = 12)			Difference Ephedrine – Difference Phenylephrine (95% CI)	*P* Value
	Pretreatment	Posttreatment	Difference Phenylephrine	Pretreatment	Posttreatment	Difference Ephedrine		
$Paco_2$, mmHg	39.0 ± 2.3	39.8 ± 3.0	0.8 ± 1.3	41.4 ± 4.5	44.7 ± 4.5	3.3 ± 1.9*	2.5 (1.2–3.9)	0.001
Pao_2, mmHg	134.3 ± 45.0	167.3 ± 52.5	33.0 ± 21.8*	129.8 ± 52.5	138.0 ± 52.5	8.3 ± 9.0*	–24.3 (–38.6 to –10.1)	0.002
MAP, mmHg	60 ± 9	81 ± 10	21 ± 6*	54 ± 13	78 ± 13	24 ± 7*	2 (–3 to 8)	0.360
Heart rate, beats per min	57 ± 6	53 ± 7	–4 ± 3*	55 ± 8	70 ± 14	15 ± 9*	19 (13 to 25)	0.0001

Data are presented as mean ± SD. Difference phenylephrine = posttreatment value of phenylephrine – pretreatment value of phenylephrine. Difference ephedrine = posttreatment value of ephedrine – pretreatment value of ephedrine. The *P* value is the statistical comparison between difference phenylephrine *versus* difference ephedrine. MAP, mean arterial blood pressure; $Paco_2$, arterial carbon dioxide partial pressure; Pao_2, arterial oxygen partial pressure.

*Significant effect of treatment within group.

Table 3. Brain Monitoring and Anesthesia

	Phenylephrine (n = 12)			Ephedrine (n = 12)			Difference Ephedrine – Difference Phenylephrine (95% CI)	*P* Value
	Pretreatment	Posttreatment	Difference Phenylephrine	Pretreatment	Posttreatment	Difference Ephedrine		
Brain monitoring								
Regional cerebral oxygen saturation, %	68 ± 7	68 ± 9	−0.5 ± 5	73 ± 9	77 ± 9	4 ± 3*	4 (1–8)	0.024
Anesthesia								
Bispectral index, %	41 ± 10	42 ± 9	0.8 ± 5	43 ± 9	48 ± 9	6 ± 5*	5 (1–9)	0.018
Propofol, mg		784 ± 150			894 ± 268		110 (−74 to 294)	0.227
Remifentanil, μg		2,272 ± 813			2,317 ± 1,000		45 (−726 to 817)	0.904
Study medication, μg/kg		12 ± 7			686 ± 481			Not applicable
Intracranial pressure and cerebral perfusion pressure								
Subdural intracranial pressure, mmHg		7 (2; 18)			8 (7; 16)		1	0.657
Cerebral perfusion pressure, mmHg		76 ± 13			72 ± 15		−4 (−17 to 8)	0.469

Data are presented as mean ± SD. Subdural ICP did not follow the normal distribution, and thus data are given as median (25th percentile; 75th percentile) and the Wilcoxon rank-sum test was applied to test whether there was any group difference. Difference phenylephrine = posttreatment value of phenylephrine – pretreatment value of phenylephrine. Difference ephedrine = posttreatment value of ephedrine – pretreatment value of ephedrine. The *P* value is the statistical comparison between difference phenylephrine *versus* difference ephedrine.

*Significant effect of treatment within group.

by a similar magnitude in terms of the pre- and posttreatment values in both groups ($P = 0.934$; fig. 4).

Contralateral Hemisphere

There was no intergroup difference in the pretreatment cerebral metabolic rate of oxygen ($P = 0.2$), cerebral blood flow ($P = 0.379$), or oxygen extraction fraction ($P = 0.177$). There was a decrease in the cerebral metabolic rate of oxygen during phenylephrine treatment and an increase, albeit not statistically significant, in the cerebral metabolic rate of oxygen during ephedrine treatment without intergroup differences (difference [95% CI], 8.2 [−2.0 to 18.5] μmol · 100 g^{-1} · min^{-1} [$P = 0.118$]; fig. 4). The cerebral blood flow increased during ephedrine infusion when compared with the increase in cerebral blood flow observed during phenylephrine infusion (difference [95% CI], 3.9 [0.7–7.0] ml · 100 g^{-1} · min^{-1} [$P = 0.019$]). The oxygen extraction fraction was reduced by the same degree in both groups with no intergroup difference ($P = 0.989$; fig. 4).

Discussion

This study shows that changes in cerebral metabolic rate of oxygen in peritumoral and contralateral regions of interest were not different between ephedrine- and phenylephrine-treated patients. However, ephedrine caused a statistically significant increase in cerebral blood flow in contralateral hemisphere and in P_{ACO_2}, regional cerebral oxygen saturation, and BIS when compared with phenylephrine.

Previous studies in anesthetized patients without cerebral pathology have shown that regional cerebral oxygen saturation decreases after phenylephrine treatment but remains unchanged after ephedrine treatment even though both agents are associated with a similar increase in MAP.[4,5,8,9] These findings may raise concerns regarding the use of phenylephrine for MAP augmentation, particularly in patients with cerebral pathology. In this study, regional cerebral oxygen saturation and cerebral metabolic rate of oxygen remained unchanged after phenylephrine treatment, but regional cerebral oxygen saturation showed a statistically significant increase after ephedrine treatment. The lack of a reduction in regional cerebral oxygen saturation after phenylephrine treatment is possibly explained by administration of phenylephrine as a continuous infusion, which is in contrast to previous studies, where phenylephrine was administered as a bolus dose.[4,6–8] Absence of a statistically significant association between regional cerebral oxygen saturation and cerebral metabolic rate of oxygen after ephedrine treatment indicates that changes in regional cerebral oxygen saturation may not adequately reflect changes in cerebral metabolic rate of oxygen. Thus, possible concerns regarding the use of phenylephrine in patients with cerebral pathology, which is based on cerebral oximetry, may not be justified. Furthermore, a clinically relevant dosage regimen of phenylephrine was not associated with a reduction in cerebral metabolic rate of oxygen, which further indicates that the drug is safe for neurosurgical procedures.

In this study, both vasopressors caused a similar increase in MAP compared with the pretreatment values, and the

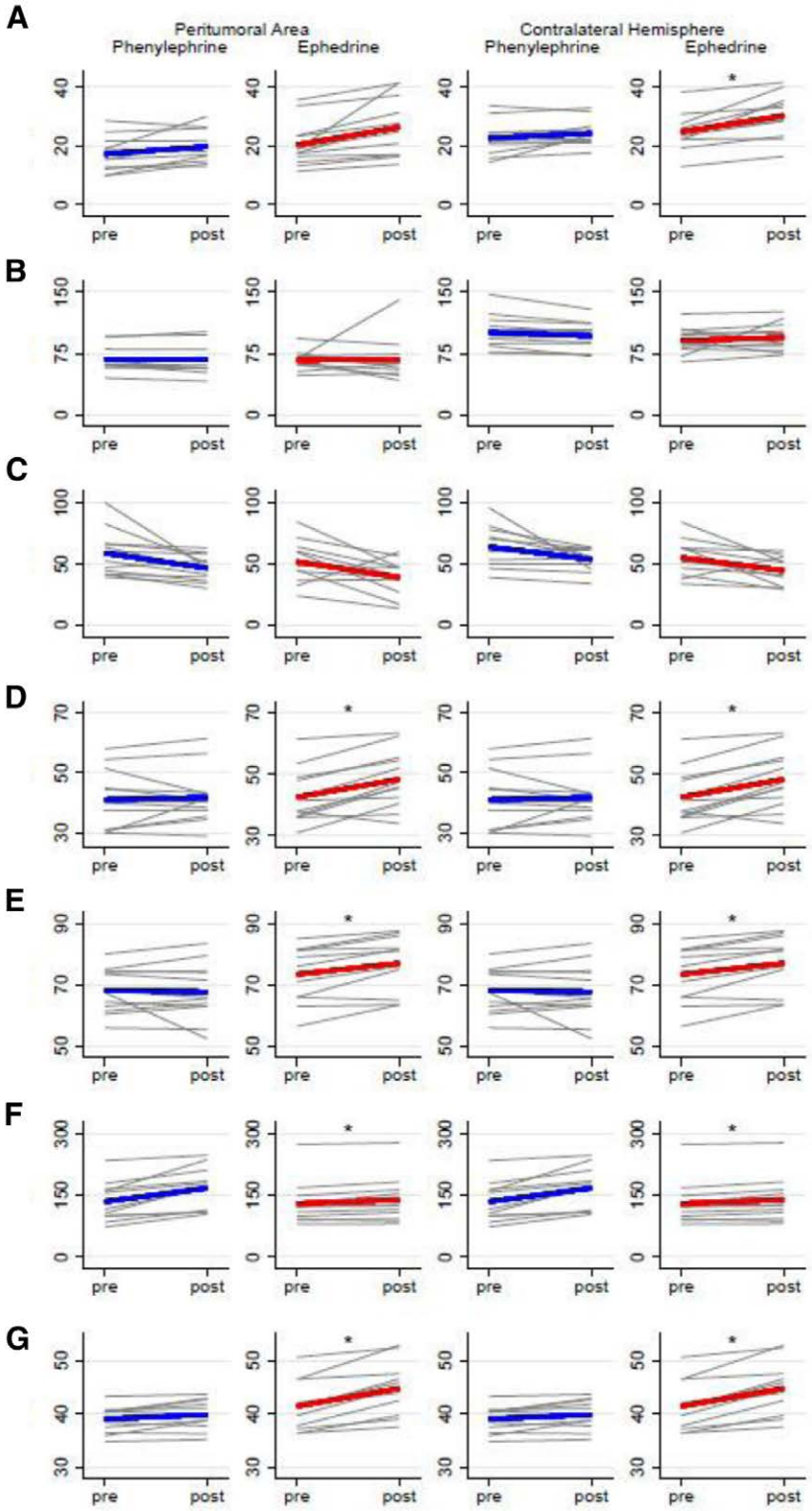

Fig 4. Line plots of (*A*) cerebral blood flow, (*B*) cerebral metabolic rate of oxygen, (*C*) oxygen extraction fraction, (*D*) bispectral index, (*E*) regional cerebral oxygen saturation, (*F*) arterial oxygen tension, and (*G*) arterial carbon dioxide tension stratified according to the region of interest (peritumoral area *vs.* contralateral hemisphere) and the study medication (phenylephrine *vs.* ephedrine). Measurements were performed before treatment (pre) and during the administration of the vasopressor posttreatment (post). Each line plot consists of measurements from 12 patients (shown in *gray*). The mean for each parameter is shown in blue for phenylephrine and red for ephedrine. Statistically significant differences between the groups are marked with an asterisk (*).

Table 4. Positron Emission Tomography/Computed Tomography-derived Parameters

	Phenylephrine (n = 12)			Ephedrine (n = 12)			Difference Ephedrine – Difference Phenylephrine (95% CI)	*P* Value
	Pretreatment	Posttreatment	Difference Phenylephrine	Pretreatment	Posttreatment	Difference Ephedrine		
Peritumoral area								
Cerebral metabolic rate of oxygen, μmol · 100g^{-1} · min^{-1}	68.2 ± 15.2	67.6 ± 18.0	–0.6 ± 4.9	67.0 ± 11.3	67.8 ± 25.7	0.8 ± 24.2	1.5 (–13.3 to 16.3)	0.839
Cerebral blood flow, ml ·100g^{-1} · min^{-1}	17.3 ± 5.8	19.9 ± 5.4	2.6 ± 3.7*	20.4 ± 7.6	26.4 ± 9.9	6.0 ± 5.9*	3,4 (–0.7 to 7.6)	0.101
Oxygen extraction fraction, %	59.3 ± 18.6	47.0 ± 10.7	–12.3 ± 16.0*	52.0 ± 17.1	39.1 ± 14.1	–12.9 ± 17.3*	–0.6 (–14.7 to 13.6)	0.934
Volume, ml		7.9 (3.7; 13.2)			5.2 (0.8; 10.8)			0.317
Contralateral hemisphere								
Cerebral metabolic rate of oxygen, μmol · 100g^{-1} · min^{-1}	100.8 ± 20.7	96.4 ± 17.7	–4.4 ± 6.9*	90.8 ± 15.9	94.6 ± 16.9	3.8 ± 15.7	8.2 (–2.0 to 18.5)	0.118
Cerebral blood flow, ml ·100g^{-1} · min^{-1}	22.7 ± 5.6	24.4 ± 4.4	1.7 ± 3.5	24.9 ± 6.2	30.4 ± 7.3	5.5 ± 4.0*	3.9 (0.7 to 7.0)	0.019
Oxygen extraction fraction (%)	64.0 ± 16.1	53.7 ± 9.1	–10.3 ± 15.0*	55.3 ± 14.6	44.9 ± 10.9	–10.4 ± 13.5*	–0.1 (–12.1 to 12.0)	0.989
Volume, ml		216.9 ± 54.7			184.3 ± 38.0		–32.6 (–72.5 to 7.2)	0.104

Data are presented as mean ± SD. Peritumoral volume did not follow the normal distribution, and thus data are given as median (25th percentile; 75th percentile) and the Wilcoxon rank-sum test was applied to test whether there was any group difference. Difference phenylephrine = posttreatment value of phenylephrine – pretreatment value of phenylephrine. Difference ephedrine = posttreatment value of ephedrine – pretreatment value of ephedrine. The *P* value is the statistical comparison between difference phenylephrine *versus* difference ephedrine. Volume define median and mean values of peritumoral area and contralateral hemisphere in ml.

*Significant effect of treatment within group.

other pretreatment physiologic parameters were comparable, suggesting presence of equivalent intergroup experimental conditions. However, phenylephrine and ephedrine produced marked differences in the systemic physiologic parameters, which may explain the observed difference in cerebral blood flow. Phenylephrine and ephedrine both caused MAP to increase, and not unexpectedly they were associated with a respective decrease and increase in heart rate because of their known cardiac and systemic effects. Despite the use of the same ventilator settings throughout the study, ephedrine was associated with a statistically significant increase in P_{ACO_2} and BIS when compared with phenylephrine. Effect of ephedrine on BIS has been described earlier and is possibly caused by increased cerebral metabolic rate of oxygen, an increase in electroencephalographic activity attributed to central stimulatory effects of ephedrine, increased CO, and changes in skin conductance.[34,35] Thus, when compared with phenylephrine infusion, ephedrine infusion was collectively associated with a simultaneous increase in cerebral blood flow, regional cerebral oxygen saturation, P_{ACO_2}, and BIS values. These differences are likely related to the different effects of the vasopressor drugs on cardiac output. Previous studies have reported that CO is maintained or increased during ephedrine treatment and reduced during phenylephrine treatment.[4,36–38] Thus, treatment with ephedrine appears to be associated with a simultaneous increase in global and cerebral blood flow in addition to an increase in global and possibly in cerebral oxygen metabolism, collectively resulting in increased carbon dioxide production. This observation confirms the previously suggested relationship between global and cerebral hemodynamics under circumstances in which changes in CO are induced by sympathomimetic agents.[4,36,39,40] However, increase in cerebral blood flow after ephedrine treatment may also be related to increase in P_{ACO_2} and changes in cerebral metabolic rate of oxygen, although these changes were insignificant; in addition, an increase in MAP in the presence of impaired cerebral autoregulation may also be associated with increase in cerebral blood flow after ephedrine treatment.

Under normal circumstances in presence of an intact blood–brain barrier, vasopressors have been reported to induce a minimal reduction in (approximately 5% to 10% decrease in cerebral blood flow) or to have no influence on normocapnic cerebral blood flow or cerebral metabolic rate of oxygen.[41] This is in contrast to the findings of the present study, in which both phenylephrine and ephedrine were associated with either a small or more pronounced increase in cerebral blood flow in both the peritumoral region of interest and the contralateral hemisphere region of interest. Several circumstances may explain this difference. Effects of exogenous phenylephrine and ephedrine on cerebral blood flow and cerebral metabolic rate of oxygen are prevented by the intact blood–brain barrier under normal conditions.

However, patients with cerebral tumors often have increased blood–brain barrier permeability, and experimental studies have demonstrated that vasopressor administration is associated with increases in both cerebral blood flow and cerebral metabolic rate of oxygen under conditions with blood–brain barrier disruption.[42,43] Stimulation of β-receptors has been suggested to be the mechanism responsible for the increase in cerebral metabolic rate of oxygen and cerebral blood flow when a vasopressor agent gains direct access to the brain.[44] Ephedrine is a combined α- and β-receptor agonist, whereas phenylephrine is a selective α-receptor agonist.[45] This difference in receptor affinity may explain the statistically significant increase in contralateral cerebral blood flow and statistically nonsignificant increase in the cerebral metabolic rate of oxygen in both regions of interest after ephedrine treatment compared with phenylephrine treatment.[46]

In both groups, the pretreatment cerebral blood flow and cerebral metabolic rate of oxygen in contralateral hemisphere region of interest were reduced by approximately 50% compared with gray matter cerebral blood flow and cerebral metabolic rate of oxygen values reported in awake human subjects, which are approximately 50 ml · 100 g^{-1} · min^{-1} and 200 μmol · 100 g^{-1} · min^{-1}, respectively.[20,47] Our findings indicate preservation of coupling of the cerebral metabolic rate of oxygen and cerebral blood flow in the pretreatment state and are in line with findings in a previous positron emission tomography study of cerebral blood flow and brain oxygen metabolism during propofol anesthesia in healthy humans. In that study, a propofol concentration producing a BIS value of 40 reduced regional cerebral blood flow and cerebral metabolic rate of oxygen values to approximately 60% of baseline awake values.[47] Other positron emission tomography studies have reported similar reductions in cerebral blood flow caused by propofol ranging from 46% to 72%.[20]

Pretreatment cerebral blood flow values in both groups were lower in the peritumoral region of interest than those in the contralateral hemisphere region of interest. However, the peritumoral area often contains both gray and white matter, and normal cerebral blood flow in white matter under awake conditions is only approximately 25 ml · 100 g^{-1} · min^{-1}. Thus, a similar percentage reduction in cerebral blood flow in both gray and white matter during propofol anesthesia may explain the lower cerebral blood flow values found in the mixed gray and white matter in the peritumoral region of interest.

In the present study, peritumoral positron emission tomography parameters were not normalized to those of a corresponding contralateral region. This comparison could possibly remove the influence of global changes in MAP and P_{ACO_2} on peritumoral measurements. However, the peritumoral region of interest is composed of both gray and white matter. Because of tumor size, tumor location, tumor infiltration into healthy brain tissue, and midline displacement, the ipsilateral peritumoral gray and white matter was considerably displaced, and the contralateral mirror of the peritumoral region of interest may not adequately reflect the peritumoral region of interest. Thus, normalization to a corresponding contralateral region of interest may not be a valid reference region.

In both groups and regions of interest, pretreatment oxygen extraction fraction was in the range from 52% to 65%, which is higher than values of approximately 30% to 50% in selected brain regions normally reported in awake healthy subjects.[47] This observation is likely explained by reduction in cerebral blood flow. However, the subsequent infusion of phenylephrine and ephedrine were associated with a statistically nonsignificant 21% and 25% reduction in oxygen extraction fraction in the peritumoral region of interest and a 16% and 19% reduction in contralateral hemisphere region of interest, respectively. The reduction in oxygen extraction fraction was associated with a comparable percentage increase in cerebral blood flow without corresponding changes in cerebral metabolic rate of oxygen. This finding suggests that infusion of phenylephrine and ephedrine may be associated with an uncoupling of the cerebral metabolic rate of the oxygen–cerebral blood flow relationship, which appeared to be present during propofol anesthesia and before vasopressor infusion.

ICP is often increased in patients with cerebral tumors and may have the potential to affect cerebral perfusion pressure, cerebral blood flow, and cerebral metabolic rate of oxygen.[1,25] In this study, subdural ICP was low and cerebral perfusion pressure was within acceptable limits in both groups without intergroup differences. These findings correspond to similar ICP and cerebral perfusion pressure measurements in patients undergoing craniotomy and appeared to be too low to be associated with intraoperative brain swelling.[1] Thus, the impact of ICP on cerebral blood flow and cerebral metabolic rate of oxygen measurements was probably limited, but an effect cannot be excluded.

This study has several limitations. First, sample size was small, which may have caused changes in cerebral metabolic rate of oxygen to have become statistically significant if additional patients were studied. Second, the majority of screened patients were not included in the study, and heterogeneity, including the uneven distribution of tumor pathology, may also have influenced the results. Furthermore, the study only included phenylephrine and ephedrine as study medications, and generalizability of our findings is limited because other vasopressors may be associated with different effects on cerebral blood flow and cerebral metabolic rate of oxygen. Possible extracranial contamination of the regional cerebral oxygen saturation signal and absence of bilateral BIS and near-infrared spectroscopy measurements and thus comparison of both hemispheres are additional weaknesses of the study.[48,49]

Conclusions

Cerebral metabolic rate of oxygen changes in the peritumoral and contralateral regions of interest were similar between ephedrine- and phenylephrine-treated patients. Ephedrine treatment was associated with an increase in regional cerebral oxygen saturation, cerebral blood flow, P_{ACO_2}, and BIS compared with phenylephrine treatment. The data indicate that this difference may be caused by ephedrine-induced stimulation of cardiac output, possibly confirming a previously suggested relationship between global and cerebral hemodynamics. The finding that regional cerebral oxygen saturation increased after ephedrine treatment without a concordant increase in cerebral metabolic rate of oxygen indicates that changes in regional cerebral oxygen saturation may not adequately reflect changes in cerebral metabolic rate of oxygen. Thus, possible concerns regarding the use of phenylephrine in patients with cerebral pathology, which is based on cerebral oximetry, may not be justified. Outcome studies are needed to further address this concern.

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Competing Interests

The authors declare no competing interests.

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