ANESTHESIOLOGY

Cerebral Macro- and Microcirculation during Ephedrine *versus* Phenylephrine Treatment in Anesthetized Brain Tumor Patients: A Randomized Clinical Trial Using Magnetic Resonance Imaging

Klaus U. Koch, M.D., Irene K. Mikkelsen, M.Sc., Ph.D., Ulrick S. Espelund, M.D., Ph.D., Hugo Angleys, M.Sc., Ph.D., Anna Tietze, M.D., Ph.D., Gorm V. Oettingen, M.D., Ph.D., Niels Juul, M.D., Leif Østergaard, M.D., M.Sc., Ph.D., D.M.Sc., Mads Rasmussen, M.D., Ph.D.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Mean arterial blood pressure may not necessarily be a good index of actual microcirculatory flow in the brain
- Brain microcirculation and oxygen delivery can be quantified by dynamic susceptibility contrast magnetic resonance imaging

What This Article Tells Us That Is New

- At equal mean arterial pressures, the use of ephedrine results in better brain microcirculation and oxygen delivery than with the use of phenylephrine

ABSTRACT

Background: This study compared ephedrine *versus* phenylephrine treatment on cerebral macro- and microcirculation, measured by cerebral blood flow, and capillary transit time heterogeneity, in anesthetized brain tumor patients. The hypothesis was that capillary transit time heterogeneity in selected brain regions is greater during phenylephrine than during ephedrine, thus reducing cerebral oxygen tension.

Methods: In this single-center, double-blinded, randomized clinical trial, 24 anesthetized brain tumor patients were randomly assigned to ephedrine or phenylephrine. Magnetic resonance imaging of peritumoral and contralateral hemispheres was performed before and during vasopressor infusion. The primary endpoint was between-group difference in capillary transit time heterogeneity. Secondary endpoints included changes in cerebral blood flow, estimated oxygen extraction fraction, and brain tissue oxygen tension.

Results: Data from 20 patients showed that mean (± SD) capillary transit time heterogeneity in the contralateral hemisphere increased during phenylephrine from 3.0 ± 0.5 to 3.2 ± 0.7 s and decreased during ephedrine from 3.1 ± 0.8 to 2.7 ± 0.7 s (difference phenylephrine *versus* difference ephedrine [95% CI], −0.6 [−0.9 to −0.2] s; $P = 0.004$). In the peritumoral region, the mean capillary transit time heterogeneity increased during phenylephrine from 4.1 ± 0.7 to 4.3 ± 0.8 s and decreased during ephedrine from 3.5 ± 0.9 to 3.3 ± 0.9 s (difference phenylephrine *versus* difference ephedrine [95%CI], −0.4[−0.9 to 0.1] s; $P = 0.130$). Cerebral blood flow (contralateral hemisphere ratio difference [95% CI], 0.3 [0.06 to 0.54]; $P = 0.018$; and peritumoral ratio difference [95% CI], 0.3 [0.06 to 0.54; $P = 0.018$) and estimated brain tissue oxygen tension (contralateral hemisphere ratio difference [95% CI], 0.34 [0.09 to 0.59]; $P = 0.001$; and peritumoral ratio difference [95% CI], 0.33 [0.09 to 0.57]; $P = 0.010$) were greater during ephedrine than phenylephrine in both regions.

Conclusions: Phenylephrine caused microcirculation in contralateral tissue, measured by the change in capillary transit time heterogeneity, to deteriorate compared with ephedrine, despite reaching similar mean arterial pressure endpoints. Ephedrine improved cerebral blood flow and tissue oxygenation in both brain regions and may be superior to phenylephrine in improving cerebral macro- and microscopic hemodynamics and oxygenation.

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The maintenance of cerebral perfusion pressure is key to the anesthetic management of patients with space-occupying brain lesions, such as tumors, because it ensures sufficient cerebral blood flow to meet brain tissues' metabolic demands.[1–3] Phenylephrine, a pure α-adrenergic agonist, and ephedrine, an indirectly acting α- and β-adrenergic agonist, are commonly administered during neurosurgical procedures to treat anesthesia-related hypotension

This article is featured in "This Month in Anesthesiology," page A1. This article is accompanied by an editorial on p. 775. This article has a related Infographic on p. A17. This article has a visual abstract available in the online version. Portions of this work were presented as part of a poster presentation at the Annual Society for Neuroscience in Anesthesiology and Critical Care (SNACC) meeting in Boston, Massachusetts, October 20, 2017, and in San Francisco, California, October 12, 2018.

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and maintain cerebral perfusion pressure.[4,5] Under some circumstances, however, mean arterial pressure (MAP) correlates poorly with microcirculatory blood flow.[6,7] Despite reaching recommended cerebral perfusion pressure endpoints, increased MAP may, paradoxically, reduce microcirculatory perfusion and impair oxygen delivery, possibly because of capillary flow disturbances.[8–11]

Microcirculation is the primary site of oxygen exchange, and brain oxygenation depends on both the macroscopic blood supply, as quantified by the cerebral blood flow, and blood's microscopic distribution across brain capillaries, as quantified by the capillary transit time heterogeneity.[12] Oxygen diffusion exchange between blood and tissue is limited by erythrocyte capillary transit time, understood as the time available for diffusion exchange before the blood returns to the heart. Maintenance of homogenous capillary flow patterns is therefore important, because abnormal flow may cause tissue hypoxia due to excessive shunting of oxygenated blood through the microcirculation.[7,10,13] Capillary transit time heterogeneity can be quantified as the SD of the distribution of erythrocyte mean transit times. Vasopressors modulate vascular smooth muscle cell tone mainly *via* α-adrenergic receptors, but these receptors are also expressed on contractile pericytes in brain capillaries.[14–16] Knowledge of vasopressors' effects on the capillary distribution of blood is therefore critical to ascertain whether augmented blood pressure is paralleled by a similar increase in brain oxygenation. For example, in patients with brain tumors, elevated intracranial pressure (ICP) and regional edema may compress individual capillaries and introduce "shunting" of oxygenated blood through the capillary bed in surrounding healthy tissue.[8,13] During administration of a vasopressor to these patients during brain tumor surgery, such brain tissue could, paradoxically, be susceptible to hypoxic injury despite the maintenance of normal cerebral perfusion pressure and cerebral blood flow if the capillary distribution of blood fails to change in parallel.[11,17,18]

Using dynamic susceptibility contrast magnetic resonance imaging (MRI), this randomized study aimed to quantify the effects of phenylephrine and ephedrine on cerebral macro- and microcirculation in brain tumor patients, measured by cerebral blood flow and capillary transit time heterogeneity. Capillary transit time heterogeneity 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 mean transit time, cerebral blood volume, cerebral blood flow, and regional cerebral oxygen saturation and calculated the resulting oxygen extraction fraction and brain tissue oxygen tension based on biophysical models. We hypothesized that capillary transit time heterogeneity in selected brain regions is greater during phenylephrine than during ephedrine. We further hypothesized that an increase in capillary transit time heterogeneity may limit oxygen uptake, causing tissue oxygen tension to decrease.

Materials and Methods

Trial Design

This study was a prospective, single-center, parallel-group, double-blinded, randomized controlled trial that enrolled patients from September 29, 2015, to June 13, 2016. The trial protocol has been published previously (July 2017).[19] Written informed consent was obtained from all participants. The trial was approved by the Central Denmark Region Committee on Health Research Ethics. The overall protocol was registered at clinicaltrials.gov (NCT02713087) on February 10, 2016, by Dr. Koch (principal investigator) and at EUDRACT (2015-001359-60) on June 16, 2015. The protocol consists of two independent randomized trials with different patient study groups and different endpoints.[19] The inclusion and exclusion criteria and applied blood pressure protocols were similar in the two trials, which differed only with regard to study cohort (two independent cohorts), imaging mode (positron emission tomography *vs.* MRI), and associated endpoints. The positron emission tomography study was recently reported in this journal, and here we report the results from the independent MRI part of the project.[20] Of note, the date of trial registration and the date of trial protocol publication occurred either at the end of the data collection period or after cessation of data collection. The late trial registration was an unfortunate error. However, no changes were made in the trial protocol throughout the study period. The trial was conducted in accordance with the Note for Guidance on Good Clinical Practice. The Good Clinical Practice Unit, Aarhus University Hospital, Aarhus, Denmark, monitored the study.

Patients and Randomization

We screened all patients aged 18 to 75 yr scheduled for elective craniotomy for supratentorial tumors with a minimum size of 3 cm (measured as the largest diameter in any plane on MRI). Participants were approached 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 physical status of IV to VI, pregnancy (positive pregnancy urine test) or breastfeeding, renal failure (estimated glomerular filtration ratio less than 60 $ml \cdot min^{-1}$ per 1.73 m^2), or the inability to give written informed consent.[21]

Patients were randomized to receive 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.[20,22] In contrast to the previous studies, in which ephedrine and phenylephrine were administered as bolus

injections, an infusion regimen was selected because of the necessity of maintaining a stable blood pressure throughout the MRI examination (lasting approximately 60 min).[5,23] The treatment allocation sequence was generated using permuted block randomization with a block size of 4 and concealed by use of sequentially numbered sealed envelopes. A third-party colleague performed allocation and concealment. 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. However, in some circumstances, the change in heart rate perhaps "may have alerted the treating physician to the treatment allegation." However, the colleagues performing the assessment, calculations, and statistics of the MRI parameters did not participate in the actual investigations and were therefore blinded to randomization.

Anesthesia, Monitoring, and ICP Measurement

On the day of surgery, patients were anesthetized in a room adjacent to the MRI 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}).[19] The Bispectral Index (BIS) was 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.[24] 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 an arterial oxygen tension (Pao_2) greater than 100 mmHg. When normoventilation was obtained, the ventilator settings were maintained throughout the MRI examination. Isotonic saline was infused at a rate of 3 ml · kg^{-1} · h^{-1}, and the patients were kept warm during the MRI examination. Oxygen saturation and heart rate were monitored. An intraarterial 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 recorded before and after the MRI examinations.[25] 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.[5,26,27] 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 in the electrode is sensitive to light absorption at a maximum depth of approximately 3 cm. The near-infrared spectroscopy technology measures contributions from both venous and arterial vessels at a 3:1 ratio.[25] Because ICP may influence cerebral blood flow and brain tissue oxygen tension, 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.[2,28]

Experimental Protocol

The experimental protocol has previously been described.[19] Pretreatment MRI examinations, including capillary transit time heterogeneity, cerebral blood flow, cerebral blood volume, and mean transit time measurements and subsequent estimation of oxygen extraction fraction and brain tissue oxygen tension based on biophysical models, 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 MRI scan sequence. The study medication was initially infused with a dedicated venous line at 30 ml/h and titrated to increase the MAP to at least 60 mmHg or by 20% relative to the pretreatment MAP.[5,20] The MRI measurement was repeated when the vasopressor treatment had raised the MAP to reach the desired plateau with stable values for 5 min. 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 gas analyses of Pao_2 and $Paco_2$ were drawn from the arterial catheter just before the infusion of study medication and initiation of the second MRI scan. After the MRI 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. The duration of the study protocol was approximately 140 min in total (fig. 1).

Neuroimaging

Each patient was examined with MRI to map brain anatomy and study hemodynamic changes caused by the vasopressors. T1-weighted and T2-FLAIR images displayed anatomic brain structures and structural changes caused by the patients' tumors (fig. 2), whereas spin echo perfusion-weighted dynamic susceptibility contrast MRI was used

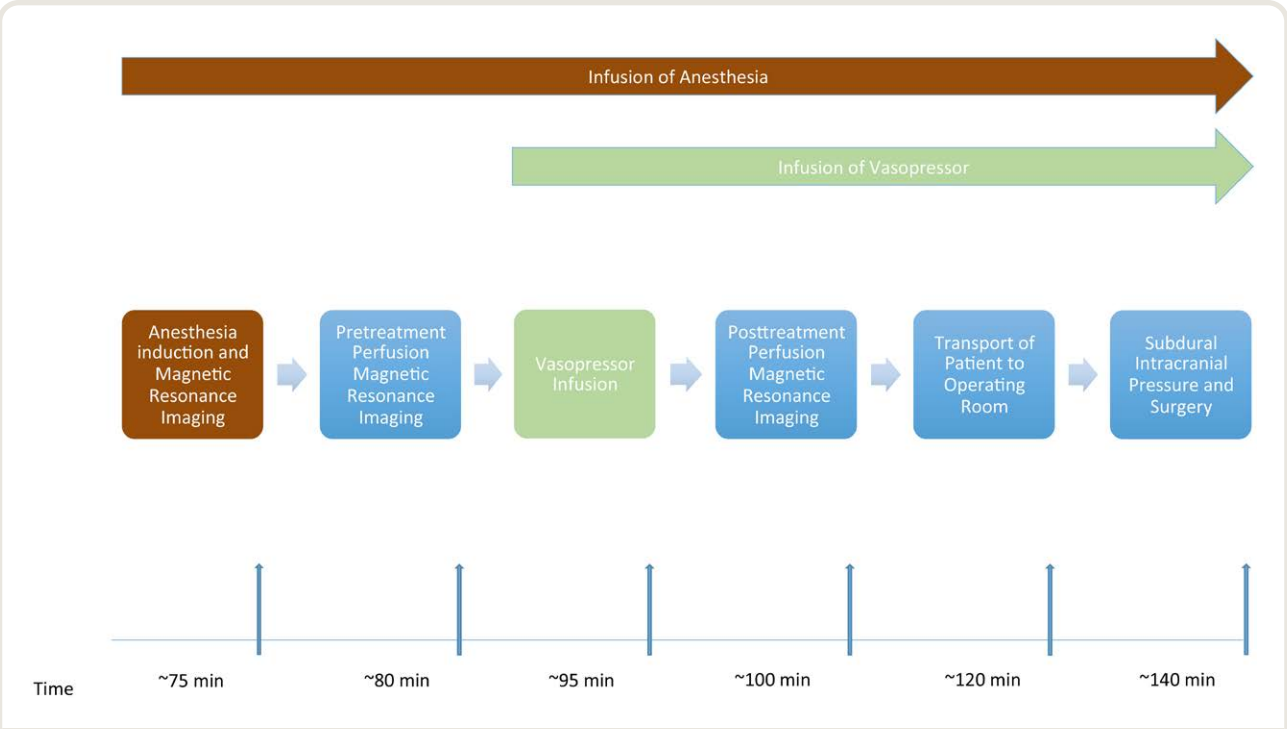

Fig. 1. Schematic time sequence diagram of the study protocol. Anesthetic preparation, induction of anesthesia, and the initial magnetic resonance imaging sequence lasted approximately 75 min. The pretreatment magnetic resonance imaging perfusion sequence lasted 5 min. Infusion of the study medication and the steady-state period until the desired effect on blood pressure was achieved lasted approximately 15 min. The posttreatment perfusion sequence (5 min) ended the magnetic resonance imaging examinations. Finally, the patient was transported to the surgical suite (approximately 20 min). Approximately 120 min passed from anesthesia induction until the patient was ready for surgery. Another 20 min elapsed before the subdural intracranial pressure measurement began.

to measure cerebral hemodynamics in each patient.[29] Two consecutive series of dynamic susceptibility contrast MRI scans were acquired, separated by the infusion of the respective study medication. For the dynamic susceptibility contrast MRI measurements, gadobutrol (Gadovist, Bayer, Germany) created susceptibility contrast by remaining intravascular in peritumor and contralateral tissue. A prebolus of 0.05 mmol/kg gadobutrol was administered to remove unwanted vascular T_1 effects, after which 0.10 mmol/kg gadobutrol was administered during each dynamic susceptibility contrast MRI session for a total dose of 0.25 mmol/kg. The contrast agent's passage through the brain was tracked dynamically across multiple image slice locations every 1.5 s.

Magnetic Resonance Imaging Analyses

Perfusion-weighted MRI data were postprocessed using fully automatic, in-house–developed modules implemented in Statistical Parametric Mapping, version 12, for MatLab (The Wellcome Center for Human Neuroimaging, United Kingdom). The perfusion parameters were calculated from concentration–time curves. The arterial input function was determined automatically with a repeated-session method that incorporates arterial input function information from both dynamic susceptibility contrast MRI sessions.[30] The arterial input function and each tissue concentration curve from the perfusion experiment were then deconvolved to achieve a flow-scaled residue function for each image unit (voxel). From this function, the cerebral blood volume, the volume of blood per unit volume of brain tissue, was determined as the area under the curve, and the cerebral blood flow, the volume of blood that flows through each unit volume of brain tissue per unit time, was taken as the maximum height of the curve. The blood's mean transit time through the tissue voxel is determined as the cerebral blood volume:cerebral blood flow ratio. The residue function is a curve that describes the fraction of contrast agent still present within the voxel vasculature at a given time after its injection into the tissue's arterial supply as an ideal, infinitely narrow bolus.[31,32] From this curve, the distribution of erythrocyte transit times through the voxel microcirculation can be determined, and thereby capillary transit time heterogeneity as the SD of this distribution.[32] The physiologic significance of these parameters in terms of tissue oxygenation was quantified as the oxygen extraction fraction and brain tissue oxygen tension and derived using the approach described by Jespersen and Østergaard.[7] Mean transit time and capillary transit time heterogeneity are

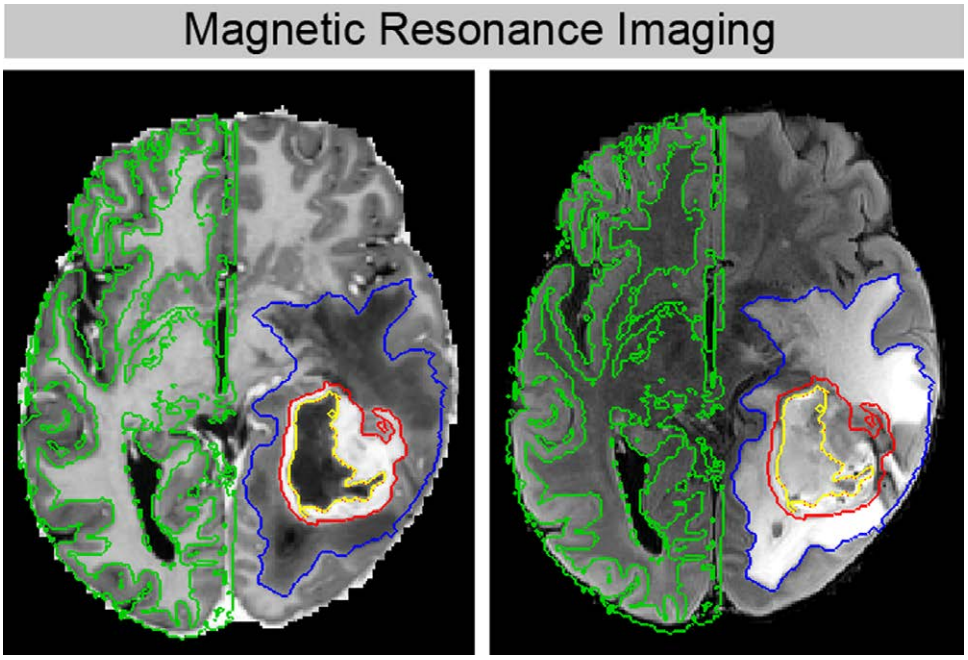

Fig. 2. Magnetic resonance images of a patient with a tumor in the left hemisphere. The regions of interest are outlined on the magnetic resonance images. *Green* indicates the contralateral hemisphere region of interest, *blue* indicates the peritumoral area region of interest, *red* indicates the tumor, and *yellow* indicates tumor necrosis.

measured in seconds, whereas all other parameters were calculated as the relative difference between the two dynamic susceptibility contrast MRI sessions.

The gray matter of the contralateral hemisphere was automatically segmented from T1-weighted MRI, and a minor manual correction was applied to account for any midline herniation. Tumors were manually outlined on T1-weighted MRI and peritumoral areas on T2-FLAIR–weighted MRI and then coregistered to perfusion maps. Peritumoral areas were corrected for any tumor overlap. A neuroradiologist validated the outlining of contrast-enhancing tumor, contralateral hemisphere, and tumor and peritumoral areas.

Impact of Microvascular Hemodynamics on Brain Tissue Oxygenation

To evaluate the impact of the flow parameters on the oxygen extraction fraction and tissue oxygen tension in the ephedrine and phenylephrine groups, we applied a biophysical model of oxygen extraction.[7] Briefly, the model requires calibration of a subject-specific rate constant k that describes the capillary wall's oxygen permeability. The value of k was determined by assuming a white matter oxygen extraction fraction of 0.525, determined under identical condition in our previous positron emission tomography study, and a brain tissue oxygen tension of 15 mmHg.[20] Note that the high, recorded oxygen extraction fraction value during propofol anesthesia (0.525 compared to ~0.35 in normal brain tissue) dictates the low brain tissue oxygen tension (15 mmHg compared to 25 mmHg in normal brain tissue), because blood is in near diffusion equilibrium with tissue at its venous exit. Then, based on the pretreatment mean transit time and capillary transit time heterogeneity measured with MRI, we estimated the pretreatment oxygen extraction fraction. This fraction was multiplied by the pretreatment cerebral blood flow measure to obtain the cerebral metabolism rate of oxygen.

Next, assuming identical pre- and posttreatment values for the cerebral metabolism rate of oxygen as determined in our positron emission tomography study, we estimated posttreatment oxygen extraction fraction by dividing it by the posttreatment cerebral blood flow, and finally, using posttreatment mean transit time and capillary transit time heterogeneity, we estimated brain tissue oxygen tension. Mean relative changes in regions of interests from before to after treatment were statistically compared between groups treated with either ephedrine or phenylephrine.[20]

Endpoints

The primary endpoint was the between-group difference in the capillary transit time heterogeneity measured in the peritumoral area and the contralateral gray matter brain tissue. The secondary endpoints were the between-group differences in cerebral blood flow, cerebral blood volume,

mean transit time, brain tissue oxygen tension, 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 capillary transit time heterogeneity in anesthetized patients. Accordingly, the sample size was based on two pieces of evidence: first, a study by Meng *et al.*[5] reporting that the 10% difference in the regional cerebral oxygen saturation between anesthetized patients treated with ephedrine and those treated with phenylephrine was clinically significant; and second, a sample size calculation used in a MRI study protocol, which has previously been described.[19] Here, the sample size calculation was based on an expected 10% difference in the capillary transit time heterogeneity between the phenylephrine and ephedrine groups.[19]

In our study, the expected 10% difference in the capillary transit time heterogeneity was translated into an estimated prevasopressor capillary transit time heterogeneity value of 3.2 s and a 10% difference yielded a mean difference of 0.32 s (difference of phenylephrine minus difference of ephedrine of 10% or more). Considering a significance level of 0.05, SD 0.2, 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.

Demographics were compared between groups by independent, one-sample *t* tests. For MRI-derived primary and secondary endpoints, the within-group changes were evaluated by ratios (posttreatment/pretreatment) and intergroup changes by ratio differences, using dependent sample *t* tests and independent, one-sample *t* tests, respectively. Secondary endpoints and variables describing physiology, anesthesia, and brain monitoring were assessed by dependent and independent sample *t* tests of differences (posttreatment minus pretreatment) for within-group and intergroup comparisons, respectively. Quantile–quantile plots were constructed to confirm that each of the tested variables followed a normal distribution, and the assumption of equal variance between tested groups was tested where appropriate. The data are given as the means ± SD unless otherwise specified, and the statistical hypothesis tests were two-sided, with $P < 0.05$ considered statistically significant. The statistical analyses and plots were performed using Stata V.12 (StataCorp, USA).

Results

Between September 29, 2015, and June 13, 2016, 24 of 233 screened patients were enrolled in the study (fig. 3). The most common reasons for study exclusion were a lack of scanner availability (78 of 233 [33%]), the unavailability of research staff (72 of 233 [31%]), failure to conform to the inclusion criteria (56 of 233 [24%]), or the patient declining to enter the study (2 of 233 [1%]). Among the 56 patients who failed to meet the inclusion criteria, the most common reasons were age and renal failure. The patient demographics in the two groups are reported in table 1. No adverse events were observed in the study, and there were no cases of unacceptable hypertension as a result of vasopressor infusion. Four patients were excluded because of technical issues involving the MRI analysis.

Comparison of Physiologic and Anesthetic Variables

The changes in physiologic and anesthetic variables are shown in tables 2 through 5. There was no significant intergroup difference between pretreatment $Paco_2$ ($P = 0.087$), Pao_2 ($P = 0.457$), MAP ($P = 0.825$), and heart rate ($P = 0.536$).

A comparable increase in MAP was observed in both groups, with no intergroup difference ($P = 0.176$). A plot of the blood pressure *versus* time is shown for each patient (fig. 4). Heart rate increased during ephedrine and decreased during phenylephrine, and the difference between the groups was significant (difference [95% CI], 21 [15 to 27] beats/min; $P < 0.0001$).

Anesthetic Depth, Cerebral Oxygen Saturation, and ICP

There was no significant intergroup difference between the pretreatment regional cerebral oxygen saturation ($P = 0.119$) and BIS ($P = 0.422$). The regional cerebral oxygen saturation decreased in both groups without intergroup significance ($P = 0.438$). There were no statistically significant differences in the dosages of propofol and remifentanil used in the two groups ($P = 0.971$ and $P = 0.173$, respectively). There was no difference in the subdural ICP and cerebral perfusion pressure between the two groups ($P = 0.591$ and $P = 0.385$; tables 5).

Cerebral Macro- and Microcirculatory Parameters

The MRI-derived parameters are shown in table 6 and figure 5.

Contralateral Hemisphere. Capillary transit time heterogeneity was greater during phenylephrine than during ephedrine treatment (difference [95% CI], −0.6 [−0.9 to −0.2] s; $P = 0.004$). The cerebral blood flow increased significantly more during ephedrine treatment than during phenylephrine treatment (ratio difference [95% CI], 0.3 [0.06 to 0.54]; $P = 0.018$; fig. 5). Cerebral blood volume increased in both the phenylephrine group and the ephedrine group, but the difference between groups was not statistically significant (ratio difference [95% CI], 0.09 [−0.08 to 0.26]; $P = 0.271$). Mean transit time was lower during ephedrine than phenylephrine treatment (difference [95%

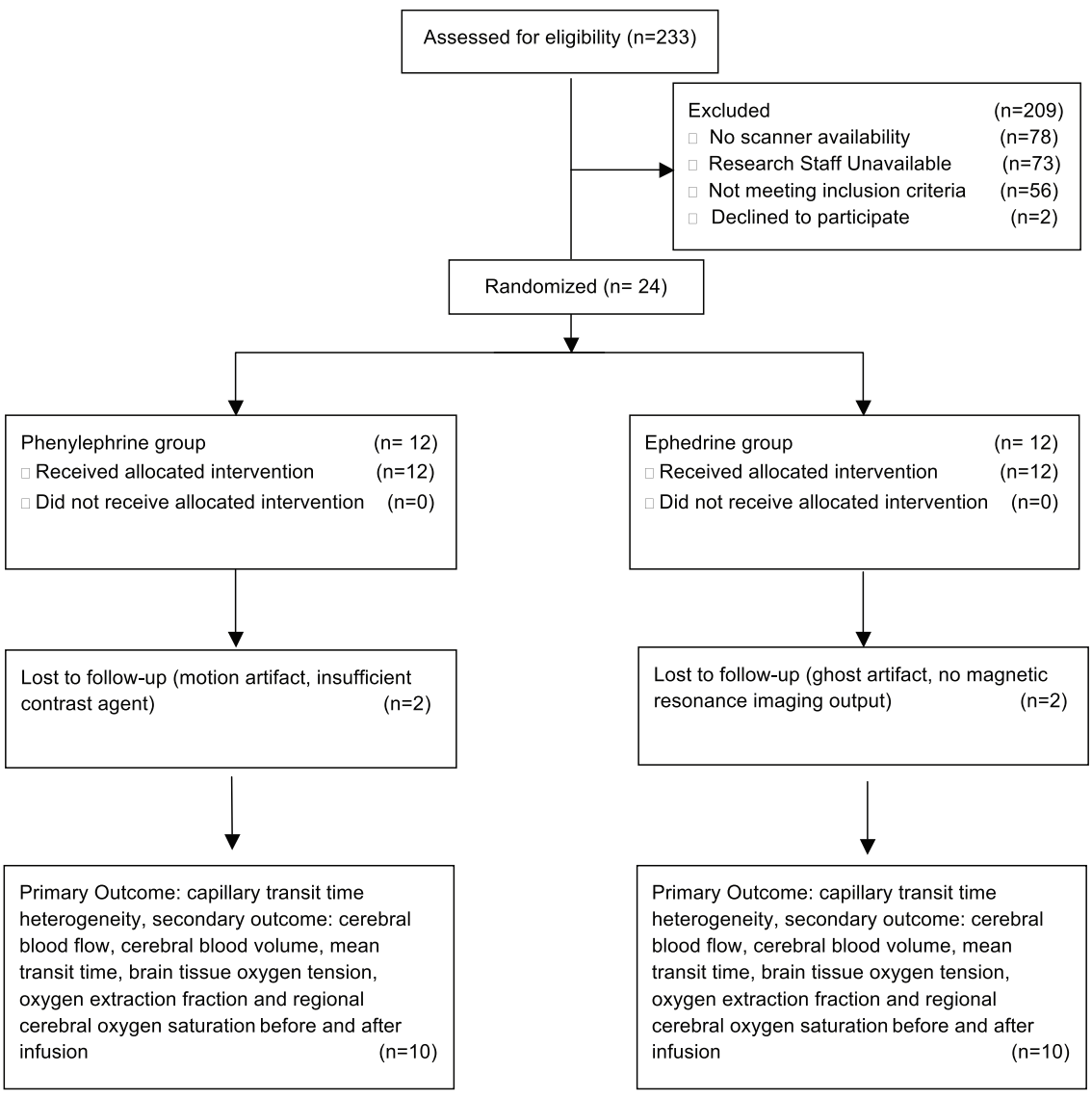

Fig. 3. Consolidated Standards of Reporting Trials (CONSORT) diagram of patient progression through the study.

CI], −0.5 [−0.9 to −0.1] s; $P = 0.009$). The contralateral tissue volume was not statistically significant between the two groups ($P = 0.659$).

Peritumoral Area. Although capillary transit time heterogeneity increased in the phenylephrine group and decreased in the ephedrine group, there was no intergroup difference (ratio difference [95% CI], −0.4 [−0.9 to 0.1] s; $P = 0.130$). Cerebral blood flow was greater during ephedrine treatment than during phenylephrine treatment (ratio difference [95% CI], 0.3 [0.06 to 0.54]; $P = 0.018$; fig. 6). Cerebral blood volume increased in both the phenylephrine and ephedrine groups, with no statistically significant difference between groups (ratio difference [95% CI], 0.14 [−0.03 to 0.32]; $P = 0.107$). Mean transit time decreased in both groups, with no statistically significant difference between groups (difference [95% CI], −0.2 [−0.7 to 0.2] s; $P = 0.240$). The peritumoral tissue volume was without statistical significance between the two groups ($P = 0.866$).

Table 1. Demographics

Demographics	Phenylephrine (n = 10)	Ephedrine (n = 10)
Age, yr	64 ± 8	56 ± 14
Sex, n (%)		
Male	5 (50)	5 (50)
Female	5 (50)	5 (50)
Weight, kg	68.6 ± 11.6	76 ± 17.3
Hypertension, n	2	3
Treated hypertension, n	2	3
Tumor pathology		
Meningeoma, n (%)	2 (20)	0 (0)
Glioblastoma, n (%)	5 (50)	6 (60)
Oligodendroglioma, n (%)	1 (10)	1 (10)
Cerebral metastasis, n (%)	2 (20)	0 (0)
Astrocytom, n (%)	0 (0)	2 (20)
Lymphoma, n (%)	0 (0)	1 (10)
Tumor size, cm^3	68.3 ± 44.6	79.3 ± 48.7

The data are presented as means ± SD for continuous variables and frequency (%) for categorical variables.

Cerebral Tissue Oxygenation

The cerebral oxygenation parameters derived from the MRI parameters are shown in table 7 and figure 5.

Contralateral Hemisphere. Ephedrine treatment was associated with a significant intergroup increase in brain tissue oxygen tension (ratio difference [95% CI], 0.34 [0.09 to 0.59]; $P = 0.001$) and a decrease in oxygen extraction fraction (ratio difference [95% CI], −0.20 [−0.33 to −0.07]; $P = 0.005$) compared to phenylephrine treatment.

Peritumoral Area. Similar to the contralateral region, brain tissue oxygen tension was greater during ephedrine than during phenylephrine treatment (ratio difference [95% CI], 0.33 [0.09 to 0.57]; $P = 0.010$). Treatment with ephedrine was associated with a significant reduction in oxygen extraction fraction compared to treatment with phenylephrine (ratio difference [95% CI], −0.17 [−0.29 to −0.05]; $P = 0.007$).

Discussion

In this double-blind randomized clinical trial, capillary transit time heterogeneity in the contralateral brain region increased during phenylephrine treatment but decreased during treatment with ephedrine, despite similar MAP endpoints being reached in both groups. A similar pattern was observed in the peritumoral region, however, without reaching statistical significance. The study further demonstrated that cerebral blood flow and indices of tissue oxygenation in both regions increased more in patients treated with ephedrine than in those treated with phenylephrine. Overall, these findings suggest that phenylephrine may disturb the microcirculation and thereby reduce oxygen extraction. In contrast, ephedrine appears to improve both cerebral macro- and microcirculation and thus oxygen extraction. Although cerebral blood flow determines the net supply of oxygenated blood to brain tissue, the uptake of oxygen from capillary blood by brain tissue critically depends on a homogeneous distribution of blood flow across the capillary bed[7,10] Biophysical modeling studies suggest that capillary flow disturbances may have a profound influence on oxygen transport in tissue, particularly in conditions with ischemic or traumatic cerebral pathology.[8,9,13]

During anesthesia, vasopressors are administered under the assumption that cerebral blood flow and oxygen supply remain sufficient, given that arterial blood pressure is maintained.[4,5] This assumption is challenged by findings in this study in which augmentations of cerebral blood flow by phenylephrine were associated with disturbance of microcirculatory flow patterns in the contralateral brain region, seemingly causing tissue oxygenation to deteriorate. A similar, albeit not statistically significant, pattern was observed in the peritumoral region, which is highly sensitive to oxygen delivery, despite a parallel decrease in blood mean transit time, which is associated with a parallel reduction in capillary transit time heterogeneity in normal microvasculature. This finding further indicates that administration of phenylephrine in clinically relevant doses may exacerbate microcirculatory flow disturbances caused by "shunting" of oxygenated blood through the capillaries. The impact of measured capillary flow patterns on brain tissue oxygen tension was estimated from MRI data using biophysical models, and data suggest that phenylephrine treatment results in smaller increases in brain tissue oxygen tension and smaller reductions in oxygen extraction fraction than does ephedrine treatment; that is, less favorable cerebral tissue oxygenation. A recent

Table 2. Physiologic Variables of Difference Ephedrine – Phenylephrine

Physiologic Variables	Pretreatment		Difference	
	Phenylephrine (n = 10)	Ephedrine (n = 10)	Ephedrine – Phenylephrine (95% CI)	*P* Value
$Paco_2$, mmHg	39.6 ± 3.9	37.1 ± 1.8	−2.5 (−5.4 to 0.4)	0.087
Pao_2, mmHg	200.4 ± 52.1	183.5 ± 47.6	−17 (−63.8 to 30)	0.457

The data are presented as means ± SD or difference (95% CI). Difference ephedrine – phenylephrine = gas tension ephedrine – gas tension phenylephrine. The *P* value is the statistical comparison between difference phenylephrine *versus* difference ephedrine.

Table 3. Physiologic Variables of Difference Ephedrine – Difference Phenylephrine

Physiologic Variables	Phenylephrine (n = 10)			Ephedrine (n = 10)			Difference Ephedrine – Difference Phenylephrine (95% CI)	*P* Value
	Pretreatment	Posttreatment	Difference Phenylephrine	Pretreatment	Posttreatment	Difference Ephedrine		
MAP, mmHg	60 ± 13	85 ± 16	25 ± 6*	61 ± 8	83 ± 9	22 ± 4*	–3 (–8 to 2)	0.176
Heart rate, beats/min	55 ± 8	50 ± 7	–5 ± 6*	58 ± 9	73 ± 12	15 ± 7*	20 (15 to 27)	0.0001

The data are presented as means ± SD or difference (95% CI). 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.

MAP, mean arterial pressure.

Table 4. Brain Monitoring

Brain Monitoring	Phenylephrine (n = 10)			Ephedrine (n = 10)			Difference Ephedrine – Difference Phenylephrine (95% CI)	*P* Value
	Pretreatment	Posttreatment	Difference Phenylephrine	Pretreatment	Posttreatment	Difference Ephedrine		
Regional cerebral oxygen saturation, %	69 ± 8	65 ± 8	–4 ± 7	75 ± 8	74 ± 7	–1 ± 8	3 (–4 to 10)	0.438

The data are presented as the means ± SD or difference (95% CI). 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.

Table 5. Brain Monitoring and Anesthesia

Variables	Phenylephrine (n = 10)	Ephedrine (n = 10)	Group Difference Ephedrine – Phenylephrine (95% CI)	*P* Value
Anesthesia				
Bispectral Index, %	46 ± 10	49 ± 7	3 (–5 to 11)	0.422
Propofol, mg/kg	10.7 ± 1.6	10.8 ± 1.5	0.02 (–1 to 1.5)	0.971
Remifentanil, μg/kg	29.6 ± 10.2	35.8 ± 9.3	6.2 (–3 to 15.4)	0.173
Study medication, μg/kg	6.4 ± 1.3	381.5 ± 145.5		NA
Intracranial pressure and cerebral perfusion pressure				
Subdural intracranial pressure, mmHg	12 ± 10	14 ± 4	2 (–6 to 11)	0.591
Cerebral perfusion pressure, mmHg	77 ± 17	70 ± 10	–6 (–21 to 9)	0.385

The data are presented as the means ± SD or difference (95% CI). 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.

NA, not applicable.

positron emission tomography study in anesthetized brain tumor patients demonstrated low pretreatment cerebral blood flow values of 17 to 23 $ml \cdot 100\,g^{-1} \cdot min^{-1}$ with high compensatory oxygen extraction values of 59 to 64%.[20] The minimal decrease in oxygen extraction (8 and 15%) induced by phenylephrine in the above study supports the notion that phenylephrine treatment may not sufficiently enhance cerebral oxygen delivery in conditions where low cerebral blood flow and cerebral pathology coexist. Under these circumstances, a further increase in cerebral perfusion pressure and cerebral blood flow to enhance oxygen delivery may result in an additional increase in capillary transit time heterogeneity and a paradoxical lowering of tissue oxygenation, in a vicious cycle.[7,8,10] Thus, administration of phenylephrine could, paradoxically, pose a risk of inducing tissue hypoxia by disturbing microcirculatory flow, despite clinically relevant MAP targets being reached.

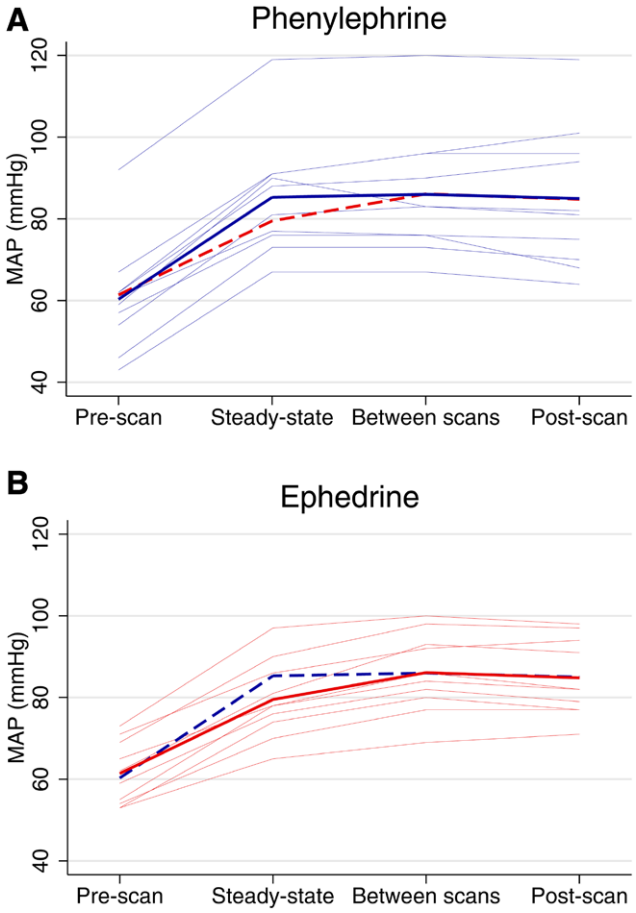

Fig. 4. Mean arterial pressure (MAP) during vasopressor treatment. The figure shows the changes in MAP over time within the (*A*) phenylephrine and (*B*) ephedrine treatment groups.

Ephedrine caused a statistically significant increase in cerebral blood flow in both peritumoral and contralateral tissue when compared to phenylephrine. This is in line with the recent positron emission tomography study[20] in which ephedrine treatment was associated with a significant increase in cerebral blood flow in anesthetized brain tumor patients. In this study, an increase in cerebral blood flow after ephedrine treatment was accompanied by a simultaneous increase in cerebral blood volume and a decrease in mean transit time in both peritumoral and contralateral regions. Although cerebral blood volume increased more during ephedrine treatment in both regions, there were no statistically significant between-group differences in the two regions. The mean transit time is given as the ratio between cerebral blood volume and cerebral blood flow, and changes in this ratio therefore reflect changes in cerebral blood flow and cerebral blood volume in the respective regions. The estimated response in brain oxygen metabolism to the measured flow changes suggests that ephedrine treatment is associated with a significant increase in brain tissue oxygen tension and a decrease in the oxygen extraction fraction. Thus, there appear to be after both phenylephrine and ephedrine treatment. Thus, regarding phenylephrine, oxygen extraction may improve little because of exacerbated "shunting" of capillary flows; while regarding ephedrine, the much greater decrease in improved oxygen extraction may be due to increased oxygen delivery and capillary flow homogenization during the increase in cerebral blood flow.

This study was not designed to examine the exact mechanisms by which the vasopressors may influence brain microcirculation. In the healthy brain, the intact blood–brain barrier normally prevents exogenous adrenergic agents from binding to adrenergic receptors, with minimal or no influence on cerebral blood flow and oxygen metabolism.[33] However, patients with brain tumors are frequently characterized by increased blood–brain barrier permeability.[34,35] Under these circumstances, the vasopressor agent may gain direct access to the brain and bind to contractile pericytes embedded in the basement membrane of cerebral capillaries.[15] The pericyte is a key cellular component in the

Table 6. Magnetic Resonance Imaging-derived Parameters

Parameters	Phenylephrine (n = 10)			Ephedrine (n = 10)			Difference Ephedrine – Difference Phenylephrine (95% CI)	*P* Value
	Pretreatment	Posttreatment	Difference Phenylephrine	Pretreatment	Posttreatment	Difference Ephedrine		
Peritumoral area								
Cerebral blood volume ratio	1.00	1.20	0.20 ± 0.16*	1.00	1.34	0.34 ± 0.21*	0.14 (–0.03 to 0.32)	0.107
Cerebral blood flow ratio	1.00	1.28	0.28 ± 0.29*	1.00	1.58	0.58 ± 0.22*	0.3 (0.06 to 0.54)	0.018
Mean transit time, s	4.3 ± 0.8	4.1 ± 0.8	–0.1 ± 0.6	3.6 ± 1.0	3.2 ± 1.0	–0.4 ± 0.2*	–0.2 (–0.7 to 0.2)	0.240
Capillary transit time heterogeneity, s	4.1 ± 0.7	4.3 ± 0.8	0.2 ± 0.6	3.5 ± 0.9	3.3 ± 0.9	–0.2 ± 0.3	–0.4 (–0.9 to 0.1)	0.130
Contralateral hemisphere								
Cerebral blood volume ratio	1.00	1.14	0.14 ± 0.16*	1.00	1.23	0.23 ± 0.19*	0.09 (–0.08 to 0.26)	0.271
Cerebral blood flow ratio	1.00	1.18	0.18 ± 0.22*	1.00	1.47	0.47 ± 0.29*	0.3 (0.06 to 0.54)	0.018
Mean transit time, s	3.0 ± 0.6	3.1 ± 0.7	0.1 ± 0.4	3.2 ± 0.9	2.7 ± 0.8	–0.5 ± 0.3*	–0.5 (–0.9 to –0.1)	0.009
Capillary transit time heterogeneity, s	3.0 ± 0.5	3.2 ± 0.7	0.2 ± 0.4	3.1 ± 0.8	2.7 ± 0.7	–0.4 ± 0.3*	–0.6 (–0.9 to –0.2)	0.004

The data are presented as means ± SD or difference (95% CI). Posttreatment values are given as a ratio ([posttreatment/pretreatment] + 1). Difference phenylephrine = posttreatment ratio of phenylephrine – pretreatment ratio of phenylephrine. Difference ephedrine = posttreatment ratio of ephedrine – pretreatment ratio of ephedrine. The *P* value is the statistical comparison between difference phenylephrine *versus* difference ephedrine.
*Significant effect of treatment within group.

active regulation of brain microvasculature expressing α-adrenergic receptors, and binding to vasopressor agents may increase capillary transit time heterogeneity.[15] Experimental studies have reported that vasopressor administration in circumstances with increased blood–brain barrier permeability is associated with direct α-adrenergic receptor–mediated vasoconstriction of cerebral vessels.[4,36,37] Similarly, increases in cerebral metabolism and cerebral blood flow through direct ß-adrenergic receptor stimulation have been reported in experimental blood–brain barrier disruption.[20,35,38,39] Ephedrine is a combined α- and ß-receptor agonist, and phenylephrine is a pure α-receptor agonist. In this study, the difference in receptor affinity between the two drugs may explain why ephedrine is associated with a significant increase in cerebral blood flow compared to phenylephrine and why phenylephrine is associated with a significant increase in capillary transit time heterogeneity compared to ephedrine.

In patients with cerebral tumors, increased ICP and local pressure from edema may compress capillaries and disturb capillary flow. In this study, mean pretreatment peritumoral capillary transit time heterogeneity was 40 and 14% higher in the phenylephrine and ephedrine groups, respectively, when compared to the contralateral region. This finding suggests that the microcirculation was disturbed in the peritumoral region before study drug administration and further aggravated by phenylephrine administration. Importantly, both subdural ICP and cerebral perfusion pressure were comparable between the two groups, and the values corresponded to measurements obtained from previous studies in similar populations.[2,3,20] Thus, the measured posttreatment differences in peritumoral capillary transit time heterogeneity between the two groups are not likely due to differences in cerebral perfusion pressure or ICP.

Studies in anesthetized patients without cerebral pathology have shown that augmentation of blood pressure with phenylephrine is associated with a decrease in regional cerebral oxygen saturation compared to ephedrine treatment.[5,40,41] In this study, regional cerebral oxygen saturation was not affected by vasopressor treatment and did not reflect the changes in cerebral blood flow and oxygen metabolism induced by ephedrine. Consistent with our findings, a similar study found that changes in regional cerebral oxygen saturation after ephedrine treatment do not adequately reflect changes in cerebral oxygen metabolism.[20] Taken together, the findings from this and the previous study may suggest that changes in regional cerebral oxygen saturation do not exclusively reflect changes in either cerebral blood flow or tissue oxygen metabolism. Rather, they may reflect changes in the balance between oxygen supply (cerebral blood flow) and consumption (cerebral metabolic rate of oxygen), as suggested by others.[5]

The main limitation of this study is the small sample size, which may explain the lack of statistically

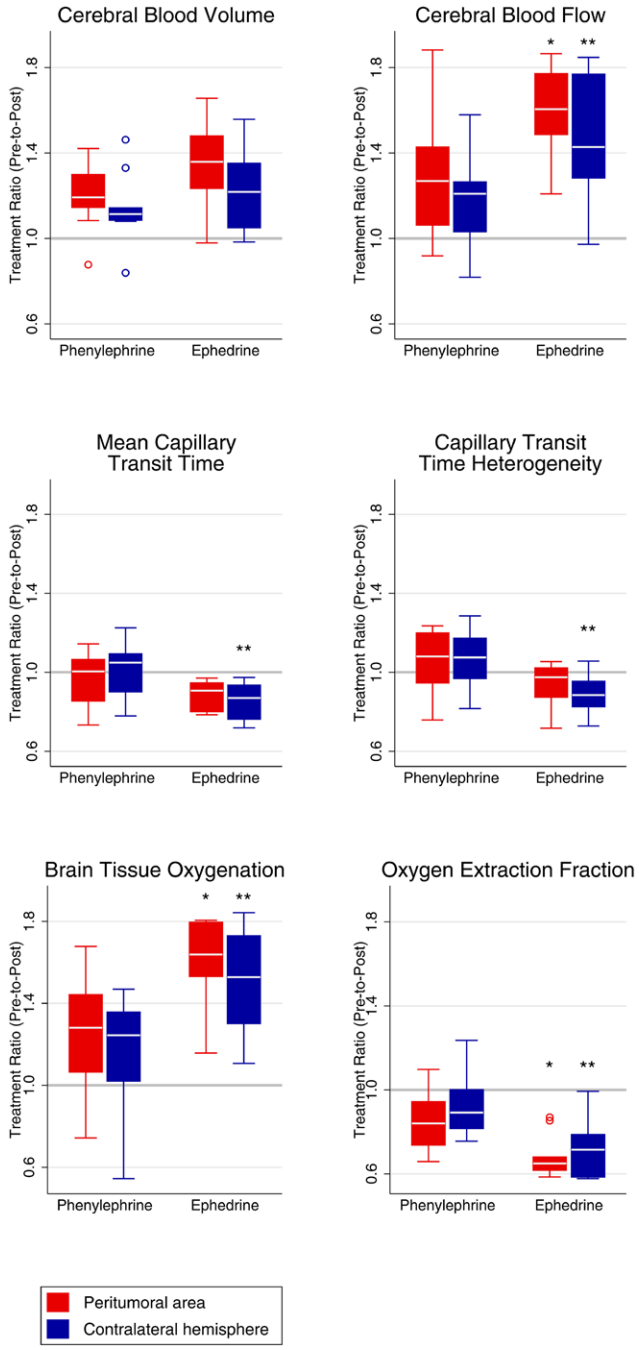

Fig. 5. Box plot of changes in peritumoral and contralateral macro- and microcirculatory magnetic resonance imaging parameters and oxygenation ratios during treatment with phenylephrine and ephedrine. Outliers are marked with *colored circles*. Statistical significance ($P < 0.05$) is marked with * for the peritumoral area and ** for the contralateral hemisphere. *Boxes* represent the interquartile range, with the median indicated as a *horizontal line*. *Whiskers* indicate the value adjacent to 1.5 times the interquartile range. The values outside the *whiskers* are plotted individually as outliers.

significant changes in peritumoral capillary transit time heterogeneity and possibly other parameters. In addition, the majority of the screened patients were not included in the study, and the uneven distribution of tumor pathology and tumor heterogeneity may have influenced the results. Other limitations are that the age of the patients may have influenced the measured flow parameters and that oxygen metabolism parameters were

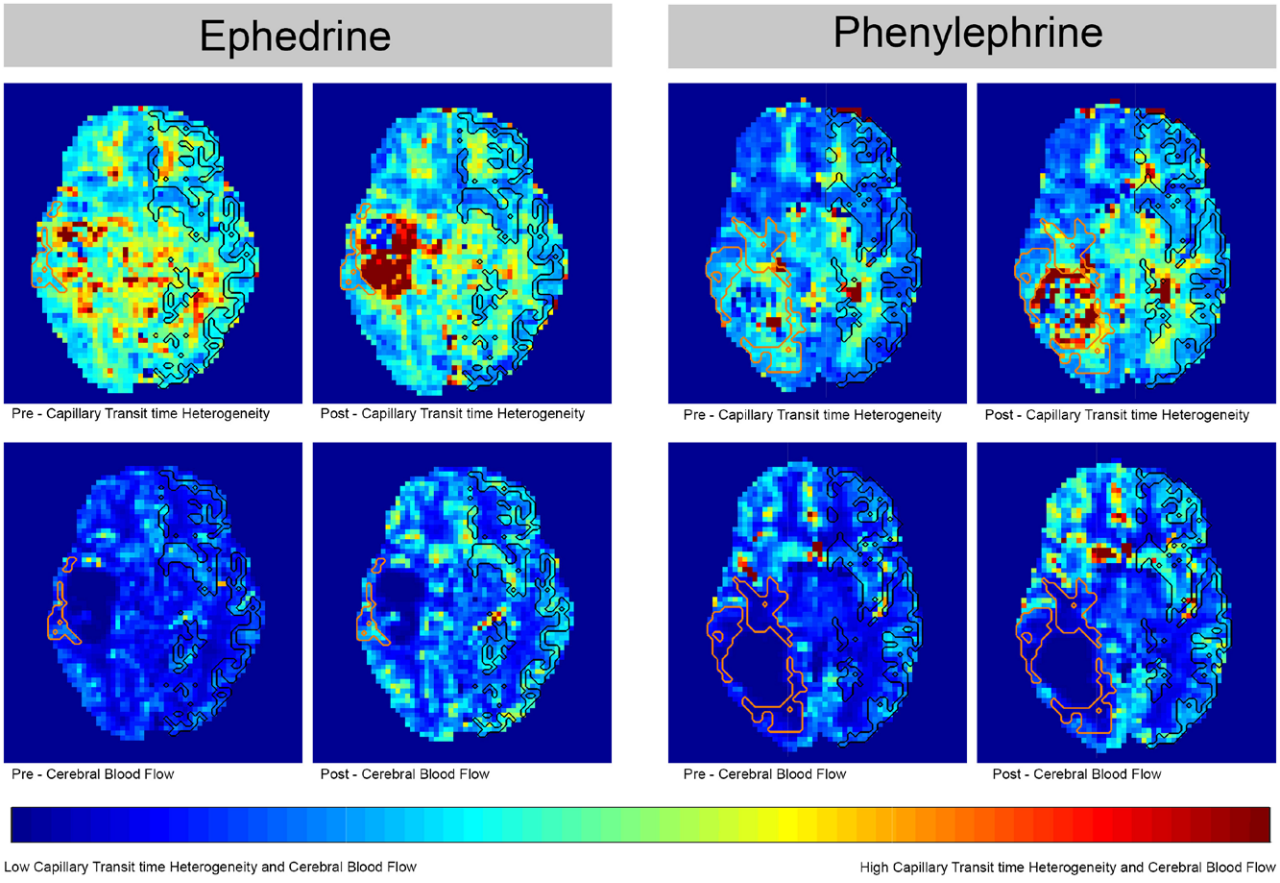

Fig. 6. Pre- and posttreatment capillary transit time heterogeneity and cerebral blood flow maps of peritumoral and contralateral regions of interest during phenylephrine and ephedrine treatment. The *color bar* indicates the spectrum from low to high values of capillary transit time heterogeneity and cerebral blood flow. The contralateral hemisphere region of interest is outlined with *black*, and the peritumoral region of interest is outlined with *orange*.

Table 7. Magnetic Resonance Imaging-derived Parameters

	Phenylephrine (n = 10)			Ephedrine (n = 10)				
Parameters	Pretreatment	Posttreatment	Difference Phenylephrine	Pretreatment	Posttreatment	Difference Ephedrine	Difference Ephedrine – Difference Phenylephrine (95% CI)	*P* Value
Peritumoral area								
Brain tissue oxygenation ratio	1.00	1.26	0.26 ± 0.28*	1.00	1.59	0.59 ± 0.22*	0.33 (0.09 – 0.57)	0.010
Oxygen extraction fraction ratio	1.00	0.85	–0.15 ± 0.14*	1.00	0.68	–0.32 ± 0.10*	–0.17 (–0.29 to –0.05)	0.007
Contralateral hemisphere								
Brain tissue oxygenation ratio	1.00	1.17	0.17 ± 0.27	1.00	1.51	0.51 ± 0.26*	0.34 (0.09 to 0.59)	0.001
Oxygen extraction fraction ratio	1.00	0.92	–0.08 ± 0.14	1.00	0.72	–0.28 ± 0.14*	–0.20 (–0.33 to –0.07)	0.005

The data are presented as means ± SD or difference (95% CI). Posttreatment values are given as a ratio ([posttreatment/pretreatment] + 1). Difference phenylephrine = posttreatment ratio of phenylephrine – pretreatment ratio of phenylephrine. Difference ephedrine = posttreatment ratio of ephedrine – pretreatment ratio of ephedrine. The *P* value is the statistical comparison between difference phenylephrine *versus* difference ephedrine.

*Significant effect of treatment within group.

not directly measured but inferred from the flow parameters. Furthermore, generalizability of our findings in terms of vasopressors in general is limited, because other vasopressors may be associated with different effects on capillary transit time heterogeneity, mean transit time, cerebral blood flow, and cerebral blood volume. Finally, extracranial contamination of the regional cerebral oxygen saturation signal and absence of bilateral near-infrared spectroscopy and BIS measurements are additional limitations of the study.[42,43]

Conclusions

Capillary transit time heterogeneity in the contralateral brain region was significantly higher during phenylephrine treatment than during ephedrine treatment, despite similar MAP targets being reached. The effects of phenylephrine on capillary flow heterogeneity were mirrored in the peritumoral region but did not reach statistical significance. Ephedrine significantly increased cerebral blood flow in both regions compared to phenylephrine. The impact of the measured flow parameters on brain oxygen metabolism was estimated, and findings suggest that ephedrine is associated with a significant improvement in both peritumoral and contralateral brain tissue oxygen tension compared to phenylephrine. Overall, our findings demonstrate that ephedrine, a combined α- and β-adrenergic agonist, is superior in improving cerebral macro- and microscopic perfusion and oxygenation compared to phenylephrine, a pure α-adrenergic agonist. Furthermore, the study raises substantial concerns regarding the use of phenylephrine for blood pressure augmentation in patients with cerebral pathology.

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Competing Interests

Dr. Østergaard is a minority shareholder in Cercare Medical A/S, Aarhus, Denmark, and serves on the scientific advisory board. The other authors declare no competing interests.

Reproducible Science

Full protocol available at: klaukoch@rm.dk. Raw data available at: klaukoch@rm.dk.

Correspondence

Address correspondence to Dr. Koch: Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark. klaukoch@rm.dk.

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