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Impact of noradrenaline versus phenylephrine on brain circulation, organ blood flow and tissue oxygenation in anesthetized patients with brain tumours: study protocol for a randomized controlled trial.

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ABSTRACT

Introduction: Vasopressor support is often preferred as an efficient and convenient way to raise the blood pressure during surgery and intensive care therapy. However, the optimal vasopressor for ensuring organ blood flow and tissue oxygen delivery during surgery remains undetermined. This study aims to assess the impact of noradrenaline versus phenylephrine, on cerebral and non-cerebral organ perfusion and oxygenation during anaesthesia in neurosurgical patients with brain tumours. The study also explores the impact of the vasopressor agents on the distribution of cardiac output between various organs.

Methods and analysis: This is an investigator-initiated, double-blinded, randomized clinical trial including 32 patients scheduled for supratentorial brain tumour surgery. The patients are randomized to receive a phenylephrine or noradrenaline infusion during preoperative positron emission tomography (PET) examinations and the following neurosurgical procedure. PET measurements of blood flow and oxygen metabolism in the brain and other organs are performed in the awake subject, during anaesthesia and following a 10% and 20 % gradual increase in blood pressure from the baseline value. The primary endpoint is the between-group difference in cerebral blood flow. Secondary endpoints include detection of ischemic brain lesions possibly associated with vasopressor treatment, changes in cerebral oxygen metabolism, non-cerebral organ blood flow and oxygen metabolism, cardiac output, regional cerebral oxygen saturation, autoregulation, and distribution of cardiac output between organs.

Ethics and dissemination: This study was approved by the Danish National Medical Ethics Committee (20 May 2022; 2203674). Results will be disseminated via peer-reviewed publication and presentation at international conferences. Trial registration number at ClinicalTrials.gov NCT06083948

STRENGTHS AND LIMITATIONS

1. The study is strengthened by the robust design, which minimizes bias, enhances the validity of findings, and allows for reliable of comparisons between effects of noradrenaline and phenylephrine.

2. The infusion of commonly used vasopressor agents and clinically relevant dosage regimes ensures the applicability of the study's results to clinical practice.

3. The study applies novel PET technology allowing for multi-organ assessments of blood flow and oxygen metabolism. PET is generally considered the "gold standard" for organ blood flow and tissue oxygenation measurements.

4. The sequential measurement of cardiac output indices under varying clinical conditions provide the possibility for a comprehensive and currently unknown understanding of vasopressor impact on flow distribution between organs.

5. The small sample size does not allow for postoperative clinical outcome assessments of the intervention. In addition, the study design does not allow for intraoperative assessments of organ blood flow and metabolism. Practical limitations include limited PET-scanner availability and complex coordination between the planning of scheduled brain surgery and PET scanner availability.

KEYWORDS

Noradrenaline. Phenylephrine. Hypotension. Vasopressors. Anesthesia. Cerebral perfusion. Organ perfusion. Cardiac Output.

INTRODUCTION

Preventing hypotension and maintaining or restoring patient hemodynamic during surgery and acute care are fundamental aspects of anaesthetic practice. Substantial evidence associates perioperative hypotension with cerebral and non-cerebral organ ischemia and dysfunction[1-6]. Vasopressor support is often preferred as an efficient and convenient way to raise the blood pressure during surgery and intensive care therapy[7-11]. The ultimate goal of the intervention is to restore/maintain blood flow to meet the metabolic demand of the brain and other organs[8,11,12]. However, the use of vasopressors *per se* may also be associated with organ injury and evidence suggests that the pharmacological profile of the vasopressor may be linked with tissue injury[13,14]. The most commonly used vasopressor agents (such as phenylephrine and noradrenaline) have different pharmacological profiles. Phenylephrine, a pure α-adrenergic agonist, primarily acts on the peripheral vasculature. In contrast, noradrenaline engages both α- and β-adrenoceptors and acts on both the heart and the peripheral vasculature[8,11]. Moreover, noradrenaline is a natural catecholamine and neurotransmitter existing in human bodies, while phenylephrine is a synthetic compound. The optimal vasopressor for ensuring organ blood flow and tissue oxygen delivery during surgery and intensive care remains undetermined[14,15].

In routine clinical practice, anesthesiologists and critical care physicians adjust their vasopressor therapy according to blood pressure[11,14]. The measured blood pressure only reflects the pressure in larger arteries and not organ perfusion and oxygen delivery to parenchymal cells[14]. Thus, blood pressure acts as a surrogate for organ perfusion with varying accuracies. Since organ blood flow and tissue oxygenation are not routinely measured, the treating physician often remains unaware whether their vasopressor therapy achieves the primary goals of maintaining adequate tissue perfusion and oxygen delivery. Evidence from our research group and others suggests that vasopressor agents may be associated with reduced microcirculatory brain perfusion and impaired tissue oxygen delivery during anaesthesia, despite reaching recommended blood pressure targets[9,10,16-19]. The data further indicates that cerebral macro- and microcirculation, tissue oxygen delivery, and cardiac output are greater with an indirectly acting α- and β-adrenergic agonist (ephedrine) compared to phenylephrine, as observed during anaesthesia in neurosurgical patients[16-19]. Collectively, the emerging evidence suggests that vasopressor agents acting on both α- and β-adrenoceptors, such as noradrenaline, may have the

potential to improve blood flow to the brain, organ blood flow, and tissue oxygen delivery in anesthetized patients compared to pure α-adrenergic agonists.

The impact of vasopressors on brain and organ circulation primarily depends on their influence on cardiac output (CO) and systemic vascular resistance (SVR)[8]. Physiologically, CO is distributed to different organs and each organ receives its share based on its metabolic demand and organ-specific perfusion-regulatory schemes[20-22]. Currently, no data are available on the influence of different vasopressor agents on the distribution of CO (i.e., blood flow) to the brain and other organs such as the myocardium, lungs, kidneys and muscle tissue, during anaesthesia. Theoretically, changes in CO would likely affect blood flow to different organs, including the brain[21-22].

The research questions of this study pertain to the potential advantages of administering a combined α- and β-adrenoceptor agonist during anaesthesia, specifically in terms of its association with improved cerebral blood flow and tissue oxygenation. Additionally, the study seeks to explore whether this compound offers enhanced blood flow and tissue oxygenation in other organs that are sensitive to changes in blood pressure during anaesthesia, in comparison to the effects of a pure α-adrenergic agonist.

HYPOTHESIS

Our hypothesis is twofold:

- Noradrenaline increases perfusion and oxygenation in diseased and healthy brain regions during anaesthesia in comparison to phenylephrine.
- Noradrenaline is associated with increased non-cerebral organ perfusion and tissue oxygenation during anaesthesia when compared to phenylephrine.

OBJECTIVES

- The primary objective is to conduct a comparative analysis of the effects of two commonly used vasopressor agents (phenylephrine vs. noradrenaline) on cerebral circulation and brain tissue oxygenation in anesthetized patients with brain pathology.

- The secondary objectives are: 1) to assess and compare the effects of the two vasopressors on blood flow and tissue oxygenation in other organs that are particularly sensitive to changes in blood pressure during anaesthesia. These organs include the heart, lungs, kidneys, and muscle tissue, 2) to assess and compare how the two vasopressors influence the distribution of cardiac output between the brain and the organs mentioned above during anaesthesia. 3) to assess and compare the relationship between mean arterial pressure and cerebral blood flow based on correlation plot and cubic penalized regression splines (i.e., static cerebral autoregulation) between noradrenaline and phenylephrine, and between normal and diseased brain regions (in addition to the global cerebral blood flow).

METHODS AND ANALYSIS

Study design and setting

The study is an investigator-initiated, single centre, double blinded randomized clinical trial. The setting for the trial is the Departments of Anaesthesia, Neurosurgery and Nuclear Medicine and PET Center, Aarhus University Hospital, Aarhus, Denmark. Patient recruitment began on 1. November 2023, and the anticipated ending date for the study is 31 December 2025. The paper is written in accordance with the standard protocol items: Recommendations for Interventional Trials (SPIRIT). See online supplementary material for the SPIRIT Checklist and figure. Trial registration: ClinicalTrials.gov NCT06083948.

Patients

The study will include 32 patients diagnosed with supratentorial brain tumours. Written informed consent will be obtained by the primary investigator or one of the co-investigators. Adult patients diagnosed with brain tumours will be screened at the outpatient clinic by attending physicians. The inclusion criteria are as follows: aged 18-75 years; scheduled for elective craniotomy for supratentorial malignant and non-malignant tumours with a minimum size of 3 cm (measured as the largest diameter in any plane on magnetic resonance images); American Society of Anesthesiologists (ASA) physical status I-III.[16,17] Exclusion criteria include: a history of allergy or intolerance to one of the

study medications; active treatment with monoamine oxidase inhibitors; pregnancy (positive pregnancy urine test) or breastfeeding, and inability to give written informed consent.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Randomization and blinding

Figure 1 shows study design and randomization. Randomizing and blinding are performed by a dedicated nurse, or a physician not involved in the experimental part of the study[16,17]. Patients and researchers are blinded to randomization. Patients are randomized in a 1:1 ratio using the in-built randomization module within the Research Electronic Data Capture (REDCap) system and a randomly varying block randomization size of 4 and 6 to receive infusion of either noradrenaline (10 mcg/ml) or phenylephrine (100 mcg/ml). The concentrations of study drugs are similar to the concentrations used in previous studies and according to institutional guidelines for the use of intraoperative vasopressor support at Aarhus University hospital. Identical syringes of 50 ml, containing either noradrenaline (10 mcg/ml) or phenylephrine (100 mcg/ml), are marked with a randomization code known only to the unblinded nurse or doctor. The study drugs are prepared immediately before administration by a nurse not involved in the actual study. The unblinded persons are responsible for documentation of study drugs, randomization–code, patient ID and blinding of drugs in a specific log. This log will only be accessible to the unblinded person. Code-break of randomization can only occur in emergencies with suspected adverse patient-reaction to a study drug. The staff involved in the experimental part of the study is unaware of randomization. The randomization code is kept without the reach of sponsor-investigator. Interpretation of imaging and calculation of flow and oxygenation parameters are performed by a blinded researcher. After the final inclusion, an independent researcher will unblind the two groups and label the groups 0 and 1. Statistical analyses will then be performed and final unblinding will take place.

Figure 1: Study design and randomization.

Anaesthesia and monitoring

The anaesthetic management is standardized. General anaesthesia with propofol and remifentanil is administered according to institutional guidelines and titrated to achieve a bispectral index (BIS) score between 40-60 which is indicative of an adequate level of anaesthesia for surgery[16,17]. A low dose of muscle relaxant (suxamethonium or rocuronium) is administered to facilitate intubation. The patients are ventilated with 40-50% oxygen in air by controlled ventilation titrated to achieve a partial pressure of carbon dioxide in arterial blood ($PaCO_2$) between 35 and 40 mmHg (4.7-6.0 kPa) and a partial pressure of oxygen in arterial blood (PaO_2) greater than 100 mmHg (13.3 kPa)[16,17]. Ventilation is adjusted according to arterial blood gas measurements. Isotonic NaCl is infused at a rate of 2-3ml/kg/hour. Temperature, ECG, oxygen saturation, heart rate, intra-arterial blood pressure and cardiac output indices acquired using LiDCO (Masimo, Irvine, CA) are continuously monitored. The depth of anaesthesia is continuously measured with BIS (Medtronic, MN). Brain tissue oxygen saturation is continuously measured with near infrared spectroscopy (NIRS) (Medtronic, MN) to allow comparison with brain oxygenation measurements determined with PET [16,17].

Experimental protocol and intervention

The experimental study protocol and flow chart are shown in figure 2. The experiment is conducted on the same day as the scheduled brain tumour surgery [16,17]. All PET examinations consist of a blood flow (using $[^{15}O]H_2O$ tracer) measurement followed by a measurement of oxygen consumption (using $[^{15}O]O_2$ tracer)[16]. Four PET examinations (including blood flow and oxygen consumption measurements) are performed.

The first PET examination (**PET 1**) is performed on the awake patient. The patient is then anesthetized, and the PET exam is repeated when the anaesthetic depth corresponds to a BIS value between 40-60 (**PET 2**). Vasopressor infusion is initiated and titrated to increase MABP to above 60 mmHg, or by 10% relative to baseline. When the blood pressure has stabilized the third PET examination (**PET 3**) is performed**.** After completion of PET 3 MABP is further increased to above 70 mmHg or by 20 % relative

to the baseline level. When the blood pressure has stabilized the fourth PET examination (**PET 4**) is performed. After completion of the PET examinations the anesthetized patient is transported to the surgical theatre and surgery is initiated. During the surgical procedure, MABP is maintained between 70-80 mmHg according to institutional guidelines. The vasopressor infusion is terminated at the time of extubation. The duration of the PET part of the study until initiation of surgery is approximately 2 hours. The 24-48-hour postoperative Magnetic Resonance Imaging (MRI) examination is conducted to assess the result of the surgical intervention and to determine whether there are any ischemic lesions possibly associated with the vasopressor agents.

The rationale for the selected PET protocol is as follows: PET 1 and 2 allow us to assess the influence of anaesthesia on organ blood flow and oxygen consumption. PET 3 and PET4 exams allow for the assessment of the effect of vasopressor infusion on organ blood flow and oxygen consumption. The MRI examination is added as a surrogate outcome measure of the vasopressor effects.

Positron emission tomography image acquisition

A Biograph Vision Quadra PET scanner (with a long axial field of view allowing for simultaneous multi-organ assessments of blood flow and oxygen consumption) and PET tracers [^{15}O]H_2O and [^{15}O]O_2 are used to measure multi-organ blood flow and oxygen consumption parameters[16,23,24].

Outcomes

The primary outcome measure is the between-group difference in the change in cerebral blood flow (ΔCBF), defined as the difference between post-treatment and pre-treatment values (ΔCBF = post-treatment value - pre-treatment value)[16,17].

Seconday outcomes include:

1. Detection of Postoperative Cerebral Ischemic Lesions: These lesions, potentially linked to vasopressor infusion, will be identified through MRI examinations conducted 24-48 hours postoperatively.

2. Absolute and relative between-group differences in brain energy consumption parameters such as

oxygen extraction fraction (OEF) and cerebral metabolic rate of oxygen ($CMRO_2$).

3. Measurements of cerebral tissue oxygen saturation ($SctO_2$).

4. Blood flow and oxygen consumption in various organs, including the kidney, liver, myocardium, spinal cord and muscle tissue.

5. Cardiac output assessments and the distribution of cardiac output across different organs.

6. Evaluation of static cerebral autoregulation.

The secondary outcomes also include the comparisons between diseased and non-diseased brain regions. In this analysis, patients themselves are their own control. We analyse the between-region differences in each patient and pool the results per group. Different vasopressor treatment is treated as a stratification factor.

Data collection and trial monitoring:

Study data are collected and managed using REDCap electronic data capture tools hosted at Aarhus University[25,26]. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

All Imaging data are stored on a server with secured and restricted access. Physiological data are initially stored on the respective monitoring devices and subsequently extracted and stored in the study database. The study is conducted according to the standards of Good Clinical Practice and is monitored by the "Good Clinical Practice Unit ", Department of Clinical Medicine, Aarhus University Hospital[16,17].

Figure 2: Experimental protocol and study flow chart.

Positron Emission Tomography and Magnetic Resonance Imaging analyses:

All patients will have a pre-operative structural MRI of the brain as part of clinical investigations performed during their preparations for surgery[16,17]. T1-weighted MRI of the brain is co-registered with PET images for each patient. Voxel wise estimation of organ blood flow and oxygen consumption is performed using the arterial blood radioactivity as the input function and a one-tissue compartment model based on previous works[16,27-29]. Brain regions of interest are defined as the tumour, peritumoural area, and contralateral hemisphere grey matter[16,17,19]. Other organs will be delineated using low-dose CT images and analysed using appropriate kinetic models[24].

Magnetic resonance imaging analyses of ischemic lesions

Diffusion weighted imaging (DWI) displays regions of reduced water mobility, which is usually ascribed to regions of cell swelling due to insufficient oxygen availability (ischemia). To obtain a quantitative measure of the potential harmful effect of the vasopressor, we will detect changes in ischemic regions by comparing the DWI images obtained prior to project enrollment with DWI obtained as a part of the routine post-surgery evaluation. Using machine-learning algorithms, we will automatically segment the pre-study and post-surgery ischemic regions. Since brain regions potentially alter position during surgery, we will attempt a non-linear co-registration of the two DWI measurements, before extracting the pre-study region from the post-surgery region to be able to report the potential volume increase. We will attempt to avoid regions that are the most affected by the surgery, since the surgery itself may also affect the DWI values. This quantitative analysis is supplemented by qualitative inspection.

Sample size and statistical analysis

No previous studies have, to our knowledge, investigated the changes in CBF based on PET measurements after phenylephrine vs. noradrenaline treatment in the same patient population. Therefore, we estimated our sample size based on the regional changes in CBF after phenylephrine vs. ephedrine treatment in a similar patient cohort as reported by Koch et al. (2020)[16]. Ephedrine and noradrenaline are both combined α- and β-adrenergic agonists and have similar pharmacological properties[8,11,16]. The study by Koch et al. reported a change in CBF of 1.7 ± 3.5 ml/100g/min after phenylephrine treatment and 5.5 ± 4.0 ml/100g/min after ephedrine treatment[16]. Given a between-

group difference in CBF = 3,8 ml/100g/min in favour of the noradrenaline group a significance level of 0.05 and a power of 80%, the study requires 16 patients in each group to detect a significant difference in CBF changes between the two vasopressors. We plan to include 16 patients in each arm to maintain a power of 80% even with a drop-out rate of 20%.

Statistical analyses: All randomized subjects with a full dataset will be included in the statistical analyses. Standard parametric and non-parametric analyses are used for paired analyses of the physiological parameters[16-19]. The percentage changes in different measurements are calculated as the post-treatment value minus pre-treatment value divided by the pre-treatment value times 100 (i.e., the relative change). The effects of vasopressor type, vasopressor dose, and CO are estimated in a generalized linear model. Static autoregulation (relationship between MABP and CBF) is assessed using correlation plots and cubic penalized regression splines between noradrenaline and phenylephrine, and between normal and diseased brain regions (in addition to the global cerebral blood flow). A detailed statistical analysis plan will be prepared prior to the start of the analyses.

ETHICS

Patients included in this study are required to receive anaesthesia for removal of their brain tumour. Thus, the patients are not exposed to any additional risk due to anaesthesia or placement of intravenous and intra-arterial catheters. The experiment and the removal of the tumour are conducted in the same anaesthesia "session". The experiment will prolong the period of which the patient is under general anaesthesia by approximately 2 hours[16,17]. With reference to our previous studies, and our experience in general, we do not find that the prolonged period of general anaesthesia will pose any additional risk to the patient[16,17]. The project has obtained approvals from the National Medical Ethics Committee (VMK) and The Danish Medicines Agency. Informed consent will be acquired from the participant prior to study enrolment.

DISCUSSION

This study will provide detailed and currently unknown information on the influence of pharmacologically different vasopressor agents on blood flow and tissue oxygenation in normal

appearing and pathologic brain regions during anaesthesia. In addition to the information on cerebral hemodynamics, the multiorgan assessment capabilities of the advanced PET technology also provide simultaneous information on blood flow and oxygen delivery to other organs which are sensitive to changes in perfusion during anaesthesia.[23] Thus, the study will provide a "global" picture of how the infusion of two commonly used vasopressor agents influence and distribute blood flow and oxygen to the body organs during anaesthesia. The results obtained from this study may have the potential to provide additional evidence-based information to inform anaesthesia and intensive care physicians in their rational choice of vasopressor therapy to patients undergoing neurosurgical and non-neurosurgical procedures.

During surgery, neurosurgery and neurointerventional procedures, blood pressure management with vasopressor agents typically aims to maintain blood pressure above or within fixed targets as defined by international guidelines, consensus guidelines or institutional guidelines[30-32]. However, studies suggest that augmenting blood pressure and cerebral perfusion pressure with an α-adrenergic agonist is associated with a "paradoxical" lowering in cerebral tissue oxygen saturation and disturbed microcirculation[9,10,16,17,19]. In contrast, a combined α- and β-adrenergic agonist (such as ephedrine) appears to be associated with improved cerebral macro- and microcirculatory blood flow and tissue oxygenation in addition to an improvement in systemic circulation[9,10,16,17,19]. This protocol aims to clarify whether noradrenaline, which is considered a more potent α- and β-adrenergic agonist than ephedrine, has similar properties to ephedrine to improve cerebral and systemic organ perfusion and tissue oxygenation when compared to a pure α-adrenergic agonist.

The study's strengths include the double-blinded randomized design and the infusion of clinically relevant vasopressor doses to achieve clinically relevant blood pressure targets. In addition, we apply PET technology, which is considered the "gold standard" for non-invasive organ blood flow and tissue oxygenation measurements. Continuous cardiac output measurements are conducted simultaneously with the PET measurements and consequently allow for the assessment of the vasopressor influence on the distribution of cardiac output between the various organs. During the PET examinations the depth of anaesthesia is titrated to a level equal to that during surgery. The PET measurements conducted during anaesthesia is therefore representative of the anaesthetic depth applied during

surgery. Limitations include the small number of participants and that we are not able to assess organ blood flow and tissue oxygenation during the surgical procedure. In this study, a post-operative MRI examination is conducted to assess cerebral ischemic lesions possibly associated with the vasopressor infusion. This assessment is a radiological outcome surrogate and may be confounded by lesions caused by the surgical procedure. In addition, the limited number of participants does not allow us to study the influence of the vasopressor treatment on surgical or other clinical outcomes.

REFERENCES

1. Mazzeffi M, Chow JH, Anders M, et al. Intraoperative hypotension and perioperative acute ischemic stroke in patients having major elective non-cardiovascular non-neurological surgery. *J Anesth*. 2021;35(2):246-53.

2. Yao J, Li S, Cui Q, et al. Intraoperative hypotension and postoperative stroke in older patients who had brain tumor resections: a retrospective cohort analysis. *World Neurosurg*. 2023;174:e72-e81.

3. Gregory A, Stapelfeldt WH, Khanna AK, et al. Intraoperative hypotension is associated with adverse clinical outcomes after noncardiac surgery. *Anesth Analg*. 2021;132(6):1654-65.

4. Ackland GL, Abbott TEF. Hypotension as a marker or mediator of perioperative organ injury: a narrative review. *Br J Anaesth*. 2022;128(6):915-30.

5. Meng L. Heterogeneous impact of hypotension on organ perfusion and outcomes: a narrative review. *Br J Anaesth*. 2021;127(6):845-61.

6. Wesselink EM, Kappen TH, Torn HM, et al. Intraoperative hypotension and the risk of postoperative adverse outcomes: a systematic review. *Br J Anaesth*. 2018;121(4):706-21.

7. Sookplung P, Siriussawakul A, Malakouti A, et al. Vasopressor use and effect on blood pressure after severe adult traumatic brain injury. *Neurocrit Care*. 2011;15:46-54.

8. Bangash MN, Kong ML, Pearse RM. Use of inotropes and vasopressor agents in critically ill patients. *Br J Pharmacol*. 2012;165(7):2015-33.

9. Meng L, Gelb AW, Alexander BS, et al. Impact of phenylephrine administration on cerebral tissue oxygen saturation and blood volume is modulated by carbon dioxide in anaesthetized patients. *Br J Anaesth*. 2012;108(5):815-22.

10. Meng L, Cannesson M, Alexander BS, et al. Effect of phenylephrine and ephedrine bolus treatment on cerebral oxygenation in anaesthetized patients. *Br J Anaesth*. 2011;107:209-17.

11. Thorup L, Koch KU, Upton RN, et al. Effects of vasopressors on cerebral circulation and oxygenation: a narrative review of pharmacodynamics in health and traumatic brain injury. *J Neurosurg Anesthesiol*. 2019;00:1-11.

12. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the management of severe traumatic brain injury, fourth edition. *Neurosurgery*. 2017;80(1):6-15.

13. Ariyarathna D, Bhonsle A, Nim J, et al. Intraoperative vasopressor use and early postoperative acute kidney injury in elderly patients undergoing elective noncardiac surgery. *Ren Fail*. 2022;44(1):648-59.

14. Karamchandani K, Dave S, Hoffmann U, et al. Intraoperative arterial pressure management: knowns and unknowns. *Br J Anaesth*. 2023;S0007-0912(23)00313-6. doi:10.1016/j.bja.2023.05.027.

15. Mets B. Should noradrenaline, rather than phenylephrine, be considered the primary vasopressor in anesthetic practice? *Anesth Analg*. 2016;122(5):1707-14.

16. Koch KU, Mikkelsen IK, Aanerud J, et al. Ephedrine versus phenylephrine effect cerebral blood flow and oxygen consumption in anesthetized brain tumor patients: a randomized clinical trial. *Anesthesiology*. 2020;133(2):304-17.

17. Koch KU, Mikkelsen IK, Espelund US, et al. Ephedrine versus phenylephrine effects on cerebral macro- and microcirculation in anesthetized brain tumor patients: a randomized clinical trial using magnetic resonance imaging. *Anesthesiology*. 2021; Nov 1;135(5):788-803. doi:10.1097/ALN.0000000000003877.

18. Koch KU, Zhao X, Mikkelsen IK, et al. Correlation between cerebral tissue oxygen saturation and oxygen extraction fraction during anesthesia: monitoring cerebral metabolic demand-supply balance during vasopressor administration. *J Neurosurg Anesthesiol*. 2023;35(2):238-42.

19. Rasmussen M, Koch KU, Espelund US, Mohamad N, et al. Blood-brain barrier permeability may influence vasopressor effects in anesthetized patients with brain tumor: An analysis of magnetic resonance imaging data. *J Neurosurg Anesthesiol*. 2024;36(4):357-362. doi:10.1097/ANA.0000000000000948.

20. Drummond JC. Cardiac output: the neglected stepchild of the cerebral blood flow physiology. *J Neurosurg Anesthesiol*. 2020;32:93-94.

21. Meng L, Hou W, Chui J, et al. Cardiac output and cerebral blood flow: the integrated regulation of brain perfusion in adult humans. *Anesthesiology*. 2015;123:1198-208.

22. Meng L, Wang Y, Zhang L, et al. Heterogeneity and variability in pressure autoregulation of organ blood flow: lessons learned over 100+ years. *Crit Care Med*. 2019;47(3):436-48.

23. Prenosil GA, Sari H, Fürstner M, et al. Performance characteristics of the Biograph Vision Quadra PET/CT system with a long axial field of view using the NEMA NU 2-2018 standard. *J Nucl Med*. 2022;63(3):476-84.

24. Knuuti J, Tuisku J, Kärpijoki H, et al. Quantitative perfusion imaging with total-body PET. *J Nucl Med*. 2023;64(Suppl 2):11S-19S.

25. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap) – a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-81.

26. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software partners. *J Biomed Inform*. 2019;103208. doi:10.1016/j.jbi.2019.103208.

27. Ohta S, Meyer E, Fujita H, et al. Cerebral [15O]water clearance in humans determined by PET: I. Theory and normal values. *J Cereb Blood Flow Metab*. 1996;16:765-80.

28. Ohta S, Meyer E, Thompson CJ, et al. Oxygen consumption of the living human brain measured after a single inhalation of positron emitting oxygen. *J Cereb Blood Flow Metab*. 1992;12:179-92.

29. Blomqvist G. On the construction of functional maps in positron emission tomography. *J Cereb Blood Flow Metab*. 1984;4:629-32.

30. Meng L, Yu W, Wang T, et al. Blood pressure targets in perioperative care. *Hypertension*. 2018;72(4):806-17. doi:10.1161/HYPERTENSIONAHA.

31. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the management of severe traumatic brain injury, fourth edition. *Neurosurgery*. 2017;80(1):6-15. doi:10.1227/NEU.0000000000001432.

32. Talke PO, Sharma D, Heyer EJ, et al. Society for Neuroscience in Anesthesiology and Critical Care expert consensus statement: anesthetic management of endovascular treatment for acute ischemic stroke. *J Neurosurg Anesthesiol*. 2014;26(2):95-108. doi:10.1097/ANA.0000000000000042.

AUTHOURS' CONTRIBUTIONS

Dr. Niwar Faisal Mohamad has prepared the IMPACT protocol manuscript in close collaboration with

Associate Professor Mads Rasmussen. The rest of the research group has subsequently reviewed the manuscript.

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DECLARATION OF INTEREST

None.

APPENDICES

Informed consent material

FIGURE LEGENDS

Figure 1: Study design and randomization.

Figure 2: Experimental protocol and study flow chart.

PET exams of Blood flow (using [^{15}O] H_2O tracer) and oxygen consumption (using [^{15}O]O_2 tracer) in brain and organs (including myocardium, kidney, lungs and limb muscle) are performed using a Biograph Vision Quadra-PET scanner with a wide axial field of view. The wide axial field of view allows for simultaneous assessments of the brain and organs.

The first PET examination (**PET 1**) is performed in the awake patient. The patient is then anesthetized, and the PET exam is repeated (**PET 2**). Vasopressor infusion is initiated and titrated to a 10 % increase in MABP relative to pre-treatment level (**PET 3**). MABP is further increased to 20 % relative to the pre-treatment level (**PET 4**). After completion of the PET examinations the anesthetized patient is transported to the surgical

theatre and surgery is performed. The vasopressor infusion is initiated after PET 2 and terminated at emergence of anaesthesia after completion of surgery. MABP, CO, BIS and NIRS are measured during PET exams and surgery. The duration of the PET part of the study until initiation of surgery is approximately 2 hours.

The 24-48 MRI examination is performed as a postoperative control of the surgical result and includes a diffusion weighted sequence to detect ischemic brain lesions possibly associated with vasopressor infusion.

MABP, mean arterial blood pressure; CO, cardiac output; BIS, bispectral index; NIRS, near infrared spectroscopy, PET, positron emission tomography; MRI, magnetic resonance imaging.

Figure 1: Study design and randomization.

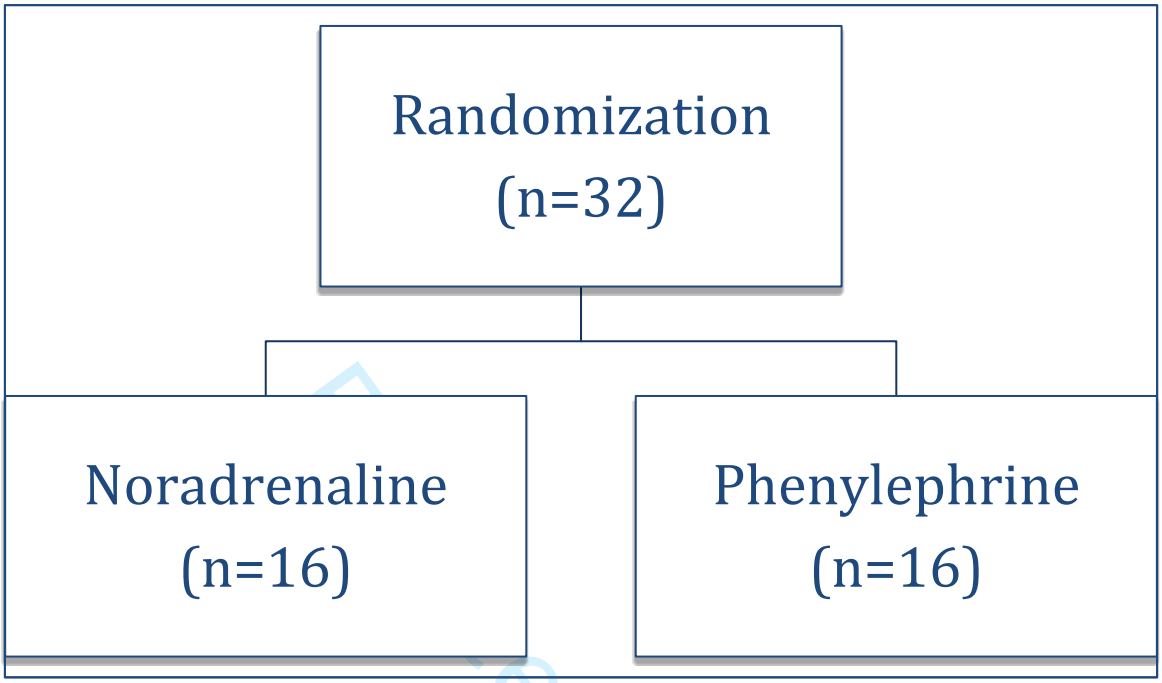
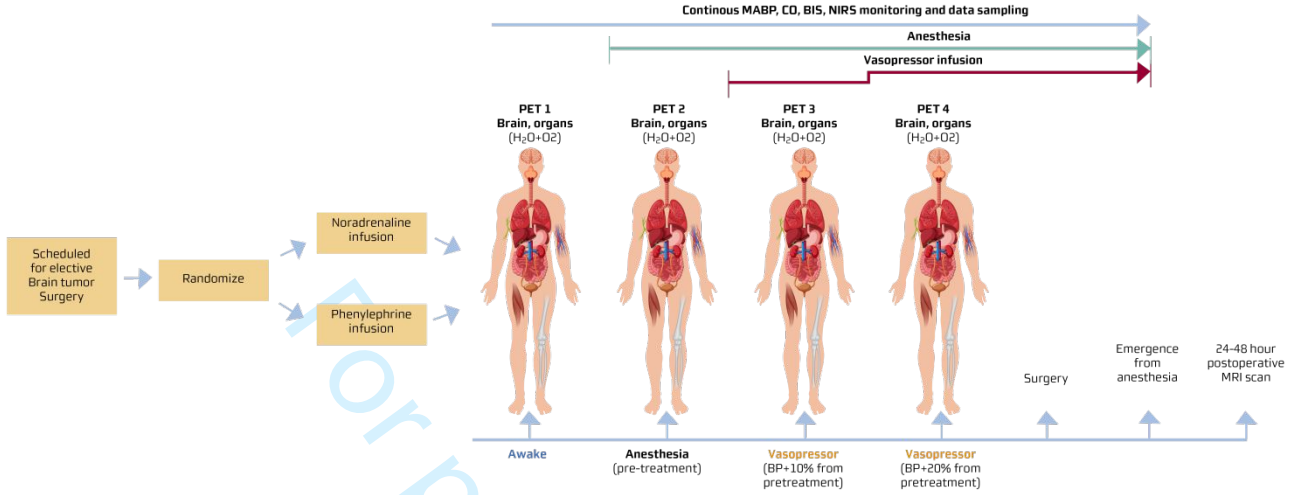


Figure 2: Experimental protocol and study flow chart.



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Impact of noradrenaline versus phenylephrine on brain circulation, organ blood flow and tissue oxygenation in anesthetized patients with brain tumours: study protocol for a randomized controlled trial.

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ABSTRACT

Introduction: Vasopressor support is often preferred as an efficient and convenient way to raise the blood pressure during surgery and intensive care therapy. However, the optimal vasopressor for ensuring organ blood flow and tissue oxygen delivery during surgery remains undetermined. This study aims to assess the impact of noradrenaline versus phenylephrine, on cerebral and non-cerebral organ perfusion and oxygenation during anaesthesia in neurosurgical patients with brain tumours. The study also explores the impact of the vasopressor agents on the distribution of cardiac output between various organs.

Methods and analysis: This is an investigator-initiated, double-blinded, randomized clinical trial including 32 patients scheduled for supratentorial brain tumour surgery. The patients are randomized to receive a phenylephrine or noradrenaline infusion during preoperative positron emission tomography (PET) examinations and the following neurosurgical procedure. PET measurements of blood flow and oxygen metabolism in the brain and other organs are performed in the awake subject, during anaesthesia and following a 10% and 20 % gradual increase in blood pressure from the baseline value. The primary endpoint is the between-group difference in cerebral blood flow. Secondary endpoints include detection of ischemic brain lesions possibly associated with vasopressor treatment, changes in cerebral oxygen metabolism, non-cerebral organ blood flow and oxygen metabolism, cardiac output, regional cerebral oxygen saturation, autoregulation, and distribution of cardiac output between organs.

Ethics and dissemination: This study was approved by the Danish National Medical Ethics Committee (20 May 2022; 2203674). Results will be disseminated via peer-reviewed publication and presentation at international conferences. Trial registration number at ClinicalTrials.gov NCT06083948

STRENGTHS AND LIMITATIONS

1. The study is strengthened by the robust design, which minimizes bias, enhances the validity of findings, and allows for reliable of comparisons between effects of noradrenaline and phenylephrine.

2. The infusion of commonly used vasopressor agents and clinically relevant dosage regimes ensures the applicability of the study's results to clinical practice.

3. The study employs PET technology allowing for multi-organ assessments of blood flow and oxygen metabolism, with PET generally regarded as the "gold standard" for these measurements.

4. The sequential measurement of cardiac output indices under varying clinical conditions provide the possibility for a comprehensive and currently unknown understanding of vasopressor impact on flow distribution between organs.

5. The study's small sample size precludes postoperative clinical outcome assessments of the intervention, while its design prevents intraoperative assessments of organ blood flow and metabolism.

KEYWORDS

Noradrenaline. Phenylephrine. Hypotension. Vasopressors. Anesthesia. Cerebral perfusion. Organ perfusion. Cardiac Output.

INTRODUCTION

Preventing hypotension and maintaining or restoring patient hemodynamic during surgery and acute care are fundamental aspects of anaesthetic practice. Substantial evidence associates perioperative hypotension with cerebral and non-cerebral organ ischemia and dysfunction[1-6]. Vasopressor support is often preferred as an efficient and convenient way to raise the blood pressure during surgery and intensive care therapy[7-11]. The ultimate goal of the intervention is to restore/maintain blood flow to meet the metabolic demand of the brain and other organs[8,11,12]. However, the use of vasopressors *per se* may also be associated with organ injury and evidence suggests that the pharmacological profile of the vasopressor may be linked with tissue injury[13,14]. The most commonly used vasopressor agents (such as phenylephrine and noradrenaline) have different pharmacological profiles. Phenylephrine, a pure α-adrenergic agonist, primarily acts on the peripheral vasculature. In contrast, noradrenaline engages both α- and β-adrenoceptors and acts on both the heart and the peripheral vasculature[8,11]. Moreover, noradrenaline is a natural catecholamine and neurotransmitter existing in human bodies, while phenylephrine is a synthetic compound. The optimal vasopressor for ensuring organ blood flow and tissue oxygen delivery during surgery and intensive care remains undetermined[14,15].

In routine clinical practice, anesthesiologists and critical care physicians adjust their vasopressor therapy according to blood pressure[11,14]. The measured blood pressure only reflects the pressure in larger arteries and not organ perfusion and oxygen delivery to parenchymal cells[14]. Thus, blood pressure acts as a surrogate for organ perfusion with varying accuracies. Since organ blood flow and tissue oxygenation are not routinely measured, the treating physician often remains unaware whether their vasopressor therapy achieves the primary goals of maintaining adequate tissue perfusion and oxygen delivery. Evidence from our research group and others suggests that vasopressor agents may be associated with reduced microcirculatory brain perfusion and impaired tissue oxygen delivery during anaesthesia, despite reaching recommended blood pressure targets[9,10,16-19]. The data further indicates that cerebral macro- and microcirculation, tissue oxygen delivery, and cardiac output are greater with an indirectly acting α- and β-adrenergic agonist (ephedrine) compared to phenylephrine, as observed during anaesthesia in neurosurgical patients[16-19]. Collectively, the emerging evidence suggests that vasopressor agents acting on both α- and β-

adrenoceptors, such as noradrenaline, may have the potential to improve blood flow to the brain, organ blood flow, and tissue oxygen delivery in anesthetized patients compared to pure α-adrenergic agonists.

The impact of vasopressors on brain and organ circulation primarily depends on their influence on cardiac output (CO) and systemic vascular resistance (SVR)[8]. Physiologically, CO is distributed to different organs and each organ receives its share based on its metabolic demand and organ-specific perfusion-regulatory schemes[20-22]. Currently, no data are available on the influence of different vasopressor agents on the distribution of CO (i.e., blood flow) to the brain and other organs such as the myocardium, lungs, kidneys and muscle tissue, during anaesthesia. Theoretically, changes in CO would likely affect blood flow to different organs, including the brain[21-22].

The research questions of this study pertain to the potential advantages of administering a combined α- and β-adrenoceptor agonist during anaesthesia, specifically in terms of its association with improved cerebral blood flow and tissue oxygenation. Additionally, the study seeks to explore whether this compound offers enhanced blood flow and tissue oxygenation in other organs that are sensitive to changes in blood pressure during anaesthesia, in comparison to the effects of a pure α-adrenergic agonist.

HYPOTHESIS

Our hypothesis is twofold:

- Noradrenaline increases perfusion and oxygenation in diseased and healthy brain regions during anaesthesia in comparison to phenylephrine.
- Noradrenaline is associated with increased non-cerebral organ perfusion and tissue oxygenation during anaesthesia when compared to phenylephrine.

OBJECTIVES

- The primary objective is to conduct a comparative analysis of the effects of two commonly used vasopressor agents (phenylephrine vs. noradrenaline) on cerebral circulation and brain

tissue oxygenation in anesthetized patients with brain pathology.

- The secondary objectives are: 1) to assess and compare the effects of the two vasopressors on blood flow and tissue oxygenation in other organs that are particularly sensitive to changes in blood pressure during anaesthesia. These organs include the heart, lungs, kidneys, and muscle tissue, 2) to assess and compare how the two vasopressors influence the distribution of cardiac output between the brain and the organs mentioned above during anaesthesia. 3) to assess and compare the relationship between mean arterial pressure and cerebral blood flow based on correlation plot and cubic penalized regression splines (i.e., static cerebral autoregulation) between noradrenaline and phenylephrine, and between normal and diseased brain regions (in addition to the global cerebral blood flow).

METHODS AND ANALYSIS

Study design and setting

The study is an investigator-initiated, single centre, double blinded randomized clinical trial. The setting for the trial is the Departments of Anaesthesia, Neurosurgery and Nuclear Medicine and PET Center, Aarhus University Hospital, Aarhus, Denmark. Patient recruitment began on 1. November 2023, and the anticipated ending date for the study is 31 December 2025. The paper is written in accordance with the standard protocol items: Recommendations for Interventional Trials (SPIRIT). See online supplementary material for the SPIRIT Checklist and figure. Trial registration: ClinicalTrials.gov NCT06083948.

Patients

The study will include 32 patients diagnosed with supratentorial brain tumours. Written informed consent will be obtained by the primary investigator or one of the co-investigators. Adult patients diagnosed with brain tumours will be screened at the outpatient clinic by attending physicians. The inclusion criteria are as follows: aged 18-75 years; scheduled for elective craniotomy for supratentorial malignant and non-malignant tumours with a minimum size of 3 cm (measured as the largest diameter in any plane on magnetic resonance images); American Society of Anesthesiologists

(ASA) physical status I-III.[16,17] Exclusion criteria include: a history of allergy or intolerance to one of the study medications; active treatment with monoamine oxidase inhibitors; pregnancy (positive pregnancy urine test) or breastfeeding, and inability to give written informed consent.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Randomization and blinding

Figure 1 shows study design and randomization. Randomizing and blinding are performed by a dedicated nurse, or a physician not involved in the experimental part of the study[16,17]. Patients and researchers are blinded to randomization. Patients are randomized in a 1:1 ratio using the in-built randomization module within the Research Electronic Data Capture (REDCap) system and a randomly varying block randomization size of 4 and 6 to receive infusion of either noradrenaline (10 mcg/ml) or phenylephrine (100 mcg/ml). The concentrations of study drugs are similar to the concentrations used in previous studies and according to institutional guidelines for the use of intraoperative vasopressor support at Aarhus University hospital. Identical syringes of 50 ml, containing either noradrenaline (10 mcg/ml) or phenylephrine (100 mcg/ml), are marked with a randomization code known only to the unblinded nurse or doctor. The study drugs are prepared immediately before administration by a nurse not involved in the actual study. The unblinded persons are responsible for documentation of study drugs, randomization–code, patient ID and blinding of drugs in a specific log. This log will only be accessible to the unblinded person. Code-break of randomization can only occur in emergencies with suspected adverse patient-reaction to a study drug. The staff involved in the experimental part of the study is unaware of randomization. The randomization code is kept without the reach of sponsor-investigator. Interpretation of imaging and calculation of flow and oxygenation parameters are performed by a blinded researcher. After the final inclusion, an independent researcher will unblind the two groups and label the groups 0 and 1. Statistical analyses will then be performed and final unblinding will take place.

Figure 1: Study design and randomization.

Anaesthesia and monitoring

The anaesthetic management is standardized. General anaesthesia with propofol and remifentanil is administered according to institutional guidelines and titrated to achieve a bispectral index (BIS) score between 40-60 which is indicative of an adequate level of anaesthesia for surgery[16,17]. A low dose of muscle relaxant (suxamethonium or rocuronium) is administered to facilitate intubation. The patients are ventilated with 40-50% oxygen in air by controlled ventilation titrated to achieve a partial pressure of carbon dioxide in arterial blood ($PaCO_2$) between 35 and 40 mmHg (4.7-6.0 kPa) and a partial pressure of oxygen in arterial blood (PaO_2) greater than 100 mmHg (13.3 kPa)[16,17]. Ventilation is adjusted according to arterial blood gas measurements. Isotonic NaCl is infused at a rate of 2-3ml/kg/hour. Temperature, ECG, oxygen saturation, heart rate, intra-arterial blood pressure and cardiac output indices acquired using LiDCO (Masimo, Irvine, CA) are continuously monitored. The depth of anaesthesia is continuously measured with BIS (Medtronic, MN). Brain tissue oxygen saturation is continuously measured with near infrared spectroscopy (NIRS) (Medtronic, MN) to allow comparison with brain oxygenation measurements determined with PET [16,17].

Experimental protocol and intervention

The experimental study protocol and flow chart are shown in figure 2. The experiment is conducted on the same day as the scheduled brain tumour surgery [16,17]. All PET examinations consist of a blood flow (using $[^{15}O]H_2O$ tracer) measurement followed by a measurement of oxygen consumption (using $[^{15}O]O_2$ tracer)[16]. Four PET examinations (including blood flow and oxygen consumption measurements) are performed.

The first PET examination (**PET 1**) is performed on the awake patient. The patient is then anesthetized, and the PET exam is repeated when the anaesthetic depth corresponds to a BIS value between 40-60. To avoid significant hypotension after anaesthesia induction, a carefully balanced anaesthesia induction is used, including administration of a crystalloid fluid bolus and if necessary

atropine (**PET 2**). Vasopressor infusion is initiated and titrated to increase MABP to above 60 mmHg, or by 10% relative to baseline. When the blood pressure has stabilized the third PET examination (**PET 3**) is performed**.** After completion of PET 3 MABP is further increased to above 70 mmHg or by 20 % relative to the baseline level. When the blood pressure has stabilized the fourth PET examination (**PET 4**) is performed. After completion of the PET examinations the anesthetized patient is transported to the surgical theatre and surgery is initiated. During the surgical procedure, MABP is maintained between 70-80 mmHg according to institutional guidelines. The vasopressor infusion is terminated at the time of extubation. The duration of the PET part of the study until initiation of surgery is approximately 2 hours. The 24-48-hour postoperative Magnetic Resonance Imaging (MRI) examination is conducted to assess the result of the surgical intervention and to determine whether there are any ischemic lesions possibly associated with the vasopressor agents.

The rationale for the selected PET protocol is as follows: PET 1 and 2 allow us to assess the influence of anaesthesia on organ blood flow and oxygen consumption. PET 3 and PET4 exams allow for the assessment of the effect of vasopressor infusion on organ blood flow and oxygen consumption. The MRI examination is added as a surrogate outcome measure of the vasopressor effects.

Positron emission tomography image acquisition

A Biograph Vision Quadra PET scanner (with a long axial field of view allowing for simultaneous multi-organ assessments of blood flow and oxygen consumption) and PET tracers $[^{15}O]H_2O$ and $[^{15}O]O_2$ are used to measure multi-organ blood flow and oxygen consumption parameters[16,23,24].

Dosimetry in the study

The total dose of radiation per patient is calculated to be 5.88 mSv.

Outcomes

The primary outcome measure is the between-group difference in the change in cerebral blood flow (ΔCBF), defined as the difference between post-treatment and pre-treatment values (ΔCBF = post-

treatment value - pre-treatment value)[16,17].

Seconday outcomes include:

1. Detection of Postoperative Cerebral Ischemic Lesions: These lesions, potentially linked to vasopressor infusion, will be identified through MRI examinations conducted 24-48 hours postoperatively.

2. Absolute and relative between-group differences in brain energy consumption parameters such as oxygen extraction fraction (OEF) and cerebral metabolic rate of oxygen ($CMRO_2$).

3. Measurements of cerebral tissue oxygen saturation ($SctO_2$).

4. Blood flow and oxygen consumption in various organs, including the kidney, liver, myocardium, spinal cord and muscle tissue.

5. Cardiac output assessments and the distribution of cardiac output across different organs.

6. Evaluation of static cerebral autoregulation.

The secondary outcomes also include the comparisons between diseased and non-diseased brain regions. In this analysis, patients themselves are their own control. We analyse the between-region differences in each patient and pool the results per group. Different vasopressor treatment is treated as a stratification factor.

Data collection and trial monitoring:

Study data are collected and managed using REDCap electronic data capture tools hosted at Aarhus University[25,26]. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

All Imaging data are stored on a server with secured and restricted access. Physiological data are initially stored on the respective monitoring devices and subsequently extracted and stored in the study database. The study is conducted according to the standards of Good Clinical Practice and is monitored by the "Good Clinical Practice Unit ", Department of Clinical Medicine, Aarhus University Hospital[16,17].

Figure 2: Experimental protocol and study flow chart.

Positron Emission Tomography and Magnetic Resonance Imaging analyses:

All patients will have a pre-operative structural MRI of the brain as part of clinical investigations performed during their preparations for surgery[16,17]. T1-weighted MRI of the brain is co-registered with PET images for each patient. Voxel wise estimation of organ blood flow and oxygen consumption is performed using the arterial blood radioactivity as the input function and a one-tissue compartment model based on previous works[16,27-29]. Brain regions of interest are defined as the tumour, peritumoural area, and contralateral hemisphere grey matter[16,17,19]. Other organs will be delineated using low-dose CT images and analysed using appropriate kinetic models[24].

Magnetic resonance imaging analyses of ischemic lesions

Diffusion weighted imaging (DWI) displays regions of reduced water mobility, which is usually ascribed to regions of cell swelling due to insufficient oxygen availability (ischemia). To obtain a quantitative measure of the potential harmful effect of the vasopressor, we will detect changes in ischemic regions by comparing the DWI images obtained prior to project enrollment with DWI obtained as a part of the routine post-surgery evaluation. Using machine-learning algorithms, we will automatically segment the pre-study and post-surgery ischemic regions. Since brain regions potentially alter position during surgery, we will attempt a non-linear co-registration of the two DWI measurements, before extracting the pre-study region from the post-surgery region to be able to report the potential volume increase. We will attempt to avoid regions that are the most affected by

the surgery, since the surgery itself may also affect the DWI values. This quantitative analysis is supplemented by qualitative inspection.

Sample size and statistical analysis

No previous studies have, to our knowledge, investigated the changes in CBF based on PET measurements after phenylephrine vs. noradrenaline treatment in the same patient population. Therefore, we estimated our sample size based on the regional changes in CBF after phenylephrine vs. ephedrine treatment in a similar patient cohort as reported by Koch et al. (2020)[16]. Ephedrine and noradrenaline are both combined α- and β-adrenergic agonists and have similar pharmacological properties[8,11,16]. The study by Koch et al. reported a change in CBF of 1.7 ± 3.5 ml/100g/min after phenylephrine treatment and 5.5 ± 4.0 ml/100g/min after ephedrine treatment[16]. Given a between-group difference in CBF = 3,8 ml/100g/min in favour of the noradrenaline group a significance level of 0.05 and a power of 80%, the study requires 15 patients in each group to detect a significant difference in CBF changes between the two vasopressors. Considering a possible dropout rate of 6%, and to increase the comparability of the two groups, we decided to recruit a total of 32 patients, with 16 patients in each arm.

Statistical analyses: All randomized subjects with a full dataset will be included in the statistical analyses. Standard parametric and non-parametric analyses are used for paired analyses of the physiological parameters[16-19]. The percentage changes in different measurements are calculated as the post-treatment value minus pre-treatment value divided by the pre-treatment value times 100 (i.e., the relative change). The effects of vasopressor type, vasopressor dose, and CO are estimated in a generalized linear model. Static autoregulation (relationship between MABP and CBF) is assessed using correlation plots and cubic penalized regression splines between noradrenaline and phenylephrine, and between normal and diseased brain regions (in addition to the global cerebral blood flow). A detailed statistical analysis plan will be prepared prior to the start of the analyses.

ETHICS AND DISSEMINATION

Patients included in this study are required to receive anaesthesia for removal of their brain tumour.

Thus, the patients are not exposed to any additional risk due to anaesthesia or placement of intravenous and intra-arterial catheters. The experiment and the removal of the tumour are conducted in the same anaesthesia "session". The experiment will prolong the period of which the patient is under general anaesthesia by approximately 2 hours[16,17]. With reference to our previous studies, and our experience in general, we do not find that the prolonged period of general anaesthesia nor the PET radiation dose (see Methods section) will pose significant additional risk to the patient[16,17]. This is furthermore supported by the obtained approvals from the Danish National Medical Ethics Committee (20 May 2022; 2203674) (VMK) and the Danish Medicines Agency. Informed consent will be acquired from the participant prior to study enrolment. Results will be disseminated via peer-reviewed publication and presentation at international conferences. Trial registration number at ClinicalTrials.gov NCT06083948

REFERENCES

1. Mazzeffi M, Chow JH, Anders M, et al. Intraoperative hypotension and perioperative acute ischemic stroke in patients having major elective non-cardiovascular non-neurological surgery. *J Anesth*. 2021;35(2):246-53.

2. Yao J, Li S, Cui Q, et al. Intraoperative hypotension and postoperative stroke in older patients who had brain tumor resections: a retrospective cohort analysis. *World Neurosurg*. 2023;174:e72-e81.

3. Gregory A, Stapelfeldt WH, Khanna AK, et al. Intraoperative hypotension is associated with adverse clinical outcomes after noncardiac surgery. *Anesth Analg*. 2021;132(6):1654-65.

4. Ackland GL, Abbott TEF. Hypotension as a marker or mediator of perioperative organ injury: a narrative review. *Br J Anaesth*. 2022;128(6):915-30.

5. Meng L. Heterogeneous impact of hypotension on organ perfusion and outcomes: a narrative review. *Br J Anaesth*. 2021;127(6):845-61.

6. Wesselink EM, Kappen TH, Torn HM, et al. Intraoperative hypotension and the risk of postoperative adverse outcomes: a systematic review. *Br J Anaesth*. 2018;121(4):706-21.

7. Sookplung P, Siriussawakul A, Malakouti A, et al. Vasopressor use and effect on blood pressure after severe adult traumatic brain injury. *Neurocrit Care*. 2011;15:46-54.

8. Bangash MN, Kong ML, Pearse RM. Use of inotropes and vasopressor agents in critically ill patients. *Br J Pharmacol*. 2012;165(7):2015-33.

9. Meng L, Gelb AW, Alexander BS, et al. Impact of phenylephrine administration on cerebral tissue oxygen saturation and blood volume is modulated by carbon dioxide in anaesthetized patients. *Br J Anaesth*. 2012;108(5):815-22.

10. Meng L, Cannesson M, Alexander BS, et al. Effect of phenylephrine and ephedrine bolus treatment on cerebral oxygenation in anaesthetized patients. *Br J Anaesth*. 2011;107:209-17.

11. Thorup L, Koch KU, Upton RN, et al. Effects of vasopressors on cerebral circulation and oxygenation: a narrative review of pharmacodynamics in health and traumatic brain injury. *J Neurosurg Anesthesiol*. 2019;00:1-11.

12. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the management of severe traumatic brain injury, fourth edition. *Neurosurgery*. 2017;80(1):6-15.

13. Ariyarathna D, Bhonsle A, Nim J, et al. Intraoperative vasopressor use and early postoperative acute kidney injury in elderly patients undergoing elective noncardiac surgery. *Ren Fail*. 2022;44(1):648-59.

14. Karamchandani K, Dave S, Hoffmann U, et al. Intraoperative arterial pressure management: knowns and unknowns. *Br J Anaesth*. 2023;S0007-0912(23)00313-6. doi:10.1016/j.bja.2023.05.027.

15. Mets B. Should noradrenaline, rather than phenylephrine, be considered the primary vasopressor in anesthetic practice? *Anesth Analg*. 2016;122(5):1707-14.

16. Koch KU, Mikkelsen IK, Aanerud J, et al. Ephedrine versus phenylephrine effect cerebral blood flow and oxygen consumption in anesthetized brain tumor patients: a randomized clinical trial. *Anesthesiology*. 2020;133(2):304-17.

17. Koch KU, Mikkelsen IK, Espelund US, et al. Ephedrine versus phenylephrine effects on cerebral macro- and microcirculation in anesthetized brain tumor patients: a randomized clinical trial using magnetic resonance imaging. *Anesthesiology*. 2021; Nov 1;135(5):788-803. doi:10.1097/ALN.0000000000003877.

18. Koch KU, Zhao X, Mikkelsen IK, et al. Correlation between cerebral tissue oxygen saturation and oxygen extraction fraction during anesthesia: monitoring cerebral metabolic demand-supply balance during vasopressor administration. *J Neurosurg Anesthesiol*. 2023;35(2):238-42.

19. Rasmussen M, Koch KU, Espelund US, Mohamad N, et al. Blood-brain barrier permeability may influence vasopressor effects in anesthetized patients with brain tumor: An analysis of magnetic

resonance imaging data. *J Neurosurg Anesthesiol*. 2024;36(4):357-362. doi:10.1097/ANA.0000000000000948.

20. Drummond JC. Cardiac output: the neglected stepchild of the cerebral blood flow physiology. *J Neurosurg Anesthesiol*. 2020;32:93-94.

21. Meng L, Hou W, Chui J, et al. Cardiac output and cerebral blood flow: the integrated regulation of brain perfusion in adult humans. *Anesthesiology*. 2015;123:1198-208.

22. Meng L, Wang Y, Zhang L, et al. Heterogeneity and variability in pressure autoregulation of organ blood flow: lessons learned over 100+ years. *Crit Care Med*. 2019;47(3):436-48.

23. Prenosil GA, Sari H, Fürstner M, et al. Performance characteristics of the Biograph Vision Quadra PET/CT system with a long axial field of view using the NEMA NU 2-2018 standard. *J Nucl Med*. 2022;63(3):476-84.

24. Knuuti J, Tuisku J, Kärpijoki H, et al. Quantitative perfusion imaging with total-body PET. *J Nucl Med*. 2023;64(Suppl 2):11S-19S.

25. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap) – a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-81.

26. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software partners. *J Biomed Inform*. 2019;103208. doi:10.1016/j.jbi.2019.103208.

27. Ohta S, Meyer E, Fujita H, et al. Cerebral [15O]water clearance in humans determined by PET: I. Theory and normal values. *J Cereb Blood Flow Metab*. 1996;16:765-80.

28. Ohta S, Meyer E, Thompson CJ, et al. Oxygen consumption of the living human brain measured after a single inhalation of positron emitting oxygen. *J Cereb Blood Flow Metab*. 1992;12:179-92.

29. Blomqvist G. On the construction of functional maps in positron emission tomography. *J Cereb Blood Flow Metab*. 1984;4:629-32.

AUTHOURS' CONTRIBUTIONS

Dr. Niwar Faisal Mohamad has prepared the IMPACT protocol manuscript in close collaboration with Associate Professor Mads Rasmussen. The rest of the research group has subsequently reviewed the manuscript.

Dr. Niwar Faisal Mohamad is the guarantor.

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DECLARATION OF INTEREST

None.

APPENDICES

Informed consent material

FIGURE LEGENDS

Figure 1: Study design and randomization.

Figure 2: Experimental protocol and study flow chart.

PET exams of Blood flow (using [^{15}O] H_2O tracer) and oxygen consumption (using [^{15}O]O_2 tracer) in brain and organs (including myocardium, kidney, lungs and limb muscle) are performed using a Biograph Vision

Quadra-PET scanner with a wide axial field of view. The wide axial field of view allows for simultaneous assessments of the brain and organs.

The first PET examination (**PET 1**) is performed in the awake patient. The patient is then anesthetized, and the PET exam is repeated (**PET 2**). Vasopressor infusion is initiated and titrated to a 10 % increase in MABP relative to pre-treatment level (**PET 3**). MABP is further increased to 20 % relative to the pre-treatment level (**PET 4**). After completion of the PET examinations the anesthetized patient is transported to the surgical theatre and surgery is performed. The vasopressor infusion is initiated after PET 2 and terminated at emergence of anaesthesia after completion of surgery. MABP, CO, BIS and NIRS are measured during PET exams and surgery. The duration of the PET part of the study until initiation of surgery is approximately 2 hours.

The 24-48 MRI examination is performed as a postoperative control of the surgical result and includes a diffusion weighted sequence to detect ischemic brain lesions possibly associated with vasopressor infusion.

MABP, mean arterial blood pressure; CO, cardiac output; BIS, bispectral index; NIRS, near infrared spectroscopy, PET, positron emission tomography; MRI, magnetic resonance imaging.

Figure 1: Study design and randomization.

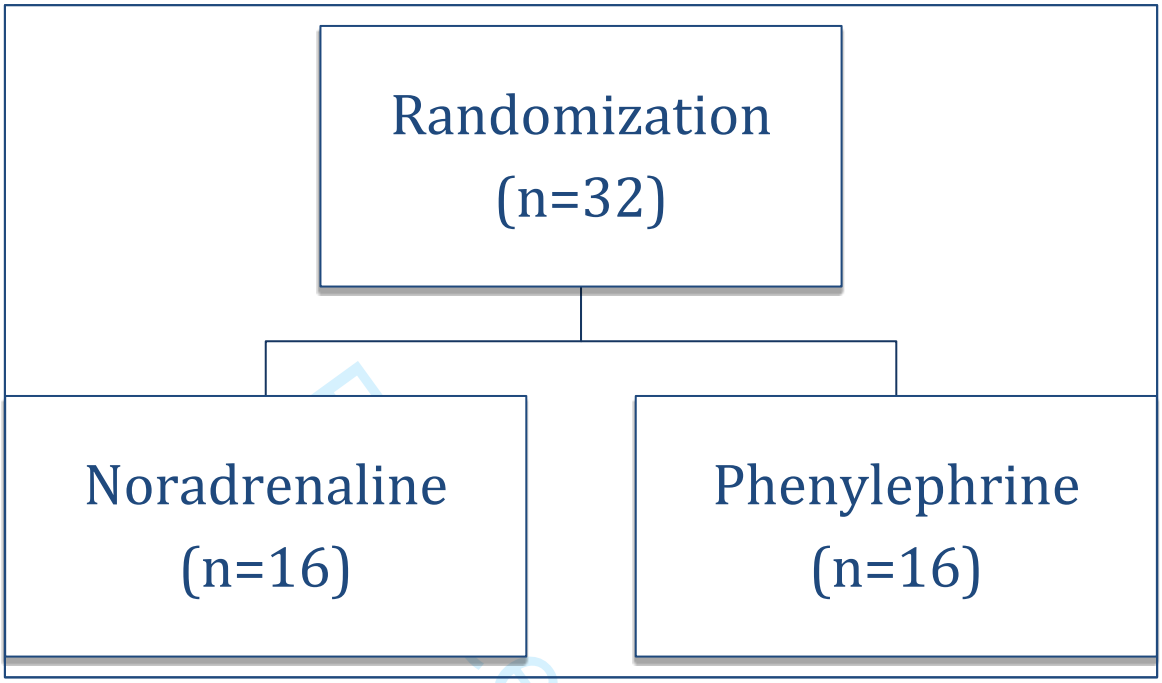
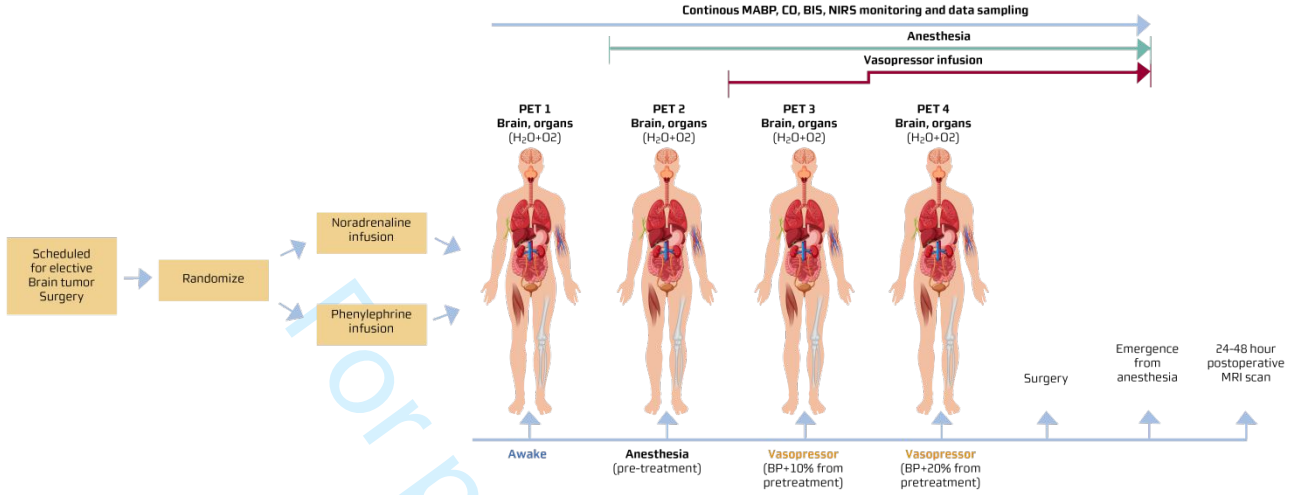


Figure 2: Experimental protocol and study flow chart.



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Impact of noradrenaline versus phenylephrine on brain circulation, organ blood flow and tissue oxygenation in anesthetized patients with brain tumours: study protocol for a randomized controlled trial.

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Impact of noradrenaline versus phenylephrine on brain circulation, organ blood flow and tissue oxygenation in anesthetized patients with brain tumours: study protocol for a randomized controlled trial.

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TRIAL REGISTRATION

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ABSTRACT

Introduction: Vasopressor support is often preferred as an efficient and convenient way to raise the blood pressure during surgery and intensive care therapy. However, the optimal vasopressor for ensuring organ blood flow and tissue oxygen delivery during surgery remains undetermined. This study aims to assess the impact of noradrenaline versus phenylephrine, on cerebral and non-cerebral organ perfusion and oxygenation during anaesthesia in neurosurgical patients with brain tumours. The study also explores the impact of the vasopressor agents on the distribution of cardiac output between various organs.

Methods and analysis: This is an investigator-initiated, double-blinded, randomized clinical trial including 32 patients scheduled for supratentorial brain tumour surgery. The patients are randomized to receive a phenylephrine or noradrenaline infusion during preoperative positron emission tomography (PET) examinations and the following neurosurgical procedure. PET measurements of blood flow and oxygen metabolism in the brain and other organs are performed in the awake subject, during anaesthesia and following a 10% and 20 % gradual increase in blood pressure from the baseline value. The primary endpoint is the between-group difference in cerebral blood flow. Secondary endpoints include detection of ischemic brain lesions possibly associated with vasopressor treatment, changes in cerebral oxygen metabolism, non-cerebral organ blood flow and oxygen metabolism, cardiac output, regional cerebral oxygen saturation, autoregulation, and distribution of cardiac output between organs.

Ethics and dissemination: This study was approved by the Danish National Medical Ethics Committee (20 May 2022; 2203674). Results will be disseminated via peer-reviewed publication and presentation at international conferences. Trial registration number at ClinicalTrials.gov NCT06083948

STRENGTHS AND LIMITATIONS

1. The study's strength lies in its randomized controlled design, which supports reliable comparisons between the effects of noradrenaline and phenylephrine.

2. The infusion of commonly used vasopressor agents and clinically relevant dosage regimes ensures the applicability of the study's results to clinical practice.

3. The study employs PET technology allowing for multi-organ assessments of blood flow and oxygen metabolism, with PET generally regarded as the "gold standard" for these measurements.

4. The sequential measurement of cardiac output indices under varying clinical conditions provide the possibility for a comprehensive and currently unknown understanding of vasopressor impact on flow distribution between organs.

5. The study's small sample size precludes postoperative clinical outcome assessments of the intervention, while its design prevents intraoperative assessments of organ blood flow and metabolism.

KEYWORDS

Noradrenaline. Phenylephrine. Hypotension. Vasopressors. Anaesthesia. Cerebral perfusion. Organ perfusion. Cardiac Output.

INTRODUCTION

Preventing hypotension and maintaining or restoring patient hemodynamic during surgery and acute care are fundamental aspects of anaesthetic practice. Substantial evidence associates perioperative hypotension with cerebral and non-cerebral organ ischemia and dysfunction[1-6]. Vasopressor support is often preferred as an efficient and convenient way to raise the blood pressure during surgery and intensive care therapy[7-11]. The ultimate goal of the intervention is to restore/maintain blood flow to meet the metabolic demand of the brain and other organs[8,11,12]. However, the use of vasopressors *per se* may also be associated with organ injury and evidence suggests that the pharmacological profile of the vasopressor may be linked with tissue injury[13,14]. The most commonly used vasopressor agents (such as phenylephrine and noradrenaline) have different pharmacological profiles. Phenylephrine, a pure α-adrenergic agonist, primarily acts on the peripheral vasculature. In contrast, noradrenaline engages both α- and β-adrenoceptors and acts on both the heart and the peripheral vasculature[8,11]. Moreover, noradrenaline is a natural catecholamine and neurotransmitter existing in human bodies, while phenylephrine is a synthetic compound. The optimal vasopressor for ensuring organ blood flow and tissue oxygen delivery during surgery and intensive care remains undetermined[14,15].

In routine clinical practice, anaesthesiologists and critical care physicians adjust their vasopressor therapy according to blood pressure[11,14]. The measured blood pressure only reflects the pressure in larger arteries and not organ perfusion and oxygen delivery to parenchymal cells[14]. Thus, blood pressure acts as a surrogate for organ perfusion with varying accuracies. Since organ blood flow and tissue oxygenation are not routinely measured, the treating physician often remains unaware whether their vasopressor therapy achieves the primary goals of maintaining adequate tissue perfusion and oxygen delivery. Evidence from our research group and others suggests that vasopressor agents may be associated with reduced microcirculatory brain perfusion and impaired tissue oxygen delivery during anaesthesia, despite reaching recommended blood pressure targets[9,10,16-19]. The data further indicates that cerebral macro- and microcirculation, tissue oxygen delivery, and cardiac output are greater with an indirectly acting α- and β-adrenergic agonist (ephedrine) compared to phenylephrine, as observed during anaesthesia in neurosurgical patients[16-19]. Collectively, the emerging evidence suggests that vasopressor agents acting on both α- and β-

adrenoceptors, such as noradrenaline, may have the potential to improve blood flow to the brain, organ blood flow, and tissue oxygen delivery in anesthetized patients compared to pure α-adrenergic agonists.

The impact of vasopressors on brain and organ circulation primarily depends on their influence on cardiac output (CO) and systemic vascular resistance (SVR)[8]. Physiologically, CO is distributed to different organs and each organ receives its share based on its metabolic demand and organ-specific perfusion-regulatory schemes[20-22]. Currently, no data are available on the influence of different vasopressor agents on the distribution of CO (i.e., blood flow) to the brain and other organs such as the myocardium, lungs, kidneys and muscle tissue, during anaesthesia. Theoretically, changes in CO would likely affect blood flow to different organs, including the brain[21-22].

The research questions of this study pertain to the potential advantages of administering a combined α- and β-adrenoceptor agonist during anaesthesia, specifically in terms of its association with improved cerebral blood flow and tissue oxygenation. Additionally, the study seeks to explore whether this compound offers enhanced blood flow and tissue oxygenation in other organs that are sensitive to changes in blood pressure during anaesthesia, in comparison to the effects of a pure α-adrenergic agonist.

HYPOTHESIS

Our hypothesis is twofold:

- Noradrenaline increases perfusion and oxygenation in diseased and healthy brain regions during anaesthesia in comparison to phenylephrine.
- Noradrenaline is associated with increased non-cerebral organ perfusion and tissue oxygenation during anaesthesia when compared to phenylephrine.

OBJECTIVES

- The primary objective is to conduct a comparative analysis of the effects of two commonly used vasopressor agents (phenylephrine vs. noradrenaline) on cerebral circulation and brain

tissue oxygenation in anesthetized patients with brain pathology.

- The secondary objectives are: 1) to assess and compare the effects of the two vasopressors on blood flow and tissue oxygenation in other organs that are particularly sensitive to changes in blood pressure during anaesthesia. These organs include the heart, lungs, kidneys, and muscle tissue, 2) to assess and compare how the two vasopressors influence the distribution of cardiac output between the brain and the organs mentioned above during anaesthesia. 3) to assess and compare the relationship between mean arterial pressure and cerebral blood flow based on correlation plot and cubic penalized regression splines (i.e., static cerebral autoregulation) between noradrenaline and phenylephrine, and between normal and diseased brain regions (in addition to the global cerebral blood flow).

METHODS AND ANALYSIS

Study design and setting

The study is an investigator-initiated, single centre, double blinded randomized clinical trial. The setting for the trial is the Departments of Anaesthesia, Neurosurgery and Nuclear Medicine and PET Center, Aarhus University Hospital, Aarhus, Denmark. Patient recruitment began on 1. November 2023, and the anticipated ending date for the study is 31 December 2025. The paper is written in accordance with the standard protocol items: Recommendations for Interventional Trials (SPIRIT). See online supplementary material for the SPIRIT Checklist and figure. Trial registration: ClinicalTrials.gov NCT06083948.

Patients

The study will include 32 patients diagnosed with supratentorial brain tumours. Written informed consent (Supplemental File 1) will be obtained by the primary investigator or one of the co-investigators. Adult patients diagnosed with brain tumours will be screened at the outpatient clinic by attending physicians. The inclusion criteria are as follows: aged 18-75 years; scheduled for elective craniotomy for supratentorial malignant and non-malignant tumours with a minimum size of 3 cm (measured as the largest diameter in any plane on magnetic resonance images); American Society of

Anaesthesiologists (ASA) physical status I-III.[16,17] Exclusion criteria include: a history of allergy or intolerance to one of the study medications; active treatment with monoamine oxidase inhibitors; pregnancy (positive pregnancy urine test) or breastfeeding, and inability to give written informed consent (Supplemental File 1).

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Randomization and blinding

Figure 1 shows study design and randomization. Randomizing and blinding are performed by a dedicated nurse, or a physician not involved in the experimental part of the study[16,17]. Patients and researchers are blinded to randomization. Patients are randomized in a 1:1 ratio using the in-built randomization module within the Research Electronic Data Capture (REDCap) system and a randomly varying block randomization size of 4 and 6 to receive infusion of either noradrenaline (10 mcg/ml) or phenylephrine (100 mcg/ml). The concentrations of study drugs are similar to the concentrations used in previous studies and according to institutional guidelines for the use of intraoperative vasopressor support at Aarhus University hospital. Identical syringes of 50 ml, containing either noradrenaline (10 mcg/ml) or phenylephrine (100 mcg/ml), are marked with a randomization code known only to the unblinded nurse or doctor. The study drugs are prepared immediately before administration by a nurse not involved in the actual study. The unblinded persons are responsible for documentation of study drugs, randomization–code, patient ID and blinding of drugs in a specific log. This log will only be accessible to the unblinded person. Code-break of randomization can only occur in emergencies with suspected adverse patient-reaction to a study drug. The staff involved in the experimental part of the study is unaware of randomization. The randomization code is kept without the reach of sponsor-investigator. Interpretation of imaging and calculation of flow and oxygenation parameters are performed by a blinded researcher. After the final inclusion, an independent researcher will unblind the two groups and label the groups 0 and 1. Statistical analyses will then be performed and

final unblinding will take place.

Figure 1: Study design and randomization.

Anaesthesia and monitoring

The anaesthetic management is standardized. General anaesthesia with propofol and remifentanil is administered according to institutional guidelines and titrated to achieve a bispectral index (BIS) score between 40-60 which is indicative of an adequate level of anaesthesia for surgery[16,17]. A low dose of muscle relaxant (suxamethonium or rocuronium) is administered to facilitate intubation. The patients are ventilated with 40-50% oxygen in air by controlled ventilation titrated to achieve a partial pressure of carbon dioxide in arterial blood ($PaCO_2$) between 35 and 40 mmHg (4.7-6.0 kPa) and a partial pressure of oxygen in arterial blood (PaO_2) greater than 100 mmHg (13.3 kPa)[16,17]. Ventilation is adjusted according to arterial blood gas measurements. Isotonic NaCl is infused at a rate of 2-3ml/kg/hour. Temperature, ECG, oxygen saturation, heart rate, intra-arterial blood pressure and cardiac output indices acquired using LiDCO (Masimo, Irvine, CA) are continuously monitored. The depth of anaesthesia is continuously measured with BIS (Medtronic, MN). Brain tissue oxygen saturation is continuously measured with near infrared spectroscopy (NIRS) (Medtronic, MN) to allow comparison with brain oxygenation measurements determined with PET [16,17].

Experimental protocol and intervention

The experimental study protocol and flow chart are shown in figure 2. The experiment is conducted on the same day as the scheduled brain tumour surgery [16,17]. All PET examinations consist of a blood flow (using $[^{15}O]H_2O$ tracer) measurement followed by a measurement of oxygen consumption (using $[^{15}O]O_2$ tracer)[16]. Four PET examinations (including blood flow and oxygen consumption measurements) are performed.

The first PET examination (**PET 1**) is performed on the awake patient. The patient is then anesthetized, and the PET exam is repeated when the anaesthetic depth corresponds to a BIS value between 40-60. To avoid significant hypotension after anaesthesia induction, a carefully balanced

anaesthesia induction is used, including administration of a crystalloid fluid bolus and if necessary atropine (**PET 2**). Vasopressor infusion is initiated and titrated to increase MABP to above 60 mmHg, or by 10% relative to baseline. When the blood pressure has stabilized the third PET examination (**PET 3**) is performed**.** After completion of PET 3 MABP is further increased to above 70 mmHg or by 20 % relative to the baseline level. When the blood pressure has stabilized the fourth PET examination (**PET 4**) is performed. After completion of the PET examinations the anesthetized patient is transported to the surgical theatre and surgery is initiated. During the surgical procedure, MABP is maintained between 70-80 mmHg according to institutional guidelines. The vasopressor infusion is terminated at the time of extubation. The duration of the PET part of the study until initiation of surgery is approximately 2 hours. The 24-48-hour postoperative Magnetic Resonance Imaging (MRI) examination is conducted to assess the result of the surgical intervention and to determine whether there are any ischemic lesions possibly associated with the vasopressor agents.

The rationale for the selected PET protocol is as follows: PET 1 and 2 allow us to assess the influence of anaesthesia on organ blood flow and oxygen consumption. PET 3 and PET4 exams allow for the assessment of the effect of vasopressor infusion on organ blood flow and oxygen consumption. The MRI examination is added as a surrogate outcome measure of the vasopressor effects.

Positron emission tomography image acquisition

A Biograph Vision Quadra PET scanner (with a long axial field of view allowing for simultaneous multi-organ assessments of blood flow and oxygen consumption) and PET tracers $[^{15}O]H_2O$ and $[^{15}O]O_2$ are used to measure multi-organ blood flow and oxygen consumption parameters[16,23,24].

Dosimetry in the study

The total dose of radiation per patient is calculated to be 5.88 mSv.

Outcomes

The primary outcome measure is the between-group difference in the change in cerebral blood flow

(ΔCBF), defined as the difference between post-treatment and pre-treatment values (ΔCBF = post-treatment value - pre-treatment value)[16,17].

Secondary outcomes include:

1. Detection of Postoperative Cerebral Ischemic Lesions: These lesions, potentially linked to vasopressor infusion, will be identified through MRI examinations conducted 24-48 hours postoperatively.

2. Absolute and relative between-group differences in brain energy consumption parameters such as oxygen extraction fraction (OEF) and cerebral metabolic rate of oxygen ($CMRO_2$).

3. Measurements of cerebral tissue oxygen saturation ($SctO_2$).

4. Blood flow and oxygen consumption in various organs, including the kidney, liver, myocardium, spinal cord and muscle tissue.

5. Cardiac output assessments and the distribution of cardiac output across different organs.

6. Evaluation of static cerebral autoregulation.

The secondary outcomes also include the comparisons between diseased and non-diseased brain regions. In this analysis, patients themselves are their own control. We analyse the between-region differences in each patient and pool the results per group. Different vasopressor treatment is treated as a stratification factor.

Data collection and trial monitoring:

Study data are collected and managed using REDCap electronic data capture tools hosted at Aarhus University[25,26]. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

All Imaging data are stored on a server with secured and restricted access. Physiological data are initially stored on the respective monitoring devices and subsequently extracted and stored in the study database. The study is conducted according to the standards of Good Clinical Practice and is monitored by the "Good Clinical Practice Unit ", Department of Clinical Medicine, Aarhus University Hospital[16,17].

Figure 2: Experimental protocol and study flow chart.

Positron Emission Tomography and Magnetic Resonance Imaging analyses:

All patients will have a pre-operative structural MRI of the brain as part of clinical investigations performed during their preparations for surgery[16,17]. T1-weighted MRI of the brain is co-registered with PET images for each patient. Voxel wise estimation of organ blood flow and oxygen consumption is performed using the arterial blood radioactivity as the input function and a one-tissue compartment model based on previous works[16,27-29]. Brain regions of interest are defined as the tumour, peritumoural area, and contralateral hemisphere grey matter[16,17,19]. Other organs will be delineated using low-dose CT images and analysed using appropriate kinetic models[24].

Magnetic resonance imaging analyses of ischemic lesions

Diffusion weighted imaging (DWI) displays regions of reduced water mobility, which is usually ascribed to regions of cell swelling due to insufficient oxygen availability (ischemia). To obtain a quantitative measure of the potential harmful effect of the vasopressor, we will detect changes in ischemic regions by comparing the DWI images obtained prior to project enrollment with DWI obtained as a part of the routine post-surgery evaluation. Using machine-learning algorithms, we will automatically segment the pre-study and post-surgery ischemic regions. Since brain regions potentially alter position during surgery, we will attempt a non-linear co-registration of the two DWI measurements, before extracting the pre-study region from the post-surgery region to be able to report the potential volume increase. We will attempt to avoid regions that are the most affected by

the surgery, since the surgery itself may also affect the DWI values. This quantitative analysis is supplemented by qualitative inspection.

Sample size and statistical analysis

No previous studies have, to our knowledge, investigated the changes in CBF based on PET measurements after phenylephrine vs. noradrenaline treatment in the same patient population. Therefore, we estimated our sample size based on the regional changes in CBF after phenylephrine vs. ephedrine treatment in a similar patient cohort as reported by Koch et al. (2020)[16]. Ephedrine and noradrenaline are both combined α- and β-adrenergic agonists and have similar pharmacological properties[8,11,16]. The study by Koch et al. reported a change in CBF of 1.7 ± 3.5 ml/100g/min after phenylephrine treatment and 5.5 ± 4.0 ml/100g/min after ephedrine treatment[16]. Given a between-group difference in CBF = 3,8 ml/100g/min in favour of the noradrenaline group a significance level of 0.05 and a power of 80%, the study requires 15 patients in each group to detect a significant difference in CBF changes between the two vasopressors. Considering a possible dropout rate of 6%, and to increase the comparability of the two groups, we decided to recruit a total of 32 patients, with 16 patients in each arm.

Statistical analyses: All randomized subjects with a full dataset will be included in the statistical analyses. Standard parametric and non-parametric analyses are used for paired analyses of the physiological parameters[16-19]. The percentage changes in different measurements are calculated as the post-treatment value minus pre-treatment value divided by the pre-treatment value times 100 (i.e., the relative change). The effects of vasopressor type, vasopressor dose, and CO are estimated in a generalized linear model. Static autoregulation (relationship between MABP and CBF) is assessed using correlation plots and cubic penalized regression splines between noradrenaline and phenylephrine, and between normal and diseased brain regions (in addition to the global cerebral blood flow). A detailed statistical analysis plan will be prepared prior to the start of the analyses.

ETHICS AND DISSEMINATION

Patients included in this study are required to receive anaesthesia for removal of their brain tumour.

Thus, the patients are not exposed to any additional risk due to anaesthesia or placement of intravenous and intra-arterial catheters. The experiment and the removal of the tumour are conducted in the same anaesthesia "session". The experiment will prolong the period of which the patient is under general anaesthesia by approximately 2 hours[16,17]. With reference to our previous studies, and our experience in general, we do not find that the prolonged period of general anaesthesia nor the PET radiation dose (see Methods section) will pose significant additional risk to the patient[16,17]. This is furthermore supported by the obtained approvals from the Danish National Medical Ethics Committee (20 May 2022; 2203674) (VMK) and the Danish Medicines Agency. Informed consent (Supplemental File 1) will be acquired from the participant prior to study enrolment. Results will be disseminated via peer-reviewed publication and presentation at international conferences. Trial registration number at ClinicalTrials.gov NCT06083948

REFERENCES

1. Mazzeffi M, Chow JH, Anders M, et al. Intraoperative hypotension and perioperative acute ischemic stroke in patients having major elective non-cardiovascular non-neurological surgery. *J Anesth*. 2021;35(2):246-53.

2. Yao J, Li S, Cui Q, et al. Intraoperative hypotension and postoperative stroke in older patients who had brain tumor resections: a retrospective cohort analysis. *World Neurosurg*. 2023;174:e72-e81.

3. Gregory A, Stapelfeldt WH, Khanna AK, et al. Intraoperative hypotension is associated with adverse clinical outcomes after noncardiac surgery. *Anesth Analg*. 2021;132(6):1654-65.

4. Ackland GL, Abbott TEF. Hypotension as a marker or mediator of perioperative organ injury: a narrative review. *Br J Anaesth*. 2022;128(6):915-30.

5. Meng L. Heterogeneous impact of hypotension on organ perfusion and outcomes: a narrative review. *Br J Anaesth*. 2021;127(6):845-61.

6. Wesselink EM, Kappen TH, Torn HM, et al. Intraoperative hypotension and the risk of postoperative adverse outcomes: a systematic review. *Br J Anaesth*. 2018;121(4):706-21.

7. Sookplung P, Siriussawakul A, Malakouti A, et al. Vasopressor use and effect on blood pressure after severe adult traumatic brain injury. *Neurocrit Care*. 2011;15:46-54.

8. Bangash MN, Kong ML, Pearse RM. Use of inotropes and vasopressor agents in critically ill patients. *Br J Pharmacol*. 2012;165(7):2015-33.

9. Meng L, Gelb AW, Alexander BS, et al. Impact of phenylephrine administration on cerebral tissue oxygen saturation and blood volume is modulated by carbon dioxide in anaesthetized patients. *Br J Anaesth*. 2012;108(5):815-22.

10. Meng L, Cannesson M, Alexander BS, et al. Effect of phenylephrine and ephedrine bolus treatment on cerebral oxygenation in anaesthetized patients. *Br J Anaesth*. 2011;107:209-17.

11. Thorup L, Koch KU, Upton RN, et al. Effects of vasopressors on cerebral circulation and oxygenation: a narrative review of pharmacodynamics in health and traumatic brain injury. *J Neurosurg Anesthesiol*. 2019;00:1-11.

12. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the management of severe traumatic brain injury, fourth edition. *Neurosurgery*. 2017;80(1):6-15.

13. Ariyarathna D, Bhonsle A, Nim J, et al. Intraoperative vasopressor use and early postoperative acute kidney injury in elderly patients undergoing elective noncardiac surgery. *Ren Fail*. 2022;44(1):648-59.

14. Karamchandani K, Dave S, Hoffmann U, et al. Intraoperative arterial pressure management: knowns and unknowns. *Br J Anaesth*. 2023;S0007-0912(23)00313-6. doi:10.1016/j.bja.2023.05.027.

15. Mets B. Should noradrenaline, rather than phenylephrine, be considered the primary vasopressor in anesthetic practice? *Anesth Analg*. 2016;122(5):1707-14.

16. Koch KU, Mikkelsen IK, Aanerud J, et al. Ephedrine versus phenylephrine effect cerebral blood flow and oxygen consumption in anesthetized brain tumor patients: a randomized clinical trial. *Anesthesiology*. 2020;133(2):304-17.

17. Koch KU, Mikkelsen IK, Espelund US, et al. Ephedrine versus phenylephrine effects on cerebral macro- and microcirculation in anesthetized brain tumor patients: a randomized clinical trial using magnetic resonance imaging. *Anesthesiology*. 2021; Nov 1;135(5):788-803. doi:10.1097/ALN.0000000000003877.

18. Koch KU, Zhao X, Mikkelsen IK, et al. Correlation between cerebral tissue oxygen saturation and oxygen extraction fraction during anesthesia: monitoring cerebral metabolic demand-supply balance during vasopressor administration. *J Neurosurg Anesthesiol*. 2023;35(2):238-42.

19. Rasmussen M, Koch KU, Espelund US, Mohamad N, et al. Blood-brain barrier permeability may influence vasopressor effects in anesthetized patients with brain tumor: An analysis of magnetic

resonance imaging data. *J Neurosurg Anesthesiol*. 2024;36(4):357-362. doi:10.1097/ANA.0000000000000948.

20. Drummond JC. Cardiac output: the neglected stepchild of the cerebral blood flow physiology. *J Neurosurg Anesthesiol*. 2020;32:93-94.

21. Meng L, Hou W, Chui J, et al. Cardiac output and cerebral blood flow: the integrated regulation of brain perfusion in adult humans. *Anesthesiology*. 2015;123:1198-208.

22. Meng L, Wang Y, Zhang L, et al. Heterogeneity and variability in pressure autoregulation of organ blood flow: lessons learned over 100+ years. *Crit Care Med*. 2019;47(3):436-48.

23. Prenosil GA, Sari H, Fürstner M, et al. Performance characteristics of the Biograph Vision Quadra PET/CT system with a long axial field of view using the NEMA NU 2-2018 standard. *J Nucl Med*. 2022;63(3):476-84.

24. Knuuti J, Tuisku J, Kärpijoki H, et al. Quantitative perfusion imaging with total-body PET. *J Nucl Med*. 2023;64(Suppl 2):11S-19S.

25. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap) – a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-81.

26. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software partners. *J Biomed Inform*. 2019;103208. doi:10.1016/j.jbi.2019.103208.

27. Ohta S, Meyer E, Fujita H, et al. Cerebral [15O]water clearance in humans determined by PET: I. Theory and normal values. *J Cereb Blood Flow Metab*. 1996;16:765-80.

28. Ohta S, Meyer E, Thompson CJ, et al. Oxygen consumption of the living human brain measured after a single inhalation of positron emitting oxygen. *J Cereb Blood Flow Metab*. 1992;12:179-92.

29. Blomqvist G. On the construction of functional maps in positron emission tomography. *J Cereb Blood Flow Metab*. 1984;4:629-32.

AUTHOURS' CONTRIBUTIONS

Dr. Niwar Faisal Mohamad has prepared the IMPACT protocol manuscript in close collaboration with Associate Professor Mads Rasmussen. The rest of the research group has subsequently reviewed the manuscript.

Dr. Niwar Faisal Mohamad is the guarantor.

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DECLARATION OF INTEREST

None.

APPENDICES

Participant informed consent material (Supplemental File 1 – "Participant Consent").

FIGURE LEGENDS

Figure 1: Study design and randomization.

Figure 2: Experimental protocol and study flow chart.

PET exams of Blood flow (using [^{15}O] H_2O tracer) and oxygen consumption (using [^{15}O]O_2 tracer) in brain and organs (including myocardium, kidney, lungs and limb muscle) are performed using a Biograph Vision

Quadra-PET scanner with a wide axial field of view. The wide axial field of view allows for simultaneous assessments of the brain and organs.

The first PET examination (**PET 1**) is performed in the awake patient. The patient is then anesthetized, and the PET exam is repeated (**PET 2**). Vasopressor infusion is initiated and titrated to a 10 % increase in MABP relative to pre-treatment level (**PET 3**). MABP is further increased to 20 % relative to the pre-treatment level (**PET 4**). After completion of the PET examinations the anesthetized patient is transported to the surgical theatre and surgery is performed. The vasopressor infusion is initiated after PET 2 and terminated at emergence of anaesthesia after completion of surgery. MABP, CO, BIS and NIRS are measured during PET exams and surgery. The duration of the PET part of the study until initiation of surgery is approximately 2 hours.

The 24-48 MRI examination is performed as a postoperative control of the surgical result and includes a diffusion weighted sequence to detect ischemic brain lesions possibly associated with vasopressor infusion.

MABP, mean arterial blood pressure; CO, cardiac output; BIS, bispectral index; NIRS, near infrared spectroscopy, PET, positron emission tomography; MRI, magnetic resonance imaging.

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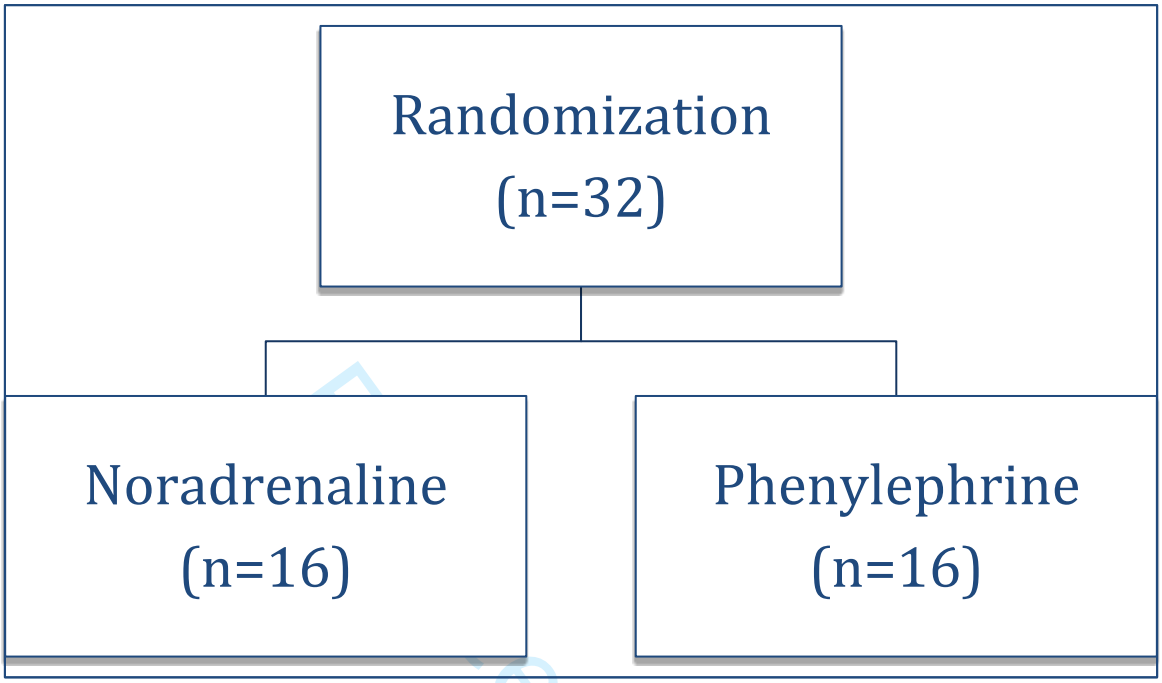

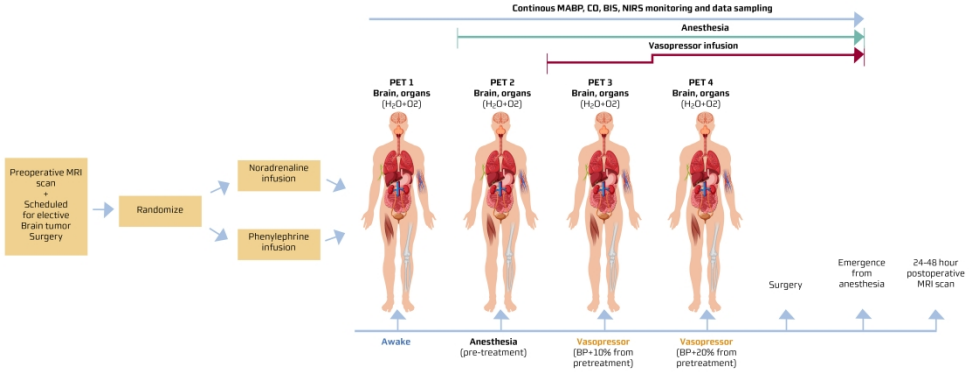

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1210x512mm (118 x 118 DPI)