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Optimal mean arterial pressure based on cerebrovascular autoregulation during and after non-cardiac surgery

Dissertation

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Content

List of abbreviations

CVA	Cerebrovascular autoregulation
CBF	Cerebral blood flow
CPP	Cerebral perfusion pressure
MAP	Mean arterial blood pressure
ICP	Intracranial pressure
20-HETE	20-hydroxyeicosatetraenoic acid
Ca^+ channels	Calcium channels
CO_2	Carbon dioxide
NO	Nitric oxide
$PaCO_2$	Partial pressure of carbon dioxide
NIRS	Near-infrared spectroscopy
rSO_2	Regional cerebral oxygen saturation
TCD	Transcranial Doppler
SAP	Systolic arterial pressure
MAPopt	Optimal mean arterial pressure
ICU	Intensive care unit
TWA	Time-weighted average
COx	Cerebral oximetry index
CSV	Comma-separated values
PACU	Post-anaesthesia care unit
CCI	Charlson comorbidity index
ASA	American Society of Anaesthesiologists
AKI	Acute kidney injury
RCT	Randomized controlled trial
AUC	Areas under curve

1. Introduction

1.1 Cerebrovascular autoregulation

Cerebrovascular autoregulation (CVA) is an intrinsic modulatory mechanism characterized by the ability to maintain relatively stable cerebral blood flow (CBF) regardless of fluctuations in cerebral perfusion pressure (CPP) or mean arterial blood pressure (MAP) (Meng and Gelb 2015).

This phenomenon was first described in 1959 by Lassen, who collected data from multiple studies and plotted the autoregulation curve accordingly (Lassen 1959). The ideal visualization of the CVA curve, with the CBF as the Y-axis against the CPP or MAP as the X-axis, incorporates two inflection points and a plateau (Figure 1). The lower inflection point corresponds to the lower limit of autoregulation, while the upper inflection point corresponds to the upper limit of autoregulation. The plateau represents the blood pressure range where changes in the CPP or MAP do not or only minimally translate into changes in the CBF.

Figure 1. The ideal visualization of CVA curve

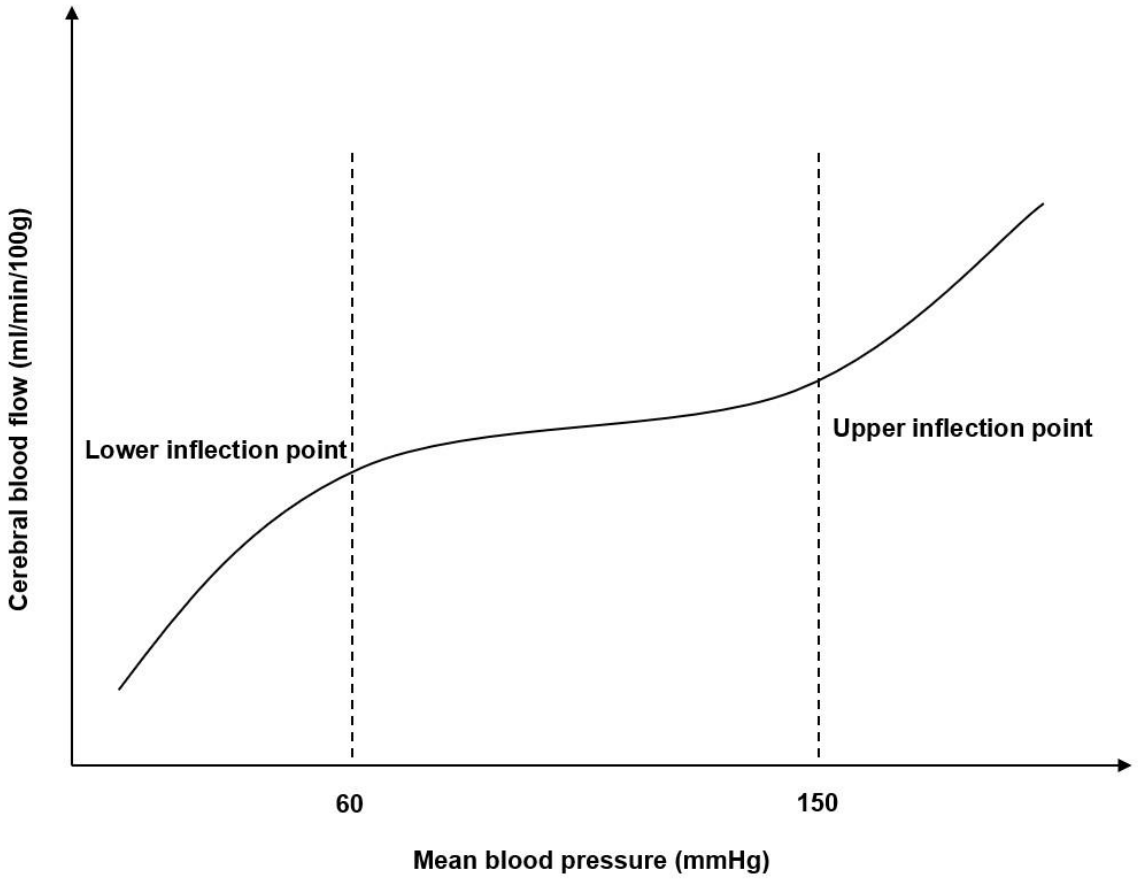

Figure 1. The lower inflection point corresponds to the lower limit of cerebrovascular autoregulation (CVA) which is around 60 mmHg and the upper inflection point corresponds to the upper limit of CVA which is around 150mmHg. The plateau is the range where the changes of blood pressure would not affect the cerebral blood flow (CBF).
Figure was drawn after Meng L, Gelb AW. Regulation of cerebral autoregulation by carbon dioxide. Anesthesiology. 2015 Jan;122 (1):196-205.

Conversely, the pressure-dependent CBF refers to the phenomenon where the CBF varies with the change in blood pressure in the same direction, which occurs in hypotension and hypertension where the CPP or MAP values bypass the lower and upper limits of autoregulation. Although CVA curves vary individually, the lower and upper limits of autoregulation are most frequently delineated around 60 and 150 mmHg or around 50 and 170 mmHg (Meng and Gelb 2015; Aaslid et al. 1989). The plateau, a crucial protective mechanism for cerebral perfusion and circulation, is most commonly depicted as CBF equals 50 ml/min/100 g despite fluctuations in arterial blood pressure within the intervals of the lower and upper limits of autoregulation (Paulson, Strandgaard, and Edvinsson 1990).

1.1.1 The physiology of cerebrovascular autoregulation

The CBF is regulated by the interaction between the CPP (= the difference between the MAP and intracranial pressure [ICP]) and cerebrovascular resistance (CVR) (Donnelly et al. 2016). It is briefly represented by an equation:

$$\text{CBF} = \frac{MAP - ICP}{CVR}$$

The CVR, meanwhile, is regulated by CVA. Generally, CVA is achieved through vasoconstriction and vasodilation, which change the arteriolar diameter. More specifically, the cerebral vasculature constricts to increase the CVR when the CPP is elevated, while the cerebral vasculature dilates to decrease the CVR when the CPP declines. The underlying mechanisms of CVA include myogenic, neurogenic, endothelial, and metabolic mechanisms. Although these factors have been studied for decades, the exact molecular mechanisms remain elusive, especially the synergistic and antagonistic interactions (Xiong et al. 2017).

1.1.1.1 Myogenic mechanism

The myogenic mechanism regulates CVA by controlling the cerebrovascular smooth muscle cells. These cells play pivotal roles in mediating vasomotor tone through contraction in response to pressure increase and relaxation in response to pressure decrease (Rivera-Lara

et al. 2017). The intraluminal pressure change stimulates ion channels on cerebrovascular smooth muscles, leading to final vasoconstriction or vasodilation (Knot and Nelson 1998).
Increased intraluminal pressure leads to more production of 20-hydroxyeicosatetraenoic acid (20-HETE), a substance which can contract the cerebral vessels by activation of calcium channels (Ca^+ channels) (David R. Harder, Narayanan, and Gebremedhin 2011). A lack of 20-HETE undermines the vasoconstriction ability, resulting in an impaired myogenic response and dysfunction of CVA (Fan et al. 2015). Elevation of the intraluminal pressure simultaneously leads to stretching of the cerebral vessels, resulting in cell membrane depolarization. Consequently, the voltage-dependent Ca^+ channels open and facilitate the influx of Ca^+, which ultimately contracts cerebrovascular smooth muscles and induces vasoconstriction (McCarron et al. 1997; Moosmang et al. 2003). Changing the Ca^+ concentration significantly affected the pressure-induced membrane potential alteration (D. R. Harder 1984). Under circumstances inhibiting the voltage-dependent Ca^+ channel or removing extracellular Ca^+, the vasoconstrictive reactivity to the intraluminal pressure increase was dramatically reduced (Knot and Nelson 1998).
In summary, the myogenic mechanism affects cerebrovascular smooth muscle cells based on their constriction and vasodilation through changes in intraluminal pressure and thus affects CVA.

1.1.1.2 Flow-induced mechanism

The flow-induced mechanism reflects how CVA is mediated by the changes in the CBF velocity. It is commonly believed that an increased CBF leads to cerebral vasoconstriction, while a decreased CBF leads to cerebral vasodilation (Toth et al. 2013). The impact of CBF on the cerebral vasculature has long been investigated (Koller and Toth 2012). The flow-induced CVA mechanism appears to have synergistic effects with the myogenic mechanism. An increased CBF velocity induces local arachidonic acid production. Metabolites, such as 20-HETE from arachidonic acid, thus activate the myogenic mechanism summarized above (Toth et al. 2011). Additionally, flow velocity-induced vasoconstriction can be eliminated by applying a 20-HETE inhibitor, and the combined impact of blood flow and intraluminal pressure exceeds the sum of these effects alone(Toth et al. 2011).

1.1.1.3 Metabolic mechanism

Considering the organ size, the cerebral metabolic rate and energy requirement are disproportionally high, resulting in a much higher blood flow demand than other organs (Fantini et al. 2016). The metabolic mechanism affects the reactivity of the cerebral vasculature in response to changes in blood levels of carbon dioxide (CO_2), oxygen, pH, nitric oxide (NO), and adenosine (Claassen et al. 2021). Among these, the effect of CO_2 has been widely studied

in several investigations and shows the most significant influence on CVA. Generally, an increase in the arterial partial pressure of CO_2 leads to cerebral vasodilation, which results in an increase in CBF. Conversely, a decrease in the arterial partial pressure of CO_2 leads to cerebral vasoconstriction, resulting in a decrease in CBF (Hoiland, Fisher, and Ainslie 2019).

Without metabolic compensation, hypercapnia results in respiratory acidosis (Meng and Gelb 2015). An acidic environment contributes to reduced Ca^{2+} channel conductivity, membrane depolarization and activation, and a reduced intracellular Ca^{2+} concentration (Boedtkjer et al. 2016; Klöckner and Isenberg 1994). Ca^{2+} channels play a key role in the myogenic mechanism described above. The reduced Ca^{2+} channel conductivity entails reduced cerebrovascular smooth muscle cell contraction, eventually leading to local cerebral vasodilation. If the MAP is beyond the autoregulatory plateau, the CBF changes by approximately 4% for every 1 mmHg change in partial pressure of carbon dioxide ($PaCO_2$) (Rangel-Castilla et al. 2008). Figure 2 shows the effect of hypercapnia at distinct levels. Increasing $PaCO_2$ leads to cerebral vasodilation. During MAP decline, the cerebral vessels dilate. However, during hypercapnia, maximal vasodilation is reached at a higher MAP compared to normocapnia. This is because decreased MAP and hypercapnia both induce cerebral vasodilation, and cerebral vessels cannot dilate limitlessly. Therefore, the lower limit of autoregulation shifts towards the right (Meng and Gelb 2015). During MAP elevation, the cerebral vessels constrict. However, during hypercapnia, maximal vasoconstriction is reached at a lower MAP compared to normocapnia. This is because increased MAP and hypercapnia have antagonistic effects on the cerebral vasculature. Therefore, the upper limit of autoregulation shifts towards the left. As hypercapnia increases, the shifts to the right and left may become more pronounced, resulting in a shorter plateau (Meng and Gelb 2015).

Hypocapnia results in cerebral vasoconstriction. This effect antagonizes the cerebral vasodilatory influence of CVA at low MAP.

However, some studies have demonstrated that extreme hypotension or low MAP resulting from blood loss, anaesthesia, or drugs overrides or even eliminates hypocapnia-induced vasoconstriction in some situations (Harper and Glass 1965; Artru 1986; Whitelaw et al. 1991). Based on Meng's deduction, the CVA curve plateau shifts downwards, while the change in the lower and upper limits of autoregulation remains unclear (Meng and Gelb 2015).

Figure 2. The ideal visualization of CVA in different hypercapnia states

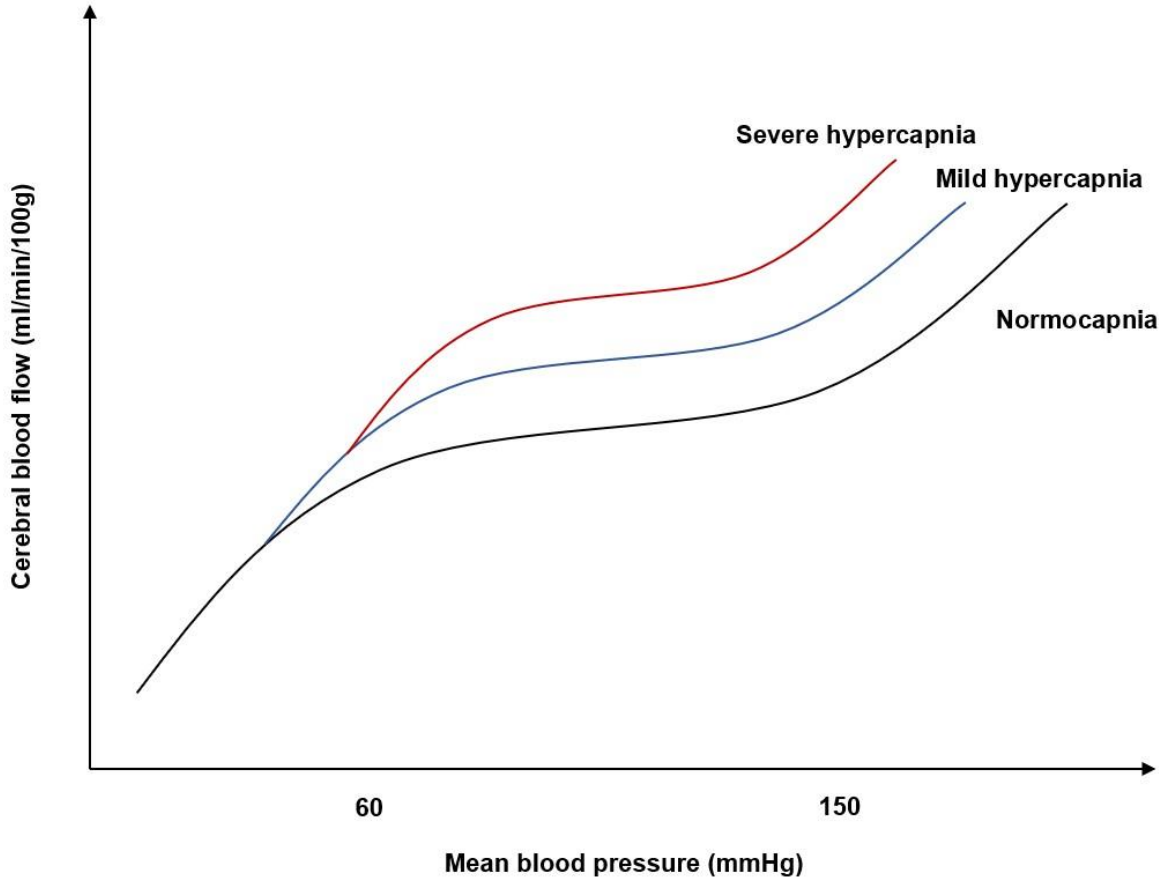

Figure 2. The effects of hypercapnia on the cerebrovascular autoregulation (CVA). The black curve represents the CVA curve during normocapnia. The blue curve represents the CVA curve during mild hypercapnia in which the plateau shortens. The red curve represents the CVA curve during severe hypercapnia in which the plateau has the shortest range compared to the normocapnia and mild hypercapnia.
Figure was drawn after Meng L, Gelb AW. Regulation of cerebral autoregulation by carbon dioxide. Anesthesiology. 2015 Jan;122 (1):196-205.

1.1.1.4 Endothelial mechanisms

Endothelial cells are a class of cells that form the superficial layer of the inner wall of blood vessels. They have different functions, including separation of the blood from the vessel wall, fluid filtration, mediation of vasomotor tone, and homeostasis (Rajendran et al. 2013). Endothelial cells regulate vasomotor tone by releasing vasoactive factors. Among these, important vasodilative molecules are NO and prostacyclin, while vasoconstrictive molecules include endothelin, thromboxane A2, angiotensin II, and superoxide (Rajendran et al. 2013). These vasoactive substances act on vascular smooth muscle cells. The release of these modulatory factors is related to a sudden change in mechanical shear stress or activation of

endothelial cell receptors according to some studies (Faraci 2011; Hill-Eubanks et al. 2014). Further evidence has shown that electrical signals spreading from endothelial cells to adjacent smooth muscle cells trigger depolarization and vasoconstriction (Hill-Eubanks et al. 2014). White determined the NO mediating function in CVA regulation by applying NO synthase in humans (R. P. White, Vallance, and Markus 2000). He implied an association between reduced NO release and impaired CVA, affirming the key role of endothelial cells in CVA regulation.
In summary, CVA results from the combined effects of multiple mechanisms, and the factors affecting CVA should be considered comprehensively in clinical practice.

1.1.2 Assessment of cerebrovascular autoregulation

CVA reflects changes in parameters such as CBF velocity or regional cerebral oxygen saturation over a certain time frame in response to MAP or CPP changes, determined by the principle of measurements. CVA can be assessed as either static or dynamic. Static CVA refers to the steady-state relationship between spontaneous changes in blood pressure and CBF. It is calculated over a long time (e.g. over 10 minutes) and represents the capacity of CPP regulation over a blood pressure range. Dynamic CVA refers to the relationship between acutely induced blood pressure changes and CBF over much shorter times (e.g. 10 seconds). This relationship demonstrates how quickly the cerebral arteries respond to pressure changes (Claassen et al. 2021; Czosnyka, Miller, and Participants in the International Multidisciplinary Consensus Conference on Multimodality Monitoring 2014). In the present study, we used continuous monitoring methods to investigate static CVA.
CVA cannot be measured directly but is calculated based on CBF and CPP. Since it is highly invasive to measure these two parameters directly, they are replaced by surrogates. Normally, MAP can be used as a surrogate for CPP because, in patients without acute brain injury and with normal ICP, MAP can be assumed to equal CPP (Rivera-Lara et al. 2017).
Multiple methods exist for assessing CBF. These methods can be separated into invasive and non-invasive. The two most common methods for non-invasive CBF assessment are assessing the blood flow velocity with transcranial Doppler sonography and assessing the local cerebral oxygen saturation with near-infrared spectroscopy. These methods are now widely used in clinical treatment and experimental research due to their portability, non-invasiveness, simplicity, and practicality.
Invasive methods include ICP, brain tissue oxygen monitoring, laser Doppler flowmetry, and thermal diffusion (Rohlwink and Figaji 2010; Rajan et al. 2009; Vajkoczy et al. 2000). These methods are generally used in invasive animal experiments or in patients with acute brain injury.

1.1.2.1 Near-infrared spectroscopy

Near-infrared spectroscopy (NIRS) measures regional cerebral oxygen saturation (rSO_2) non-invasively (Rivera-Lara et al. 2017). Jöbsis was the first to report the application of NIRS in monitoring the cerebral and myocardial oxygenation status (Jöbsis 1977). This measurement assumes that penetrating near-infrared wavelengths are barely absorbed by the skin, scalp, and muscles (Jöbsis 1977). The wavelength spectrum of NIRS is around 700–1,000 nm (Rivera-Lara et al. 2017). This wavelength is mainly absorbed by molecules called chromophores in cerebral vessels. Chromophores are constituted by oxyhaemoglobin, deoxyhaemoglobin, and cytochrome-c-oxidase (Roldán and Kyriacou 2021). Different chromophores have different absorption rates. Thus, NIRS can determine the oxygenation of local brain areas based on this difference. The oxyhaemoglobin absorption spectrum ranges from 700 to 1,150 nm, while that of deoxyhaemoglobin ranges from 650 to 1,000 nm (Jöbsis 1977). The devices used for NIRS detection select the wavelength spread from 700 to 850 to cover most of the oxyhaemoglobin and deoxyhaemoglobin absorption spectra and avoid other mixing factors (Murkin and Arango 2009). NIRS relies on a calculation based on the Beer-Lambert law, which correlates the attenuation of emitted light to the tissue-specific absorption coefficient, light travelling distance, and chromophore concentration (Roldán and Kyriacou 2021).

Based on this principle, a NIRS sensor attached to the forehead emits constant near-infrared light to the brain. This light passes through human tissues and is mainly absorbed by oxyhaemoglobin and deoxyhaemoglobin. Reflected light is detected by the receiver, and the degree of attenuation is used to calculate the regional cerebral oxygen saturation. These continuous NIRS devices assume that alterations in the oxyhaemoglobin and deoxyhaemoglobin proportions are the major influencing factors for the change in light intensity (Roldán and Kyriacou 2021).

1.1.2.2 Transcranial Doppler

Transcranial Doppler (TCD) measures the CBF velocity based on the Doppler principle. TCD application has been recorded as early as the 1980s (Aaslid, Markwalder, and Nornes 1982). It was designed to insonate basal cerebral arteries with low-frequency transducer probes. Regarding CVA assessment, the middle cerebral artery is normally used to measure the CBF velocity through the temporal bone window. The waves emitted by the probe pass through the skull and soft tissues and are reflected by the moving red blood cells. The difference between back and forth waves, termed the “Doppler shift frequency”, is calculated to derive the blood flow speed (Purkayastha and Sorond 2012). The blood flow velocity is affected by the cerebral vasculature diameter, while vasodilation and constriction are controlled by multiple mechanisms described above. Thus, understanding the relationship between blood flow

velocity and the CPP or MAP can indirectly reflect CVA.

TCD is frequently used for CVA assessment. However, using TCD for CVA measurement and other clinical applications has disadvantages. TCD operation requires highly experienced and well-trained users to find the target arteries. Based on the previous study, middle cerebral arteries cannot be located through temporal bone windows in 4% of patients (Arnolds and von Reutern 1986). Intraoperative monopolar electric knife operation and various low-frequency signals can also generate background noise and affect the accuracy of TCD data.

1.2 Perioperative optimal blood pressure

Perioperative blood pressure management is crucial for not only the safety but also the prognosis of surgical patients. Individual intraoperative and postoperative optimal blood pressure varies dramatically between patients. Personalized blood pressure management may positively impact patient prognosis (Saugel and Sessler 2021). However, opinions diverge on defining the individual optimal blood pressure during surgery and anaesthesia.

1.2.1 Intraoperative blood pressure

Although patients require different intraoperative blood pressures to meet the perfusion of tissues and organs, consensus statements on intraoperative blood pressure management have been made to guide anaesthesiologists' daily work. Generally, the MAP should be sustained above 60–70 mmHg throughout the surgery (Sessler et al. 2019). An absolute MAP below 65 mmHg is normally considered an intraoperative intervention threshold (Sessler et al. 2019). No consensus exists on the definition of intraoperative hypotension. Various hypotension thresholds were set based on a retrospective cohort study. The most frequent definitions include the following: 1. systolic arterial pressure (SAP) below 80 mmHg; 2. SAP decreasing by more than 20% from baseline values; 3. the overall SAP below 100 mmHg and SAP decreasing by more than 30% below baseline values (Bijker et al. 2007). In contrast to methods considering the baseline blood pressure, monitoring the absolute blood pressure is much easier to manage in practice. Salmasi et al. showed that absolute and relative MAP management share comparable efficiency in distinguishing postoperative outcomes including myocardial and acute kidney injury (Salmasi et al. 2017).

However, the definition of intraoperative hypotension might not apply to all patients, especially those who have already developed chronic hypertension. The intervention limit (65 mmHg) may be unsuitable for them since the organ perfusion regulation mechanism has changed to adapt to a hypertensive state (Song, Li, and Jiang 2022). Similar to intraoperative hypotension, the definition of intraoperative hypertension has no global consensus (Sessler et al. 2019). Convincing evidence to associate intraoperative blood pressure elevation with adverse outcomes remains equivocal. In a study of 797 patients undergoing non-cardiac surgery, Reich

et al. analyzed influencing factors related to adverse outcomes in operations lasting longer than 220 minutes using multiple logistic regression models. The results showed that intraoperative hypertension (MAP > 100 mmHg and SAP > 160 mmHg) was the independent risk factor (Reich et al. 2002). Conversely, Monk *et al*. performed a retrospective cohort study of 18,756 patients to associate intraoperative hypertension or hypotension with 30-day mortality. The results indicated that hypotension (MAP decrease >50% for >5 min) but not hypertension (MAP increase from 30% to 50%) was related to 30-day mortality (Monk et al. 2015). Abbott et al. indicated that a maximum SAP exceeding 160 mmHg was associated with myocardial injury after non-cardiac surgery (OR, 1.16, $p < 0.05$) and myocardial infarction (OR, 1.34, $p < 0.05$) but, paradoxically and unexpectedly, reduced mortality (OR, 0.76, $p < 0.05$)(Abbott et al. 2018). This evidence suggests that it is difficult and unconvincing to develop a consensus definition of intraoperative hypertension. Appropriate increases (20% of baseline) in intraoperative blood pressure may improve postoperative cognitive performance (Heyer et al. 2014). However, an excessive rise in MAP likewise increases the chance of perioperative intracranial haemorrhage (Sessler et al. 2019). Therefore, it is equally important to set individualized intraoperative blood pressure upper limits in intraoperative MAP management. Notably, intraoperative blood pressure fluctuations can also impact postoperative outcomes. Hirsch et al. indicated an association between increased intraoperative blood pressure fluctuation and a higher likelihood of postoperative delirium through prospective observational research on non-cardiac surgical patients (Hirsch et al. 2015).

1.2.2 Postoperative blood pressure

Few trials have separately examined the relationship between postoperative hypotension and adverse outcomes without considering the impact of intraoperative hypotension, although postoperative hypotension can cause adverse outcomes regarding clinical plausibility. A consensus has been achieved by the Perioperative Quality Initiative to guide clinical practice: 1. A postoperative SAP < 90 mmHg is associated with myocardial injury, acute kidney injury, and all-cause death, and the severity is a function of duration and magnitude. 2. For patients with preoperative chronic hypertension, the thresholds of postoperative SAP to prevent injury exceed 90 mmHg (McEvoy et al. 2019).

Postoperative hypotension is common in surgical patients and usually occurs within the first 3 days after surgery, especially on the first day (Roshanov et al. 2017). Notably, it can be difficult to distinguish whether the adverse outcomes are due to intraoperative or postoperative hypotension or both (Sessler et al. 2019).

Postoperative hypertension, referring to an emergent blood pressure rise, occurs frequently and is associated with many adverse outcomes, including stroke, myocardial infarction, and

bleeding (McEvoy et al. 2019). Whether a threshold exists to define postoperative hypertension remains unclear. A postoperative SAP exceeding 180 mmHg appears to predict mortality and cardiac arrest for surgical patients (Smith et al. 2014). Nevertheless, more experiments are needed to confirm the threshold's effectiveness.

As with postoperative hypotension, frequent bedside monitoring is crucial. A target blood pressure above 10% of the preoperative MAP estimation is considered beneficial (McEvoy et al. 2019).

1.2.3 Perioperative optimal blood pressure based on cerebral autoregulation

According to the CVA theory, optimal mean arterial pressure (MAPopt) is defined as the blood pressure at which the CVA reaches the minimal pressure passiveness. Specifically, the MAPopt provides the optimal conditions for the autoregulatory capacity of the cerebral vessels (Rivera-Lara et al. 2017). This concept was broadly applied in studies to assess the individual MAPopt and CBF during cardiovascular surgery (Hori, Hogue, et al. 2016).

Hori et al. found that an intraoperative MAP exceeding the CVA-based MAPopt was associated with the incidence and severity of postoperative delirium, indicating that identification and blood pressure management based on CVA-based MAPopt is important and necessary for clinical practice (Hori, Max, et al. 2016).

A prospective randomized clinical trial from the same group revealed that surgical patients whose average postoperative MAP in the intensive care unit (ICU) was higher than the CVA-based MAPopt had lower levels of glial fibrillary acidic protein, a substance indicating stroke or brain injury, compared to the group in which the patients' average postoperative MAP in ICU was below the CVA-based MAPopt (Hori et al. 2015).

All these studies demonstrated the relationship between the CVA-based MAPopt and postoperative outcomes, indicating the potential role of the CVA-based MAPopt in future clinical applications.

2. Aim of the study

CVA-based MAPopt appears a promising tool for individualized perioperative blood pressure management. As detailed above, significant differences exist between intraoperative and postoperative blood pressure management. We speculate that these differences also exist between intraoperative and postoperative MAPopt. The relationship between intra- and postoperative MAP and the magnitude and duration of hypotension below the CVA-based MAPopt is unclear. Therefore, we aimed to determine intraoperative and postoperative CVA-based MAPopt values, as well as the intraoperative and postoperative time-weighted average (TWA) MAP below the CVA-based MAPopt during non-cardiac surgery. Additionally, we aimed to determine factors influencing the intra- and postoperative TWA-MAP below the CVA-based MAPopt.

This study aimed to

1. Compare intraoperative and postoperative CVA-based MAPopt;
2. Compare the intraoperative and postoperative TWA-MAP below the CVA-based MAPopt;
3. Identify factors influencing the intraoperative and postoperative TWA-MAP below the CVA-based MAPopt.

3. Hypotheses

1. The intraoperative CVA-based MAPopt is lower than the postoperative CVA-based MAPopt.
2. The intraoperative TWA-MAP below the CVA-based MAPopt exceeds the postoperative TWA-MAP below the CVA-based MAPopt.

4. Material and methods

4.1 Study registration and ethical information

The study was registered and approved by the Ethics Committee of the Hamburg Chamber of Physicians on January 14, 2019 (registration number PV5980). Each patient was informed about all study procedures and related risks. Written informed consent was obtained before performing any study-related procedure.

4.2 Patient enrolment

This is a sub-study of an ongoing single-centre prospective cohort study, which aims to explore the correlation between TCD and NIRS as methods for intraoperative CVA assessment. Starting on August 09, 2021, patients scheduled for non-cardiac surgery at the University Medical Center Hamburg-Eppendorf who fulfilled the inclusion criteria are being enrolled in the main study. Patients enrolled between the start of the study and May 27, 2022, were included in the present sub-study.

4.2.1 Inclusion criteria

Patients were considered eligible if

1. They were scheduled for non-cardiac surgery with an expected duration of >120 minutes;
2. They received general anaesthesia;
3. They had an indication for invasive blood pressure monitoring or consented to have an arterial line for study purposes;
4. The intraoperative blood loss was expected to exceed 500 ml
   or they had preoperative anaemia (haemoglobin concentration <12 mg/dl in women, <14 mg/dl in men);
5. They had excellent knowledge of the German language to complete the neuropsychological assessment for postoperative cognitive dysfunction;
6. They gave written consent to study participation.

4.2.2 Exclusion criteria

Patients were not included if the following applied:

1. Pregnancy;
2. Age < 18 years;
3. Contraindications against invasive blood pressure monitoring (e.g. skin infection at puncture sites);
4. History of cerebrovascular events (ischemic stroke, transient ischemic attack).

4.3 Anaesthesiological management

General anaesthesia was induced, starting with the application of an intravenous opioid such as sufentanil (0.3–1 µg/kg) or remifentanil (0.3–0.5 µg/kg), followed by propofol (1.5–2.5 mg/kg) according to the standard clinical anaesthesia management. After administering a muscle relaxant, endotracheal intubation was performed.

Propofol (4–8 mg/kg) or inhalative sevoflurane with an age-adjusted targeted minimum alveolar concentration of 1 was used to maintain general anaesthesia intraoperatively (Katoh and Ikeda 1987). Patients received positive pressure ventilation with a tidal volume of 6–8 ml/kg. The respiratory rate was adjusted to a targeted expiratory CO_2 of 35–42 mmHg.

Norepinephrine and crystalloid fluids were administered intravenously to maintain the MAP within a physiological range if the mean blood pressure dropped below the threshold of 65 mmHg.

An arterial monitoring catheter (Leader-Cath, VYGON GmbH & Co. KG, Aachen, Germany) was placed in either the left or the right radial artery and connected to a compatible arterial monitoring system (Combitrans UKE EXAdyn, B. Braun Melsung, Germany). The blood pressure calibration line was placed at heart level around the left midaxillary area. The blood pressure monitor was recalibrated each time the patient's intraoperative position was changed.

4.4 Intraoperative cerebral autoregulation measurement

4.4.1 Intraoperative regional cerebral oxygen saturation measurement

After induction of general anaesthesia, the right side of the forehead was cleaned and degreased with an alcoholic disinfectant. If the right side was unavailable, the left side was used. Excess disinfectant was wiped off carefully, waiting until the skin was completely dry. A compatible sensor (INVOS™ Cerebral/Somatic Oximetry Adult Sensors, Medtronic, Minneapolis, Minnesota) was then attached to the forehead area and tightly fitted to the skin to prevent light from the environment from reaching the sensor. Sensors were placed to cover as much skin as possible, and the edge of the sensor was placed at the midline of the forehead according to the manufacturer's instructions. The rSO_2 was measured and recorded with a NIRS monitor (INVOS™ 5100 Cerebral Oximeter, Medtronic, Minneapolis, Minnesota). When the measurement started, the NIRS monitor was automatically calibrated and the real-time rSO_2 values were displayed on the screen.

4.4.2 Intraoperative cerebral oximetry index measurement

Cerebral autoregulation was assessed as the cerebral oximetry index (COx) based on the correlation of the MAP and rSO_2 values (Moerman et al. 2015). Generally, the MAP and rSO_2 data were recorded over a certain time (e.g. 300 s). The change in these two data sets was used for the calculation with the Pearson correlation by specific real-time software. The COx normally ranges from −1 to 1. When the COx is positive and close to 1, this indicates that CBF passively changes with the CPP or MAP. At this stage, CVA is impaired. When the COx is negative or close to 0, this indicates that the change in CBF is independent of the CPP or MAP (Rivera-Lara et al. 2017).

A bedside GE monitor (GE Healthcare Systems, GE Healthcare, United States), which monitors vital indicators such as heart rate and arterial pressure intraoperatively, was used to record MAP. A GE monitor with intraoperative real-time invasive blood pressure monitoring and an INVOS monitor with intraoperative real-time rSO_2 values were connected to a laptop, and the data were processed with a specialized software (ICM+ software, Cambridge Enterprise ICM+ , Cambridge, UK). ICM+ software, which provides real-time analysis from multiple bedside monitoring sources, was invented and developed by a team from Cambridge University (Smielewski et al. 2012). The relevant configurations for this study were completed with the assistance of the software developer.

The Pearson correlation coefficients of the MAP and rSO_2 values were calculated at 10-second intervals. These were averaged over 300 seconds, resulting in an autoregulation index (COx). The level of this index between −1 and +1 provides information about cerebral autoregulatory capacity, with a value below 0.3 indicating intact cerebral autoregulation.

Realtime COx, MAP, and rSO_2 curves were plotted in different colours and recorded.

The CVA-based MAPopt was defined as the MAP at which the COx is lowest, indicating optimal autoregulation capacity.

Intraoperative measurements lasted at least 2 hours. Any interruptions of MAP or NIRS measurements for any reason were recorded.

4.5 Postoperative cerebral autoregulation measurement

Postoperatively, patients were transferred to the post-anaesthesia care unit (PACU) or an intermediate care unit (IMC). Patients transferred to the PACU or the IMC were extubated in the operation room. Patients transferred to the ICU were extubated later in the ICU in some cases. Study-related recordings of invasive blood pressure and NIRS were paused during transport and restarted immediately after the patients arrived in the PACU or IMC. For patients transferred to the ICU, recordings of invasive blood pressure and NIRS were restarted after extubation. The MAP, rSO_2, and COx were measured and calculated as described for the intraoperative period. Correlation coefficients were calculated at 10-second intervals, averaged

over a moving period of a 300-second time window. Postoperative measurements lasted at least 1 hour. Any interruptions of MAP or NIRS measurements for any reason were recorded.

4.6 Data collection

The raw CVA data and configuration files were saved after each measurement. Raw data were exported as comma-separated values (CSV) files. The SAP, diastolic blood pressure, MAP, rSO_2, and COx values were recorded in time intervals of 1 minute. Baseline characteristics of relevant surgical patients, including age, sex, height, weight, disease history (hypertension, myocardial infarction, heart failure, peripheral vascular disease, pulmonary disease, ulcer disease, liver disease, diabetes mellitus, chronic kidney disease, solid tumours and lymphomas) along with perioperative parameters including intraoperative blood loss, haemoglobin concentration, anaesthesia medication (angiotensin-converting enzyme inhibitors, angiotensin 1 receptor antagonists, beta blockers, other antihypertensive drugs, thiazide diuretics, loop diuretics, aldosterone antagonists) were retrieved from electronic data management systems and documented in a separate Excel file.

4.7 Determination of CVA-based MAPopt

Raw CVA data for each measurement were imported into the ICM+ affiliated calculation program. Blood pressures were filtered for artefacts by excluding MAP values exceeding 150 mmHg and below 30 mmHg and their corresponding COx values.

Multiple methods exist for calculating the CVA-based MAPopt. The second-order polynomial formula, also known as a U-shaped curve, is the most common way to determine the CVA-based MAPopt based on the COx values. The formula constructs a parabolic curve to maximally fit all the data with the MAP or CPP as the X-axis and COx or Mx as the Y-axis. The CVA-based MAPopt is thus defined as the X-axis value at the lowest point of this parabolic curve (Figure 3).

Another method for assessing the CVA-based MAPopt is to find the lowest cerebral autoregulation index, which is easy to use but less exact and objective than determining a U-shaped curve. All the data are pooled on the coordinate axis, and the CVA-based MAPopt is defined as the blood pressure with the lowest COx or Mx (Figure 3).

Figure 3. Exemplary visualization of the determination of CVA-based MAPopt pressure with two methods

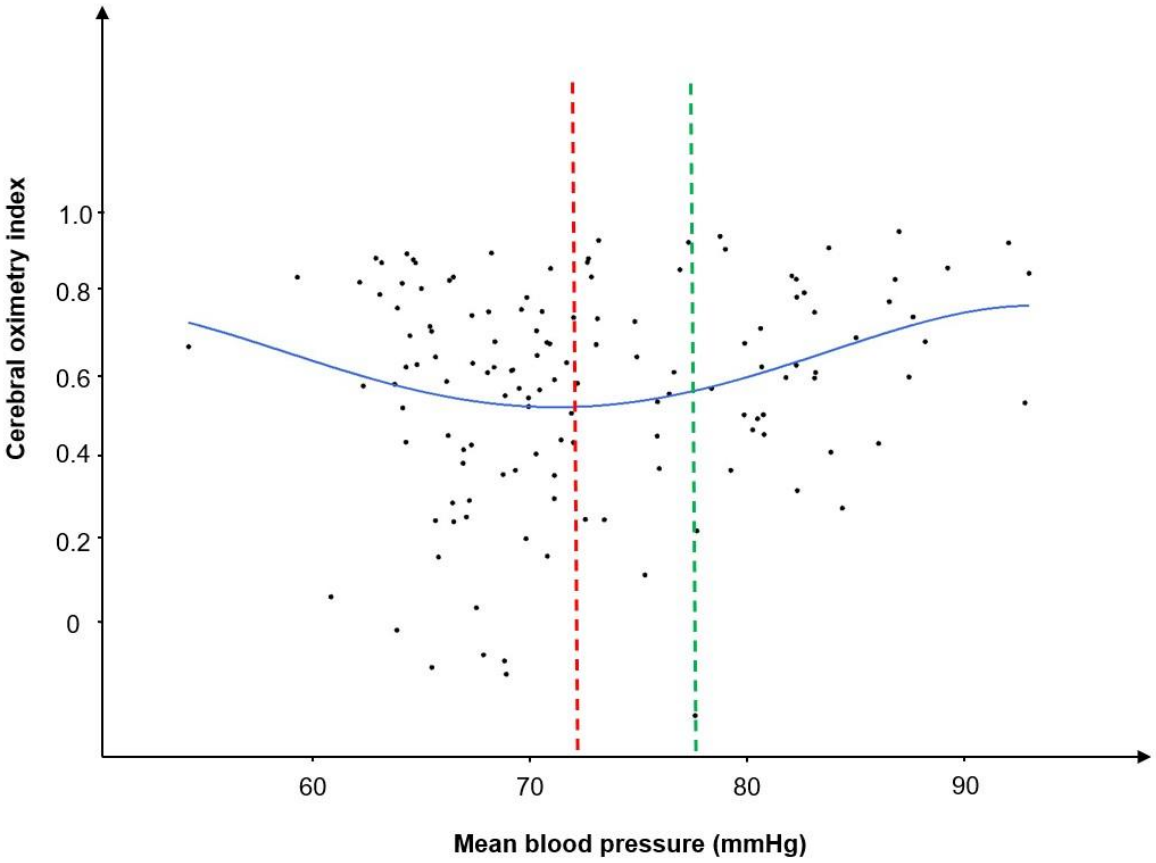

Figure 3. The scatter plot representing the COx (Y-axis) and corresponding MAP data (X-axis) of one of our study patients (n=1). The black dots represent the individual data in the measurement intraoperatively. The blue parabolic curve represents the U-shape curve calculated according to the second-order polynomial formula. The red dashed line represents the CVA-based MAPopt determined by U-shape curve. The green dashed line represents the CVA-based MAPopt determined by the lowest cerebral oximetry index.

COx: cerebral oximetry index. MAP: mean arterial blood pressure. CVA-based MAPopt: cerebrovascular autoregulation based optimal MAP.

In the present study, the CVA-based MAPopt was calculated using the ICM+ software based on the second-order polynomial formula theory. The filtered MAP values were allocated to the X-axis in bins of 2 mmHg intervals. The COx was categorized and averaged for each MAP bin. Any bin containing below 1% of the total data was eliminated from the analysis.

A U-shaped curve was then formed to fit all the data as closely as possible based on the coordinates with the MAP as the X-axis and COx as the Y-axis. The MAP at the lowest point of this parabolic curve was considered the CVA-based MAPopt for this measurement, since at

this level, the MAP indicated the lowest correlation with the rSO_2. One intraoperative and one postoperative CVA-based MAPopt value were calculated for each patient if the data were suitable to draw a curve. The U-shaped curve is shown in Figure 4.

Figure 4. The U-shape curve calculated by the ICM+ software

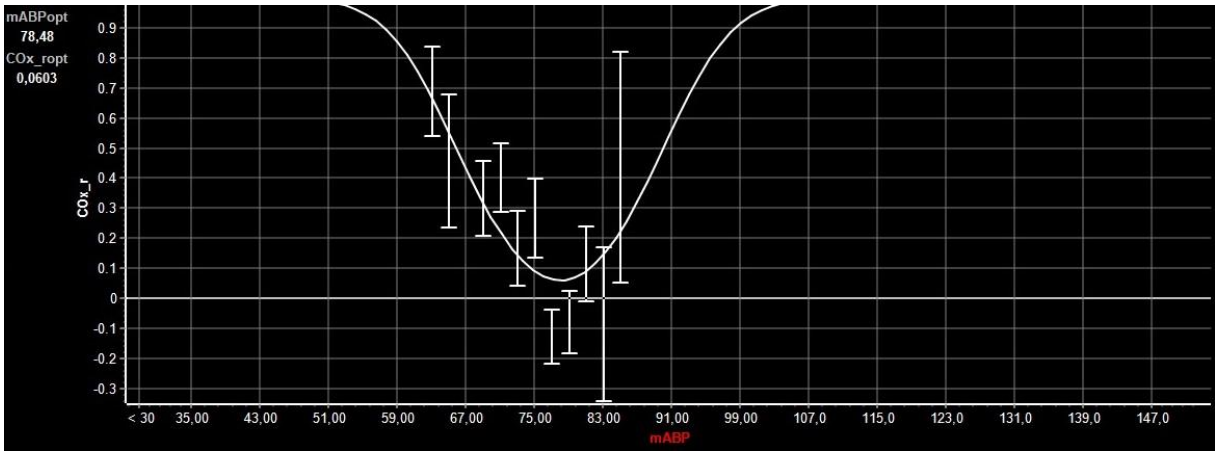

Figure 4. The U-shape curve was calculated from one of our patients (Patient No. 008). The COx is shown on the Y-axis, MAP is shown on the X-axis. The vertical bars represent the 25th – 75th quartile values of COx in each MAP bin and the U-shape curve was made to fit most of the values. The CVA-based MAPopt pressure was 78.48 mmHg in this case.

COx: cerebral oximetry index. MAP: mean arterial blood pressure. CVA-based MAPopt: cerebrovascular autoregulation based optimal MAP.

4.8 Time-weighted average MAP below the CVA-based MAPopt

The TWA-MAP below the CVA-based MAPopt was defined as the area between the MAP curve and the threshold of the CVA-based MAPopt (Figure 5). The area size corresponds to the magnitude and duration of hypotension below the CVA-based MAPopt. A greater severity and longer duration of hypotension lead to a larger area size, namely a greater TWA-MAP below the CVA-based MAPopt.

The TWA-MAP below the CVA-based MAPopt was calculated as the total sum of the irregular enclosed areas divided by the entire measurement time. Each irregular area could in turn be divided into the sum of the areas of several trapezoids. The lengths of the two bottom edges of the trapezoid were the difference between the CVA-based MAPopt and the two adjacent MAP values, respectively (Maheshwari et al. 2018). Since the recording time interval was 1 minute, the height of the trapezoid was documented as 1. Therefore, the area of the trapezoid was calculated based on the formula,

4. Materials and methods

$$\text{Trapezoid area} = \frac{(a+b)\times h}{2},$$

and the irregular area is presented as the sum of the trapezoids inside:

$$\text{Irregular area} = \sum_{i=1}^{i=k} (Trapezoid\ 1 + Trapezoid\ 2 + \cdots + Trapezoid\ k)$$

The TWA-MAP below the CVA-based MAPopt is expressed as the formula below:

$$\text{TWA-MAP below the CVA-based MAPopt} = \frac{\sum_{i=1}^{i=k} (Area\ 1 + Area\ 2 + \ldots + Area\ k)}{Entire\ measurement\ time}$$

Each patient had two TWA-MAPs below the CVA-based MAPopt values if the corresponding CVA-based MAPopt values could be extracted from the ICM+ software.

Figure 5. The visualization of how to calculate TWA-MAP below CVA-based MAPopt

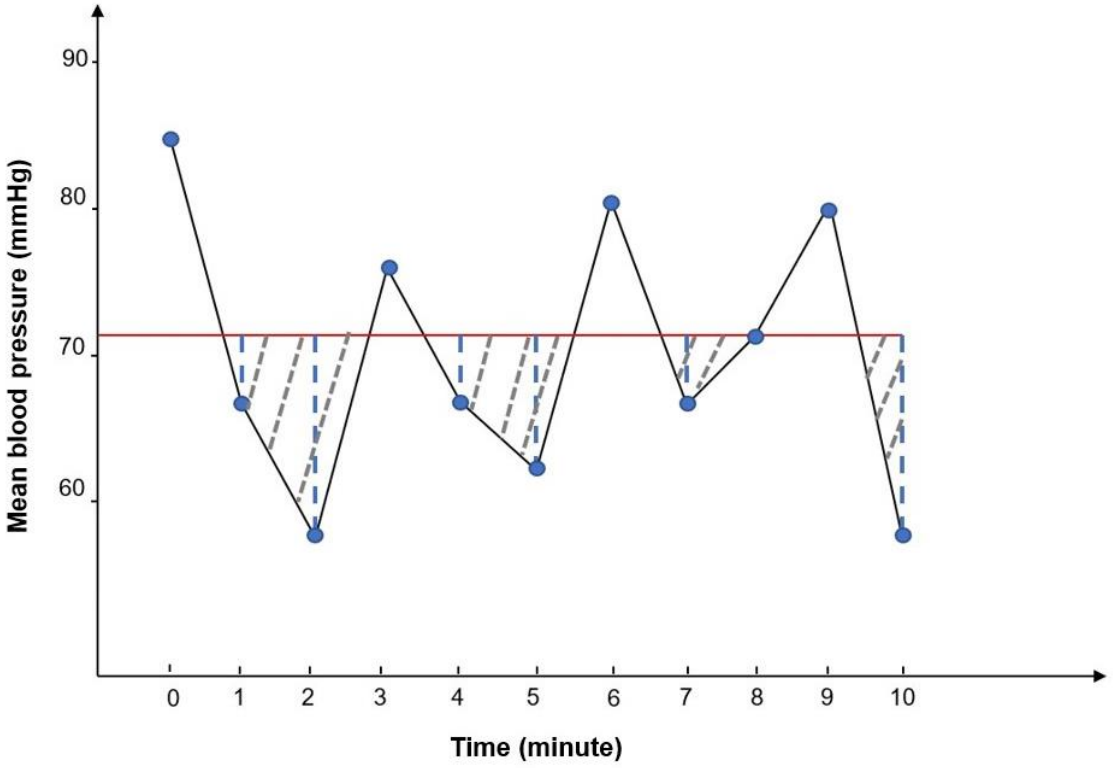

Figure 6. The blue solid dots represent the MAP values recorded every minute of one of our study patients (n=1). The red line represents the MAPopt of this patient. The shadow areas represented the TWA-MAP below CVA-based MAPopt. The vertical blue dashed lines separate the areas into several triangles and trapezoids.

TWA-MAP below CVA-based MAPopt: Time-weighted average mean arterial blood pressure below cerebrovascular autoregulation based optimal mean arterial blood pressure. MAP: mean arterial blood pressure.

4.9 Power calculation

The analysis of the present sub-study was performed after the consecutive inclusion of 201 patients in the main study. Of these patients, 161 could be included in the analysis of the sub-study. We performed a post-hoc power analysis based on a comparable study by Hori et al.(Hori, Max, et al. 2016). The inclusion of 161 patients resulted in a power of 99% to detect a difference in an intraoperative MAP of 5 ± 10.7 mmHg, considering a type I error of 5%.

4.10 Statistical analysis

All analyses were performed with SPSS Version 24 (IBM SPSS Statistics, IBM Corporation). The tables and plots were depicted with SPSS Version 24, Microsoft Excel or R Version 3.5.1 (The R Foundation).

Means and standard deviations were used to report continuous variables. Absolute numbers and percentages were used to represent categorical descriptive variables. Continuous statistics were analyzed for their normality of distribution with Q-Q plots, and the homogeneity of variances was determined with Levene's test. A comparison between normally distributed continuous variables was performed with a Student's t-test, while a comparison between non-normally distributed continuous variables was performed using the Wilcoxon signed-rank test for matched samples.

Two multivariable general linear models were constructed to determine factors associated with the TWA-MAP below the CVA-based MAPopt, with the intraoperative and postoperative TWA-MAPs below the CVA-based MAPopt as the dependent variables. Both the intraoperative and postoperative TWA-MAPs below the CVA-based MAPopt were transformed using a logarithmic function to ensure a normal distribution. We included variables that were considered clinically relevant, such as age, body mass index, Charlson comorbidity index (CCI), sex, American Society of Anesthesiologists (ASA) physical status classification, hypertension, type of surgery, sevoflurane for anaesthesia maintenance, duration of surgery, change in the haemoglobin before and after surgery, and the dose of noradrenaline as the independent variables, which were fixed effects in the model. The models were reduced following a backwards stepwise approach: In each step, the variable with the highest p-value was excluded from the model. The model reduction was continued until only variables with p-values below 0.05 remained. The normal distribution of the residuals was tested; p-values < 0.05 were considered statistically significant in this study.

5. Results

5.1 Study population

From August 09, 2021, to May 27, 2022, 544 patients scheduled for non-cardiac surgery were screened for study inclusion. Of these 544 patients, 334 were found ineligible for study participation. Of the remaining 210 patients, 19 did not complete the measurement. In total, 191 patients were included in this study, and data were extracted from intraoperative and postoperative measurements. Of the 191 patients who received study-related CVA measurements, the data could not be analyzed in 30 cases. In conclusion, data from 161 patients were included in the final analysis of the present sub-study. The flow chart in Figure 6 shows the entire procedures in which the patients were enrolled in this study.

Figure 6. The flow chart of study participants

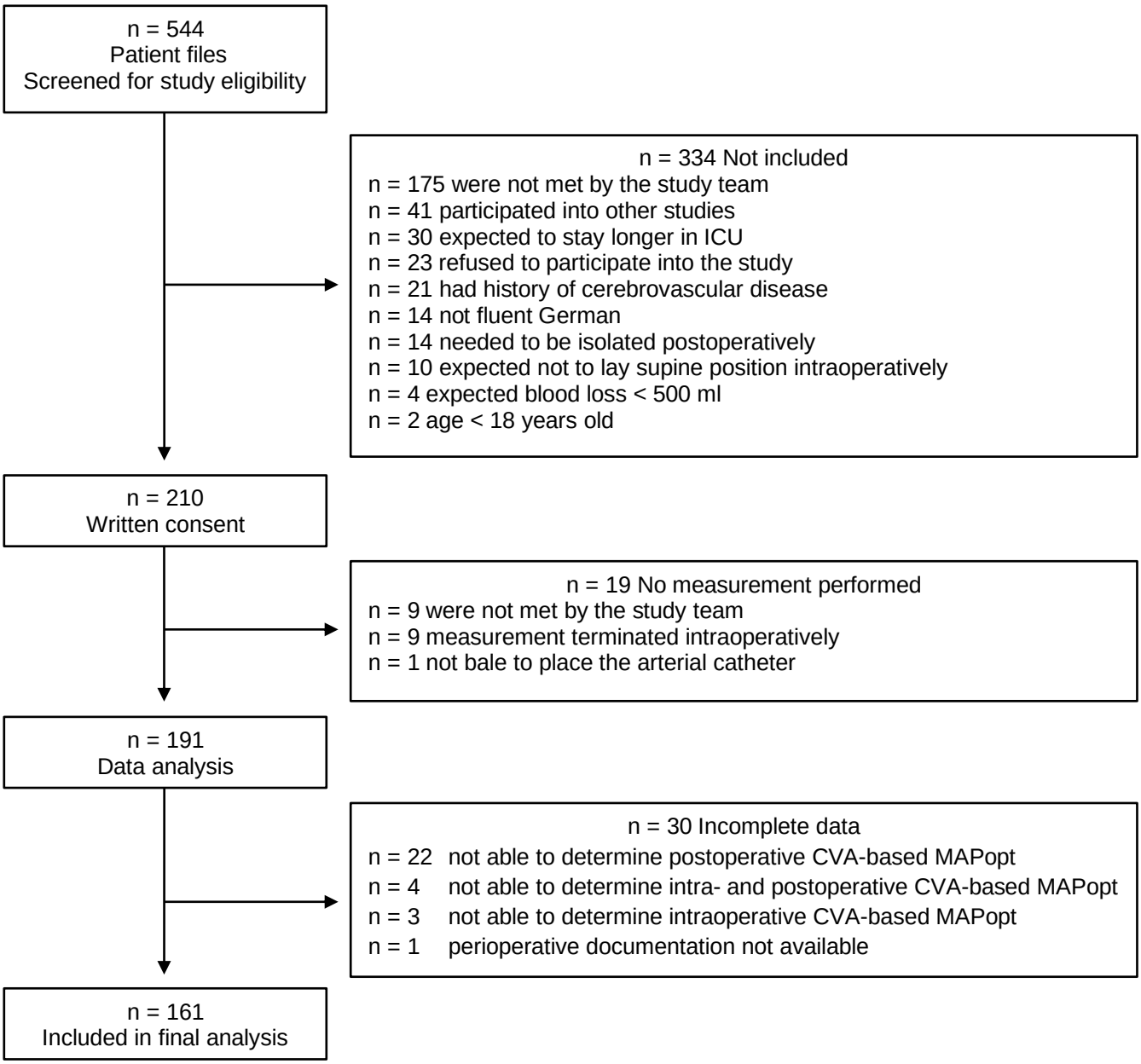

Figure 7. Flow of Identification and inclusion study participants throughout the study.
ICU: Intensive care unit. CVA-based MAPopt: Cerebrovascular autoregulation based optimal mean arterial blood pressure

5.2 Baseline characteristics

The mean age of the patients in this study was 65 ± 10 years. Male patients (87.6%) accounted for the majority. Half of the study population (50.3%) had a preoperative history of hypertension. Two-thirds of the study population (65.8%) had mild systemic disease and one-third (33.5%) had severe systemic disease, according to the ASA classification. The average CCI score was 3 ± 1. Details of medical and medication histories are presented in Table 1.

Table 1. Baseline characteristics of study participants

	n=161
Age (years)	65 ± 10
Sex	
Male	141 (87.6%)
Female	20 (12.4%)
BMI	26.7 ± 3.9
ASA physical status classification	
I	1 (0.6%)
II	106 (65.8%)
III	54 (33.6 %)
Pre-existing medication	
ACE inhibitor	37 (23%)
AT1 receptor antagonist	35 (21.7%)
Beta blocker	33 (20.5%)
Other antihypertensive drugs	31 (19.3%)
Thiazide diuretic	14 (8.7%)
Loop diuretics	5 (3.1%)
Aldosterone antagonist	4 (2.5%)
Medical history	
Hypertension	81 (50.3%)
Myocardial infarction	21 (13%)
Heart failure	6 (3.7%)
Peripheral vascular disease	5 (3.1%)
Pulmonary disease	21 (13%)
Ulcer disease	5 (3.1%)
Liver disease	5 (3.1%)
Diabetes mellitus*	23 (14.4%)
Moderate to severe CKD	3 (1.9%)
Solid tumor	153 (95%)
Lymphoma	3 (1.9%)
CCI without age	3 ± 1

Table 1. Data are presented as mean ± SD or n (%).

* : There is 1 missing data in this variable. SD: standard deviation; BMI: Body mass index; CCI: Charlson Comorbidity Index; pAOD: peripheral artery occlusive disease; OSAS: obstructive sleep apnea syndrome; ASA classification: American Society of Anaesthesiologists Classification; Continuous variables were represented as Mean ± SD while categorical variables were represented as Number (%).

5.3 Perioperative parameters

The majority of surgeries were open laparotomies (96.3%). The most common type of surgery was open retropubic prostatectomy (74.5%). The mean blood loss was 760 ± 496 ml, and the change in haemoglobin was 3 ± 1.2 (Table 2). Detailed perioperative parameters are documented in Table 2.

Table 2. Perioperative parameters of study patients

	n=161
Surgery	
Duration of surgery (min)	197 ± 85
Blood loss (ml)	760 ± 496
△haemoglobin (g/dL)	3 ± 1.2
Preoperative haemoglobin (g/dL)	14.2 ± 1.5
Postoperative haemoglobin (g/dL)	11.2 ± 1.5
Surgical specialty	
Prostatectomy	120 (74.5%)
General surgery	20 (12.4%)
Urology (other than prostatectomy)	13 (8.1%)
Gynaecology	8 (5%)
Laparoscopic surgery	6 (3.7%)
Anaesthesia	
Premedication with benzodiazepines	1 (0.6%)
Intraoperative medication	
Sevoflurane	124 (77%)
Remifentanil	11 (6.8%)
Sufentanil, cumulative (µg)	90 ± 22
Clonidine (mg)	3 ± 18
Noradrenaline (µg/kg/min)*	0.2 ± 0.12
Colloids (ml)	311 ± 562
Crystalloids (ml)	2799 ± 984
Total fluid intake (ml)	3413 ± 1678
Blood transfusion (number of RBCC)	
0	152 (94.4%)
1 - 3	6 (3.7%)
>3	3 (1.9%)
Postoperative medication	
Pethidine, cumulative (mg)	15.2 ± 15.4
Piritramide, cumulative (mg)	4.24 ± 4.32
Peridural anaesthesia	28 (17.4%)
Postoperative management	
ICU/IMC planned	33 (20.5%)
ICU/IMC unplanned	1 (0.6%)
Normal wards	127 (78.9%)
Length of hospital stay (days)	8 ± 10

Table 2. Data are presented in mean ± SD or n (%).*highest rate during surgery. RBCC: Red blood cell concentrate. △haemoglobin: Change of haemoglobin from before to after surgery. ICU: Intensive care unit. IMC: Intermediate care unit.

5.4 Comparison of intraoperative and postoperative CVA-based MAPopt

The median for the intraoperative CVA-based MAPopt was 77.85 (IQR: 72.78, 84.13) mmHg, while the median for the postoperative CVA-based MAPopt was 85.10 (IQR: 77.91, 95.06) mmHg (Figure 7). The results show a statistically significant difference between intraoperative and postoperative CVA-based MAPopt values ($p < 0.001$).

Figure 7. Comparison of intraoperative and postoperative CVA-based MAPopt

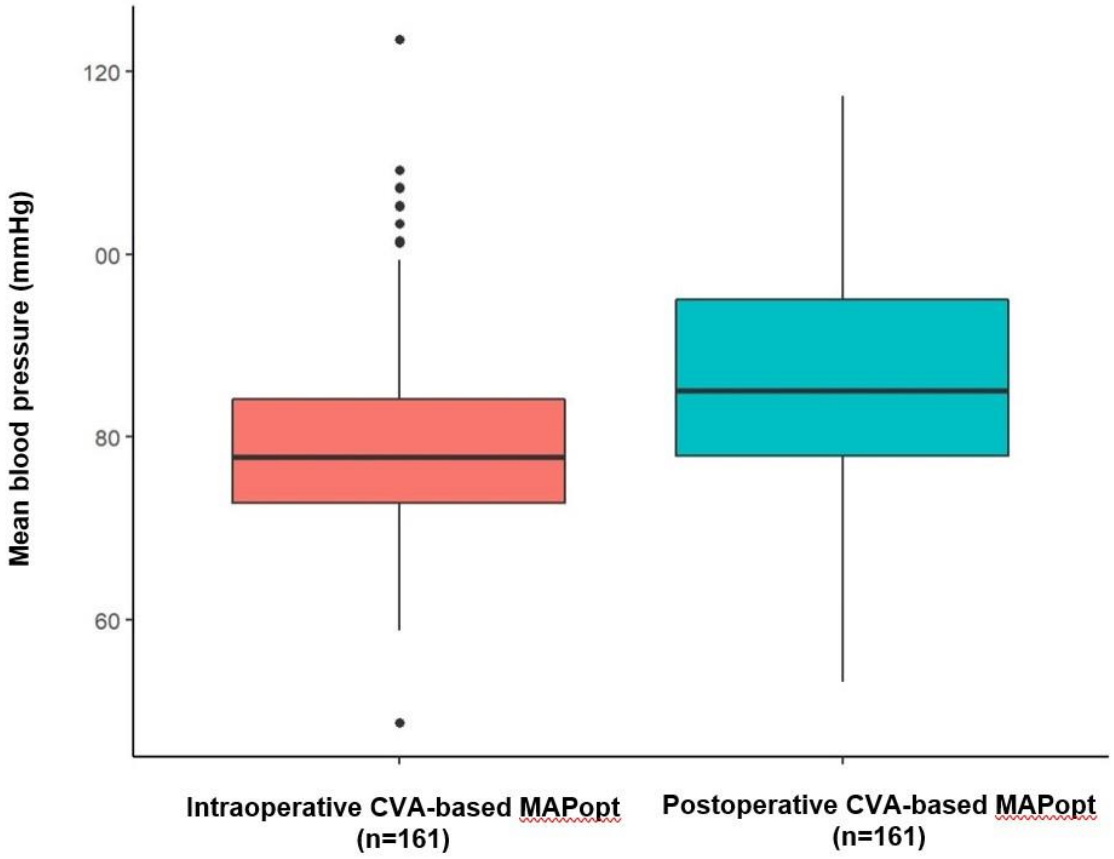

Figure 7. The upper border line of the box represents the 75th quantile. The middle line in the box represents the median. The lower border line of the box represents the 25th quantile. The upper and lower vertical bars represents the upper and lower whiskers. The bigger points mark the outliers.

Intraoperative CVA-based MAPopt: Intraoperative cerebrovascular autoregulation based optimal mean arterial blood pressure; Postoperative CVA-based MAPopt: Postoperative cerebrovascular autoregulation based optimal mean arterial blood pressure.

5.5 Comparison between intraoperative and postoperative TWA-MAP below CVA-based MAPopt

The median intraoperative TWA-MAP below the CVA-based MAPopt was 2.59 (IQR: 0.93, 5.41) mmHg. The median postoperative TWA-MAP below the CVA-based MAPopt was 4.26 (IQR: 1.06, 8.73) mmHg (Figure 8). The results show that the difference between the mean intra- and postoperative TWA-MAPs below the CVA-based MAPopt was not statistically significant (p = 0.118).

Figure 8. Comparison of intraoperative and postoperative TWA-MAP below CVA-based MAPopt.

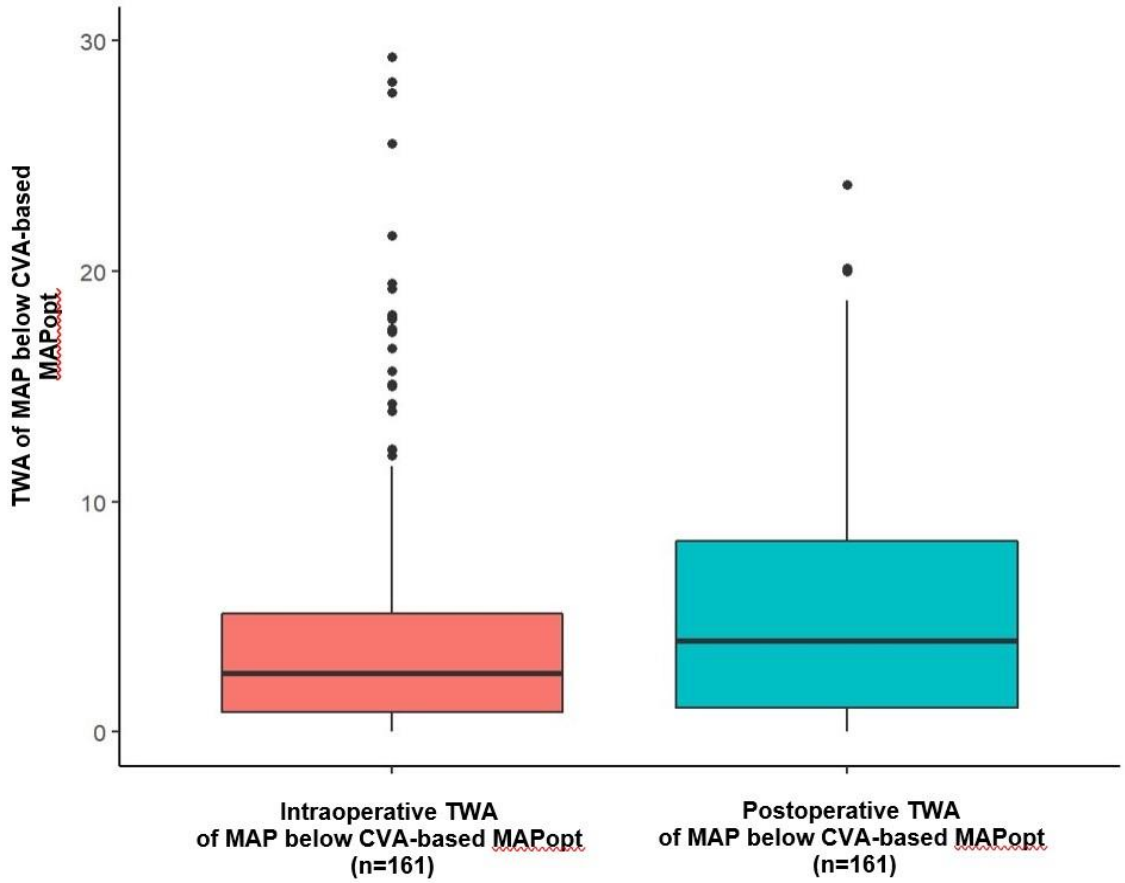

Figure 8. The upper border line of the box represents the 75th quantile. The middle line in the box represents the median. The lower border line of the box represents the 25th quantile. The upper and lower vertical bars represents the upper and lower whiskers. The bigger points marked the outliers. The limit of y axis was set as 30 in order to fit the intuition. Outliers above 30 were not shown in this figure.

TWA-MAP below CVA-based MAPopt: Intraoperative time-weighted average mean arterial blood pressure below cerebrovascular autoregulation based optimal mean arterial blood pressure.

5.6 Factors associated with intraoperative TWA-MAP below CVA-based MAPopt

Table 3 displays the results of the initial multivariable model investigating the factors associated with the intraoperative TWA-MAP below the CVA-based MAPopt before stepwise backwards reduction.

Sevoflurane for anaesthesia maintenance was the only variable significantly associated with the intraoperative TWA-MAP below the CVA-based MAPopt.

Table 3. Results of the initial multivariable general linear models of intraoperative TWA-MAP below CVA-based MAPopt

Parameter	B	95% CI low	95% CI up	P
Intercept	0.730	-2.416	3.875	0.647
Age	-0.005	-0.030	0.021	0.714
CCI	-0.177	-0.381	0.027	0.089
Sex (Male vs. Female)	0.511	-0.426	1.448	0.283
ASA physical status (1 and 2 vs. 3)	-0.508	-1.089	0.073	0.086
Hypertension (No hypertension vs. hypertension)	-0.169	-0.677	0.338	0.511
Type of surgery (No prostatectomy vs. prostatectomy)	0.756	-0.178	1.690	0.112
Sevoflurane (No sevoflurane vs. sevoflurane)	0.958	0.389	1.527	0.001*
BMI (kg/m^2)	0.005	-0.060	0.071	0.873
Duration of surgery (min)	0.001	-0.003	0.005	0.603
△haemoglobin (g/dL)	0.106	-0.088	0.300	0.281
Noradrenaline (µg/kg/min)	-1.335	-3.513	0.843	0.228

Table 3. Results of the initial multivariable general linear models of intraoperative TWA-MAP below CVA-based MAPopt.

* : statistical significance (P < 0.05); CCI: Charlson Comorbidity Index; BMI: Body mass index; ASA: American Society of Anaesthesiologists Classification; △haemoglobin: The change of the haemoglobin before and after surgeries; TWA-MAP below CVA-based MAPopt: time-weighted average mean arterial blood pressure below cerebrovascular autoregulation based optimal mean arterial blood pressure; B: Regression coefficient; CI: Confidence interval.

5. Results

Table 4 displays the results of the reduced multivariable model investigating factors associated with the intraoperative TWA-MAP below the CVA-based MAPopt after model reduction. Sevoflurane versus propofol for anaesthesia maintenance and the type of surgery remained in the final model as the only variables significantly associated with the intraoperative TWA-MAP below the CVA-based MAPopt. Propofol for anaesthesia maintenance was associated with a larger TWA-MAP below the CVA-based MAPopt than sevoflurane. Additionally, non-prostatectomy surgeries were associated with a larger intraoperative TWA-MAP below the CVA-based MAPopt than prostatectomy.

Table 4. Results of reduced multivariable general linear models of intraoperative TWA-MAP below CVA-based MAPopt

Parameter	B	95% CI - low	95% CI - up	P
Intercept	0.446	0.151	0.741	0.003*
Type of surgery (No prostatectomy vs. prostatectomy)	0.571	0.053	1.089	0.031*
Sevoflurane (No sevoflurane vs. sevoflurane)	0.921	0.384	1.457	0.001*

Table 4 Results of reduced multivariable general linear models of intraoperative TWA-MAP below CVA-based MAPopt.

* : statistical significance (P < 0.05); TWA-MAP below CVA-based MAPopt: time-weighted average mean arterial blood pressure below cerebrovascular autoregulation based optimal mean arterial blood pressure; B: Regression coefficient; CI: Confidence interval.

5. Results

Table 5 displays the results of the initial multivariable model investigating factors associated with the postoperative TWA-MAP below the CVA-based MAPopt before model reduction.
Unlike the intraoperative TWA-MAP below the CVA-based MAPopt model, the statistical significance of the postoperative corrected model exceeded 0.05. The model revealed no variables significantly associated with the postoperative TWA-MAP below the CVA-based MAPopt.

Table 5. Results of the initial multivariable general linear models of postoperative TWA-MAP below CVA-based MAPopt

Parameter	B	95% CI - low	95% CI - up	P
Intercept	2.114	-1.499	5.728	0.647
Age	-0.011	-0.041	0.018	0.714
CCI without Age	0.093	-0.141	0.327	0.089
Gender (Male vs. Female)	0.503	-0.574	1.579	0.283
ASA (ASA 1 and 2 vs. ASA 3)	0.415	-1.089	-0.252	1.083
Hypertension (No hypertension vs. hypertension)	-0.435	-0.677	-1.017	0.148
Type of surgery (No prostatectomy vs. prostatectomy)	0.470	-0.178	-0.603	1.543
Sevoflurane (No sevoflurane vs. sevoflurane)	-0.039	0.389	-0.533	0.775
BMI	-0.002	-0.060	-0.114	0.036
Duration surgery (min)	0.067	-0.003	-0.007	0.002
△haemoglobin (g/dL)	-0.008	-0.088	-0.156	0.289
Noradrenalin (µg/kg/min)	-0.039	-3.513	-2.510	2.494

Table 5. Results of the initial multivariable general linear models of postoperative TWA-MAP below CVA-based MAPopt: time-weighted average mean arterial blood pressure below cerebrovascular autoregulation based optimal mean arterial blood pressure; CCI: Charlson Comorbidity Index; BMI: Body mass index; ASA: American Society of Anaesthesiologists

Table 6 displays the results of the reduced multivariable model investigating factors associated with the postoperative TWA-MAP below the CVA-based MAPopt after model reduction.
The reduced model revealed no variables significantly associated with the postoperative TWA-MAP below the CVA-based MAPopt.

Table 6. Results of reduced multivariable general linear models of postoperative TWA-MAP below CVA-based MAPopt

Parameter	B	95% CI - low	95% CI - up	P
Intercept	1.143	0.787	1.499	0.000
Hypertension (No hypertension vs. hypertension)	-0.352	-0.856	0.153	0.171

Table 6. Results of reduced multivariable general linear models of postoperative TWA-MAP below CVA-based MAPopt. B: Regression coefficient; CI: Confidence interval.

6. Discussion

6.1. Summary

This prospective cohort study showed that 1) the intraoperative MAPopt from this study popuation was significantly lower than the postoperative MAPopt. 2) No statistically significant difference was found between the TWA-MAP below the intraoperative MAPopt and the TWA-MAP below the postoperative MAPopt. 3) The type of medications used for anaesthesia maintenance and the type of surgery were associated with a TWA-MAP below the intraoperative MAPopt. 4) None of the investigated variables was associated with a TWA-MAP below the postoperative MAPopt.

6.2. Individualized versus non-individualized MAP

Maintaining intraoperative blood pressure, especially preventing intraoperative hypotension, is a major concern for clinical practitioners. However, in seeking optimal blood pressure thresholds, researchers struggle to meet the contending claims of clinical practicability and individualized treatment.

6.2.1. Non-individualized MAP

Regarding a practical approach, a consensus was reached that an intraoperative MAP below 65 mmHg is regarded as an intervention threshold (Sessler et al. 2019). Multiple studies have shown an association between an intraoperative MAP below 65 mmHg and adverse outcomes (Salmasi et al. 2017; Walsh et al. 2013).

A clear relationship between intraoperative hypotension and postoperative acute kidney injury (AKI) or myocardial injury has been confirmed (Salmasi et al. 2017; Walsh et al. 2013). The retrospective cohort study from Salmasi et al. indicated that controlling the intraoperative MAP above 65 mmHg significantly reduced the incidence of postoperative AKI and myocardial injury (Salmasi et al. 2017). Similar to this conclusion, Walsh et al. revealed that even short exposure to an intraoperative MAP below 55 mmHg greatly increased the risk of developing postoperative AKI and myocardial injury, and this risk was positively correlated with the exposure time (Walsh et al. 2013). Interestingly, one randomized controlled trial (RCT) did not support the conclusion that targeting a higher intraoperative MAP on non-cardiac surgical patients (MAP ≥ 75 mmHg) could improve the postoperative adverse events including 30-day AKI incidence compared with the controlled group (MAP ≥ 65 mmHg) (Wanner et al. 2021).

A more recent multicentre retrospective cohort study illustrated the association of intraoperative hypotension and adverse postoperative cardiac and cerebrovascular outcomes when stratifying the intraoperative hypotension into different levels (≤75, ≤65, ≤55 mmHg).

Simultaneously, this study emphasized the relationship between the magnitude of hypotension and the likelihood of adverse events, concluding that no evident safe period for hypotension existed (Gregory et al. 2021). Wesselink et al. indicated the association between organ injury and MAP < 80 mmHg for over 10 minutes (Wesselink et al. 2018). This threshold is much higher than the commonly accepted “safe” intraoperative MAP thresholds, indicating that managing intraoperative MAPs for all the patients with established thresholds may be insufficient.

However, whether intraoperative hypotension contributes to the development of postoperative cognitive dysfunction remains elusive. One RCT performed on cardiopulmonary bypass patients found a favourable outcome regarding postoperative cognitive function in the high MAP group (80–90 mmHg) compared to the low MAP group (60–70 mmHg) (Siepe et al. 2011). However, a recent systematic review and meta-analysis on this topic showed no significant correlation between intraoperative hypotension and postoperative cognitive dysfunction (van Zuylen et al. 2021; Feng et al. 2020). Notably, the huge methodological variety of included studies was also mentioned in the systematic review (van Zuylen et al. 2021). First, postoperative cognitive functions were tested in different ways, from mini-mental state examination to electroencephalograms (Yao et al. 2006; Deiner et al. 2015). Second, the timing of the screening for postoperative cognitive functions varied from 7 days to 1 month (Kim et al. 2016; Evered et al. 2018). Third, the definition of hypotension differed between studies (van Zuylen et al. 2021). All these factors contributed to the methodological heterogeneity. In summary, it is plausible to link intraoperative hypotension with postoperative cognitive disorders, however, more concrete evidence from RCTs regarding the relationship between intraoperative hypotension and postoperative cognitive dysfunction is needed.

6.2.2. Individualized MAP

Although setting the pathological MAP threshold to 65 mmHg is both highly feasible in clinical practice and reasonable regarding adverse outcomes, it is evident that this threshold might be inadequate for many patients. For example, patients with chronic hypertension appear to require higher blood pressure to guarantee adequate organ perfusion (Song, Li, and Jiang 2022). It is thus generally accepted that for patients with chronic hypertension, the lower limit of the intraoperative MAP should be raised to adapt the altered blood flow autoregulation mechanisms in different organs (Song, Li, and Jiang 2022). Different methods are applied to determine individual blood pressure thresholds. One approach is to consider preoperative blood pressure.

An RCT showed that controlling the intraoperative SAP within 10% of preoperative resting values could improve postoperative outcomes compared to the standard management (Futier et al. 2017). Another RCT was performed by Langer et al. on 101 elderly patients who

underwent non-cardiac surgery. Qualifying patients were allocated to a target group (intraoperative MAP of each patient exceeding 90% of their own preoperative MAP) and a usual care group (intraoperative MAP managed based on the routine practice). The results showed no association between postoperative hypotension and postoperative cognitive dysfunction or delirium (Langer et al. 2019). It is noteworthy that the intraoperative MAP of patients in the usual care group in this study was relatively high (85 ± 11 mmHg) compared to the target group (92 ± 9 mmHg) and compared with recommended blood pressure targets. Thus, the intraoperative MAP in the usual care group may not have been sufficiently low to entail an adverse outcome.

However, using preoperative blood pressures is not always feasible in the perioperative setting. First, no established definition of preoperative blood pressure exists that can be used as the baseline blood pressure. These preoperative blood pressures were either measured shortly before the induction of general anaesthesia or measured at varying time points before surgery (Bijker et al. 2007). A recent study found a weak correlation between preinduction MAP and daytime MAP assessed with repeated ambulatory blood pressure measurements, suggesting preinduction MAP was not an ideal surrogate for preoperative blood pressures (Saugel et al. 2019). Second, blood pressure is affected by multiple factors, such as stress, medication, and environment. Measuring blood pressure at different time points may give different results, obscuring the true preoperative blood pressures (James and Pickering 1993). Furthermore, manual blood pressure measurement can be inaccurate in practice, leading to false preoperative blood pressures (Handler 2009).

In addition to the difficult assessment of preoperative blood pressures, it must be acknowledged that blood pressure thresholds may not only vary between individuals. Indeed, according to the individual's specific situation, different blood pressure thresholds may relate to optimal organ perfusion. For example, the MAPopt required for the same patient is evidently different during exercise and resting states (W. B. White, Lund-Johansen, and Omvik 1990). To meet the oxygen consumption for exercise, the body raises blood pressure through the autonomic nervous system (Guyton 1961). During surgery and anaesthesia, the neuronal activity is reduced (Hudetz 2012). The depression of cerebral metabolic activity during general anaesthesia has been identified by downgrading the signal transmission in different parts of the brain (Cavazzuti et al. 1991; Vutskits and Xie 2016). The CBF needed to deliver oxygen and nutrition to the brain may thereby differ between anaesthesia and the awake state.

Optimizing the intraoperative MAP by assessing cardiac output is another way to achieve an individual BP management goal. Fluid responsiveness and other haemodynamic indicators are used to evaluate the cardiac output and oxygen delivery, guiding clinicians to optimize the MAP accordingly (Saugel, Vincent, and Wagner 2017). This theory was supported by a study which found that patients with higher cardiac output were more likely to survive high-risk

surgeries (Shoemaker et al. 1982).

Besides the methods described above, assessing the CVA-based MAPopt may be an elegant way of considering these inter- and intra-individual variations in blood pressure thresholds. With this approach, it is possible to assess the MAP needed for optimal autoregulation (CVA-based MAPopt) as well as whether the actual MAP differs from the CVA-based MAPopt. Intraoperative CVA-based MAPopt-guided blood pressure management is feasible and has been performed in research settings (Brown et al. 2019).

6.3. Intraoperative CVA-based MAPopt

In the present study, we determined individualized intraoperative and postoperative MAPopt values based on the CVA concept. We assumed that the MAPopt was the MAP which enabled the highest autoregulatory capacity, that is, when the COx was closest to 0. We aimed to assess whether the individual CVA-based MAPopt differs between the intra- and postoperative periods. The median intraoperative CVA-based MAPopt in this study sample was 77.85 (IQR: 72.78, 84.13) mmHg. The large MAP distribution reveals the vast individual variety in intraoperative CVA-based MAPopt, confirming that individually oriented blood pressure management is critical for anaesthesiologists during surgery (Sessler et al. 2019). This result is consistent with previous studies. Hori et al. applied ultrasound-tagged NIRS to determine the CVA-based MAPopt intraoperatively in cardiac surgery patients, aiming to associate postoperative AKI with different MAP levels. The intraoperative CVA-based MAPopt in this study sample was 71 mmHg (Hori, Hogue, et al. 2016). The difference between this study and ours may be explained by the sampling error and patient enrolment, since our study investigated the intraoperative CVA-based MAPopt on non-cardiac surgery patients.

While a few studies have used CVA to investigate optimal intraoperative blood pressure, our results appear comparable to previous studies investigating the association between predefined MAP thresholds and adverse outcomes.

An RCT conducted by Gold et al. showed that patients who received cardiopulmonary bypass at higher MAP (80–100 mmHg) had a significantly lower incidence of postoperative cardiac and neurological complications than those in the lower MAP group (50–60 mmHg) (Gold et al. 1995). Another RCT indicated that maintaining a higher MAP ranging from 80–90 mmHg was associated with a favourable postoperative cognitive function, confirming the opinions of Gold in the previous study (Siepe et al. 2011). Wu et al. found that patients whose intraoperative MAP was controlled between 80–95 mmHg presented the fewest incidences of postoperative AKI, hospital-acquired pneumonia, ICU admission, and prolonged length of hospital stay compared to the 65–79 mmHg and 96–110 mmHg groups (Wu et al. 2017).

The results from the above experiments indicate that an intraoperative MAP in the 80–100 mmHg range was the most favourable for surgical patients. Although none of these studies

used CVA to ascertain the optimal intraoperative MAP, and, conversely, we did not assess an association with adverse outcomes, the optimal intraoperative MAP range results of the above-mentioned studies were very close to our findings for the CVA-based MAPopt.

6.4. Postoperative CVA-based MAPopt

The median postoperative CVA-based MAPopt in this study sample was 85.10 (IQR: 77.91, 95.06) mmHg. It is more difficult to compare this finding to previous studies, since most studies did not directly determine the postoperative MAPopt or examine its prognostic impact.

6.5. Comparison between intra- and postoperative OP CVA-based MAPopt

In our study sample, the postoperative CVA-based MAPopt was significantly higher than the intraoperative CVA-based MAPopt. The above-mentioned study by Hori et al. found the postoperative CVA-based MAPopt to be 75 mmHg (Hori, Hogue, et al. 2016). This finding is comparable to ours, although the absolute values were slightly lower than our findings, the pattern of significantly higher postoperative MAP than intraoperative MAP (about 7%) was very close to our results.

The fact that CVA-based MAPopt is lower intraoperatively than postoperatively suggests that the brain can guarantee optimal CVA on a lower MAP during anaesthesia and surgery than postoperatively (Hori et al. 2017). It is plausible to assume that intraoperative anaesthetic agents, such as propofol and sevoflurane, reduce the neuronal activity and therefore result in a lower need for oxygen and nutrients. Studies have shown that propofol administration decreased the cerebral metabolism by 30%–70% in different parts of the brain (Alkire et al. 1995). More studies indicated the effects of global cerebral suppression in anaesthesia agents other than propofol and sevoflurane (Alkire et al. 1997; Veselis et al. 1997). Since the cerebral metabolism is coupled with the CBF, this resulted in a low intraoperative CBF demand (Claassen et al. 2021). Schlünzen et al. and Kaisti et al. investigated the change in blood flow and metabolism in distinct areas or in the entire brain by using positron emission tomography during anaesthesia. Both Schlünzen et al. and Kaisti et al. indicated that administering propofol significantly decreased the CBF and cerebral metabolism (Schlünzen et al. 2012; Kaisti et al. 2003). This may translate into a lower intraoperative CVA-based MAPopt compared to the postoperative CVA-based MAPopt, as we demonstrated in our study.

6.6. TWA-MAP below CVA-based MAPopt

The TWA-MAP below the CVA-based MAPopt reflects the extent to which the patients' MAP fell below their individual CVA-based MAPopt values. In the present study, we found a median intraoperative TWA-MAP below the CVA-based MAPopt of 2.59 (IQR: 0.93, 5.41) mmHg and a median postoperative TWA-MAP below the CVA-based MAPopt of 4.26 (IQR: 1.06, 8.73) mmHg.

Anaesthesiologists providing care for patients included in the present study adhered to the standard clinical procedure for perioperative blood pressure management, which targets a predefined MAP threshold of at least 65 mmHg. The calculated CVA-based MAPopt was higher than 65 mmHg both intra- and postoperatively.

Our study is comparable to the aforementioned study of Hori et al., who investigated the areas under curve (AUC) of the intraoperative MAP below the CVA-based MAPopt (Hori, Hogue, et al. 2016). The raw numbers of our studies are not directly comparable, since Hori et al. analyzed the AUC of the MAP below the CVA-based MAPopt, whereas we analyzed the TWA (AUC normalized to the measurement duration) of the MAP below the CVA-based MAPopt. Additionally, Hori et al. compared the AUC of the MAP below the CVA-based MAPopt between two cohorts (no postoperative AKI vs postoperative AKI), whereas in the present sub-study, we did not assess a postoperative outcome. However, Hori et al. found an association between a larger AUC of the MAP below the CVA-based MAPopt and the incidence of postoperative AKI, while simultaneously, they found no significant association between the AUC of the MAP below predefined MAP thresholds (i.e. 60, 70, 80 mmHg) and postoperative AKI (Hori, Hogue, et al. 2016). This finding suggests that the CVA-based MAPopt may be an appropriate approach to guide perioperative blood pressure management. Another study from this group investigated the relationship between surgical patients' MAP excursions from the CVA-based MAPopt and postoperative delirium. MAP excursions below or above the CVA-based MAPopt were defined as AUC < CVA-based MAPopt or AUC > CVA-based MAPopt. They concluded AUC > CVA-based MAPopt was associated with postoperative delirium on Day 2 (Hori, Max, et al. 2016).

To our knowledge, there is no such study applying the exact same method to explore TWA-MAP below the CVA-based MAPopt and thus, we cannot conclude if the results of our study show relatively small or large TWA-MAP below predefined thresholds to others. We suggest that more studies are needed to relate the clinical outcomes with the TWA-MAP below the CVA-based MAPopt.

6.7. Difference between intra- and postoperative TWA-MAP below CVA-based MAPopt

The difference between intra- and postoperative TWA-MAP below the CVA-based MAPopt was not statistically significant ($p = 0.118$).

This result is interesting. While the intra- and postoperative CVA-based MAPopt values differed significantly, the attending anaesthesiologists used a predefined minimal MAP target of 65 mmHg in both settings. Still, the TWA-MAP below the CVA-based MAPopt did not differ significantly. A possible explanation may be that anaesthetic medication causes both peripheral vasodilation, resulting in lower MAP, and reduced neuronal activity, which may result in a lower CVA-based MAPopt (Hudetz 2012; McKeage and Perry 2003). After the effects of the anaesthetic medication subside, both the MAP and CVA-based MAPopt may return to higher levels (McKeage and Perry 2003; Behne, Wilke, and Harder 1999).

This finding suggests that although intra- and postoperative blood pressure management differ, they do not differ regarding their effects on the TWA-MAP below the CVA-based MAPopt. Assuming that a low TWA-MAP below the CVA-based MAPopt reflects appropriate blood pressure, we conclude that neither method of blood pressure management placed the patients in an overall disadvantageous situation.

We found no studies comparing intraoperative and postoperative TWA-MAPs below the CVA-based MAPopt.

6.8. Factors with potential influence on TWA-MAP below intraoperative CVA-based MAPopt

To explore the factors' potential effect on the intraoperative TWA-MAP below MAPopt, we investigated the association with clinically relevant variables. We found that the type of surgery and the type of anaesthetic for anaesthesia maintenance were associated with the intraoperative TWA-MAP below MAPopt. Specifically, surgeries other than prostatectomy and the use of propofol for intraoperative maintenance were associated with a greater TWA-MAP below MAPopt.

Since no studies have specifically investigated the TWA-MAP below the CVA-based MAPopt, we compare our results to studies that have investigated factors influencing intraoperative and postoperative MAP instead of focusing the values themselves. Administering anaesthetic agents during the maintenance phase can decrease the intraoperative MAP, and this effect differs depending on the specific agents.

In the present study, the attending anaesthesiologists used either propofol or sevoflurane for anaesthesia maintenance. Propofol is an intravenous anaesthetic agent acting as a positive allosteric modulator on $GABA_A$ receptors, which facilitates the transmission of GABA (γ-

aminobutyric acid) between synapses and thereby promotes sedation and sleep (Brohan and Goudra 2017; Shaye et al. 2021). Sevoflurane is a volatile anaesthetic agent administered by inhalation. By decreasing the signal correlation between different parts of the brain, sevoflurane breaks down the connectivity with increasing concentrations (Palanca, Avidan, and Mashour 2017).

Propofol results in intraoperative hypotension by attenuating the sympathetic nervous system as well as the baroreflex regulatory mechanism (T. J. Ebert et al. 1992). Other mechanisms involve endogenous vasoactive factors (Tsikas, Jordan, and Engeli 2015). Propofol has been shown to decrease the SAP by up to 30% (Hilton, Dev, and Major 1986). Administering sevoflurane also induces a decrease in the MAP. This can be explained by the reduced cardiac output and decreased peripheral resistance (Thomas J. Ebert, Harkin, and Muzi 1995). Similar to other volatile anaesthesia agents, sevoflurane presents a dose-dependent tendency to decrease the MAP but is weaker than isoflurane and desflurane (Thomas J. Ebert, Harkin, and Muzi 1995). Although both anaesthetic agents reduce the MAP, the effect of propofol appears stronger than that of sevoflurane (Bharti, Chari, and Kumar 2012; Husedzinović et al. 2003). Bharti et al. compared the effects of propofol and sevoflurane on the haemodynamic response during microlaryngeal surgery. They found a more severe decrease in MAP in the propofol group (16 ± 9 mmHg) than in the sevoflurane group (12 ± 7 mmHg; $p < 0.05$). Notably, eight patients in the propofol groups experienced intraoperative hypotension compared to only two patients in the sevoflurane groups (Bharti, Chari, and Kumar 2012). Similar results were obtained by Husedzinović et al. when they investigated the haemodynamic change caused by propofol and sevoflurane in myocardial contractility patients. They found that propofol depressed the cardiac output more severely than sevoflurane and concluded that sevoflurane maintained better haemodynamic stability during surgeries (Husedzinović et al. 2003). In our study, either propofol or sevoflurane was used as the intraoperative agent for anaesthesia maintenance. Our results showed that using propofol as the anaesthetic agent for anaesthesia maintenance was associated with a larger TWA-MAP below MAPopt, consistent with the results of Bharti and other studies who showed that compared to sevoflurane, using propofol alone may decrease the intraoperative MAP more severely(Bharti, Chari, and Kumar 2012).

In the present sub-study, most of our patients underwent open prostatectomy in the supine position, performed at a highly specialized prostate cancer centre. All other surgeries were performed at the central surgical facilities of the University Medical Centre Hamburg-Eppendorf, which focuses on highly complex major oncological surgeries. To consider these different settings, we dichotomized the type of surgery into prostatectomy and major abdominal surgery (including general, gynaecological, and urological surgery).

In our study, major abdominal surgeries were related to a larger TWA-MAP below the CVA-based MAPopt compared to prostatectomy. Various factors may explain this finding. Prostate

cancer is among the most common cancers in developed countries, with 1.6 million cases diagnosed globally in 2015 (Global Burden of Disease Cancer Collaboration et al. 2017). Radical prostatectomy is recommended for localized prostate cancer and reduces mortality (Wilt et al. 2021). This curative treatment is recommended for patients whose comorbidity-adjusted life expectancy exceeds 10 years since prostate cancer is slow growing and the benefits of the operation may only present after 10 years (Brawley, Mohan, and Nein 2018). Compared to prostate cancer, other solid tumours are operated on at various cancer stages and include patients with higher perioperative risk (Pope et al. 2006). This information emphasizes that prostate cancer patients are usually “healthier” and may have lower perioperative risks than patients with other solid tumours.

Additionally, prostatectomy is a highly standardized surgical procedure. Based on our results, we assumed that the highly standardized surgery type and good perioperative physical conditions resulted in prostatectomy patients experiencing less overall magnitude and duration of MAP below the CVA-based MAPopt than patients undergoing other surgery types.

6.10. Discussion of methods

The assessment of CVA and CVA-based MAPopt is relatively new, and different methods are available (Rivera-Lara et al. 2017).

6.10.1. Calculation of MAPopt

To date, no consensus exists on a gold standard for calculating the CVA-based MAPopt. The CVA-based MAPopt is calculated either as the bottom of a U-shaped curve depicting MAP values and corresponding COx values or as the MAP corresponding to the lowest COx, even if the data do not present the typical parabolic form (Rivera-Lara et al. 2017). In the present study, we used the U-shaped curve to determine the CVA-based MAPopt, since this method is more commonly applied (Rivera-Lara et al. 2017). Additionally, we believe that compared to the U-shaped curve, determining the CVA-based MAPopt with the lowest Cox is less exact in cases where two or more approximate minimal Cox are presented within a wide span of blood pressures (e.g. two minimal Cox at 70 and 100 mmHg) (Rivera-Lara et al. 2017). Despite the accuracy of the U-shaped curve method, it has limitations. Extreme outliers (too low or too high) may bias the curve because all the data are used in the calculation if no filter procedures are applied. We aimed to solve this problem by eliminating evident artefacts of MAP values, which were greater than 150 mmHg and below 30 mmHg. Furthermore, the method ignores the time weight of the collected data. We aimed to correct this error by excluding data representing below 1% of the complete measurement time. Another disadvantage of the method is that a CVA-based MAPopt cannot always be retrieved, especially if the monitoring time window is too short or if the data distribution does not result in a parabola. We tried to minimize this effect by setting the bin at 2 mmHg, which resulted in more data points for use

in the U-shaped curve calculations compared to bins of 5 mmHg.

6.10.2. AUC versus TWA-MAP below CVA-based MAPopt

Intra- or postoperative hypotension is assessed in different ways, such as the time below a predefined blood pressure threshold, the AUC of the respective blood pressure threshold, or the TWA blood pressure below the blood pressure threshold. The extent and duration of intraoperative hypotension are related to enormous adverse outcomes, including myocardial injury, AKI, delirium, and perioperative death (Sessler et al. 2019). Among these, myocardial injury and AKI are the major components. Rather than dichotomous identification of intraoperative hypotension (hypotension or no hypertension), modern randomized researchers prefer to consider certain exposure times. The degree of hypotension multiplied by the cumulative exposure time constitutes the AUC. Exploring the association between the AUC and adverse outcomes revealed more persuasive evidence than the onset of intraoperative hypotension alone (Hori, Max, et al. 2016). In the present study, we used the TWA, which corresponds to the AUC divided by the measurement duration. This normalization allows adjustment for the duration of surgery, which is important since prolonged surgeries are more likely to cause greater AUC (Saugel and Sessler 2021).

7. Limitations

Our study has several limitations. First, we included many more male patients (87.6%) than female patients (12.4%) due to partial enrolment at a prostate cancer centre. In considering the methodological feasibility, i. e. the TCD , we enrolled only the patients who had surgery in the supine position, which could cause bias in patient selection. Second, based on the clinical practice, age, CCI, gender, dichotomized ASA, hypertension, dichotomized type of surgery, sevoflurane, BMI, surgery duration, change in haemoglobin, and noradrenaline were used as independent variables to build the multivariable general linear models. However, we cannot be sure that all the potentially confounding variables were considered for this heterogeneous patient cohort. Third, we did not adjust for the doses of sevoflurane and propofol. Instead, the variable was only dichotomized as “propofol or sevoflurane for anaesthesia maintenance” in our study. Some studies have shown that the effect of sevoflurane and propofol on CVA is dose-dependent. Fourth, this study presents the results from a single-centre observation. Multicentre data are needed to confirm our findings, and further RCTs are recommended to generalize the experimental findings.

8. Conclusion

Patients experience lower intraoperative CVA-based MAPopt than postoperative CVA-based MAPopt, which requires different blood pressure management in different perioperative periods. The application of propofol for anaesthesia maintenance and major abdominal surgery are associated with lower intraoperative MAP.

9. References

Aaslid, R., K. F. Lindegaard, W. Sorteberg, and H. Nornes. 1989. 'Cerebral Autoregulation Dynamics in Humans'. *Stroke* 20 (1): 45–52. https://doi.org/10.1161/01.str.20.1.45.

Aaslid, R., T. M. Markwalder, and H. Nornes. 1982. 'Noninvasive Transcranial Doppler Ultrasound Recording of Flow Velocity in Basal Cerebral Arteries'. *Journal of Neurosurgery* 57 (6): 769–74. https://doi.org/10.3171/jns.1982.57.6.0769.

Abbott, Tom E. F., Rupert M. Pearse, R. Andrew Archbold, Tahania Ahmad, Edyta Niebrzegowska, Andrew Wragg, Reitze N. Rodseth, Philip J. Devereaux, and Gareth L. Ackland. 2018. 'A Prospective International Multicentre Cohort Study of Intraoperative Heart Rate and Systolic Blood Pressure and Myocardial Injury After Noncardiac Surgery: Results of the VISION Study'. *Anesthesia and Analgesia* 126 (6): 1936–45. https://doi.org/10.1213/ANE.0000000000002560.

Alkire, M. T., R. J. Haier, S. J. Barker, N. K. Shah, J. C. Wu, and Y. J. Kao. 1995. 'Cerebral Metabolism during Propofol Anesthesia in Humans Studied with Positron Emission Tomography'. *Anesthesiology* 82 (2): 393–403; discussion 27A. https://doi.org/10.1097/00000542-199502000-00010.

Alkire, M. T., R. J. Haier, N. K. Shah, and C. T. Anderson. 1997. 'Positron Emission Tomography Study of Regional Cerebral Metabolism in Humans during Isoflurane Anesthesia'. *Anesthesiology* 86 (3): 549–57. https://doi.org/10.1097/00000542-199703000-00006.

Arnolds, B. J., and G. M. von Reutern. 1986. 'Transcranial Doppler Sonography. Examination Technique and Normal Reference Values'. *Ultrasound in Medicine & Biology* 12 (2): 115–23. https://doi.org/10.1016/0301-5629(86)90016-5.

Artru, A. A. 1986. 'Partial Preservation of Cerebral Vascular Responsiveness to Hypocapnia during Isoflurane-Induced Hypotension in Dogs'. *Anesthesia and Analgesia* 65 (6): 660–66.

Behne, M., H. J. Wilke, and S. Harder. 1999. 'Clinical Pharmacokinetics of Sevoflurane'. *Clinical Pharmacokinetics* 36 (1): 13–26. https://doi.org/10.2165/00003088-199936010-00002.

Bharti, Neerja, Promila Chari, and Parag Kumar. 2012. 'Effect of Sevoflurane versus Propofol-Based Anesthesia on the Hemodynamic Response and Recovery Characteristics in Patients Undergoing Microlaryngeal Surgery'. *Saudi Journal of Anaesthesia* 6 (4): 380–84. https://doi.org/10.4103/1658-354X.105876.

Bijker, Jilles B., Wilton A. van Klei, Teus H. Kappen, Leo van Wolfswinkel, Karel G. M. Moons, and Cor J. Kalkman. 2007. 'Incidence of Intraoperative Hypotension as a Function of the Chosen Definition: Literature Definitions Applied to a Retrospective Cohort Using Automated Data Collection'. *Anesthesiology* 107 (2): 213–20. https://doi.org/10.1097/01.anes.0000270724.40897.8e.

Boedtkjer, Ebbe, Kristoffer B. Hansen, Donna M. B. Boedtkjer, Christian Aalkjaer, and Walter F. Boron. 2016. 'Extracellular HCO3- Is Sensed by Mouse Cerebral Arteries: Regulation of Tone by Receptor Protein Tyrosine Phosphatase γ'. *Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism* 36 (5): 965–80. https://doi.org/10.1177/0271678X15610787.

Brawley, Stephen, Ravinder Mohan, and Christopher D. Nein. 2018. 'Localized Prostate Cancer: Treatment Options'. *American Family Physician* 97 (12): 798–805.

Brohan, Janette, and Basavana G. Goudra. 2017. 'The Role of GABA Receptor Agonists in Anesthesia and Sedation'. *CNS Drugs* 31 (10): 845–56. https://doi.org/10.1007/s40263-017-0463-7.

Brown, Charles H., Karin J. Neufeld, Jing Tian, Julia Probert, Andrew LaFlam, Laura Max, Daijiro Hori, et al. 2019. 'Effect of Targeting Mean Arterial Pressure During Cardiopulmonary Bypass by Monitoring Cerebral Autoregulation on Postsurgical Delirium Among Older Patients: A Nested Randomized Clinical Trial'. *JAMA Surgery* 154 (9): 819–26. https://doi.org/10.1001/jamasurg.2019.1163.

Cavazzuti, M., C. A. Porro, A. Barbieri, and A. Galetti. 1991. 'Brain and Spinal Cord Metabolic Activity during Propofol Anaesthesia'. *British Journal of Anaesthesia* 66 (4): 490–95. https://doi.org/10.1093/bja/66.4.490.

Claassen, Jurgen A. H. R., Dick H. J. Thijssen, Ronney B. Panerai, and Frank M. Faraci. 2021. 'Regulation of Cerebral Blood Flow in Humans: Physiology and Clinical Implications of Autoregulation'. *Physiological Reviews* 101 (4): 1487–1559. https://doi.org/10.1152/physrev.00022.2020.

Czosnyka, Marek, Chad Miller, and Participants in the International Multidisciplinary Consensus Conference on Multimodality Monitoring. 2014. 'Monitoring of Cerebral Autoregulation'. *Neurocritical Care* 21 Suppl 2 (December): S95-102. https://doi.org/10.1007/s12028-014-0046-0.

Deiner, Stacie, Xiaodong Luo, Jeffrey H. Silverstein, and Mary Sano. 2015. 'Can Intraoperative Processed EEG Predict Postoperative Cognitive Dysfunction in the Elderly?' *Clinical Therapeutics* 37 (12): 2700–2705. https://doi.org/10.1016/j.clinthera.2015.11.004.

Donnelly, Joseph, Karol P. Budohoski, Peter Smielewski, and Marek Czosnyka. 2016. 'Regulation of the Cerebral Circulation: Bedside Assessment and Clinical Implications'. *Critical Care (London, England)* 20 (1): 129. https://doi.org/10.1186/s13054-016-1293-6.

Ebert, T. J., M. Muzi, R. Berens, D. Goff, and J. P. Kampine. 1992. 'Sympathetic Responses to Induction of Anesthesia in Humans with Propofol or Etomidate'. *Anesthesiology* 76 (5): 725–33. https://doi.org/10.1097/00000542-199205000-00010.

Ebert, Thomas J., Christopher P. Harkin, and Michael Muzi. 1995. 'Cardiovascular Responses to Sevoflurane: A Review'. *Anesthesia & Analgesia* 81 (6S): 11S.

Evered, L., B. Silbert, D. S. Knopman, D. A. Scott, S. T. DeKosky, L. S. Rasmussen, E. S. Oh, et al. 2018. 'Recommendations for the Nomenclature of Cognitive Change Associated with Anaesthesia and Surgery-2018'. *British Journal of Anaesthesia* 121 (5): 1005–12. https://doi.org/10.1016/j.bja.2017.11.087.

Fan, Fan, Aron M. Geurts, Sydney R. Murphy, Mallikarjuna R. Pabbidi, Howard J. Jacob, and Richard J. Roman. 2015. 'Impaired Myogenic Response and Autoregulation of Cerebral Blood Flow Is Rescued in CYP4A1 Transgenic Dahl Salt-Sensitive Rat'. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology* 308 (5): R379-390. https://doi.org/10.1152/ajpregu.00256.2014.

Fantini, Sergio, Angelo Sassaroli, Kristen T. Tgavalekos, and Joshua Kornbluth. 2016. 'Cerebral Blood Flow and Autoregulation: Current Measurement Techniques and Prospects for Noninvasive Optical Methods'. *Neurophotonics* 3 (3): 031411. https://doi.org/10.1117/1.NPh.3.3.031411.

Faraci, Frank M. 2011. 'Protecting against Vascular Disease in Brain'. *American Journal of Physiology. Heart and Circulatory Physiology* 300 (5): H1566-1582. https://doi.org/10.1152/ajpheart.01310.2010.

Feng, Xiaojin, Jialing Hu, Fuzhou Hua, Jing Zhang, Lieliang Zhang, and Guohai Xu. 2020. 'The Correlation of Intraoperative Hypotension and Postoperative Cognitive Impairment: A Meta-Analysis of Randomized Controlled Trials'. *BMC Anesthesiology* 20 (1): 193. https://doi.org/10.1186/s12871-020-01097-5.

Futier, Emmanuel, Jean-Yves Lefrant, Pierre-Gregoire Guinot, Thomas Godet, Emmanuel Lorne, Philippe Cuvillon, Sebastien Bertran, et al. 2017. 'Effect of Individualized vs Standard Blood Pressure Management Strategies on Postoperative Organ Dysfunction Among High-Risk Patients Undergoing Major Surgery: A Randomized Clinical Trial'. *JAMA* 318 (14): 1346–57. https://doi.org/10.1001/jama.2017.14172.

Global Burden of Disease Cancer Collaboration, Christina Fitzmaurice, Christine Allen, Ryan M. Barber, Lars Barregard, Zulfiqar A. Bhutta, Hermann Brenner, et al. 2017. 'Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study'. *JAMA Oncology* 3 (4): 524–48. https://doi.org/10.1001/jamaoncol.2016.5688.

Gold, J. P., M. E. Charlson, P. Williams-Russo, T. P. Szatrowski, J. C. Peterson, P. A. Pirraglia, G. S. Hartman, F. S. Yao, J. P. Hollenberg, and D. Barbut. 1995. 'Improvement of Outcomes after Coronary Artery Bypass. A Randomized Trial Comparing Intraoperative High versus Low Mean Arterial Pressure'. *The Journal of Thoracic and Cardiovascular Surgery* 110 (5): 1302–11; discussion 1311-1314. https://doi.org/10.1016/S0022-5223(95)70053-6.

Gregory, Anne, Wolf H. Stapelfeldt, Ashish K. Khanna, Nathan J. Smischney, Isabel J. Boero, Qinyu Chen, Mitali Stevens, and Andrew D. Shaw. 2021. 'Intraoperative Hypotension Is Associated With Adverse Clinical Outcomes After Noncardiac Surgery'. *Anesthesia and Analgesia* 132 (6): 1654–65. https://doi.org/10.1213/ANE.0000000000005250.

Guyton, A. C. 1961. 'Physiologic Regulation of Arterial Pressure'. *The American Journal of Cardiology* 8 (September): 401–7. https://doi.org/10.1016/0002-9149(61)90159-x.

Handler, Joel. 2009. 'The Importance of Accurate Blood Pressure Measurement'. *The Permanente Journal* 13 (3): 51–54. https://doi.org/10.7812/TPP/09-054.

Harder, D. R. 1984. 'Pressure-Dependent Membrane Depolarization in Cat Middle Cerebral Artery'. *Circulation Research* 55 (2): 197–202. https://doi.org/10.1161/01.res.55.2.197.

Harder, David R., Jayashree Narayanan, and Debebe Gebremedhin. 2011. 'Pressure-Induced Myogenic Tone and Role of 20-HETE in Mediating Autoregulation of Cerebral Blood Flow'. *American Journal of Physiology. Heart and Circulatory Physiology* 300 (5): H1557-1565. https://doi.org/10.1152/ajpheart.01097.2010.

Harper, A. M., and H. I. Glass. 1965. 'Effect of Alterations in the Arterial Carbon Dioxide Tension on the Blood Flow through the Cerebral Cortex at Normal and Low Arterial Blood Pressures'. *Journal of Neurology, Neurosurgery, and Psychiatry* 28 (5): 449–52. https://doi.org/10.1136/jnnp.28.5.449.

Heyer, Eric J., Joanna L. Mergeche, Zirka H. Anastasian, Minjae Kim, Kaitlin A. Mallon, and E. Sander Connolly. 2014. 'Arterial Blood Pressure Management during Carotid Endarterectomy and Early Cognitive Dysfunction'. *Neurosurgery* 74 (3): 245–51; discussion 251-253. https://doi.org/10.1227/NEU.0000000000000256.

Hill-Eubanks, David C., Albert L. Gonzales, Swapnil K. Sonkusare, and Mark T. Nelson. 2014. 'Vascular TRP Channels: Performing under Pressure and Going with the Flow'. *Physiology (Bethesda, Md.)* 29 (5): 343–60. https://doi.org/10.1152/physiol.00009.2014.

Hilton, P., V. J. Dev, and E. Major. 1986. 'Intravenous Anaesthesia with Propofol and Alfentanil. The Influence of Age and Weight'. *Anaesthesia* 41 (6): 640–43. https://doi.org/10.1111/j.1365-2044.1986.tb13061.x.

Hirsch, J., G. DePalma, T. T. Tsai, L. P. Sands, and J. M. Leung. 2015. 'Impact of Intraoperative Hypotension and Blood Pressure Fluctuations on Early Postoperative Delirium after Non-Cardiac Surgery'. *British Journal of Anaesthesia* 115 (3): 418–26. https://doi.org/10.1093/bja/aeu458.

Hoiland, Ryan L., Joseph A. Fisher, and Philip N. Ainslie. 2019. 'Regulation of the Cerebral Circulation by Arterial Carbon Dioxide'. *Comprehensive Physiology* 9 (3): 1101–54. https://doi.org/10.1002/cphy.c180021.

Hori, Daijiro, Charles Hogue, Hideo Adachi, Laura Max, Joel Price, Christopher Sciortino, Kenton Zehr, John Conte, Duke Cameron, and Kaushik Mandal. 2016. 'Perioperative Optimal Blood Pressure as Determined by Ultrasound Tagged near Infrared Spectroscopy and Its Association with Postoperative Acute Kidney Injury in Cardiac Surgery Patients'. *Interactive Cardiovascular and Thoracic Surgery* 22 (4): 445–51. https://doi.org/10.1093/icvts/ivv371.

Hori, Daijiro, Laura Max, Andrew Laflam, Charles Brown, Karin J. Neufeld, Hideo Adachi, Christopher Sciortino, et al. 2016. 'Blood Pressure Deviations From Optimal Mean Arterial Pressure During Cardiac Surgery Measured With a Novel Monitor of Cerebral Blood Flow and Risk for Perioperative Delirium: A Pilot Study'. *Journal of Cardiothoracic and Vascular Anesthesia* 30 (3): 606–12. https://doi.org/10.1053/j.jvca.2016.01.012.

Hori, Daijiro, Yohei Nomura, Masahiro Ono, Brijen Joshi, Kaushik Mandal, Duke Cameron, Masha Kocherginsky, and Charles W. Hogue. 2017. 'Optimal Blood Pressure during Cardiopulmonary Bypass Defined by Cerebral Autoregulation Monitoring'. *The Journal of Thoracic and Cardiovascular Surgery* 154 (5): 1590-1598.e2. https://doi.org/10.1016/j.jtcvs.2017.04.091.

Hori, Daijiro, Masahiro Ono, Thomas E. Rappold, John V. Conte, Ashish S. Shah, Duke E. Cameron, Hideo Adachi, Allen D. Everett, and Charles W. Hogue. 2015. 'Hypotension After Cardiac Operations Based on Autoregulation Monitoring Leads to Brain Cellular Injury'. *The Annals of Thoracic Surgery* 100 (2): 487–93. https://doi.org/10.1016/j.athoracsur.2015.03.036.

Hudetz, Anthony G. 2012. 'General Anesthesia and Human Brain Connectivity'. *Brain Connectivity* 2 (6): 291–302. https://doi.org/10.1089/brain.2012.0107.

Husedzinović, Ino, Dinko Tonković, Stjepan Barisin, Nikola Bradić, and Stojanka Gasparović. 2003. 'Hemodynamic Differences in Sevoflurane versus Propofol Anesthesia'. *Collegium Antropologicum* 27 (1): 205–12.

James, G. D., and T. G. Pickering. 1993. 'The Influence of Behavioral Factors on the Daily Variation of Blood Pressure'. *American Journal of Hypertension* 6 (6 Pt 2): 170S-173S. https://doi.org/10.1093/ajh/6.6.170s.

Jöbsis, F. F. 1977. 'Noninvasive, Infrared Monitoring of Cerebral and Myocardial Oxygen Sufficiency and Circulatory Parameters'. *Science (New York, N.Y.)* 198 (4323): 1264–67. https://doi.org/10.1126/science.929199.

Kaisti, Kaike K., Jaakko W. Långsjö, Sargo Aalto, Vesa Oikonen, Hannu Sipilä, Mika Teräs, Susanna Hinkka, Liisa Metsähonkala, and Harry Scheinin. 2003. 'Effects of Sevoflurane, Propofol, and Adjunct Nitrous Oxide on Regional Cerebral Blood Flow, Oxygen Consumption, and Blood Volume in Humans'. *Anesthesiology* 99 (3): 603–13. https://doi.org/10.1097/00000542-200309000-00015.

Katoh, T., and K. Ikeda. 1987. 'The Minimum Alveolar Concentration (MAC) of Sevoflurane in Humans'. *Anesthesiology* 66 (3): 301–3. https://doi.org/10.1097/00000542-198703000-00006.

Kim, Jeongmin, Jae-Kwang Shim, Jong Wook Song, Eui-Kyung Kim, and Young Lan Kwak. 2016. 'Postoperative Cognitive Dysfunction and the Change of Regional Cerebral Oxygen Saturation in Elderly Patients Undergoing Spinal Surgery'. *Anesthesia and Analgesia* 123 (2): 436–44. https://doi.org/10.1213/ANE.0000000000001352.

Klöckner, U., and G. Isenberg. 1994. 'Calcium Channel Current of Vascular Smooth Muscle Cells: Extracellular Protons Modulate Gating and Single Channel Conductance'. *The Journal of General Physiology* 103 (4): 665–78. https://doi.org/10.1085/jgp.103.4.665.

Knot, H. J., and M. T. Nelson. 1998. 'Regulation of Arterial Diameter and Wall [Ca2+] in Cerebral Arteries of Rat by Membrane Potential and Intravascular Pressure'. *The Journal of Physiology* 508 (Pt 1) (April): 199–209. https://doi.org/10.1111/j.1469-7793.1998.199br.x.

Koller, Akos, and Peter Toth. 2012. 'Contribution of Flow-Dependent Vasomotor Mechanisms to the Autoregulation of Cerebral Blood Flow'. *Journal of Vascular Research* 49 (5): 375–89. https://doi.org/10.1159/000338747.

Langer, Thomas, Alessandro Santini, Francesco Zadek, Manuela Chiodi, Paola Pugni, Valentina Cordolcini, Barbara Bonanomi, et al. 2019. 'Intraoperative Hypotension Is Not Associated with Postoperative Cognitive Dysfunction in Elderly Patients Undergoing General Anesthesia for Surgery: Results of a Randomized Controlled Pilot Trial'. *Journal of Clinical Anesthesia* 52 (February): 111–18. https://doi.org/10.1016/j.jclinane.2018.09.021.

Lassen, N. A. 1959. 'Cerebral Blood Flow and Oxygen Consumption in Man'. *Physiological Reviews* 39 (2): 183–238. https://doi.org/10.1152/physrev.1959.39.2.183.

Maheshwari, Kamal, Sandeep Khanna, Gausan Ratna Bajracharya, Natalya Makarova, Quinton Riter, Syed Raza, Jacek B. Cywinski, Maged Argalious, Andrea Kurz, and Daniel I. Sessler. 2018. 'A Randomized Trial of Continuous Noninvasive Blood Pressure Monitoring During Noncardiac Surgery'. *Anesthesia and Analgesia* 127 (2): 424–31. https://doi.org/10.1213/ANE.0000000000003482.

McCarron, J. G., C. A. Crichton, P. D. Langton, A. MacKenzie, and G. L. Smith. 1997. 'Myogenic Contraction by Modulation of Voltage-Dependent Calcium Currents in Isolated Rat Cerebral Arteries'. *The Journal of Physiology* 498 (Pt 2) (January): 371–79. https://doi.org/10.1113/jphysiol.1997.sp021864.

McEvoy, Matthew D., Ruchir Gupta, Elena J. Koepke, Aarne Feldheiser, Frederic Michard, Denny Levett, Julie K. M. Thacker, et al. 2019. 'Perioperative Quality Initiative Consensus Statement on Postoperative Blood Pressure, Risk and Outcomes for Elective Surgery'. *British Journal of Anaesthesia* 122 (5): 575–86. https://doi.org/10.1016/j.bja.2019.01.019.

McKeage, Kate, and Caroline M. Perry. 2003. 'Propofol: A Review of Its Use in Intensive Care Sedation of Adults'. *CNS Drugs* 17 (4): 235–72. https://doi.org/10.2165/00023210-200317040-00003.

Meng, Lingzhong, and Adrian W. Gelb. 2015. 'Regulation of Cerebral Autoregulation by Carbon Dioxide'. *Anesthesiology* 122 (1): 196–205. https://doi.org/10.1097/ALN.0000000000000506.

Moerman, Annelies T., Valerie M. Vanbiervliet, Astrid Van Wesemael, Stefaan M. Bouchez, Patrick F. Wouters, and Stefan G. De Hert. 2015. 'Assessment of Cerebral Autoregulation Patterns with Near-Infrared Spectroscopy during Pharmacological-Induced Pressure Changes'. *Anesthesiology* 123 (2): 327–35. https://doi.org/10.1097/ALN.0000000000000715.

Monk, Terri G., Michael R. Bronsert, William G. Henderson, Michael P. Mangione, S. T. John Sum-Ping, Deyne R. Bentt, Jennifer D. Nguyen, Joshua S. Richman, Robert A. Meguid, and Karl E. Hammermeister. 2015. 'Association between Intraoperative Hypotension and Hypertension and 30-Day Postoperative Mortality in Noncardiac Surgery'. *Anesthesiology* 123 (2): 307–19. https://doi.org/10.1097/ALN.0000000000000756.

Moosmang, Sven, Verena Schulla, Andrea Welling, Robert Feil, Susanne Feil, Jörg W. Wegener, Franz Hofmann, and Norbert Klugbauer. 2003. 'Dominant Role of Smooth Muscle L-Type Calcium Channel Cav1.2 for Blood Pressure Regulation'. *The EMBO Journal* 22 (22): 6027–34. https://doi.org/10.1093/emboj/cdg583.

Murkin, J. M., and M. Arango. 2009. 'Near-Infrared Spectroscopy as an Index of Brain and Tissue Oxygenation'. *British Journal of Anaesthesia* 103 Suppl 1 (December): i3-13. https://doi.org/10.1093/bja/aep299.

Palanca, B. J. A., M. S. Avidan, and G. A. Mashour. 2017. 'Human Neural Correlates of Sevoflurane-Induced Unconsciousness'. *British Journal of Anaesthesia* 119 (4): 573–82. https://doi.org/10.1093/bja/aex244.

Paulson, O. B., S. Strandgaard, and L. Edvinsson. 1990. 'Cerebral Autoregulation'. *Cerebrovascular and Brain Metabolism Reviews* 2 (2): 161–92.

Pope, D., H. Ramesh, R. Gennari, G. Corsini, M. Maffezzini, H. J. Hoekstra, D. Mobarak, et al. 2006. 'Pre-Operative Assessment of Cancer in the Elderly (PACE): A Comprehensive Assessment of Underlying Characteristics of Elderly Cancer Patients Prior to Elective Surgery'. *Surgical Oncology* 15 (4): 189–97. https://doi.org/10.1016/j.suronc.2007.04.009.

Purkayastha, Sushmita, and Farzaneh Sorond. 2012. 'Transcranial Doppler Ultrasound: Technique and Application'. *Seminars in Neurology* 32 (4): 411–20. https://doi.org/10.1055/s-0032-1331812.

Rajan, Vinayakrishnan, Babu Varghese, Ton G. van Leeuwen, and Wiendelt Steenbergen. 2009. 'Review of Methodological Developments in Laser Doppler Flowmetry'. *Lasers in Medical Science* 24 (2): 269–83. https://doi.org/10.1007/s10103-007-0524-0.

Rajendran, Peramaiyan, Thamaraiselvan Rengarajan, Jayakumar Thangavel, Yutaka Nishigaki, Dhanapal Sakthisekaran, Gautam Sethi, and Ikuo Nishigaki. 2013. 'The Vascular Endothelium and Human Diseases'. *International Journal of Biological Sciences* 9 (10): 1057–69. https://doi.org/10.7150/ijbs.7502.

Rangel-Castilla, Leonardo, Jaime Gasco, Haring J. W. Nauta, David O. Okonkwo, and Claudia S. Robertson. 2008. 'Cerebral Pressure Autoregulation in Traumatic Brain Injury'. *Neurosurgical Focus* 25 (4): E7. https://doi.org/10.3171/FOC.2008.25.10.E7.

Reich, David L., Elliott Bennett-Guerrero, Carol A. Bodian, Sabera Hossain, Wanda Winfree, and Marina Krol. 2002. 'Intraoperative Tachycardia and Hypertension Are Independently Associated with Adverse Outcome in Noncardiac Surgery of Long Duration'. *Anesthesia and Analgesia* 95 (2): 273–77, table of contents. https://doi.org/10.1097/00000539-200208000-00003.

Rivera-Lara, Lucia, Andres Zorrilla-Vaca, Romergryko G. Geocadin, Ryan J. Healy, Wendy Ziai, and Marek A. Mirski. 2017. 'Cerebral Autoregulation-Oriented Therapy at the Bedside: A Comprehensive Review'. *Anesthesiology* 126 (6): 1187–99. https://doi.org/10.1097/ALN.0000000000001625.

Rohlwink, Ursula K., and Anthony A. Figaji. 2010. 'Methods of Monitoring Brain Oxygenation'. *Child's Nervous System: ChNS: Official Journal of the International Society for Pediatric Neurosurgery* 26 (4): 453–64. https://doi.org/10.1007/s00381-009-1033-1.

Roldán, María, and Panayiotis A. Kyriacou. 2021. 'Near-Infrared Spectroscopy (NIRS) in Traumatic Brain Injury (TBI)'. *Sensors (Basel, Switzerland)* 21 (5): 1586. https://doi.org/10.3390/s21051586.

Roshanov, Pavel S., Bram Rochwerg, Ameen Patel, Omid Salehian, Emmanuelle Duceppe, Emilie P. Belley-Côté, Gordon H. Guyatt, et al. 2017. 'Withholding versus Continuing Angiotensin-Converting Enzyme Inhibitors or Angiotensin II Receptor Blockers before Noncardiac Surgery: An Analysis of the Vascular Events In Noncardiac Surgery PatIents COhort EvaluatioN Prospective Cohort'. *Anesthesiology* 126 (1): 16–27. https://doi.org/10.1097/ALN.0000000000001404.

Salmasi, Vafi, Kamal Maheshwari, Dongsheng Yang, Edward J. Mascha, Asha Singh, Daniel I. Sessler, and Andrea Kurz. 2017. 'Relationship between Intraoperative Hypotension, Defined by Either Reduction from Baseline or Absolute Thresholds, and Acute Kidney and Myocardial Injury after Noncardiac Surgery: A Retrospective Cohort Analysis'. *Anesthesiology* 126 (1): 47–65. https://doi.org/10.1097/ALN.0000000000001432.

Saugel, Bernd, Philip C. Reese, Daniel I. Sessler, Christian Burfeindt, Julia Y. Nicklas, Hans O. Pinnschmidt, Daniel A. Reuter, and Stefan Südfeld. 2019. 'Automated Ambulatory Blood Pressure Measurements and Intraoperative Hypotension in Patients Having Noncardiac Surgery with General Anesthesia: A Prospective Observational Study'. *Anesthesiology* 131 (1): 74–83. https://doi.org/10.1097/ALN.0000000000002703.

Saugel, Bernd, and Daniel I. Sessler. 2021. 'Perioperative Blood Pressure Management'. *Anesthesiology* 134 (2): 250–61. https://doi.org/10.1097/ALN.0000000000003610.

Saugel, Bernd, Jean-Louis Vincent, and Julia Y. Wagner. 2017. 'Personalized Hemodynamic Management'. *Current Opinion in Critical Care* 23 (4): 334–41. https://doi.org/10.1097/MCC.0000000000000422.

Schlünzen, L., N. Juul, K. V. Hansen, and G. E. Cold. 2012. 'Regional Cerebral Blood Flow and Glucose Metabolism during Propofol Anaesthesia in Healthy Subjects Studied with Positron Emission Tomography'. *Acta Anaesthesiologica Scandinavica* 56 (2): 248–55. https://doi.org/10.1111/j.1399-6576.2011.02561.x.

Sessler, Daniel I., Joshua A. Bloomstone, Solomon Aronson, Colin Berry, Tong J. Gan, John A. Kellum, James Plumb, et al. 2019. 'Perioperative Quality Initiative Consensus Statement on Intraoperative Blood Pressure, Risk and Outcomes for Elective Surgery'. *British Journal of Anaesthesia* 122 (5): 563–74. https://doi.org/10.1016/j.bja.2019.01.013.

Shaye, Hamidreza, Benjamin Stauch, Cornelius Gati, and Vadim Cherezov. 2021. 'Molecular Mechanisms of Metabotropic GABAB Receptor Function'. *Science Advances* 7 (22): eabg3362. https://doi.org/10.1126/sciadv.abg3362.

Shoemaker, W. C., P. L. Appel, K. Waxman, S. Schwartz, and P. Chang. 1982. 'Clinical Trial of Survivors' Cardiorespiratory Patterns as Therapeutic Goals in Critically Ill Postoperative Patients'. *Critical Care Medicine* 10 (6): 398–403. https://doi.org/10.1097/00003246-198206000-00015.

Siepe, Matthias, Thomas Pfeiffer, Andreas Gieringer, Silke Zemann, Christoph Benk, Christian Schlensak, and Friedhelm Beyersdorf. 2011. 'Increased Systemic Perfusion Pressure during Cardiopulmonary Bypass Is Associated with Less Early

Postoperative Cognitive Dysfunction and Delirium'. *European Journal of Cardio-Thoracic Surgery: Official Journal of the European Association for Cardio-Thoracic Surgery* 40 (1): 200–207. https://doi.org/10.1016/j.ejcts.2010.11.024.

Smielewski, Peter, Zofia Czosnyka, Magdalena Kasprowicz, John D. Pickard, and Marek Czosnyka. 2012. 'ICM+: A Versatile Software for Assessment of CSF Dynamics'. *Acta Neurochirurgica. Supplement* 114: 75–79. https://doi.org/10.1007/978-3-7091-0956-4_13.

Smith, M. E. Beth, Joseph C. Chiovaro, Maya O'Neil, Devan Kansagara, Ana Quinones, Michele Freeman, Makalapua Motu'apuaka, and Christopher G. Slatore. 2014. *Early Warning System Scores: A Systematic Review*. VA Evidence-Based Synthesis Program Reports. Washington (DC): Department of Veterans Affairs. http://www.ncbi.nlm.nih.gov/books/NBK259026/.

Song, Qiliang, Jipeng Li, and Zongming Jiang. 2022. 'Provisional Decision-Making for Perioperative Blood Pressure Management: A Narrative Review'. *Oxidative Medicine and Cellular Longevity* 2022: 5916040. https://doi.org/10.1155/2022/5916040.

Toth, Peter, Anna Csiszar, Zsuzsanna Tucsek, Danuta Sosnowska, Tripti Gautam, Akos Koller, Michal Laniado Schwartzman, William E. Sonntag, and Zoltan Ungvari. 2013. 'Role of 20-HETE, TRPC Channels, and BKCa in Dysregulation of Pressure-Induced Ca2+ Signaling and Myogenic Constriction of Cerebral Arteries in Aged Hypertensive Mice'. *American Journal of Physiology-Heart and Circulatory Physiology* 305 (12): H1698–1708. https://doi.org/10.1152/ajpheart.00377.2013.

Toth, Peter, Bernadett Rozsa, Zsolt Springo, Tamas Doczi, and Akos Koller. 2011. 'Isolated Human and Rat Cerebral Arteries Constrict to Increases in Flow: Role of 20-HETE and TP Receptors'. *Journal of Cerebral Blood Flow & Metabolism* 31 (10): 2096–2105. https://doi.org/10.1038/jcbfm.2011.74.

Tsikas, Dimitrios, Jens Jordan, and Stefan Engeli. 2015. 'Blood Pressure-Lowering Effects of Propofol or Sevoflurane Anaesthesia Are Not Due to Enhanced Nitric Oxide Formation or Bioavailability'. *British Journal of Clinical Pharmacology* 79 (6): 1030–33. https://doi.org/10.1111/bcp.12568.

Vajkoczy, P., H. Roth, P. Horn, T. Lucke, C. Thomé, U. Hubner, G. T. Martin, et al. 2000. 'Continuous Monitoring of Regional Cerebral Blood Flow: Experimental and Clinical Validation of a Novel Thermal Diffusion Microprobe'. *Journal of Neurosurgery* 93 (2): 265–74. https://doi.org/10.3171/jns.2000.93.2.0265.

Veselis, R. A., R. A. Reinsel, B. J. Beattie, O. R. Mawlawi, V. A. Feshchenko, G. R. DiResta, S. M. Larson, and R. G. Blasberg. 1997. 'Midazolam Changes Cerebral Blood Flow in Discrete Brain Regions: An H2(15)O Positron Emission Tomography Study'. *Anesthesiology* 87 (5): 1106–17. https://doi.org/10.1097/00000542-199711000-00015.

Vutskits, Laszlo, and Zhongcong Xie. 2016. 'Lasting Impact of General Anaesthesia on the Brain: Mechanisms and Relevance'. *Nature Reviews. Neuroscience* 17 (11): 705–17. https://doi.org/10.1038/nrn.2016.128.

Walsh, Michael, Philip J. Devereaux, Amit X. Garg, Andrea Kurz, Alparslan Turan, Reitze N. Rodseth, Jacek Cywinski, Lehana Thabane, and Daniel I. Sessler. 2013. 'Relationship between Intraoperative Mean Arterial Pressure and Clinical Outcomes after Noncardiac Surgery: Toward an Empirical Definition of Hypotension'. *Anesthesiology* 119 (3): 507–15. https://doi.org/10.1097/ALN.0b013e3182a10e26.

Wanner, Patrick M., Dirk U. Wulff, Mirjana Djurdjevic, Wolfgang Korte, Thomas W. Schnider, and Miodrag Filipovic. 2021. 'Targeting Higher Intraoperative Blood Pressures Does Not Reduce Adverse Cardiovascular Events Following Noncardiac Surgery'. *Journal of the American College of Cardiology* 78 (18): 1753–64. https://doi.org/10.1016/j.jacc.2021.08.048.

Wesselink, E. M., T. H. Kappen, H. M. Torn, A. J. C. Slooter, and W. A. van Klei. 2018. 'Intraoperative Hypotension and the Risk of Postoperative Adverse Outcomes: A Systematic Review'. *British Journal of Anaesthesia* 121 (4): 706–21. https://doi.org/10.1016/j.bja.2018.04.036.

White, R. P., P. Vallance, and H. S. Markus. 2000. 'Effect of Inhibition of Nitric Oxide Synthase on Dynamic Cerebral Autoregulation in Humans'. *Clinical Science (London, England: 1979)* 99 (6): 555–60.

White, W. B., P. Lund-Johansen, and P. Omvik. 1990. 'Assessment of Four Ambulatory Blood Pressure Monitors and Measurements by Clinicians versus Intraarterial Blood Pressure at Rest and during Exercise'. *The American Journal of Cardiology* 65 (1): 60–66. https://doi.org/10.1016/0002-9149(90)90026-w.

Whitelaw, A., B. R. Karlsson, K. Haaland, I. Dahlin, P. A. Steen, and M. Thoresen. 1991. 'Hypocapnia and Cerebral Ischaemia in Hypotensive Newborn Piglets'. *Archives of Disease in Childhood* 66 (10 Spec No): 1110–14. https://doi.org/10.1136/adc.66.10_spec_no.1110.

Wilt, Timothy J., Kristen E. Ullman, Eric J. Linskens, Roderick MacDonald, Michelle Brasure, Elizabeth Ester, Victoria A. Nelson, Jayati Saha, Shahnaz Sultan, and Philipp Dahm. 2021. 'Therapies for Clinically Localized Prostate Cancer: A Comparative Effectiveness Review'. *The Journal of Urology* 205 (4): 967–76. https://doi.org/10.1097/JU.0000000000001578.

Wu, Xiujuan, Zongming Jiang, Jing Ying, Yangyang Han, and Zhonghua Chen. 2017. 'Optimal Blood Pressure Decreases Acute Kidney Injury after Gastrointestinal Surgery in Elderly Hypertensive Patients: A Randomized Study: Optimal Blood Pressure Reduces Acute Kidney Injury'. *Journal of Clinical Anesthesia* 43 (December): 77–83. https://doi.org/10.1016/j.jclinane.2017.09.004.

Xiong, Li, Xiuyun Liu, Ty Shang, Peter Smielewski, Joseph Donnelly, Zhen-ni Guo, Yi Yang, et al. 2017. 'Impaired Cerebral Autoregulation: Measurement and Application to Stroke'. *Journal of Neurology, Neurosurgery & Psychiatry* 88 (6): 520–31. https://doi.org/10.1136/jnnp-2016-314385.

Yao, Xin-hua, Bao Wang, Zhen-ke Xiao, Pu Zhou, Chen-yan Chen, and Zhao-hui Qing. 2006. '[Acute normovolemic hemodilution combined with controlled hypotension in patients undergoing liver tumorectomy]'. *Nan Fang Yi Ke Da Xue Xue Bao = Journal of Southern Medical University* 26 (6): 828–30.

Zuylen, Mark L. van, Annerixt Gribnau, Manouk Admiraal, Werner Ten Hoope, Denise P. Veelo, Markus W. Hollmann, Benedikt Preckel, and Jeroen Hermanides. 2021. 'The Role of Intraoperative Hypotension on the Development of Postoperative Cognitive Dysfunction: A Systematic Review'. *Journal of Clinical Anesthesia* 72 (September): 110310. https://doi.org/10.1016/j.jclinane.2021.110310.

10. Abstract

Background: Cerebrovascular autoregulation (CVA) maintains steady cerebral brain blood flow despite changes in perfusion pressure, a mechanism which is crucial during surgery and anaesthesia. Perioperative measurement of CVA allows for the determination of CVA-based optimal mean arterial blood pressure (MAPopt), which is defined as the blood pressure at which the CVA reaches maximal activity. The aim of this study was to compare intra- and postoperative CVA-based MAPopt and time-weighted average (TWA)-MAP below the CVA-based MAPopt. In addition, this study aimed to assess factors associated with intra- and postoperative TWA-MAP below the CVA-based MAPopt.

Methods: This sub-study of an ongoing single-centre prospective cohort study was conducted between August 2021 and May 2022. Adult patients scheduled for non-cardiac surgery of >120 minutes with general anaesthesia, invasive blood pressure monitoring and pre-existing anaemia or expected blood loss >500ml were enrolled. CVA was assessed through correlation between MAP and regional cerebral oxygen saturation detected by near-infrared spectroscopy. Each patient was assessed intra- and postoperatively. CVA-based MAPopt was defined as MAP with the lowest correlation with cerebral oxygen saturation . TWA-MAP was calculated as the area between the MAP and the MAPopt curve, normalized to the duration of CVA assessment. Factors associated with the intra- and postoperative TWA-MAP below the CVA-based MAPopt were analysed using multivariable general linear models.

Results: The final analysis included 161 patients. The median intra- and postoperative CVA-based MAPopt differed significantly (77.85 (IQR: 72.78, 84.13) mmHg versus 85.10 (IQR: 77.91, 95.06) mmHg, $p < 0.001$). The median intra- and postoperative TWA-MAP below the CVA-based MAPopt did not differ significantly (2.59 (IQR: 0.93, 5.41) mmHg versus 4.26 (IQR: 1.06, 8.73) mmHg, $p = 0.118$). Propofol for anaesthesia maintenance was associated with a larger intraoperative TWA-MAP below the CVA-based MAPopt.

Conclusion: Intraoperative CVA-based MAPopt is lower than postoperative CVA-based MAPopt, which might require different blood pressure management in different perioperative periods. The application of propofol for anaesthesia maintenance and major abdominal surgery are associated with lower intraoperative MAP.

10. Zusammenfassung

Hintergrund: Die Zerebrovaskuläre Autoregulation (CVA) ist ein wichtiger Mechanismus, der den zerebralen Blutfluss trotz Veränderungen des cerebralen Perfusionsdrucks stabil hält. Die perioperative Messung der CVA ermöglicht die Bestimmung des CVA-basierten optimalen mittleren arteriellen Blutdrucks (MAPopt). Der CVA-basierte MAPopt entspricht dem systemischen Blutdruck, bei dem die CVA maximal ausgeprägt ist. Ziel der Studie war es, den intra- und postoperative CVA-basierte MAPopt zu vergleichen, den intra- und postoperativen zeitgewichteten Mittelwert (TWA)-MAP unterhalb des CVA-basierten MAPopt zu vergleichen, sowie zu untersuchen, welche Faktoren mit einem intra- und postoperativen TWA-MAP unterhalb des CVA-basierten MAPopt assoziiert sind.

Methoden: Diese Sub-Studie einer laufenden Single-Centre-Studie wurde zwischen August 2021 und Mai 2022 durchgeführt. Eingeschlossen wurden erwachsene Patienten, die sich einer nicht-kardiochirurgische Operation (>120 Minuten) unter Vollnarkose und mit invasiver Blutdruckmessung unterzogen und eine präoperative Anämie aufwiesen, bzw. der erwartete intraoperativen Blutverlust >500 ml entsprach. Die Berechnung CVA erfolgte durch kontinuierliche Korrelation des MAPs mit der auf Nahinfrarot-Spektroskopie basierenden regionalen zerebralen Sauerstoffsättigung. Der CVA-basierter MAPopt wurde definiert, als der MAP bei dem die Korrelation mit der zerebralen Sauerstoffsättigung am niedrigsten war. Der TWA-MAP wurde berechnet als Fläche zwischen der MAP- und der MAPopt-Kurve, normiert auf die Dauer der CVA-Messung. Faktoren, welche mit dem intra- und postoperativen TWA-MAP unterhalb des CVA-basierten MAPopt assoziiert waren, wurden mit multivariablen allgemeinen linearen Modellen analysiert.

Ergebnisse: Die Analyse umfasste 161 Patienten. Der mediane intra- und postoperative CVA-basierte MAPopt unterschieden sich signifikant (77,85 (IQR: 72,78, 84,13) mmHg versus 85,10 (IQR: 77,91, 95,06) mmHg; $p < 0,001$). Der mittlere intra- und postoperative TWA-MAP unterhalb des CVA-basierten MAPopt unterschieden sich nicht signifikant (2,59 (IQR: 0,93, 5,41) mmHg versus 4,26 (IQR: 1,06, 8,73) mmHg; $p = 0,118$). Die Verwendung von Propofol zur Aufrechterhaltung der Narkose war mit einem größeren intraoperativen TWA-MAP unterhalb des CVA-basierten MAPopt assoziiert.

Schlussfolgerung: Der intraoperative CVA-basierte MAPopt ist niedriger als der postoperative CVA-basierte MAPopt, Während sich der intra- und postoperative TWA-MAP unterhalb des CVA-basierten MAPopt nicht signifikant unterscheiden. Die Anwendung von Propofol zur Anästhesieaufrechterhaltung ist mit einem größeren intraoperativen TWA-MAP unterhalb des CVA-basierten MAPopt assoziiert.

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12. Curriculum Vitae

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13. Eidesstattliche Erklärung

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.

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