Limits of cerebrovascular autoregulation during and after major non-cardiac surgery

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List of abbreviations

ABP	Arterial blood pressure
ACE	Angiotensin-Converting Enzyme
ACh	Acetylcholine
AIDS	Acquired Immunodeficiency Syndrome
AKI	Acute kidney injury
ARI	Autoregulatory index
ASA	American Society of Anesthesiologists
AT1	Angiotensin II Type 1
AUC	Area under the curve
BCP	Beach chair position
BMI	Body mass index
BIS	Bispectral Index
CBF	Cerebral blood flow
CBFV	Cerebral blood flow velocity
CCI	Charlson comorbidity index
CFIx	Cerebral flow index correlation index
CKD	Chronic Kidney Disease
CO_2	Carbon dioxide
COx	Cerebral oximetry index
CPB	Cardiopulmonary bypass
CPP	Cerebral perfusion pressure
CVA	Cerebrovascular autoregulation

Abbreviations

CVR	Cerebrovascular resistance
dCA	Dynamic cerebral autoregulation
HVx	Haemoglobin volume index
ICP	Intracranial pressure
ICU	Intensive care unit
LDP	Lateral decubitus position
LLA	The lower limit of cerebrovascular autoregulation
MAP	Mean arterial blood pressure
MCA	Middle cerebral artery
mmHg	millimeter of mercury
MMOM	Major morbidity and operative mortality
Mx	Mean Flow Index
NIRS	Near-infrared spectroscopy
O_2	Oxygen
OLT	Orthotopic liver transplantation
OSAS	Obstructive Sleep Apnea Syndrome
OxyHb	Oxygenated hemoglobin
PACU	Post-anesthesia care unit
PACU24	Extended PACU providing overnight stay
$PaCO_2$	Partial pressure of carbon dioxide
PEARS	Personalized External Aortic Root Support
RALP	Robotic-assisted laparoscopic radical prostatectomy
RBCC	Red Blood Cell Concentrate

Abbreviations

rCBF	Regional cerebral blood flow
RoR	Rate of Regulation
rSO_2	Regional cerebral oxygen saturation
SBP	Systolic blood pressure
SD	Standard Deviation
TCD	Transcranial Doppler
TFA	Transfer function analysis
TWA	Time-weighted average
ULA	The upper limit of cerebrovascular autoregulation

1. Introduction

1.1 Concept of cerebrovascular autoregulation

Cerebrovascular autoregulation, known as CVA, functions as a vital safeguard within the cerebral circulatory system, maintaining a stable cerebral blood flow (CBF) irrespective of fluctuations in cerebral perfusion pressure (CPP) or arterial blood pressure (ABP). This mechanism is crucial for sustaining the cerebral oxidative metabolism (Xiong et al. 2017; Liu et al. 2022).

Initially, the prevailing belief was that CBF was unregulated, passively adjusted by CPP or ABP, an idea rooted in the Monro-Kellie doctrine. This doctrine states that due to the confined space of the brain within the skull, the different parts of the brain must maintain a certain volume balance (Friedland and Iadecola 1991).

In 1868, Donders first proposed that CBF could be actively adjusted in response to cognitive stimulation, such as neuronal activity. This concept, now recognized as neurovascular coupling or functional hyperemia, was a significant step in understanding the cerebral vascular reactions to mental processes (Donders 1868).

The year 1890 saw an experiment by Roy and Sherrington, who injected a homogenized brain solution into a dog and observed an increase in brain volume. This was indicative of an increase in CBF without a corresponding rise in ABP (Roy and Sherrington 1890). This experiment provided the first empirical evidence supporting the metabolic theory of neurovascular coupling. Although the study could not measure CBF directly, it inferred its changes from alterations in brain volume or increases in cerebral venous pressure, noting that CBF changes might be less pronounced or revert to baseline more rapidly than ABP changes.

Fog later provided foundational evidence that supported and expanded the concept of autoregulation (Fog 1938). Using a cranial window technique on anesthetized cats, Fog observed rapid changes in the diameters of pial arteries and arterioles in response to controlled changes in ABP, shedding more light on CVA.

In 1959, Lassen articulated the concept of CVA in a review that is often considered

the starting point of autoregulation studies in humans (Lassen 1959). The work of Lassen presented a comprehensive approach linking systemic hemodynamics with the regulation of CBF. The influential paper included the now-famous Lassen Curve, which correlated CBF with ABP across various studies and individuals. This curve showed a plateau in CBF across a wide range of ABP values, from a mean arterial blood pressure (MAP) of 50 to 150 millimeter of mercury (mmHg), demonstrating the maintenance of CBF despite significant ABP variations. Lassen introduced the term autoregulation to emphasize the importance of local regulatory mechanisms. The curve also included a descending line indicating the "lower limit of cerebrovascular autoregulation (LLA)", while the concept of the "upper limit of cerebrovascular autoregulation (ULA)" emerged in later research. Perspective on CVA of Lassen was significantly validated by subsequent studies, primarily based on observations from preclinical models, especially when ABP changes were gradual (Fitch et al. 1976; Jones et al. 1976; Chemtob et al. 1990; Hauerberg 1998; Pesek et al. 2014). These studies collectively identified a blood pressure range where CBF remained relatively stable, with some data suggesting or clearly showing the upper and lower limits of CVA.

The classic correlation between ABP and CBF, as previously mentioned, is now commonly referred to as static CVA (Tiecks et al. 1995; Panerai 1998, 2008; Van Beek et al. 2008). The concept of dynamic cerebral autoregulation (dCA) was first introduced by Aaslid in 1989 (Aaslid et al. 1989). While CVA is often divided into static and dynamic components, this division is more of an experimental framework than a physiological difference. "Static" refers to measurements taken when ABP and CBF have reached a steady state, often over extended periods to determine mean values. In contrast, "dynamic" captures the immediate adjustments in CBF following a change in ABP, observable within seconds during events like postural changes, coughing, or physical activity (Panerai et al. 1998, 2001, 2003; Tzeng and Ainslie 2014).

1.2 Physiology of cerebrovascular autoregulation

The foundational rules of blood flow dynamics indicate that the flow of blood to the brain is governed by the pressure difference across the cerebral blood vessels and the resistance caused by the blood vessels. Specifically, the driving force behind CBF is not just the CPP, which is determined by the difference between ABP and intracranial pressure (ICP), but also the resistance offered by the small cerebral vessels, referred to as cerebrovascular resistance (CVR). This relationship can be expressed in a basic formula: CBF = (ABP − ICP)/CVR (Early et al. 1974; Czosnyka et al. 1997; Ursino and Lodi 1997; Vavilala et al. 2002; Donnelly et al. 2016).

The resistance of the cerebral vessels, which reflects the tension of the smooth muscles in their walls, is partly dependent on the MAP. When there is a rise or fall in CPP, the myogenic reflex responds by causing the vessels to constrict or dilate, respectively. Assuming that ICP remains unchanged, CPP can be approximated by MAP. This allows for the assessment of changes in CBF across various blood pressures to determine the cerebral autoregulatory capabilities (Silverman and Petersen 2024).

1.3 Mechanism of cerebrovascular autoregulation

Maintaining CBF in line with the body metabolic needs involves a complex interplay of physiological factors. CVA adjusts vascular resistance in response to ABP changes to maintain a stable blood flow. Within the framework of CVA, a variety of mechanisms are activated, each contributing to the regulation of CBF through different pathways, including myogenic, neurogenic, endothelial, and metabolic mechanisms (Vu et al. 2024).

1.3.1 Myogenic mechanism

The myogenic response is a natural characteristic of vascular smooth muscle cells that line the cerebral arteries and arterioles, allowing them to automatically adjust to shifts in the pressure within the blood vessels and separate from any neurohormonal influences. The level of myogenic tone in the blood vessels of the brain is directly related to ABP; an increase in pressure within the blood vessel leads to a heightened

myogenic tone, causing the vessels to constrict, while a decrease in pressure results in reduced myogenic tone, leading to vessel dilation (Davis and Hill 1999). The concept of myogenic tone being pressure-dependent was first put forward by Bayliss in 1902. Although it has been over a century, the complete mechanisms behind this response are still not entirely understood (Bayliss 1902).

Based on numerous animal studies, it is hypothesized that the myogenic response begins with changes in the tension of the vascular smooth muscle wall due to variations in pressure, which then activate mechanosensitive ion channels, causing alterations in the membrane electrical potential (Bülbring 1955; Kirber et al. 1992; VanBavel and Mulvany 1994; Knot and Nelson 1995; Nelson et al. 1997; Ohya et al. 1998). This leads to the depolarization of the vascular smooth muscle cell membrane, opening voltage-operated calcium channels, and allowing Ca^{2+} to flow into the cell (Harder 1984; Hill and Meininger 1994; Wesselman et al. 1996). The resulting rise in Ca^{2+} concentration inside the cell is a crucial part of the myogenic response. The increased levels of Ca^{2+} bind to calmodulin and activate myosin light chain kinase, which phosphorylates myosin light chains, increasing the sensitivity of the contractile machinery to Ca^{2+} and causing the actin-myosin filaments to contract, resulting in the constriction of the blood vessel (Hill et al. 1990; Osol et al. 1991, 1993; VanBavel et al. 1998).

The myogenic response is also subject to various feedback mechanisms that can regulate it, such as the release of relaxing factors from the endothelium (like nitric oxide) and the activation of potassium channels that can hyperpolarize the cell membrane, counteracting the depolarizing effects of increased pressure (Huang et al. 1996; Toyoda et al. 1997; Faraci and Heistad 1998; Shin and Hong 2004; Kusano et al. 2010; Rocha et al. 2020).

In terms of CVA, the myogenic mechanism helps to adjust the resistance of the blood vessels in response to changes in ABP. When blood pressure rises, the cerebral arteries constrict to prevent an overabundance of blood flow, and when blood pressure falls, the cerebral arteries dilate to keep blood flow stable (Johnson 1986; Davis 1988). This response has its limits range, since there is a maximal dilation and a maximal

constriction that can be achieved, meaning that autoregulation has both a lower threshold (maximum dilation) and an upper threshold (maximum constriction). Damage to the myogenic mechanisms can interfere with the CVA, potentially playing a role in the development of several neurological disorders, including traumatic brain injury, stroke, and neurodegenerative diseases (Carlson et al. 2024).

1.3.2 Neurogenic mechanism

Neurogenic mechanism is the neural processes that influence the diameter and tension of the cerebral blood vessels. It involves both the central and peripheral nervous systems and are carried out by a variety of neurotransmitters and neuromodulators (Hotta 2016). It is important to note that the exact nature of neurogenic mechanisms is intricate and not yet completely understood.

The peripheral nervous system includes nerves that originate from peripheral ganglia outside the skull, which are somatic sensory nerves and the autonomic nervous system comprising sympathetic and parasympathetic branches (Hamel 2006). This system supplies nerves to the large intracranial and pial vessels on the surface of the brain and is capable of managing the overall blood flow to the brain. This is achieved through autonomic vascular regulation, which affects the diameter of the blood vessels via its autonomic nervous system components (Sato et al. 1994). Sympathetic activation generally leads to vasoconstriction and a reduction in blood flow, while parasympathetic activation can cause vasodilation and an increase in blood flow (Beishon et al. 2022; Koep et al. 2022).

The central nervous system consists of nerves that originate in the brain and extend through it to reach the parenchymal vessels. Given the specialized functions of different brain regions, regional cerebral blood flow (rCBF) must be suitably distributed. This rCBF can be regulated by changes in the diameter of the penetrating arteriole that links the pial arteriole on the cerebral surface to the intraparenchymal capillary (Hotta 2016). For instance, the cholinergic vasodilative system which originates in the basal forebrain specifically targets the neocortex and hippocampus (Sato and Sato 1992). This vasodilative response, which is independent of blood

pressure and brain glucose metabolism changes, takes place at the parenchymal penetrating arterioles to significantly boost cortical rCBF (Hotta et al. 2013).

Various neurotransmitters also play a role in the neurogenic regulation of CBF, including glutamate, γ-aminobutyric acid, acetylcholine, and norepinephrine. Depending on the receptors they bind to and the intracellular signaling pathways they trigger, these neurotransmitters can either raise or lower CBF (Morillo et al. 1997; Hamel 2006).

1.3.3 Endothelial mechanism

The inner lining of all blood vessels, including arteries, arterioles, capillaries, venules, and veins, is composed of a layer called the endothelium. Endothelial cells are crucial for various functions such as cell growth and angiogenesis, managing the exchange of fluids, maintaining the body homeostasis, controlling blood flow, and influencing vasoconstriction or vasodilation (Rajendran et al. 2013).

Endothelial cells regulate the tightness or relaxation of blood vessels through multiple pathways. One method involves the release of chemical signals that influence the nearby vascular muscle cells. Additionally, endothelial cells can transmit electrical signals to the smooth muscle cells through structures known as myoendothelial gap junctions (Aydin et al. 1991; Faraci and Heistad 1998; Hill-Eubanks et al. 2014).

A group of molecules produced by the endothelium have been found to directly impact the contraction of vascular muscle. Nitric oxide is a key example; it is a strong vasodilator that can spread to the smooth muscle cells beneath it, leading to the relaxation and dilation of the blood vessels. This process helps to counteract the effects of high blood pressure and to maintain a stable CBF. Conversely, endothelin-1 is a powerful vasoconstrictor that can reduce CBF when blood pressure is low, preventing excessive blood flow to the brain (Ashby and Mack 2021).

Furthermore, endothelial cells are sensitive to changes in shear stress-the force applied by the blood flow against the endothelial lining. Variations in shear stress can stimulate the release of substances that either widen or narrow the blood vessels, thus

adjusting their diameter to suit the current conditions (Faraci 2011; Vittum et al. 2024).

1.3.4 Metabolic mechanism

The control of CBF is closely linked to the cerebral metabolic processes. Metabolism implies that the reduction in tissue oxygen (O_2), the increase in carbon dioxide (CO_2), as well as the change in pH, play a role in this coupling (Claassen et al. 2021). Beyond O_2 and CO_2, metabolic changes might also impact CBF through the local production of other substances that affect blood vessels, such as adenosine, nitric oxide, prostanoids, and potassium ions (Iadecola 2017).

CO_2 is particularly pivotal in the metabolic regulation of CVA for its notably influence on blood vessels. Typically, an elevation in the arterial partial pressure of CO_2 ($PaCO_2$) causes the vasodilation, increasing CBF, and *vice versa* (Hoiland et al. 2019). This mechanism helps to align CBF with the cerebral metabolic demands.

Research indicates that for every mmHg increase in $PaCO_2$ beyond the norm, CBF rises 3-6% correspondingly. Similarly, each mmHg decrease in $PaCO_2$ results in a 1-3% decrease in CBF (Yoshihara 1995; Rangel-Castilla et al. 2008; Willie et al. 2012).

It is believed that the tone of the small arteries (arterioles) does not react directly to changes in CO_2 but rather to the changes in extracellular pH that result from CO_2 variations. The hypothesis is that arterial CO_2 affects pH, which in turn affects nitric oxide synthase enzymes, thereby influencing the tone of the blood vessels (Murkin 2007).

Numerous studies have explored the impact of both low (hypocapnia) and high (hypercapnia) CO_2 levels on both static and dynamic autoregulation under various conditions.

Hypercapnia leads to the dilation of cerebral blood vessels. It shifts the autoregulation plateau upward, moving the LLA to the right and the ULA to the left (Meng and Gelb 2015).Studies have shown that static CVA is compromised in hypercapnia (Perry et al. 2014); and dCA, as measured by phase angle, is also impaired following CO_2

inhalation (Carrera et al. 2009). Hypercapnia has been observed to significantly impact neurovascular coupling both at rest and during stimulation, with suggestions that it impairs the metabolic aspect of autoregulation (Maggio et al. 2013, 2014).

Hypocapnia, on the other hand, results in the constriction of cerebral blood vessels. This counters the vasodilatory effect of CVA at low MAP. Hypocapnia has been shown to lower the autoregulation plateau, with minimal change in the LLA and no clear change in the ULA (Meng and Gelb 2015). dCA, as measured by the Rate of Regulation (RoR), has been found to improve in hypocapnia (Ogoh et al. 2010).

In addition to the effects of arterial CO_2 levels, there has been considerable interest in the role of arterial O_2 levels. It is important to note that separating the effects of arterial CO_2 and O_2 levels is not always straightforward. Decreased oxygen partial pressures can increase CBF, but this effect is only observed under severe hypoxemia, where the partial pressure of O_2 is less than 50 mmHg. Such condition leads to CBF increase due to a reduction in vascular smooth muscle tone, which regulated via the activation of membrane potassium channels and inhibition of transmembrane calcium flux (Mcdowall 1966; Bonnet et al. 1991; Pearce et al. 1992). Mild hypoxia is known to impair dynamic CVA and reduce steady-state cerebral blood flow velocity (CBFV), as measured by transfer function analysis (TFA) and by both TFA and RoR (Bailey et al. 2009; Nishimura et al. 2010; Katsukawa et al. 2012). CVA is also impaired in acute hypoxia, as measured during rest and rapid cuff deflation with the autoregulatory index (ARI) (Subudhi et al. 2009). However, Ainslie et al. found that in healthy individuals, CVA improved during acute hypoxia, as indicated by an increase in low-frequency gain (Ainslie et al. 2008).

In conclusion, CVA is the outcome of multiple interacting mechanisms, and a comprehensive consideration of the factors affecting it is essential in clinical practice.

1.4 Assessment of cerebrovascular autoregulation

Impaired CVA heightens the possibility of inadequate blood flow (hypoperfusion) or excessive blood flow (hyperemia) to the brain. Precise evaluation and surveillance of CVA can offer valuable insights for clinical decision-making and therapeutic

interventions (Aaslid et al. 1989; Czosnyka et al. 1996). To assess CVA, it is necessary to track CBF concurrently with changes in CPP, which can occur naturally or be deliberately induced, and in the latter case, through either pharmacological or non-pharmacological means (Vavilala et al. 2002). Under normal circumstances, mean arterial blood pressure (MAP) serves as a surrogate for CPP because direct measurement of CPP is quite invasive. For patients who have not suffered an acute brain injury and have normal ICP, it is reasonable to consider MAP as equivalent to CPP (Rivera-Lara et al. 2017). To begin with, the pivotal element in evaluating CVA is the necessity for precise and quantitative measurements of CBF.

1.4.1 Methods of measuring cerebral blood flow

1.4.1.1 Transcranial Doppler ultrasound

In recent years, Transcranial Doppler ultrasound (TCD) has emerged as the preferred option for nearly all CVA measurements in studies. This preference is due to the excellent temporal resolution of TCD, which enables to capture high-frequency and continuous data that can be integrated with other modalities such as ABP to quantify CVA. TCD is portable, non-invasive, and can be feasibly used in various settings such as emergency rooms, critical care units, or operating theaters.

The validation of TCD for measuring CBFV in the middle cerebral artery (MCA) was first conducted by Aaslid et al. (Aaslid et al. 1982). TCD operates by using low-frequency transducer probes to insonate basal cerebral arteries. For CVA assessment, the MCA is commonly utilized to measure CBFV through the temporal bone window. The emitted waves pass through the skull and soft tissues and are reflected by the velocity of moving red blood cells, creating a "Doppler shift frequency" that is calculated by the difference between back and forth waves to determine blood flow speed (Purkayastha and Sorond 2013).

It is important to note that TCD measures CBFV, not CBF. Converting between the two requires knowledge of the dynamic cross-sectional area of the vessel or the cerebral vasculature diameter, while vasodilation and constriction are controlled by multiple mechanisms described above. Understanding the relationship between CBFV

and CPP or MAP can indirectly reflect CVA. The autoregulation status can be quantified using the ARI, which scales autoregulation from 0 (none) to 9 (maximal) (Tiecks et al. 1995).

However, TCD use for CVA measurement and other clinical applications comes with several limitations. Initially, the use of TCD demands operators who are not only highly skilled but also extensively trained, capable of accurately locating the target arteries. Following that, findings from extensive research indicate that in 3% to 5% of patients across all age brackets, the temporal bone windows necessary for examination with 2-MHz probes are either missing or not adequately developed. This prevalence is significantly higher among the elderly (Arnolds and Von Reutern 1986; Grolimund et al. 1987; Hennerici et al. 1987). Additionally, the operation of monopolar electric knives during surgery and the presence of numerous low-frequency signals can create interference in the form of background noise, potentially compromising the precision of TCD measurements. Lastly, as previously noted, TCD measures the velocity of CBF but does not account for the diameter of the blood vessels (or their cross-sectional area). Consequently, any alterations in the vessel diameter that occur during the course of interventions and measurements can lead to inaccuracies in the estimation of CBF using TCD.

1.4.1.2 Near-Infrared Spectroscopy

More recently, Near-Infrared Spectroscopy (NIRS) has gained interest for noninvasively measuring regional cerebral oxygen saturation (rSO_2). The simplicity and cost-effectiveness of the measurement process, combined with the possibility of achieving high spatial and temporal resolution, and the versatility of data provided, make NIRS an appealing method for various applications.

In 1977, Jöbsis pioneered the application of NIRS for in vivo monitoring of brain perfusion and oxygenation (Jöbsis 1977). This non-invasive optical technique is designed to track changes in the concentration of biological chromophores present within tissues. Capitalizing on the ability of near-infrared light, with wavelengths ranging from 700 to 1000 nm, to pass through bone and penetrate a few millimeters

into the brain, NIRS measures the absorption by chromophores such as oxygenated hemoglobin (OxyHb) and deoxygenated hemoglobin. As the light propagates through the brain tissue, the degree of absorption is directly related to the concentration of the chromophores and the distance the light covers within the tissue. This relationship is articulated by the modified Beer-Lambert Law, which takes into account the scattering of light within the cerebral architecture (Delpy DT and Cope M 1997). NIRS assesses the variation in light attenuation at multiple wavelengths, enabling it to deduce the concentration changes of OxyHb and deoxygenated hemoglobin. These measurements are indicative of rSO_2 and reflect the equilibrium between oxygen supply and metabolic demand. Consequently, NIRS has proven to be highly responsive to shifts in the cerebral oxygenation levels (Roldán and Kyriacou 2021).

A NIRS device typically comprises a laser diode that emits near-infrared light into the brain and a sensor that detects the significantly diminished light that returns. These components are housed within a single probe, usually positioned a few centimeters apart. The probe is typically affixed to the forehead, avoiding the central sinus areas. This setup allows the probe to sample a broad spectrum of tissue types, encompassing the skin, underlying fat, skull, cerebrospinal fluid, and brain tissue, as well as the various blood vessels present within. Consequently, the signal obtained is a composite derived from all these different sources, which must be factored into the signal interpretation. The nature of this composite signal is heavily influenced by the distance between the laser diode and the sensor. Greater separation allows for deeper light penetration and a higher proportion of photons reaching the brain. Conversely, a smaller distance is preferable for maintaining an adequate signal-to-noise ratio. Thus, the optimal spacing between the diode and sensor is a balance between obtaining a significant signal contribution from the cerebral cortex, which necessitates a larger gap, and ensuring a clear, noise-free signal, which is facilitated by a smaller gap. This balance is crucial for accurately interpreting the NIRS data and obtaining reliable measurements of cerebral oxygenation and blood flow.

NIRS technology was initially employed to measure CBF by Edwards and colleagues in 1988 (Edwards et al. 1988). This approach fundamentally utilized OxyHb as an

indicator, in conjunction with the Kety-Schmidt methodological framework. To elicit fluctuations in OxyHb levels, arterial saturation is intentionally altered, such as by inhaling pure oxygen, which leads to elevated arterial oxygen saturation and, consequently, an increase in OxyHb. With several presuppositions, it becomes possible to formulate a calculation for precise perfusion levels. Consequently, CBF can be assessed non-invasively, with the added necessity of only one supplementary measurement: arterial saturation.

1.4.1.3 Other methods of measuring cerebral blood flow

A significant development in this domain was the nitric oxide technique pioneered by Kety (Kety and Schmidt 1948). This approach is based on the Fick principle, which is about the conservation of mass, and it involves measuring the variations in the concentrations of nitrous oxide in cerebral arteries and veins following its inhalation. The Kety-Schmidt technique provides an average CBF measurement over a period of 10 to 15 minutes. A variation of this method was later introduced by Lassen and Ingvar in 1961, who utilized the intra-arterial injection of radioactive isotopes like Krypton-85 or Xenon-133 (Lassen and Ingvar 1961). By employing a camera to record the intracerebral concentration of the tracer, the authors were able to deduce both global and regional CBF estimates. Since then, almost all subsequent imaging methodologies have been developed based on the same tracer principle for quantifying CBF.

Another crucial advancement took place from the 1970s onward with the introduction of techniques that were safe for human use, beginning with computed tomography, followed by positron emission tomography, and magnetic resonance imaging (Wintermark et al. 2005; Payne S 2018). These methodologies have greatly enhanced our understanding of cerebrovascular system anatomy, physiology, and pathophysiology, and they are currently instrumental in diagnosing and researching diseases that impact cerebral circulation. Despite the continuous technological progress that has provided more detailed insights and high spatial resolution of CBF data, along with the capacity to assess absolute CBF, these methods still suffer from

inadequate temporal resolution for capturing rapid CBF changes due to physiological or pathophysiological stimuli. Furthermore, they are not ideal for bedside monitoring due to size constraints and radiation exposure (Rostami et al. 2014).

In addition to the non-invasive CBF measurement techniques previously discussed, there exist several invasive alternatives. These include ICP monitoring, brain tissue oxygenation assessment, laser Doppler flowmetry, and thermal diffusion methods (Vajkoczy et al. 2000; Rajan et al. 2009; Rohlwink and Figaji 2010). Such methods are advantageous for their durability in extended cerebral circulation surveillance and are predominantly utilized in invasive animal research or in the care of patients with severe conditions, attributable to their invasive characteristics.

1.4.2 Techniques for analyzing cerebrovascular autoregulation

Since the 1980s, the advent of TCD technology, combined with many techniques for ABP measurement, has enabled the continuous and simultaneous acquisition of both CBFV and ABP data. This has been achieved with high temporal resolution and at a relatively low cost. Beyond just CBFV, other intracranial parameters often play a significant role in dynamic vasoregulatory assessments. These include rSO_2 measured by NIRS and ICP as monitored through cerebrospinal fluid drainage systems. The core principle underlying these dynamic measurements is consistent across different methodologies: the input signal is represented by changes in blood pressure or volume, and the output signal is the resulting alteration within the intracranial compartment. By using spontaneous oscillations in ABP and CBF, researchers have developed a variety of mathematical methods to understand the relationship between these two critical variables. These analysis techniques are categorized into those that operate in the time domain and those that operate in the frequency domain.

1.4.2.1 Time domain analysis

Time domain analysis involves assessing the correlation between ABP and cerebral output signals (Kostoglou et al. 2024). In this background information, RoR, ARI, and the correlation coefficients are included for detailed description.

RoR

The RoR, first introduced by Aaslid et al. in 1989, is an early metric used to quantify CVA. It measures the speed of CBFV reverting to its baseline after a change in ABP by thigh cuff deflation (Aaslid et al. 1989). RoR values are influenced by carbon dioxide levels ($PaCO_2$), with an inverse relationship observed as $PaCO_2$ levels rise. However, its reliability can be compromised by noise in the data and the specifics of the testing procedure, which may affect repeatability and patient tolerance.

ARI

The ARI, proposed by Tiecks et al., is a scale ranging from 0 (no dynamic CVA) to 9 (optimal CVA). It is derived from a model based on a second-order differential equation that evaluates the response of CBFV to changes in ABP, considering both past and present values. The simplicity of ARI has contributed to its broad application across numerous studies (Tiecks et al. 1995).

Time Correlation Method

The correlation coefficient, introduced by Czosnyka et al. in 1996, is a widely utilized metric for assessing CVA (Czosnyka et al. 1996). It calculates Pearson's correlation coefficient between consecutive samples of CPP and CBFV, known as Mx.

There are also many studies calculating the Pearson correlation coefficient between 30 consecutive, time-averaged (10 sec) values of ABP and CBF or its surrogates. The resulting coefficient provides an estimate of autoregulatory function respective to each variable. The coefficient for CBFV measured by TCD is Mxa (Czosnyka et al. 2009), for regional cerebral oxygenation derives from NIRS is termed the cerebral oximetry index (COx) or tissue oxygenation index, for total haemoglobin concentration derived from NIRS is haemoglobin volume index (HVx), while for cerebral flow index derived from ultrasound-tagged near infrared is cerebral flow index correlation index (CFIx) (Brady et al. 2007; Lee et al. 2009; Blaine Easley et al. 2013; Murkin et al. 2015). These coefficients range from -1 (perfect negative correlation) to 1 (perfect positive correlation), with 0 indicating no correlation. A positive correlation suggests impaired CVA, reflecting a direct relationship between ABP and CBF, whereas a zero value suggests intact CVA where CBF is not influenced by ABP changes. Each index has a unique threshold for impaired CVA, varying from

0.069 to 0.46, depending on the devices used for CBF or surrogate measurement (Rivera-Lara et al. 2017).

Another significant index is the pressure reactivity index (PRx), which is derived from ABP and invasive ICP measurements, serving as a surrogate for cerebral blood volume (Czosnyka et al. 1996). A positive correlation with PRx indicates a passive transmission of ABP fluctuations to cerebral blood volume and ICP, while a negative correlation suggests active cerebrovascular counter-regulation and preserved vasoreactivity. PRx offers the advantage of continuous, easy measurement in any patient equipped with a parenchymal ICP monitor, an ABP line, and suitable analysis software.

1.4.2.2 Frequency domain analysis

Frequency domain analysis is a technique for examining the dynamic interplay between ABP and indicators of CBF, such as CBFV, within the frequency domain. One specific approach within frequency domain analysis is TFA, which investigates how the CBF regulation is influenced by the different frequency components of ABP oscillations (Panerai et al. 2023).

TFA assesses dynamic CVA by treating it as a linear time-invariant system with ABP as the input and CBFV as the output. It uses spontaneous fluctuations in ABP and CBFV and applies a fast Fourier transform to generate spectral estimates. TFA assumes that dynamic CVA functions as a high-pass filter, permitting high-frequency ABP changes to influence CBFV while reducing the impact of low-frequency changes (Meel-van Den Abeelen et al. 2014). TFA yields three principal parameters: gain, phase and coherence.

The first one is gain, which measures the extent to which ABP fluctuations are transmitted to CBFV. A low gain suggests effective CVA, while a high gain indicates impaired CVA. The second one is phase, which describes the temporal delay between changes in ABP and CBFV. A larger phase shift suggests that the cerebrovascular system is effectively buffering the pressure changes. The third one is coherence, which indicates the linear relationship between ABP and CBFV. Coherence values

above 0.5 are generally considered acceptable and are essential for confirming the linearity assumption of TFA (Diehl et al. 1995; Blaber et al. 1997; Zhang et al. 1998; Mahony et al. 2000). However, the reliability of TFA can be affected by data quality, analysis settings, and nonstationary behavior in the data. Organizations such as the Cerebrovascular Research Network provide guidelines to improve the robustness of TFA analysis (Panerai et al. 2023).

To summarize, TFA is a valuable instrument for evaluating how the cerebral circulation responds to ABP changes in a frequency-dependent manner, offering detailed insights into the function of CVA and its variations under different conditions.

In conclusion, the assessment of CVA primarily revolves around two parameters: CBF and ABP. For measuring CBF non-invasively, the most common methods are TCD, which assesses CBFV, and NIRS, which assesses rSO_2. These methods are favored for their portability, non-invasive nature, ease of use, and practicality in both clinical and research settings. For assessing CVA, time domain analysis and frequency domain analysis are two most techniques. The correlation coefficient between ABP and CBF such as Mx and COx are widely used in clinical practice.

1.5 The limits of cerebrovascular autoregulation

The limits of CVA refer to the lower and upper thresholds of CPP or ABP within which the cerebral vasculature can effectively adjust to maintain stable CBF, when exceeding this range, CBF becomes pressure-dependent. ABP is commonly used as a surrogate for CPP, assuming that the ICP or central venous pressure are within normal or low range as mentioned above.

The LLA, also known as the breakpoint, is the ABP threshold below which a decrease in pressure results in a corresponding decrease in CBF, risking cerebral ischemia. Conversely, the ULA is the point at which the autoregulatory capacity is overwhelmed, and further increases in ABP lead to increased CBF, potentially causing hyperperfusion injury.

In healthy adults, the typical range for CVA is between 50 and 150 mmHg of CPP or 60 and 160 mmHg of mean arterial pressure (Armstead 2016). It is important to

recognize that these values represent the "normal" range for the autoregulatory mechanism to maintain stable CBF despite fluctuations in blood pressure. However, the precise values for the LLA and ULA can vary significantly among individuals and may be affected by factors such as sex, comorbidities, and specific conditions. For instance, studies have reported substantial interindividual variability in the LLA, ranging from 30 to 90 mmHg in adults and 20-55 mmHg in children during cardiopulmonary bypass (CPB) (Joshi et al. 2012; Hori et al. 2017). These findings align with earlier research that indicated the LLA can vary between 33 and 113 mmHg (Drummond 1997). In terms of the ULA, Hori D et al. found that the MAP at the ULA ranges from 68 to 102 mmHg in adults during CPB (Hori et al. 2014). Additionally, Rivera-Lara et al. determined the median ULA to be 93.5 mmHg for intensive care unit (ICU) patients (Rivera-Lara et al. 2018). This variability underscores the importance of considering individual differences when assessing and managing CVA.

2. Aim of the study

The primary aim of this study is to conduct a comprehensive investigation into the limits of CVA during and after major non-cardiac surgery, with a specific focus on comparing the numerical thresholds at which autoregulation is compromised, as well as the time-weighted average (TWA) of mean arterial pressure (TWA-MAP) that exceeds these limits. This research will contribute to a deeper understanding of the cerebrovascular response to major non-cardiac surgery, inform clinical practice to optimize patient safety, and pave the way for future research into cerebrovascular protection in the perioperative setting. The specific objectives of this research are as follows:

1. To identify and quantify the specific lower and upper limits of CVA both during and after surgery.
2. To compare the numerical values of the lower and upper limits of CVA during surgery to those observed in the postoperative period.
3. To calculate the TWA-MAP that exceeds the autoregulatory limits for both the intraoperative and postoperative phases to assess the cumulative exposure to cerebrovascular autoregulatory failure.
4. To evaluate the differences between the TWA-MAP values that surpass the CVA thresholds during surgery and those observed after the surgery.

3. Hypothesis

1. The numerical limits of CVA will not differ significantly between the intraoperative and postoperative periods.

2. The time-weighted average of mean arterial pressure that exceeds the autoregulatory limits will be higher during surgery compared to the postoperative period.

4. Material and methods

4.1 Study registration and ethical information

On January 14, 2019, the Ethics Committee of the Hamburg Chamber of Physicians authorized and approved the study under the registration number PV5980. Each patient was informed about all research procedures and associated risks. Prior to performing any study-related procedure, written informed consent was obtained.

4.2 Study population

This is a sub-study of a single-center prospective cohort study that intends to investigate the relationship between TCD and NIRS as intraoperative CVA assessment techniques. Starting August 9, 2021, patients scheduled for non-cardiac surgery at the University Medical Center Hamburg-Eppendorf who met the inclusion criteria were enrolled in the main study. The present sub-study includes patients who were enrolled between the start date of the study and September 29, 2023.

4.2.1 Inclusion criteria

Eligibility for the study was determined based on the following criteria:

1. Participants were scheduled for non-cardiac surgical procedures anticipated to last more than 120 minutes;
2. They were undergoing general anesthesia for the surgery;
3. They either had a clinical need for invasive blood pressure monitoring or had consented to the insertion of an arterial line specifically for the study;
4. It was expected that they would experience blood loss exceeding 500 ml during surgery, or they had a preoperative diagnosis of chronic anemia, defined as a hemoglobin concentration below 12 g/dl for women and below 14 g/dl for men;
5. They possessed a strong command of the German language, necessary for conducting the postoperative neuropsychological assessment aimed at detecting cognitive dysfunction;
6. They provided their informed written consent to participate in the study.

4.2.2 Exclusion criteria

Patients were excluded from the study if any of the following conditions were met:

1. They were pregnant;
2. They were under the age of 18 years;
3. They had contraindications for invasive blood pressure monitoring, such as skin infections at potential puncture sites;
4. They had a history of cerebrovascular events, including ischemic stroke or transient ischemic attack.

4.3 Anesthesia management

As per the conventional clinical anesthesia care, general anesthesia was induced by administering an intravenous opioid such as sufentanil (0.3-1 ug/kg) or remifentanil (0.3-0.5 ug/kg), and then propofol (1.5-2.5 mg/kg). A muscle relaxant was given, and then endotracheal intubation was carried out.

To maintain general anesthesia throughout surgery, either inhalating sevoflurane with an age-adjusted targeted minimum alveolar concentration of 1 or propofol (4-8 mg/kg) were employed. A tidal volume of 6-8 ml/kg was administered during positive pressure ventilation. To achieve a specified expiratory CO_2 of 35-42 mmHg, the respiratory rate was modified accordingly. If the mean blood pressure fell below the threshold of 65 mmHg, intravenous norepinephrine and crystalloid fluids were given to maintain the MAP above 65 mmHg.

Either the left or the right radial artery was used to insert an arterial monitoring catheter (Leader-Cath, VYGON GmbH & Co. KG, Aachen, Germany), which was then connected to an appropriate arterial monitoring system (Combitrans UKE EXAdyn, B. Braun Melsung, Germany). Around the left midaxillary area, at heart level, was where the blood pressure calibration line was positioned. Every time the intraoperative position of the patient was modified, the blood pressure monitor was recalibrated.

4.4 Intraoperative cerebrovascular autoregulation measurement

Following the initiation of general anesthesia, the forehead on the right side of the patient was meticulously cleaned and degreased using an alcohol-based disinfectant. If the right side was not accessible, the left side was utilized instead.

Any surplus disinfectant was meticulously removed, and the process involved waiting for the skin to be fully dry. Subsequently, an adhesive NIRS probe (INVOS™ Cerebral/Somatic Oximetry Adult Sensors, Medtronic, Minneapolis, Minnesota) was affixed to the frontal region of the skull. The probe was securely fitted to the skin to ensure that no external light could affect the sensor. Specifically, the NIRS sensor was positioned over the frontal scalp, above the eyebrows and just below the hairline, with the edge of the sensor aligned with the midline of the forehead, adhering to the manufacturer guidelines. This positioning method avoids the need for shaving eyebrows or the hairline and does not disrupt standard clinical procedures. The rSO_2 was then measured and documented using a NIRS monitor (INVOS™ 5100 Cerebral Oximeter, Medtronic, Minneapolis, Minnesota). Upon initiation of the measurement, the NIRS monitor automatically calibrated itself, and the real-time rSO_2 values were displayed on the monitor screen.

A GE bedside monitor (GE Healthcare Systems, GE Healthcare, United States) was utilized for recording MAP. This monitor, equipped with real-time invasive blood pressure monitoring capabilities, and an INVOS monitor that provides real-time regional oxygen saturation values, were both interfaced with a laptop. The data collected were then analyzed using a dedicated software program (ICM+ software, Cambridge Enterprise ICM+, Cambridge, UK). The ICM+ software, capable of performing real-time analysis from various patient monitoring devices, was created and refined by a team at Cambridge University (Smielewski et al. 2012). The necessary software settings for this research were finalized with the support of the software developers.

The correlation between MAP and rSO_2 was determined at intervals of 10 seconds.

The values obtained were then averaged over a period of 300 seconds to generate an autoregulation index, denoted as COx. This index serves as a dependable proxy for CBF in the context of autoregulation monitoring (Brady et al. 2007, 2010). The index value, ranging from -1 to +1, indicates the state of the cerebral autoregulatory capacity. A value less than 0.3 suggests that CVA is functioning properly. When CBF is within the autoregulatory limits and is not influenced by CPP or MAP, COx tends towards zero or becomes negative. Conversely, if MAP falls outside the limits of CVA, CBF will change passively with CPP or MAP, indicating impaired CVA. In such cases, COx increases, becoming positive and potentially approaching 1.

The intraoperative monitoring period was extended to a minimum of 2 hours. Throughout this time, the real-time curves for COx, MAP, and rSO_2 were graphed using distinct colors and documented. Additionally, any instances where the MAP or NIRS measurements were disrupted for any reason were meticulously noted.

4.5 Postoperative cerebrovascular autoregulation measurement

Following surgery, patients were transferred to post-anesthesia care unit (PACU), or an extended PACU (PACU24) providing overnight stay or ICU. Patients were extubated in the operating room before being moved to the PACU or PACU24. Invasive blood pressure measurements and the NIRS recordings pertaining to the study were stopped during transport and resumed as soon as the patients reached the PACU or PACU24. Following transfer, some patients were extubated later in ICU, and invasive blood pressure and NIRS recordings were resumed.

Consistent with the intraoperative procedures, the MAP, rSO_2, and COx were measured and calculated using the same methodology. A dynamic 300-second window was employed to calculate the average correlation coefficients, which were updated every 10 seconds. The postoperative monitoring was conducted for at least 60 minutes. Any disruptions to the MAP or NIRS measurements, regardless of the reason, were meticulously logged.

4.6 Data collection

After each session of data collection, the unprocessed CVA data and the relevant configuration files were saved. These raw data sets were subsequently exported in a format known as comma-separated values. The measurements of systolic arterial pressure, diastolic blood pressure, MAP, rSO_2, and COx were taken at one-minute intervals.

Additionally, clinical characteristics about the study participants were collected. This included demographic information such as age, sex, height, and weight, as well as a comprehensive medical history. The medical history encompassed a range of conditions: hypertension, myocardial infarction, heart failure, peripheral vascular disease, pulmonary disease, ulcer disease, liver disease, diabetes mellitus, chronic kidney disease, solid tumors, and lymphomas. The medication history included angiotensin-converting enzyme inhibitors, angiotensin 1 receptor antagonists, beta blockers, other antihypertensive drugs, thiazide diuretics, loop diuretics, and aldosterone antagonists. Furthermore, parameters related to the perioperative period were also extracted. This included details on surgery types, duration of the surgery, intraoperative blood loss and hemoglobin concentration, as well as the types of anesthesia medications administered. These data were retrieved from electronic health record systems and meticulously documented in a dedicated Excel spreadsheet.

4.7 Determination of limits of cerebrovascular autoregulation

Unprocessed 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. There are several approaches to calculate the LLA and the ULA based on CVA. The most frequently utilized method is the second-degree polynomial equation, often depicted as a "U-shaped" graph, which was used in the present study.

The process began by creating a parabolic curve that closely aligns with all the data, with MAP on the X-axis and COx on the Y-axis. To achieve this, the MAP values that

have been sifted through were arranged in bins of 2 mmHg along the X-axis, and the COx values were grouped and averaged within each MAP interval. Any data bin that represents less than 1% of the total dataset was excluded from the analysis. Subsequently, a U-shaped curve was crafted to closely align with the data points, based on the MAP and COx coordinates. The LLA was defined by drawing a straight horizontal line at cut-off values (COx, 0.3), as illustrated in Figure 1 using the ICM+ software. The X-coordinate of the point at which the straight line meets the U-shaped curve on the left side (at which the COx decreased from ≥ 0.3 to < 0.3) was defined as the LLA, on the right side (at which the COx increased from < 0.3 to ≥ 0.3) was defined as ULA. If no intersection was observed, the value was considered to be absent. For each patient, intraoperative and postoperative values of the LLA and the ULA were computed, if the data quality was sufficient to generate a curve.

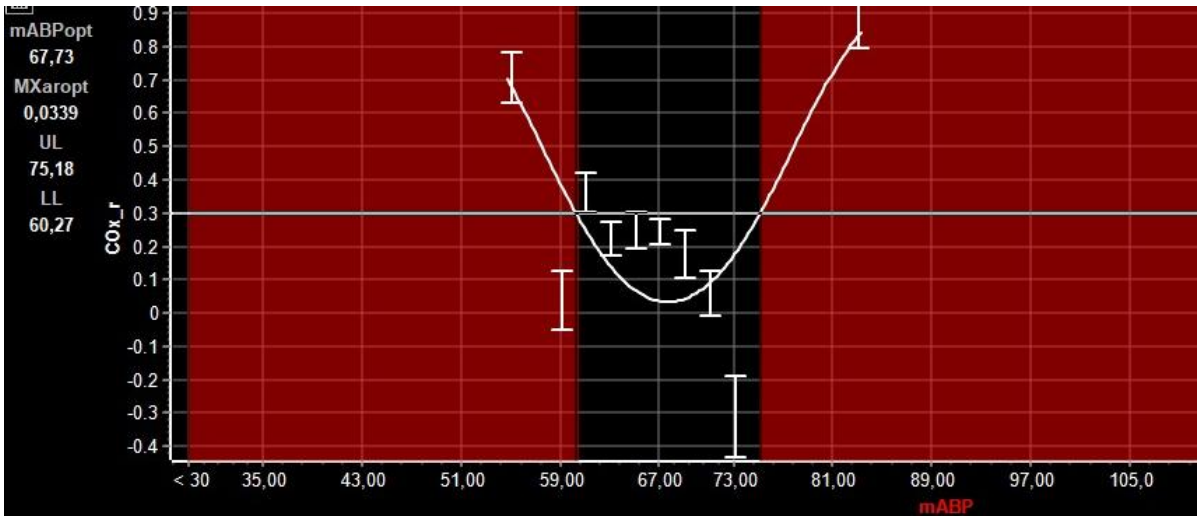

Figure 1. The U-shape curve calculated by the ICM+ software

The U-shaped curve was derived from data one example patient. In the graph, COx is depicted on the Y-axis, while MAP is represented on the X-axis. The vertical bars indicate the interquartile range, specifically the 25th to 75th percentile values of COx for each MAP interval. The U-shaped curve is designed to closely match the majority of the data points. For this particular patient, the LLA was determined to be 60.27 mmHg, and the ULA was 75.18 mmHg.

Abbreviations: COx: cerebral oximetry index; MAP: mean arterial blood pressure; LLA: the lower limit of cerebrovascular autoregulation; ULA: the upper limit of cerebrovascular autoregulation.

4.8 Determination of time-weighted average mean arterial blood pressure outside the limits of cerebrovascular autoregulation

The calculation of TWA-MAP below the LLA involved a process where the area under the curve (AUC) for MAP values that were below the LLA was divided by the total duration of the monitoring period (Maheshwari et al. 2020). The AUC was determined by summing the product of the magnitude and duration by which MAP was below the LLA per hour of measurement time (expressed in mmHg h) (Hori et al. 2014).

Similarly, the TWA-MAP exceeding the ULA was calculated by normalizing the total dose of MAP above the ULA with respect to the monitoring time. The total dose is mathematically defined as the sum of the product of the MAP values above the ULA and the duration for which these values were sustained (also expressed in mm Hg h) (Nakano et al. 2021).

For each patient, the time-weighted averages of MAP values that were either below the LLA or above the ULA were determined, provided that the respective autoregulation limits were established.

4.9 Exploration of factors with potential influence on the limits of cerebrovascular autoregulation and time-weighted average mean arterial blood pressure beyond the limits of cerebrovascular autoregulation

Eight linear regression models were developed to identify factors linked to both intraoperative and postoperative CVA limits and TWA-MAP values that exceed these limits.

For the intraoperative models, two models focused on intraoperative CVA limits and another two models examined intraoperative TWA-MAP values that surpass CVA limits. The dependent variables in these models included intraoperative LLA,

intraoperative ULA, TWA-MAP below LLA, and TWA-MAP above ULA. Independent variables were chosen that have potential influence on intraoperative CVA limits or TWA-MAP beyond CVA limits based on clinical experience and literature reading. They encompassed baseline characteristics including age, sex, body mass index (BMI); medical history data including American Society of Anesthesiologists (ASA) physical status, arterial hypertension, presence of obstructive sleep apnea syndrome (OSAS); surgery and anesthesia related factors containing preoperative hemoglobin levels, use of sevoflurane for anesthesia, noradrenaline dosage, blood loss, crystalloid and colloid administration, blood transfusion, and surgery duration. These indicators were then analyzed for collinearity. If 2 or more factors were tested with collinearity, multiple researchers would discuss the indicators with collinearity and select the more suitable one to be included in the regression analysis.

For the postoperative models, two models were designed to identify factors associated with postoperative CVA limits and the remaining two models aimed to determine factors related to postoperative TWA-MAP values that exceed CVA limits. The dependent variables in these models were postoperative LLA, postoperative ULA, TWA-MAP below LLA, and TWA-MAP above ULA. Independent variables were selected for their potential to impact postoperative CVA limits or TWA-MAP beyond CVA, as determined by clinical knowledge and literature review. They comprised baseline characteristics including age, sex, BMI, ASA physical status, arterial hypertension, OSAS status; surgery and anesthesia related factors including change in hemoglobin from pre- to post-surgery, sevoflurane for anesthesia maintenance, noradrenaline dosage, blood loss, crystalloid and colloid administration, blood transfusion, and surgery duration. Subsequently, these metrics were tested for collinearity. A group of researchers deliberated over the collinear indicators and decided the most appropriate one to incorporate into the definitive model.

4.10 Statistical analysis

The data collected for this study were represented using descriptive statistics to

summarize and organize the information. For continuous variables, mean±SD was applied to describe normalized data while median (First Quartile (Q1), Third Quartile (Q3)) was used to describe unnormalized data. Categorical data were summarized using percentages. The normality of the distribution of continuous variables was assessed using the Shapiro-Wilk test, which is robust for small sample sizes. The Levene's test was employed to test for homogeneity of variance across groups.

For comparing the means between two independent groups, the independent samples t-test was used when the assumptions of normality and homogeneity of variance were passed. For non-parametric data, the Mann-Whitney U test was applied.

Eight linear regression models above were simplified by employing a backward elimination method, where at each stage, the variable with the highest *p*-value was removed until only those with *p*-values less than 0.05 remained.

All statistical analyses were conducted using SPSS Version 25 (IBM SPSS Statistics, IBM Corporation). The threshold for statistical significance was established at $p < 0.05$ for all tests. For the creation of tables and graphs, SPSS Version 25, Microsoft Excel, or R Version 4.2.2 (The R Foundation) were utilized.

5. Results

5.1 Study population

Between August 9, 2021, and September 29, 2023, a total of 509 patients were selected as eligible candidates with written consents. Among them, 28 patients subsequently withdrew for various reasons, including 4 patients who were unable to have an arterial catheter placed, 12 whose surgeries were cancelled or rearranged, and 12 whose surgery duration was too short to be included. Of the remaining 481 patients who underwent the study-related CVA assessments, 46 patients were unable to complete the intraoperative or postoperative measurements and clinical data of 1 patient were unavailable, which led to calculation that included data from 434 patients. Finally, 11 participants could not have their intra- and postoperative limits of CVA determined. The remaining 423 participants were included in the final data analysis of the study.

The process of patient enrollment in the study is detailed in Figure 2, which provides a visual representation of the comprehensive steps taken to include participants in the research.

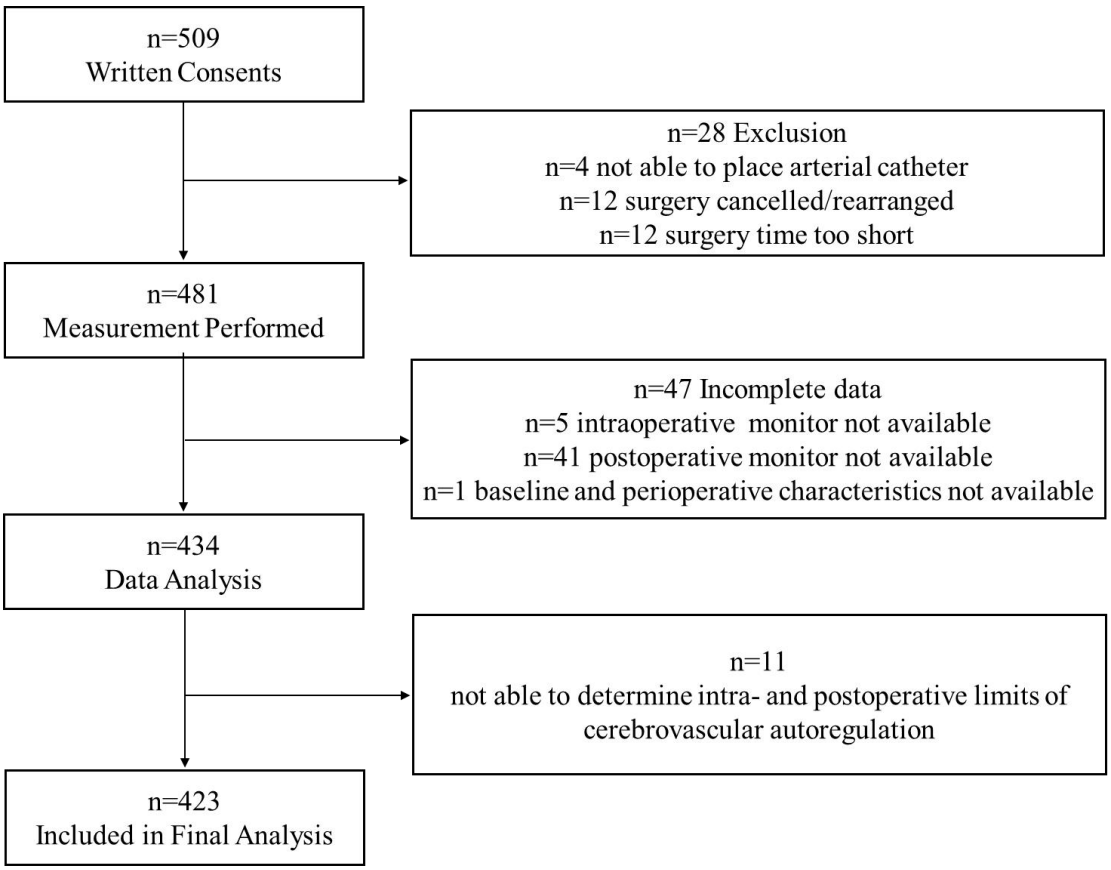

Figure 2. The flow chart of study participants

5.2 Baseline characteristics

The average age of the participants in this study was 62.96±12.34 years, and 62.9% were male. 51.3% of the study group had a medical history of arterial hypertension prior to the operation. In terms of the ASA classification, over half of the participants, 53.4%, were classified with mild systemic disease, while 43.5% had severe systemic conditions. The median CCI score was 2.00 (2.00, 4.00). Further details regarding the medical and medication histories of the participants are outlined in Table 1.

5. Results

Table 1. Baseline characteristics of study participants

Count of involved patients	n=423
Age, yr, mean±SD	62.96±12.34
Sex, n (%)	
Male	266 (62.9)
Female	157 (37.1)
BMI, kg/m^2, median (Q1, Q3)	25.57 (23.18, 28.81)
ASA classification, n (%)	
I	10 (2.4)
II	226 (53.4)
III	184 (43.5)
IV	3 (0.7)
Medical history, n (%)	
Arterial hypertension	217 (51.3)
Myocardial infarction	30 (7.1)
Heart failure	9 (2.1)
Cerebrovascular diseases	4 (0.9)
Dementia*	1 (0.2)
Peripheral vascular disease	19 (4.5)
Pulmonary disease	35 (8.3)
OSAS	43 (10.2)
Collagenosis*	9 (2.1)
Ulcer disease	10 (2.4)
Liver disease	21 (4.8)
Diabetes mellitus	60 (14.2)
Hemiplegia	1 (0.2)
Moderate to severe CKD	13 (3.1)
Solid tumor	387 (91.5)
Leukemia	0 (0)
Lymphoma	5 (1.2)

AIDS	1 (0.2)
Medication history, n (%)	
ACE inhibitor	85 (20.1)
AT1 receptor antagonist	87 (20.6)
Beta blocker	96 (22.7)
Other antihypertensive drugs	74 (17.5)
Thiazide diuretics	32 (7.6)
Loop diuretics	21 (5.0)
Aldosterone antagonist	9 (2.1)
Oral antidiabetic drugs	41 (9.7)
Insulin	18 (4.3)
Lipid reducers	88 (20.8)
Aspirin	61 (14.4)
Anticonvulsant drugs*	7 (1.7)
Antidepressants	28 (6.6)
Neuroleptics	6 (1.4)
L-Dopa dopamine agonists	4 (0.9)
Others	232 (54.8)
CCI without age**, median (Q1, Q3)	2.00 (2.00, 4.00)

Continuous variables are presented as mean±SD or median (Q1, Q3) while categorical variables are presented as n (% within group).

*: There is 1 missing data in this variable.

**: There are 2 missing data in this variable.

Abbreviations: SD: Standard Deviation; Q1: First Quartile; Q3: Third Quartile; BMI: Body Mass Index; ASA classification: American Society of Anesthesiologists Classification; OSAS: Obstructive Sleep Apnea Syndrome; CKD: Chronic Kidney Disease; AIDS: Acquired Immunodeficiency Syndrome; ACE: Angiotensin-Converting Enzyme; AT1: Angiotensin II Type 1; CCI: Charlson Comorbidity Index.

5.3 Perioperative parameters

The median length of the surgical procedures in this study was 193.00 (155.00, 278.00) minutes. Urological surgery was the predominant type of operation, accounting for 46.1% of the total surgeries performed. The median blood loss

recorded was 500.00 (300.00, 10000.00) ml, and the median decrease in hemoglobin levels was 2.60 (1.80, 3.40) g/dL. A substantial majority of the patients, 69.3%, were administered sevoflurane for anesthesia. A comprehensive list of perioperative parameters is provided in Table 2.

Table 2. Perioperative parameters of study patients

Count of involved patients	n=423
Surgery	
Duration of surgery, min, median (Q1, Q3)	193.00 (155.00, 278.00)
Blood loss**, ml, median (Q1, Q3)	500.00 (300.00, 1000.00)
△ haemoglobin*, g/dL, median (Q1, Q3)	2.60 (1.80, 3.40)
Preoperative haemoglobin, g/dL, median (Q1, Q3)	13.60 (12.20, 14.70)
Postoperative haemoglobin*, g/dL, median (Q1, Q3)	10.80 (9.50, 11.70)
Surgery type	
Urology surgery, n (%)	195 (46.1)
General surgery, n (%)	137 (32.4)
Gynaecology surgery, n (%)	78 (18.4)
Thoracic surgery, n (%)	2 (0.5)
Others, n (%)	11 (2.6)
Anesthesia	
Premedication with benzodiazepines, n (%)	3 (0.7)
Depth of anesthesia monitoring, n (%)	238 (56.3)
Peridural Anesthesia, n (%)	205 (48.5)
Intraoperative medication	
Sevoflurane, n (%)	293 (69.3)
Remifentanil*, n (%)	162 (38.3)
Clonidine, n (%)	28 (6.6)
Sufentanil, cumulative, µg, median (Q1, Q3)	80.00 (55.00, 95.00)
Noradrenaline, µg/kg/min,median (Q1, Q3)	0.18 (0.11, 0.27)
Colloids, n (%)	135 (31.9)

Crystalloids, ml, median (Q1, Q3)	3000.00 (2000.00, 3530.00)
Total fluid intake, ml, median (Q1, Q3)	3324.00 (2639.00, 4790.00)
Blood transfusion(number of RBCC), n (%)	
0	364 (86.1)
1-3	36 (8.5)
>3	23 (5.4)
Postoperative medication, n (%)	
Pethidine, n (%)	114 (26.7)
Piritramide, n (%)	202 (47.8)
Postoperative management	
ICU/PACU24 planned, n (%)	209 (49.4)
ICU/PACU24 unplanned, n (%)	2 (0.5)
PACU, n (%)	212 (50.1)
Length of hospital stay*, days, median (Q1, Q3)	8.00 (5.00, 14.00)

Continuous variables are presented as median (range) or median (Q1, Q3) while categorical variables are presented as n (% within group).

*: There is 1 missing data in this variable.

**:There are 2 missing data in this variable.

Abbreviations: Q1: First Quartile; Q3: Third Quartile; △ haemoglobin: Change of haemoglobin from before to after surgery; RBCC: Red Blood Cell Concentrate; ICU: Intensive Care Unit; PACU: Post-anesthesia care unit; PACU24: Extended post-anesthesia care unit providing overnight stay.

5.4 Perioperative limits of cerebrovascular autoregulation and time-weighted average mean arterial blood pressure beyond the limits of cerebrovascular autoregulation

Among the patients with available monitoring data, the intraoperative LLA was successfully determined in 71.4% of cases, while the intraoperative ULA was identifiable in 63.6% of the patients. Postoperatively, the LLA was identifiable in 70.2% of the patients, and the ULA was detectable in 59.6%. These percentages also apply to the TWA-MAP values that exceeded the CVA limits. Table 3 offers a

comprehensive documentation of detailed values of perioperative limits of CVA and perioperative TWA of MAP that surpassed these limits.

Table 3. Perioperative limits of cerebrovascular autoregulation and time-weighted average mean arterial blood pressure beyond the limits of cerebrovascular autoregulation

	Intraoperative	Postoperative
LLA, mmHg, median (Q1, Q3)	69.40 (63.94, 76.21)	71.09 (62.94, 79.52)
ULA, mmHg, median (Q1, Q3)	86.06 (79.42, 93.64)	87.42 (77.07, 97.69)
TWA of MAP < LLA, mmHg, median (Q1, Q3)	0.43 (0.11, 1.36)	0.14 (0.00, 0.74)
TWA of MAP > ULA, mmHg, median (Q1, Q3)	1.19 (0.43, 2.32)	0.29 (0.03, 0.86)

Abbreviations: Q1: First Quartile; Q3: Third Quartile; LLA: the Lower Limit of Cerebrovascular Autoregulation; ULA: the Upper Limit of Cerebrovascular Autoregulation; TWA: Time-Weighted Average; MAP: Mean Arterial Blood Pressure.

5.5 Comparison of intraoperative and postoperative limits of cerebrovascular autoregulation

Of the patients who had both intraoperative and postoperative monitoring data available, both intraoperative and postoperative LLA could be determined in 48.5% of them, and both intraoperative and postoperative ULA could be identified in 39.0%. This set of paired data was utilized for comparing the CVA limits between the intraoperative and postoperative phases. The findings indicated that the variances in the intraoperative and postoperative LLA (p=0.343) and ULA (p=0.322) were not statistically significant.

Table 4. Comparison of intraoperative and postoperative limits of cerebrovascular autoregulation

	LLA, mmHg, median (Q1, Q3)	ULA, mmHg, median (Q1, Q3)
Intraoperative	68.82 (64.01, 76.34)	85.93 (79.39, 93.47)
Postoperative	70.89 (62.94, 79.70)	88.25 (78.31, 97.74)
P	0.343	0.322

Abbreviations: Q1: First Quartile; Q3: Third Quartile; LLA: the Lower Limit of Cerebrovascular Autoregulation; ULA: the Upper Limit of Cerebrovascular Autoregulation.

Statistic method: Mann-Whitney U test

5.6 Comparison between intraoperative and postoperative time-weighted average mean arterial blood pressure beyond the limits of cerebrovascular autoregulation

The proportions for paired TWA-MAP that were below the LLA and above the ULA were identical to those for the LLA and ULA, respectively, as previously indicated. Table 5 demonstrates a statistically significant disparity between the intraoperative and postoperative TWA-MAP values that are beneath the LLA (p<0.001). In congruence, the difference between the intraoperative and postoperative TWA-MAP values that surpass the ULA also holds statistical significance (p<0.001).

Table 5. Comparison between intraoperative and postoperative time-weighted average mean arterial blood pressure beyond the limits of cerebrovascular autoregulation

	TWA of MAP < LLA, mmHg, median (Q1, Q3)	TWA of MAP > ULA, mmHg, median (Q1, Q3)
Intraoperative	0.45 (0.11, 1.18)	1.25 (0.43, 2.35)
Postoperative	0.15 (0.00, 0.67)	0.27 (0.03, 0.81)
P	< 0.001*	< 0.001*

*: statistical significance (P < 0.05).

Statistic method: Mann-Whitney U test.

Abbreviations: Q1: First Quartile; Q3: Third Quartile; LLA: the Lower Limit of Cerebrovascular Autoregulation; ULA: the Upper Limit of Cerebrovascular Autoregulation; TWA: Time-Weighted Average; MAP: Mean Arterial Blood Pressure.

5.7 Factors associated with perioperative limits of cerebrovascular autoregulation

5.7.1 Factors associated with the intraoperative lower limit of cerebrovascular autoregulation

Table 6 presents the findings from the initial linear regression analysis, which explores the factors correlated with the intraoperative LLA prior to the application of

stepwise backwards elimination. In this preliminary model, sex (p<0.001) and preoperative hemoglobin levels (p=0.022) are identified as the variables that have a significant correlation with the LLA (all details in Table 6).

Table 6. Results of the initial linear regression model of the intraoperative lower limit of cerebrovascular autoregulation

Parameter	B	95% CI low	95% CI up	*P*
Intercept	64.97	44.31	85.63	<0.001*
Age (yr)	0.10	-0.05	0.24	0.184
Sex (Male)	7.22	3.36	11.09	<0.001*
BMI (kg/m^2)	0.28	-0.09	0.65	0.143
ASA classification	0.06	-3.26	3.37	0.974
Arterial hypertension	-1.00	-4.66	2.66	0.591
OSAS	1.77	-3.94	7.48	0.542
Preoperative haemoglobin (g/dL)	-1.23	-2.28	-0.18	0.022*
Sevoflurane	2.27	-1.49	6.03	0.236
Noradrenalin (µg/kg/min)	-2.04	-16.85	12.77	0.786
Blood loss (ml)	0.00	-0.01	0.01	0.764
Crystalloids (ml)	0.00	-0.01	0.01	0.351
Colloids	-3.34	-7.67	0.98	0.129
Blood transfusion	6.26	-0.56	13.07	0.072
Duration of surgery (min)	0.01	-0.02	0.03	0.810

*: statistical significance (P < 0.05).

Abbreviations: BMI: Body Mass Index; ASA classification: American Society of Anesthesiologists Classification; OSAS: Obstructive Sleep Apnea Syndrome; B: Regression coefficient; CI: Confidence interval.

Table 7 displays the findings from a streamlined linear regression analysis focused on determinants linked to the intraoperative LLA. The final refined model identifies sex (p<0.001), preoperative haemoglobin levels (p=0.002), and the occurrence of blood transfusion (p=0.007) as key variables that significantly correlate with the intraoperative LLA. Male patients show a higher intraoperative LLA than their female

counterparts (B=7.41). There is a tendency for patients with reduced preoperative haemoglobin levels to exhibit an increased intraoperative LLA (B=-1.48). Furthermore, those who underwent blood transfusion demonstrate a more elevated intraoperative LLA in contrast to patients who did not received blood transfusion (B=6.59). All details are shown in Table 7.

Table 7. Results of reduced linear regression model of intraoperative lower limit of cerebrovascular autoregulation

Parameter	B	95% CI low	95% CI up	*P*
Intercept	76.74	63.73	89.74	<0.001*
Sex (Male)	7.41	3.84	10.99	<0.001*
BMI (kg/m^2)	0.32	-0.01	0.65	0.055
Preoperative haemoglobin (g/dL)	-1.48	-2.43	-0.50	0.002*
Blood transfusion	6.59	1.80	11.38	0.007*

*: statistical significance ($P < 0.05$).

Abbreviations: BMI: Body Mass Index; B: Regression coefficient; CI: Confidence interval.

5.7.2 Factors associated with the intraoperative upper limit of cerebrovascular autoregulation

Table 8 delineates the results from the preliminary linear regression assessment aimed at pinpointing variables connected to the intraoperative ULA. Prior to engaging in the stepwise backward elimination process, this original model was utilized. In this initial examination, sex (p=0.003), BMI (p=0.006), and the use of sevoflurane (p=0.018) surface as factors with a statistically significant correlation to the intraoperative ULA (all details in Table 8).

Table 8. Results of the initial linear regression model of the intraoperative upper limit of cerebrovascular autoregulation

Parameter	B	95% CI low	95% CI up	*P*
Intercept	69.73	50.75	88.72	<0.001*
Age (yr)	0.04	-0.09	0.18	0.504

Sex (Male)	-5.49	-9.12	-1.86	0.003*
BMI (kg/m^2)	0.48	0.14	0.82	0.006*
ASA classification	2.99	0.02	5.97	0.048
Arterial hypertension	0.10	-3.24	3.45	0.951
OSAS	-3.23	-8.56	2.11	0.234
Preoperative haemoglobin (g/dL)	0.13	-0.79	1.05	0.785
Sevoflurane	-4.26	-7.77	-0.75	0.018*
Noradrenalin (µg/kg/min)	3.66	-11.52	18.83	0.636
Blood loss (ml)	0.00	-0.01	0.01	0.963
Crystalloids (ml)	0.00	-0.01	0.01	0.789
Colloids	0.43	-3.74	4.60	0.838
Blood transfusion	1.68	-5.02	8.38	0.622
Duration of surgery (min)	-0.01	-0.03	0.01	0.582

*: statistical significance ($P < 0.05$).

Abbreviations: BMI: Body Mass Index; ASA classification: American Society of Anesthesiologists Classification; OSAS: Obstructive Sleep Apnea Syndrome; B: Regression coefficient; CI: Confidence interval.

Table 9 shows the refined findings of a linear regression model that scrutinizes the intraoperative ULA following the reduction process. In this analysis, being male (as opposed to female) emerges as a significantly negative predictor, signifying that male patients tend to have a reduced intraoperative ULA (p=0.001, B=-5.15). Patients undergoing surgery with sevoflurane anesthesia were likely to experience a decrease in intraoperative ULA compared to those who did not receive sevoflurane anesthesia (p=0.022, B=-3.76). Conversely, an elevated ASA classification (p=0.030, B=2.98) and an increased BMI (p=0.008, B=0.41) correlate with a higher ULA.

Table 9. Results of reduced linear regression model of intraoperative upper limit of cerebrovascular autoregulation

Parameter	B	95% CI low	95% CI up	*P*
Intercept	75.84	65.78	85.90	<0.001*

Sex (Male)	-5.15	-8.16	-2.14	0.001*
BMI (kg/m^2)	0.41	0.11	0.71	0.008*
ASA classification	2.98	0.29	5.67	0.030*
Sevoflurane	-3.76	-6.96	-0.56	0.022*

*: statistical significance ($P < 0.05$).

Abbreviations: BMI: Body Mass Index; ASA classification: American Society of Anesthesiologists Classification; B: Regression coefficient; CI: Confidence interval.

5.7.3 Factors associated with the postoperative lower limit of cerebrovascular autoregulation

Table 10 captures the results of the preliminary linear regression analysis conducted to identify factors associated with the postoperative LLA, before the application of the stepwise backward elimination method. In this initial evaluation, there are no variables found to have a statistically significant relationship with the postoperative LLA.

Table 10. Results of the initial linear regression model of the postoperative lower limit of cerebrovascular autoregulation

Parameter	B	95% CI low	95% CI up	*P*
Intercept	58.73	39.04	78.41	<0.001*
Age	0.11	-0.06	0.29	0.192
Sex (Male)	3.43	-0.94	7.80	0.123
BMI (kg/m^2)	0.15	-0.29	0.58	0.508
ASA classification	-0.47	-4.17	3.23	0.803
Arterial hypertension	1.34	-2.92	5.61	0.536
OSAS	5.42	-1.45	12.28	0.121
△ haemoglobin (g/dL)	1.33	-0.21	2.87	0.089
Noradrenalin (µg/kg/min)	3.36	-12.61	19.32	0.679
Blood loss (ml)	-0.01	-0.01	0.01	0.227
Crystalloids (ml)	-0.01	-0.01	0.01	0.286
Colloids	-3.84	-8.66	0.98	0.118

Blood transfusion	-0.09	-8.86	8.68	0.984
Duration of surgery (min)	0.10	-0.02	0.04	0.566

*: statistical significance ($P < 0.05$).

Abbreviations: BMI: Body Mass Index; ASA classification: American Society of Anesthesiologists Classification; OSAS: Obstructive Sleep Apnea Syndrome; △ haemoglobin: Change of haemoglobin from before to after surgery; B: Regression coefficient; CI: Confidence interval.

Table 11 outlines the outcomes from a streamlined linear regression model examining the postoperative LLA, following the model reduction process. The model indicates that the change in haemoglobin levels (denoted as △ haemoglobin) from the preoperative period to the postoperative period (in grams per deciliter) (p=0.042, B=1.45) exhibit significantly positive associations with the postoperative LLA.

Table 11. Results of reduced linear regression model of postoperative lower limit of cerebrovascular autoregulation

Parameter	B	95% CI low	95% CI up	*P*
Intercept	59.52	49.03	70.00	<0.001*
Age	0.13	-0.03	0.29	0.100
Sex	3.64	-0.33	7.61	0.072
OSAS	6.18	-0.24	12.60	0.059
△ haemoglobin (g/dL)	1.45	0.06	2.84	0.042*
Blood loss (ml)	-0.01	-0.01	0.00	0.072
Colloids	-3.89	-8.25	0.48	0.081

*: statistical significance ($P < 0.05$).

Abbreviations: OSAS: Obstructive Sleep Apnea Syndrome; △ haemoglobin: Change of haemoglobin from before to after surgery; B: Regression coefficient; CI: Confidence interval.

5.7.4 Factors associated with the postoperative upper limit of cerebrovascular autoregulation

Table 12 lists the findings from an initial linear regression analysis aimed at discovering factors that might be linked to the postoperative ULA, which was conducted prior to the implementation of the stepwise backward elimination

technique. In this preliminary assessment, it is determined that there are no variables with a statistically significant association to the postoperative ULA.

Table 12. Results of the initial linear regression model of the postoperative upper limit of cerebrovascular autoregulation

Parameter	B	95% CI low	95% CI up	*P*
Intercept	93.89	74.68	113.09	<0.001*
Age	0.02	-0.15	0.20	0.782
Sex (Male)	3.73	-0.80	8.25	0.106
BMI (kg/m^2)	0.07	-0.39	0.53	0.766
ASA classification	-0.76	-4.64	3.11	0.699
Arterial hypertension	-2.37	-6.78	2.03	0.290
OSAS	0.39	-7.59	8.36	0.924
△ haemoglobin (g/dL)	-0.16	-1.74	1.42	0.844
Noradrenalin (µg/kg/min)	-3.78	-21.75	14.18	0.679
Blood loss (ml)	0.01	-0.01	0.01	0.321
Crystalloids (ml)	-0.01	-0.01	0.01	0.339
Colloids	1.04	-4.22	6.30	0.698
Blood transfusion	-3.53	-12.72	5.65	0.449
Duration of surgery (min)	-0.02	-0.05	0.01	0.231

*: statistical significance ($P < 0.05$).

Abbreviations: BMI: Body Mass Index; ASA classification: American Society of Anesthesiologists Classification; OSAS: Obstructive Sleep Apnea Syndrome; △ haemoglobin: Change of haemoglobin from before to after surgery; B: Regression coefficient; CI: Confidence interval.

Table 13 exhibits the refined outcomes of a streamlined linear regression model focused on the postoperative ULA, following the reduction of the initial model. The duration of surgery is identified with a significantly inverse relationship to the postoperative ULA (p=0.005, B=-0.03). Additionally, the model reveals that male patients exhibit a higher postoperative ULA compared to female patients (p=0.042, B=4.26).

Table 13. Results of reduced linear regression model of postoperative upper limit of cerebrovascular autoregulation

Parameter	B	95% CI low	95% CI up	*P*
Intercept	92.71	86.62	98.80	<0.001*
Sex (Male)	4.26	0.16	8.37	0.042*
Duration of surgery (min)	-0.03	-0.05	-0.10	0.005*

*: statistical significance ($P < 0.05$).

Abbreviations: B: Regression coefficient; CI: Confidence interval.

5.8 Factors associated with perioperative time-weighted average mean arterial blood pressure beyond the limits of cerebrovascular autoregulation

5.8.1 Factors associated with intraoperative time-weighted average mean arterial blood pressure below the lower limit of cerebrovascular autoregulation

Table 14 encapsulates the findings of a preliminary linear regression model that scrutinized the intraoperative TWA-MAP falling below the LLA, prior to the application of stepwise backward elimination. Within this initial analysis, sex (p=0.002, B=4.21), the presence of OSAS (p=0.027, B=4.38), and the administration of blood transfusion (p=0.019, B=5.57) are identified as factors that exhibit a positive and statistically significant link to the intraoperative TWA-MAP below the LLA. Conversely, preoperative haemoglobin levels are found to have a significant inverse association with the intraoperative TWA-MAP below the LLA (p=0.001, B=-1.23).

Table 14. Results of the initial linear regression model of the intraoperative time-weighted average mean arterial blood pressure below the lower limit of cerebrovascular autoregulation

Parameter	B	95% CI low	95% CI up	*P*
Intercept	9.97	-4.11	24.05	0.164

Age	0.03	-0.07	0.12	0.585
Sex (Male)	4.21	1.58	6.84	0.002*
BMI (kg/m^2)	0.08	-0.18	0.33	0.556
ASA classification	-0.49	-2.75	1.77	0.668
Arterial hypertension	0.63	-1.87	3.12	0.621
OSAS	4.38	0.50	8.27	0.027*
Preoperative haemoglobin (g/dL)	-1.23	-1.94	-0.51	0.001*
Sevoflurane	0.63	-1.93	3.19	0.630
Noradrenalin (µg/kg/min)	4.33	-5.77	14.42	0.399
Blood loss (ml)	0.00	-0.01	0.01	0.831
Crystalloids (ml)	0.01	-0.01	0.01	0.442
Colloids	-2.67	-5.62	0.28	0.076
Blood transfusion	5.57	0.93	10.21	0.019*
Duration of surgery (min)	0.00	-0.02	0.02	0.972

*: statistical significance ($P < 0.05$).

Abbreviations: BMI: Body Mass Index; ASA classification: American Society of Anesthesiologists Classification; OSAS: Obstructive Sleep Apnea Syndrome; B: Regression coefficient; CI: Confidence interval.

Table 15 depicts the findings from a streamlined linear regression model which applied to the TWA-MAP values below the LLA, subsequent to model reduction. The variables that demonstrate a positive and statistically significant association with the intraoperative TWA-MAP below the LLA include sex (with males showing higher TWA-MAP below the LLA compared to females) (p=0.001, B=4.25), the status of OSAS (where patients with OSAS exhibit higher TWA-MAP below the LLA than those without) (p=0.009, B=4.82), and the administration of blood transfusion (where recipients have higher TWA-MAP below the LLA than non-recipients) (p<0.001, B=6.13). In contrast, preoperative haemoglobin levels are inversely and significantly related to the intraoperative TWA-MAP below LLA, indicating that an increase in preoperative haemoglobin levels is associated with a lower TWA-MAP below the LLA (p<0.001, B=-1.26).

Table 15. Results of reduced linear regression model of intraoperative time-weighted average mean arterial blood pressure below the lower limit of cerebrovascular autoregulation

Parameter	B	95% CI low	95% CI up	*P*
Intercept	15.33	7.30	23.36	<0.001*
Sex (Male)	4.25	1.80	6.69	0.001*
OSAS	4.82	1.22	8.41	0.009*
Preoperative haemoglobin (g/dL)	-1.26	-1.88	-0.63	<0.001*
Blood transfusion	6.13	2.87	9.39	<0.001*

*: statistical significance ($P < 0.05$).

Abbreviations: OSAS: Obstructive Sleep Apnea Syndrome; B: Regression coefficient; CI: Confidence interval.

5.8.2 Factors associated with intraoperative time-weighted average mean arterial blood pressure above the upper limit of cerebrovascular autoregulation

Table 16 illustrates the findings of an initial linear regression model that is utilized to analyze the intraoperative TWA-MAP values exceeding the ULA, prior to undergoing stepwise backward elimination. In this preliminary assessment, it concluded that no variables exhibit a statistically significant correlation with the intraoperative TWA-MAP beyond the ULA.

Table 16. Results of the initial linear regression model of the intraoperative time-weighted average mean arterial blood pressure above the upper limit of cerebrovascular autoregulation

Parameter	B	95% CI low	95% CI up	*P*
Intercept	-1.49	-6.40	3.42	0.551
Age	0.03	-0.01	0.06	0.083
Sex (Male)	0.25	-0.69	1.19	0.607
BMI (kg/m^2)	0.03	-0.06	0.12	0.482
ASA classification	-0.06	-0.82	0.71	0.888
Arterial hypertension	-0.53	-1.40	0.34	0.230
OSAS	0.44	-0.94	1.82	0.534
Preoperative haemoglobin (g/dL)	0.06	-0.18	0.30	0.611
Sevoflurane	0.03	-0.88	0.94	0.945
Noradrenalin (µg/kg/min)	-0.39	-4.31	3.54	0.847
Blood loss (ml)	0.00	-0.01	0.00	0.191
Crystalloids (ml)	0.00	-0.01	0.00	0.541
Colloids	-0.10	-1.18	0.98	0.859
Blood transfusion	1.53	-0.21	3.26	0.084
Duration of surgery (min)	0.002	-0.003	0.01	0.370

*: statistical significance ($P < 0.05$).

Abbreviations: BMI: Body Mass Index; ASA classification: American Society of Anesthesiologists Classification; OSAS: Obstructive Sleep Apnea Syndrome; B: Regression coefficient; CI: Confidence interval.

Table 17 reveals the refined outcomes of a streamlined linear regression model that scrutinizes the TWA-MAP when it surpasses the ULA, following the reduction of the model. In this condensed model, none of the variables exhibit a statistically significant correlation with intraoperative TWA-MAP that exceeds ULA.

Table 17. Results of reduced linear regression model of intraoperative time-weighted average mean arterial blood pressure above the upper limit of cerebrovascular autoregulation

Parameter	B	95% CI low	95% CI up	*P*
Intercept	1.79	1.42	2.17	< 0.001*

*: statistical significance ($P < 0.05$).
Abbreviations: B: Regression coefficient; CI: Confidence interval.

5.8.3 Factors associated with postoperative time-weighted average mean arterial blood pressure below the lower limit of cerebrovascular autoregulation

Table 18 demonstrates the findings from an initial linear regression model that evaluates the postoperative TWA-MAP as it falls below the LLA, prior to the execution of stepwise backward elimination. Among the variables examined, age (p=0.033) and the presence of OSAS (p=0.022) emerge as the factors that exhibit a statistically significant association with the postoperative TWA-MAP below the LLA.

Table 18. Results of the initial linear regression model of the postoperative time-weighted average mean arterial blood pressure below the lower limit of cerebrovascular autoregulation

Parameter	B	95% CI low	95% CI up	*P*
Intercept	-7.47	-19.90	4.96	0.238
Age	0.12	0.01	0.23	0.033*
Sex (Male)	-0.02	-2.78	2.74	0.989
BMI (kg/m^2)	-0.08	-0.36	0.19	0.548
ASA classification	0.78	-1.56	3.11	0.514
Arterial hypertension	0.53	-2.16	3.22	0.699
OSAS	5.09	0.76	9.43	0.022*
△ haemoglobin (g/dL)	0.29	-0.68	1.26	0.554
Noradrenalin (µg/kg/min)	-1.34	-11.42	8.74	0.794
Blood loss (ml)	-0.01	-0.01	0.01	0.384
Crystalloids (ml)	0.00	-0.001	0.01	0.842
Colloids	-1.70	-4.74	1.34	0.272
Blood transfusion	0.58	-4.96	6.12	0.837
Duration of surgery (min)	0.01	-0.01	0.02	0.577

*: statistical significance ($P < 0.05$).

Abbreviations: BMI: Body Mass Index; ASA classification: American Society of Anesthesiologists Classification; OSAS: Obstructive Sleep Apnea Syndrome; △ haemoglobin: Change of haemoglobin from before to after surgery; B: Regression coefficient; CI: Confidence interval.

Table 19 conveys the findings of a reduced linear regression model that was applied to analyze the postoperative TWA-MAP below the LLA, following the reduction of the model. The model reveals that age (p=0.020, B=0.11) is positively correlated with the outcome in a statistically significant manner, suggesting a slight increase in the postoperative TWA-MAP below the LLA with each additional year of age. Furthermore, the status of OSAS (p=0.015, B=4.96) is identified as a significant predictor, with patients diagnosed with OSAS demonstrating a higher postoperative TWA-MAP below the LLA when compared to patients without OSAS.

Table 19. Results of reduced linear regression model of postoperative time-weighted average mean arterial blood pressure below the lower limit of cerebrovascular autoregulation

Parameter	B	95% CI low	95% CI up	*P*
Intercept	-6.18	-12.38	0.01	0.050
Age	0.11	0.02	0.21	0.020*
OSAS	4.96	0.96	8.95	0.015*

*: statistical significance ($P < 0.05$).
Abbreviations: OSAS: Obstructive Sleep Apnea Syndrome; B: Regression coefficient; CI: Confidence interval.

5.8.4 Factors associated with postoperative time-weighted average mean arterial blood pressure above the upper limit of cerebrovascular autoregulation

Table 20 displays the findings from a preliminary linear regression model which designed to explore factors correlated with the postoperative TWA-MAP exceeding the ULA, prior to the application of stepwise backward elimination. Within this initial analysis, the volume of blood loss (p=0.011, B=0.01) is identified as the sole variable

that exhibit a statistically significant association with the postoperative TWA-MAP above the ULA.

Table 20. Results of the initial linear regression model of the postoperative time-weighted average mean arterial blood pressure above the upper limit of cerebrovascular autoregulation

Parameter	B	95% CI low	95% CI up	*P*
Intercept	0.13	-4.13	4.39	0.952
Age	0.01	-0.03	0.05	0.693
Sex (Male)	-0.84	-1.84	0.17	0.102
BMI (kg/m^2)	0.01	-0.10	0.11	0.928
ASA classification	-0.27	-1.13	0.59	0.536
Arterial hypertension	0.92	-0.06	1.89	0.066
OSAS	-0.63	-2.40	1.14	0.486
△ haemoglobin (g/dL)	-0.17	-0.52	0.19	0.354
Noradrenalin (µg/kg/min)	3.94	-0.05	7.93	0.053
Blood loss (ml)	0.01	0.00	0.01	0.011*
Crystalloids (ml)	0.00	0.00	0.01	0.514
Colloids	-0.33	-1.50	0.84	0.579
Blood transfusion	-1.83	-3.87	0.21	0.078
Duration of surgery (min)	-0.01	-0.01	0.01	0.796

*: statistical significance ($P < 0.05$).

Abbreviations: BMI: Body Mass Index; ASA classification: American Society of Anesthesiologists Classification; OSAS: Obstructive Sleep Apnea Syndrome; △ haemoglobin: Change of haemoglobin from before to after surgery; B: Regression coefficient; CI: Confidence interval.

Table 21 presents the refined outcomes of a linear regression model that scrutinizes factors linked to the postoperative TWA-MAP surpassing the ULA, following the reduction of the model. The model indicates that sex (p=0.048, B=-0.93) has a significant negative relationship with the outcome, implying that male patients tend to exhibit a reduced TWA-MAP above the ULA in comparison to female patients. Patients suffering from arterial hypertension are more likely to exhibit elevated

postoperative TWA-MAP beyond the ULA, in contrast to patients who do not have arterial hypertension (p=0.048, B=0.89). There is also a positive correlation between the dosage of noradrenalin and the TWA-MAP exceeding the ULA, indicating that, an increase in noradrenalin dosage (p=0.023, B=3.89) is likely to result in an increase in TWA-MAP above the ULA. Additionally, blood loss (p=0.016, B=0.01) demonstrates statistical significance with the outcome, suggesting that an increase in blood loss is associated with a modest rise in the postoperative TWA-MAP above the ULA.

Table 21. Results of reduced linear regression model of postoperative time-weighted average mean arterial blood pressure above the upper limit of cerebrovascular autoregulation

Parameter	B	95% CI low	95% CI up	*P*
Intercept	-0.03	-1.04	0.98	0.953
Sex (Male)	-0.93	-1.85	-0.01	0.048*
Arterial hypertension	0.89	0.01	1.77	0.048*
Noradrenalin (µg/kg/min)	3.89	0.53	7.24	0.023*
Blood loss (ml)	0.01	0.00	0.01	0.016*
Blood transfusion	-1.59	-3.45	0.26	0.092

*: statistical significance ($P < 0.05$).

Abbreviations: B: Regression coefficient; CI: Confidence interval.

6. Discussion

6.1 Summary

This prospective cohort study made a deep exploration on the LLA, ULA, and TWA-MAP beyond the limits of CVA, which are all vital important parameters for perioperative measurement on patients. These results provided evidence for more personalized decisions in clinic and better outcome of patients.

6.2 Perioperative limits of cerebrovascular autoregulation

6.2.1 Intraoperative limits of cerebrovascular autoregulation

The median intraoperative lower and upper limits of CVA in this study sample were 69.40 and 86.06 mmHg, respectively.

These results are consistent with previous studies to some extent, especially the case for the intraoperative LLA values. All these findings also contribute to a growing body of evidence suggesting that the LLA is much higher than previously assumed 40 mmHg, which was derived from the average of two data points identified as LLA on the Lassen Curve (Lassen 1959). The possible reasons for this could be different sample size and different calculation methods of the limits of CVA. Here are some relevant previous studies that can substantiate the claim. For non-cardiac surgery research, Goettel and colleagues calculated that the ULA was 70±14 mmHg in 84 older patients (over 65 years) and 73±19 mmHg in 49 younger patients (18-40 years) undergoing major non-cardiac surgery (Goettel et al. 2016). Zhang and team enrolled 80 patients undergoing robotic-assisted laparoscopic radical prostatectomy and calculated the LLA, which was 67.8±8.9 mmHg for 40 middle-aged patients and 71.2±12.5 mmHg for 40 elderly patients (Zhang et al. 2021a). For cardiac surgery investigation, Hori et al. conducted CVA monitoring in 614 patients during CPB, reporting an adjusted mean LLA of 65±12 mmHg and ULA of 84±11 mmHg (Hori et al. 2017). There were also many other researches studying the intraoperative limits of CVA which are presented in Table 22 to facilitate a more intuitive comparison. To sum

up, this study along with previous research, all provided a new perspective on the numerical values of intraoperative LLA and ULA.

The consistency between the values of the CVA limits the present study obtained and the data obtained in previous studies could be related to the consistent correlation coefficient method employed. This further validates the correlation coefficient method as a reliable tool for determining the intraoperative LLA and ULA. Although the studies mentioned above employed different equipment (such as TCD or NIRS) and various cerebral indices (such as Mx, COx, HVx or CFIx) to measure and evaluate CVA (details in Table 22), the core computational method remains correlation coefficient. There were also many studies reporting a high degree of agreement among these measures. In a laboratory setting using a piglet model, Brady and colleagues discovered a strong correlation between the COx and the monitoring of CVA, which was based on laser Doppler techniques (Brady et al. 2007). This team also observed a significant correlation and good agreement between Mx and COx during CPB (Brady et al. 2010). In a study of sepsis patients, Pfister and colleagues noted that NIRS waveforms at frequencies below 0.04 Hz showed a high degree of coherence with the CBFV as measured by TCD (Pfister et al. 2008). Ono and colleagues found a correlation and good agreement between COx, derived from a prototype NIRS-based monitor, and Mx in 70 patients undergoing CPB (Ono et al. 2013b). Blaine Easley and colleagues reported that Mx and HVx showed good agreement in identifying the LLA and the optimal blood pressure for patients during CPB (Blaine Easley et al. 2013). Additionally, a feasibility study conducted by Murkin and colleagues demonstrated a high level of concordance between CFIx and the Mx derived from TCD for the detection of CVA and LLA (Murkin et al. 2015).

On the other hand, the data above indicate a broad range of MAP at both the LLA and the ULA in each study. This underscores the significant variability in CVA limits among individuals, indicating that in many cases, CBF could be pressure-dependent during surgical procedures. This highlights the importance of personalized CVA-based, blood pressure management for anesthesiologists, as it is essential for preventing intraoperative hypotension or hypertension to ensure optimal patient outcomes.

6. Discussion

Intraoperative hypotension, which is identified by a substantial decline in blood pressure during surgical procedures, can negatively impact patient outcomes, especially in suboptimal organ perfusion conditions. It is typically recognized when the mean arterial pressure falls below 65 mmHg or experiences a decrease of over 20-30% from the baseline values (Bijker and Moons 2007; Sessler et al. 2019). The precise values that trigger intervention might differ based on factors such as the initial blood pressure levels of the patient, the surgical procedure being performed, and any coexisting medical conditions (Meng et al. 2018). A multitude of studies have demonstrated a correlation between intraoperative hypotension and detrimental postoperative effects, including acute kidney injury (AKI) and heart damage, as well as increased mortality rates in non-cardiac surgical patients (Walsh et al. 2013; Sun and Beattie 2015; Wesselink et al. 2018; Khanna et al. 2019; Saugel and Sessler 2021). Intraoperative hypertension, marked by abnormally high blood pressure during surgical procedures, can lead to several risks including increased bleeding, hypertensive encephalopathy, and the worsening of pre-existing cardiovascular conditions. There is no universally consensus on the threshold of intraoperative intraoperative hypertension (Sessler et al. 2019). Moreover, research connecting intraoperative hypertension with postoperative outcomes is limited, and the findings from existing studies are not consistent. Reich et al. conducted an analysis of factors influencing adverse outcomes in patients undergoing non-cardiac surgeries that lasted over 220 minutes. Their results indicated that intraoperative systolic blood pressures (SBP) above 160 mmHg were an independent risk factor for negative surgical outcomes, which were defined as a hospital stay of more than 10 days with a morbid condition or death (Reich et al. 2022). Abbott et al. suggested that a maximum SBP exceeding 160 mmHg was linked to myocardial injury following non-cardiac surgery and myocardial infarction. However, paradoxically and unexpectedly (Abbott et al. 2018). In contrast, Monk and colleagues conducted a retrospective cohort study to examine the relationship between intraoperative hypertension or hypotension and 30-day mortality. They found that SBP above 180 mmHg or mean arterial pressure above 130 mmHg for more than 5 minutes did not correlate with 30-day mortality

(Monk et al. 2015). This body of evidence illustrates the challenge and difficulty in establishing a consensus definition for intraoperative hypertension, as the impact of blood pressure thresholds on patient outcomes appears to be complex and not clearly defined. All above underscores the need for a more personalized and nuanced approach to blood pressure management that takes the unique CVA of each patient into consideration.

However, the LLA and the ULA values observed in present study still slightly differ from that in others. This small variance could be attributed to factors such as the size and demographics of the study samples, the use of distinct measurement instruments, and variations in research methodologies. Consequently, further investigations are warranted to determine the limits of CVA using a variety of techniques, specifically for patients undergoing non-cardiac surgery. This will help in refining the understanding of how these limits can be accurately assessed in diverse clinical settings.

Table 22. Characteristics of previous publications calculating the intraoperative limits of cerebrovascular autoregulation

Study	n	Surgery Type	Index	Intraoperative LLA (mmHg)	Intraoperative ULA (mmHg)
Present study	423	Non-cardiac surgery	COx	69.40 (63.94, 76.21)[c]	86.06 (79.42, 93.64)[c]
(Brady et al. 2010)	60	CPB	Mx	45-80[a]	
(Joshi et al. 2012)	232	CPB	Mx	66 (40-90)[b]	
(Ono et al. 2013a)	348	CPB	COx	With AKI: 69±16; Without AKI: 63±15	
(Ono et al. 2013b)	70	CPB	MX, COx	Mx: 63±11; COx: 59±9	
(Ono et al. 2014)	450	CPB	COx	With MMOM: 71±12; Without MMOM: 69±14	
(Hori et al. 2017)	614	CPB	COx	65±12	84±11
(Nomura et al. 2018)	346	CPB	Mx	66.3±11.9	
(Brown et al. 2019)	199	CPB	Mx	Stand care: 68.7±11.3; Autoregulation targeted: 66±10.9	
(Hogue et al. 2021)	460	CPB	Mx	Usual Care: 66.4±11.2; Autoregulation: 67.4±12.4	
(Blaine Easley et al. 2013)	109	CPB	Mx, HVx	Mx: 66±13; HVx: 66±12	
(Murkin et al. 2015)	20	CPB	Mx, CFIx	Mx: 48.5±11.1; CFIx:48.0±12.1	
(Gergelé et al. 2021)	5	CPB	Mx	Mx10s: 70±2.5; Mx2s: 73±3.5	
(Liu et al. 2021)	79	CPB	Mx	66.5±10.2	
(Kho et al. 2022)	20	PEARS	Mx	56 (47, 74)[c]	
(Hori et al. 2021)	66	CPB	COx	46±13.3	
(Melvin et al. 2022)	55	CPB	COx, HVx	COx: 63±18; HVx: 66±20	COx: 108±22; HVx: 109±12
(Liu et al. 2022)	240	CPB	COx, Mx	COx: 65.6±8.3; Mx: 68.2±8.4	
(Gavish et al. 2023)	181	CPB	Mx	64.3±13.0	
(Desebbe et al. 2023)	55	CPB	Mx	qLLA: 66 (61, 71)[c]; rLLA: 66 (66, 71)[c]	
(Hori et al. 2014)	491	CPB	COx		90±12
(NORNES 1977)	21	intracranial surgery		Grade I and II: 62 (35-85)[b]; Grade III: 76 (60-95)[b]	
(Nissen et al. 2009)	33	OLT	ScO2	69 (50-90)[b]	
(Zheng et al. 2012)	9	OLT	Mx	40-85[a]	
(Laflam et al. 2015)	218	shoulder surgery	COx	LDP: 65 (55, 75)[c]; BCP: 70 (55, 80)[c]	

(Goettel et al. 2016)	49	major non-cardiac surgery	Mx	Older: 73±14; Younger: 66±12	Older: 70±14; Younger: 73±19
(Zhang et al. 2021a)	80	RALP	COx	Elderly: 71.2±12.5; Middle-aged: 67.8±8.9	Elderly: 111.3±8.9; Middle-aged: 116.4±10.5

Values are presented as mean±SD or range or mean (range) or median (Q1, Q3); [a]: range; [b]: mean (range); [c]: median (Q1, Q3).

Abbreviations: SD: Standard Deviation; Q1: First Quartile; Q3: Third Quartile; COx: Cerebral oximetry index; Mx: Mean Flow Index; CFIx: Cerebral flow index correlation index; HVx: Haemoglobin volume index; CPB: Cardiopulmonary bypass; PEARS: Personalized External Aortic Root Support; AKI: Acute kidney injury; MMOM: Major morbidity and operative mortality; ScO2: frontal lobe cerebral oxygenation; LLA: the lower limit of cerebrovascular autoregulation; ULA: the upper limit of cerebrovascular autoregulation; qLLA: the quick determination of LLA using Mx2s; rLLA: the reference LLA using Mx10s; OLT: Orthotopic liver transplantation; LDP: Lateral decubitus position; BCP: Beach chair position; RALP: Robotic-assisted laparoscopic radical prostatectomy

6.2.2 Postoperative limits of cerebrovascular autoregulation

The median postoperative lower and upper limits in this study sample were 71.09 and 87.42 mmHg, respectively. It is challenging to compare these results with earlier studies because only one study has specifically determined the postoperative limits of CVA and looked into how this might predict outcomes.

Chan et al. measured the LLA and ULA by calculating an index called tissue oxygenation index which was derived from the relationship between the COx (measured by NIRS) and the MAP for 108 adult patients undergoing cardiac surgery. The authors aimed to check the patients on the day 0 after surgery (within two hours after the patients were moved to the ICU) and on postoperative day 1 to see if there was a link between postoperatively impaired CVA and the onset of delirium following cardiac surgery. The median LLA was 67.2 (64.6, 71.6) mmHg on postoperative day 0 and 65.5 (61.0, 70.6) mmHg on postoperative day 1. The ULA was 86.0±10.3 mmHg on postoperative day 0 and 84.7±11.6 mmHg on postoperative day 1 (Chan and Aneman 2019).

The findings in this study are similar to what we found. Moreover, the values provide anesthesiologists some reference to perform individual postoperative blood pressure management, which is currently under debate and lack of a wide-accepted agreement.

Postoperative hypotension, which frequently occurs in the first few days following surgery, is identified by a considerable decrease in blood pressure (Sessler et al. 2018). This condition may result in inadequate tissue oxygenation and could potentially lead to organ dysfunction, such as AKI, myocardial ischemia, or cerebral hypoperfusion (Khanna et al. 2019; Liem et al. 2020). Importantly, differentiating whether the negative outcomes are a consequence of intraoperative or postoperative hypotension, or a combination of both, can be challenging (Sessler et al. 2019). The Perioperative Quality Initiative has reached a consensus to guide clinical practice, which includes the following points: 1. A postoperative SBP below 90 mmHg is linked to myocardial injury, AKI, and all-cause mortality. The degree of risk is related to both the duration and the extent of the blood pressure drop. 2. For patients with chronic hypertension prior to surgery, the postoperative SBP thresholds to prevent injury are considered to be above 90 mmHg (McEvoy et al. 2019). Conversely, postoperative hypertension, defined by high blood pressure in the period immediately after surgery, can result in several adverse outcomes, such as stroke, heart attack, and bleeding(McEvoy et al. 2019). It might be tentatively defined as a SBP of 190 mmHg or higher and/or a diastolic blood pressure of 100 mmHg or higher on two consecutive readings after the surgery (Varon 2008). The existing clinical experience-guided postoperative blood pressure management lacks personalized management, using a uniform target to maintain the blood pressure within a specific range, which can easily lead to the patient experiencing postoperative hypertension or hypotension.

In conclusion, it is essential to conduct more research in this area to determine the exact LLA and ULA in patients after surgery due to the limited number of studies and the potential for this kind of research to aid in postoperative blood pressure management.

6.2.3 Factors influencing intraoperative and postoperative limits of cerebrovascular autoregulation

In this study, a number of factors that had a significant connection with the intraoperative and postoperative limits of CVA were identified.

1). Several variables were identified that had a significant relationship with the intraoperative LLA, including sex, hemoglobin level before surgery, and the requirement of blood transfusions during the operation.

2). The factors that were found to have an impact on the intraoperative ULA were sex, BMI, their classification according to the ASA physical status, and whether the patients recieved sevoflurane anesthesia.

3). For the postoperative LLA, the sole factor that showed a significant association was the change in hemoglobin levels between the preoperative and postoperative periods.

4). The postoperative ULA showed a significant correlation with sex and the duration of surgery.

Sex

Sex was observed to have an impact not only on the intraoperative LLA and the ULA, but also on the postoperative ULA. Specifically, male patients showed a higher intraoperative LLA and a lower intraoperative ULA than their female counterparts. This suggests that female individuals may have a superior capacity to tolerate lower or higher CBF during the surgery, indicating more effective CVA. Consistent with our findings, previous studies have reported higher cerebral flow velocity, enhanced cerebral vasomotor reactivity, and greater cerebrovascular responsiveness in females (Ackerstaff et al. 1990; Karnik et al. 1996; Kastrup et al. 1997). Wang and colleagues discovered that young adult females exhibited lower coherence of the MCA transfer function in the low-frequency band when tested in an upright position, pointing to better CBF autoregulation (Wang et al. 2005). Deegan and colleagues, in a study of the elderly, found that women had a higher baseline MCA blood flow velocity, more robust responsiveness to CO_2, stronger vasoconstriction activity, and a higher autoregulation index than men, indicating superior CVA in older women than men (Deegan et al. 2009). The authors have hypothesized several reasons for the improved CVA observed in females including 1) variations in the number of reactive blood vessels, 2) differences in blood vessel diameters, 3) hormonal influences, and 4)

variations in brain metabolic rates. In contrast, the postoperative ULA was found to be higher in male patients compared to females. This result contradicts the above findings, so all these hypotheses have yet to be empirically confirmed and require additional research for validation.

Hemoglobin

Hemoglobin levels play a crucial role in determining the limits of CVA. Notably, patients with lower preoperative hemoglobin levels were found to have a higher intraoperative LLA. Moreover, those with a smaller decrease in hemoglobin from the preoperative to the postoperative period showed a lower postoperative LLA. Hemoglobin, the main oxygen carrier in red blood cells, is essential for ensuring that sufficient oxygen reaches brain tissue. When hemoglobin levels fall, as in cases of anemia, the blood oxygen-carrying capacity is compromised, which may adversely affect cerebral metabolic functions and reduce the ability of small resistance arteries to dilate. This can disrupt the cerebrovascular autoregulatory mechanisms, making them less effective at managing CBF (Lee and Hung 2001; Sekhon et al. 2012; Hoiland et al. 2016). In this scenario, it is plausible that patients with lower preoperative hemoglobin levels might need higher blood pressure to maintain sufficient CBF, thereby increasing the intraoperative LLA. Furthermore, it could also explain the observation that patients with a smaller change in hemoglobin levels between the preoperative and postoperative periods exhibit a lower postoperative LLA, which means patients were less likely to experience CVA dysfunction. Further research is required to fully understand this phenomenon.

Blood transfusion

Additionally, patients who received blood transfusions during surgery showed a significantly higher intraoperative LLA compared to those who did not undergo transfusion. Sekhon and colleagues examined the impact of red blood cell (RBC) transfusion on CVA, as indicated by the Pressure Reactivity Index (PRx), in 28 patients with severe traumatic brain injury. The authors discovered that RBC

transfusion in these patients led to a deterioration in PRx, suggesting a negative effect on CVA (Sekhon et al. 2015). This aligns with our findings. The exact reason why CVA is compromised by RBC transfusion remains elusive. It might be due to the fact that a transfusion increases the viscosity of the blood, which can alter the flow dynamics within the cerebral vasculature and potentially decrease CBF (Bisschops et al. 2014). Furthermore, sudden changes in viscosity due to hemoconcentration or hemodilution seem to disrupt CVA, and RBC transfusion has been linked to endothelial dysfunction, which could impair microcirculatory flow (Weinberg et al. 2011; Sriram et al. 2012; Neuman et al. 2015). However, Vavilala and colleagues presented a contrasting case report. The authors utilized the ARI to measure the autoregulatory capacity and calculated the LLA in an anemic child undergoing lower extremity surgery. After a blood transfusion, CVA was preserved, and the LLA was reduced (Vavilala et al. 2001). The authors speculated that the mechanism behind this could be attributed to hemodilution, which typically increases CBF, a reflex increase in flow to compensate for the reduced oxygen-carrying capacity, and a viscosity-mediated direct increase in flow (Strebel et al. 1995; Mühling et al. 1999). In summary, if a blood transfusion effectively raises the hemoglobin level, it can enhance the blood oxygen-carrying capacity, potentially improving cerebral metabolic function and supporting the autoregulatory mechanisms that maintain CBF.

Besides, other aspects such as excessive high blood viscosity due to over-transfusion and significant hemodilution due to rapid transfusion could also increase resistance in the smaller cerebral vessels and disrupt the balance of oxygen and carbon dioxide in the blood, ultimately impairing CVA. Thus, the relationship between blood transfusion and CVA is intricate and necessitates further research. Careful management is essential to ensure that the cerebral blood supply is neither hindered by inadequate oxygenation nor overwhelmed by excessive blood volume or viscosity changes.

BMI

In our research, a higher BMI was found to be linked with an elevated intraoperative

ULA. The connection between BMI and ULA is complex and can be affected by multiple elements. However, this correlation can be understood when considering the impact of obesity on the cardiovascular and cerebrovascular systems. Obesity frequently coincides with elevated blood pressure (Seravalle and Grassi 2017), which might shift the autoregulatory curve, including the ULA, to higher values. This suggests that the brain could handle higher blood pressures before the autoregulatory mechanism fails. A systematic review examining the link between obesity and CBF revealed an increase in blood flow in certain brain regions among obese individuals. The authors of this review hypothesized possible pathological or physiological causes for these changes (Qiao et al. 2022).

Additionally, individuals with obesity are more likely to suffer from obstructive sleep apnea (Gami et al. 2003). The conditions of hypopnea and hypoxemia caused by obstructive sleep apnea can lead to reduced cerebral perfusion. Meanwhile, an increase in CBF in specific subcortical areas, such as the putamen, globus pallidus, amygdala, and hippocampus, may serve as a protective mechanism for vital brain regions, particularly during periods of wakeful rest (Baril et al. 2015). Another study pointed out that a higher BMI is also associated with chronically elevated $PaCO_2$ and reduced arterial oxygen partial pressure (Littleton and Tulaimat 2017). Therefore, the increased CBF in certain brain regions among obese patients might be a compensatory response to hypoxia.

In this context, obesity could result in a state where the brain is subjected to a blood flow surplus, potentially leading to hyperperfusion and the subsequent risks and complications. This scenario might push the ULA to higher levels. However, other research has indicated an inverse relationship between higher BMI and CBF. Dorrance and colleagues discovered that obesity might lead to a reduction in CBF, thereby impairing the functionality of cerebral arteries (Dorrance et al. 2014). There are several potential physiological explanations for these findings. Firstly, obesity can impair insulin-mediated vasodilation and reduce vasomotor reactivity, irrespective of insulin resistance. This can lead to a selective suppression of the vasodilator pathway and an over-activation of the vasoconstrictor pathway, causing cerebrovascular

dysfunction (Katakam et al. 2012; Rodríguez-Flores et al. 2014; Van Sloten et al. 2020). Secondly, obesity-induced reactive oxygen species and oxidative stress can result in endothelial damage, contributing to the impairment of cerebral perfusion (Martínez 2006; Chrissobolis and Faraci 2008). Thirdly, obesity is characterized by a low-grade chronic inflammatory state, with adipocytes acting as a source of pro-inflammatory cytokines that can lead to endothelial dysfunction and damage to cerebral small vessels (Fernández-Sánchez et al. 2011; Low et al. 2019). Lastly, the dysregulation of baroreflex control of blood pressure due to diet-induced obesity may result in brain hypoperfusion (Laosiripisan et al. 2015). In conclusion, the link between BMI and CBF is intricate and affected by a multitude of factors. Further investigation is essential to gain a comprehensive understanding of the mechanisms underlying this relationship and its clinical significance.

ASA classification

Our findings also indicated that a higher ASA classification is associated with an increased intraoperative ULA while there is a scarcity of studies examining the link between ASA classification and the ULA. The ASA Physical Status Classification System is a recognized instrument for evaluating an overall health of the patient before surgical procedures (Horvath et al. 2021). An elevated ASA class signifies the presence of more severe systemic illnesses or health conditions that could impact the capacity to withstand surgery and anesthesia. These conditions may subsequently influence the physiological reactions of the patient, including the potential to alter the ULA.

Sevoflurane

In the present study, patients who recieved sevoflurane anesthesia showed lower intraoperative ULA, which means the ABP during the surgery of the patients was more likely to surpass the ULA and the patients were more likely to experience impaired CVA. This finding is to some extent in agreement with one published report, which found that sevoflurane could cause a global declining tendency in regional CBF

when it was titrated to keep a constant hypnotic depth (Kaisti et al. 2003). However, the majority of studies confirmed that sevoflurane does not affect CVA. Sevoflurane is a volatile anesthetic with a relatively low blood partition coefficient that permits rapid induction and recovery from anesthesia (Gupta et al. 1997). Among inhaled agents sevoflurane appears to preserve CVA at all doses, whereas with other agents CVA is impaired in a dose-related manner (Miletich et al. 1976; Schlünzen et al. 2006). This contradictory finding means that more research is needed to confirm.

Duration of surgery

Ultimately, our study revealed that the longer time the patient underwent surgery, the lower postoperative ULA value was. Unfortunately, there is currently no direct evidence to suggest this. We could attempt to explain it from the following perspective: prolonged surgery may lead to the use of vasoactive drugs, hypotensive events, and tissue hypoxia, all of which could impact the reactivity and autoregulatory capacity of cerebral blood vessels, leading to a lower ULA during the surgery. We provide our own relevant conclusions for this relationship between the duration of surgery and the postoperative ULA, and therefore hope that more research will support this view.

6.3 Intraoperative versus postoperative limits of cerebrovascular autoregulation

In this study population, there was no statistically significant variation between the LLA and the ULA when comparing the intraoperative and postoperative phases. A possible explanation is that for most patients, postoperative monitoring began immediately upon transfer to the PACU or PACU24 after surgery. The effects of intraoperative factors continue into the postoperative period, such as the use of anesthetic drugs during surgery and the impact of intraoperative blood loss on blood pressure.

6. Discussion

There is a lack of direct comparative studies examining the exact values of CVA limits between the periods of surgery and post-surgery. However, we could infer from related research that has investigated shifts in CVA using different parameters.

Schmieder and colleagues evaluated dCA by calculating the ARI perioperatively using TCD and the thigh cuff method in 50 neurosurgery patients with intracranial tumors. dCA was found maintained post-surgery if the clinical condition of the patient was favorable (Schmieder et al. 2000). A similar outcome was reported by Sharma and colleagues, who measured CVA in 35 patients with supratentorial tumors undergoing elective craniotomy. The transient hyperemic response of the MCA was used to calculate the transient hyperemic response ratio, with a value greater than 1.1 indicating normal autoregulation. The team found that CVA remained intact before and after tumor resection in their patient group. Furthermore, preoperative impaired CVA correlated with postoperative impairment, with all seven patients showing preoperative issues also having postoperative issues (Sharma et al. 2010). These two studies align with our findings in that CVA remains stable post-surgery.

However, there are also studies that suggest an improvement in CVA following surgery. Nakano and colleagues characterized CVA using NIRS during and after surgery for 134 cardiac surgical patients, noting that the prevalence of globally impaired CVA was higher in the operating room than in the ICU (Nakano et al. 2021). Dütsch and colleagues monitored CBFV in 16 patients with temporal lobe epilepsy 3-4 months before and after surgery, finding that the low-frequency transfer function gain decreased and the phase angle increased post-surgery, indicating improved CVA (Dütsch et al. 2004).

The majority of these studies suggest that CVA is either preserved or enhanced following surgery. This variability in outcomes may be attributed to the type of surgery performed and the methodologies and criteria applied in assessing changes in CVA.

6.4 Perioperative time-weighted average mean arterial blood pressure beyond the limits of cerebrovascular autoregulation

6.4.1 Intraoperative time-weighted average mean arterial blood pressure beyond the limits of cerebrovascular autoregulation

In current research, the median TWA-MAP below the LLA during surgery was 0.43 mmHg, the median intraoperative TWA-MAP above the ULA was 1.19 mmHg. The present study employed the TWA measure, which corresponds to the AUC divided by the length of the measurement duration. This normalization accounts for variations in the duration of surgery, a critical factor given that longer surgeries are more likely to result in a higher AUC (Saugel and Sessler 2021). Upon standardizing the units, it becomes evident that the TWA values obtained in this study are comparable to the outcomes of the previously mentioned studies.

Several studies have also quantified the Area Under the Curve (AUC) or the normalized AUC of MAP when it extends beyond the limits of CVA during surgical procedures. Hori and colleagues calculated the AUC of MAP excursions below the LLA in 66 patients undergoing cardiovascular surgery. The median AUC was 4.55 (2.62, 9.44), and 1.23 (0.04, 2.92) mmHg×h in patients with and without AKI respectively (Hori et al. 2021). Ono and colleagues adjusted the intraoperative AUC below the LLA by measuring periods where MAP dipped below the LLA were quantified by the degree of pressure decrease and the length of time it persisted, and expressed in units of mmHg×min per hour. The median AUC-MAP below LLA was 2.4 (1.1, 5.7) mmHg×min/h for patients who did not experience major morbidity and operative mortality (MMOM), and 6.5 (2.1, 15.4) mmHg×min/h for those patients with MMOM. The team concluded that the AUC below the LLA was independently associated with MMOM after cardiac surgery (Ono et al. 2014). Somewhat differently, Nakano and colleagues normalized the intraoperative AUC below the LLA (the product of the magnitude and duration of MAP below the LLA) or above the ULA (the product of the magnitude and duration of MAP above the ULA) . The median

normalized AUC below the LLA and above the ULA were 3.1 (1.6, 5.6) and 1.1 (0.6, 2.7) mmHg×h per hour, respectively. The authors also indicated that blood pressure levels outside the autoregulation limits in the operating room were correlated with the incidence of delirium (Nakano et al. 2021).Further researches are advocated to establish a connection between clinical outcomes and the TWA-MAP that extends beyond the limits of CVA.

6.4.2 Postoperative time-weighted average mean arterial blood pressure beyond the limits of cerebrovascular autoregulation

In the present study, the median postoperative TWA-MAP below the LLA was 0.14 mmHg, and the median postoperative TWA-MAP above the ULA was 0.29 mmHg.

There was only one study that calculated the time and duration of MAP surpassing the postoperative limits of CVA. Nakano and colleagues characterized CVA using NIRS in 134 cardiac surgical patients during surgery and the early ICU phase. In the ICU, the median normalized per hour of monitoring for the product of the magnitude and duration of MAP below the LLA and above the ULA were 0.5 (0.1, 1.4) and 0.4 (0.1, 0.9) mmHg×h per hour, respectively (Nakano et al. 2021).

The discrepancy of the findings between Nakano team and the present study could be attributed to sampling variability and differences in patient populations, as the later research focused on the TWA-MAP beyond the CVA limits in patients undergoing non-cardiac surgery.

6.4.3 Factors with the values of time-weighted average mean arterial blood pressure beyond limits of cerebrovascular autoregulation

To delve into how various factors might influence the levels of TWA-MAP that exceed the limits of CVA, we examined the connections with several clinically significant variables. Here are the findings:

1). The intraoperative TWA-MAP below the LLA correlated with factors such as the sex, the presence of OSAS, blood transfusion received during surgery, and hemoglobin levels prior to the operation.

2). There were no factors linked to the intraoperative TWA-MAP above the ULA.

3). Postoperative TWA-MAP below the LLA was found to be related to the age and OSAS status.

4). For the postoperative TWA-MAP above the ULA, associations were observed with sex, the staus of arterial hypertension, the amount of blood loss during surgery, and the amount of noradrenalin administered.

Given that the TWA-MAP beyond the limits of CVA is determined using the LLA and the ULA, any elements that impact the LLA and ULA will correspondingly affect the TWA-MAP. Therefore, the factors influencing the LLA and ULA, which have already been discussed, will not be reiterated in this context.

Age

Our research indicated a slight increase in the postoperative TWA-MAP below the LLA with each additional year of age. This suggests that older patients may be at a higher risk of compromised CVA relative to their younger counterparts, specifically in terms of being more prone to inadequate cerebral perfusion and the potential for cerebral ischemia. Impaired CVA has been observed in several conditions that are more common in older individuals, such as ischemic stroke and carotid stenosis (White and Markus 1997; Eames et al. 2002). Consequently, the brains of these patients are less well-protected against the impacts of rapid blood pressure fluctuations. However, the dominant view in the literature is that CVA remains unaffected by age (Carey et al. 2003; Van Beek et al. 2008). For instance, one study has reported that neither the lower and upper limits of cerebral blood flow autoregulation nor the autoregulatory range are influenced by the age of patients under anesthesia (Goettel et al. 2016). This finding contradicts our results, underscoring the need for further studies to explore this discrepancy.

OSAS

In our study, patients diagnosed with OSAS exhibited a higher intraoperative and postoperative TWA-MAP below the LLA than those without OSAS. This indicates

that patients with OSAS are at an elevated risk of impaired CVA and cerebral ischemia, both during and after surgery. Urbano et al. observed a reduction in CBFV in awake patients with OSAS, with a diminished cerebrovascular response to hypotension, while the vasodilatory response to hypercapnia remained intact. Their findings point to an increased susceptibility to cerebral ischemia and shearing stress on cerebral vessels during periods of low blood pressure and surges in blood pressure due to obstructive apneas during sleep (Urbano et al. 2008). Other studies have also reported impaired CVA in patients with OSAS (Nasr et al. 2009; Zhang et al. 2021b), corroborating our findings.

However, the evidence regarding the impairment of CVA in OSAS patients is limited. One possible reason could be the concurrent condition of hypercapnia, a state of having higher than normal levels of carbon dioxide in the blood, which is known to exert a substantial influence on CVA (Tsivgoulis and Alexandrov 2009). A number of investigations have demonstrated that patients with OSAS had a weakened response of their cerebral blood vessels to CO_2. This indicates that there were inherent issues with CVA even when the end-tidal PCO_2 was within the normal range while the patients were conscious (Furtner et al. 2009; Virtanen et al. 2012; Schytz et al. 2013). Moreover, studies indicate that in individuals with OSAS, both the chemical and mechanical aspects of cerebrovascular regulation are considerably impacted. This implies that the ability of the cerebral blood vessels to respond to changes in chemical composition and mechanical forces in the blood, such as blood pressure, is significantly disrupted in patients with OSAS (Virtanen et al. 2012; Schytz et al. 2013). Individuals suffering from OSAS demonstrate irregularities in the vasodilation that are both dependent and independent of the endothelium, along with a muted reaction in the cerebral blood vessels to oxygen deprivation. This suggests that their ability of vasodilation in response to both direct endothelial stimulation and other stimuli is impaired, and their response of cerebrovascular system to low oxygen levels is diminished (Kato et al. 2000; Foster et al. 2007; Jelic et al. 2008).

The elevated likelihood of experiencing cerebrovascular incidents, including strokes in patients with OSAS, is due to several factors. The impaired CVA makes these

patients more susceptible to drops in ABP and the subsequent risk of cerebral ischemia. Additionally, fluctuations in ABP, particularly when there are sharp increases, can result in an overabundance of blood flow through the cerebral vessels. This excessive flow can cause damage to the endothelial lining of the capillaries, further contributing to the risk of stroke (Koehler et al. 2014; Li et al. 2014). Nevertheless, as alluded to earlier, the instances of hypopnea and hypoxemia stemming from obstructive sleep apnea can result in reduced blood flow to the brain. Conversely, there may be an augmentation of CBF in particular subcortical regions, including the putamen, globus pallidus, amygdala, and hippocampus, that could serve to selectively protect vital areas of the brain. This protective mechanism is a consistent finding that is typically observed during periods of wakeful relaxation (Baril et al. 2015). These seemingly contradictory results underscore the necessity for further research to clarify the complex relationship between OSAS, CVA, and associated cerebrovascular risks.

Arterial hypertension

In the present study, patients with arterial hypertension had a higher postoperative TWA-MAP exceeding the ULA which means that those patients are more likely to suffer from impaired CVA. This finding is somewhat similar to the conclusions of some other studies (Immink et al. 2004; Marmarelis et al. 2020). The underlying mechanism might involve hypertension causing alterations in the structure and function of the walls of the cerebral arterioles, including increased stiffness, arteriolar narrowing, and a decrease in the production of endothelial nitric oxide, causing a rise in cerebrovascular resistance and an elevation in pulse pressure, which in turn can lead to a decrease in CBF and a diminished CVA (Nobili et al. 1993; Avolio et al. 2018). However, this perspective was not universally accepted, there were also studies that reported intact CVA in individuals with arterial hypertension (Eames 2003; Machado et al. 2020). These conflicting findings may be related to the subjects selected and the evaluation methods of CVA used.

Noradrenalin

There is a positive correlation between the dosage of noradrenalin and the postoperative TWA-MAP exceeding the ULA, indicating that, an increase in noradrenalin dosage is likely to result in an increase in TWA-MAP above the ULA. Noradrenaline, an endogenous catecholamine, has a mix of alpha- and beta-agonist properties, but its primary effect is alpha-adrenergic, leading to significant arterial and venous vasoconstriction (Costa et al. 2022). Traditionally, vasoconstrictors are not thought to significantly alter intracerebral hemodynamics (Olesen 1972). However, Strebel and colleagues noted that during anesthesia, an increase in MAP due to norepinephrine was linked to an increase in CBF, suggesting impaired autoregulation. The authors attributed this more to the effects of anesthetics than to the vasoactive agents themselves (Strebel et al. 1998). A separate study also discovered that in meningitis patients, increasing MAP through norepinephrine infusion led to an increase in CBF, indicative of disturbed autoregulation (Møller et al. 2004). While the findings in this area are not entirely consistent, our study indicates that patients who received a higher dose of noradrenaline had a higher postoperative TWA-MAP that exceeded the ULA. This implies that these patients could tolerate a higher MAP before the onset of impaired CVA. More research is indeed needed in this field to confirm their interrelationship.

6.5 Intraoperative versus postoperative time-weighted average mean arterial blood pressure beyond limits of cerebrovascular autoregulation

In this study,the intraoperative TWA-MAP below the LLA was statistically higher than the postoperative TWA-MAP below the LLA. The same pattern was noted for the TWA of MAP above the ULA, with the intraoperative TWA being statistically higher than the postoperative TWA. Thes findings are similar to another study. Nakano and colleagues, in their evaluation of CVA using NIRS in 134 cardiac surgery patients during surgery and early ICU care, reported that the normalized measure of MAP below the LLA, accounting for both magnitude and duration, was more

pronounced in the operating room than in the ICU. A similar trend for the normalized exposure of MAP above the ULA between the two monitoring periods were also found in this research (Nakano et al. 2021).

A potential explanation for this observed phenomenon could be the differences in clinical interventions applied during the intraoperative and postoperative phases. The more frequent use of vasoactive medications and anesthetics during surgery might impact the cerebral ability to autoregulate blood flow, increasing the risk of complications such as cerebral ischemia or edema (Dagal and Lam 2009; Slupe and Kirsch 2018; Park et al. 2024). Additionally, the goals of fluid and blood pressure management differ between the intraoperative and postoperative periods. As previously noted, the volume of crystalloid fluids administered and the occurrence of blood transfusions can influence CBF. Generally, a larger amount of crystalloid is given during surgery compared to the postoperative period, and blood transfusions are typically carried out in the operating room.

Overall, our study revealed the values of intraoperative and postoperative limits of CVA, which provided anesthesiologists a reference for individualized perioperative blood pressure management. The study also found that there were no statistically significant differences between the intraoperative and postoperative periods for both the LLA and the ULA, which further indicated that CVA remained stable after surgery for this study sample. The TWA-MAP that fell below the LLA and above the ULA during surgery were significantly higher when compared to the corresponding postoperative values, which may suggest that the extent to which intraoperative blood pressure exceeds the limits of CVA is more likely to be associated with adverse patient outcomes than the extent to which postoperative blood pressure exceeds the limits of CVA. The present study also indicated many factors associated with the periopertaive limits of CVA and TWA-MAP beyond the limits of CVA, which could help clinicians better understand the factors affecting the limits of CVA, thereby making better clinical decisions to prevent patients from having blood pressure below the LLA or above the ULA. All these findings are solid evidence for the research about CVA and perioperative monitoring and patient caring.

7. Limitations

This research has a number of limitations that should be taken into account. Firstly, due to methodological considerations, specifically the use of TCD, only patients who underwent surgery in the supine position were included. This criterion may have introduced a bias in the selection of participants. Secondly, not all patients exhibited clear limits of CVA, which could be attributed to the fact that patients in our clinical context were not subjected to extreme blood pressure variations, both low and high. Thirdly, when constructing linear regression models to evaluate factors associated with the perioperative limits of CVA and TWA-MAP beyond those limits, we could not guarantee that we accounted for all potential confounding variables in our diverse patient group. Fourthly, we did not adjust for the dosages of sevoflurane and propofol, merely categorizing the variable as "use of propofol or sevoflurane for anesthesia maintenance." It is important to note that some studies have indicated that the impact of these anesthetic agents on CVA is contingent on dosage. Lastly, our study reports findings from a single-center observation. To substantiate our results, multicenter data are essential, and further randomized controlled trials are advised to assess the association between the limits of CVA and neurocognitive outcomes such as delirium.

8. Abstract

Background: Cerebrovascular Autoregulation (CVA) is a vital mechanism that ensures a constant cerebral blood flow (CBF) even when perfusion pressure fluctuates. This process is especially critical during surgical and anesthetic procedures. The perioperative assessment of CVA helps to identify the lower limit of cerebrovascular autoregulation (LLA) and the upper limit of cerebrovascular autoregulation (ULA), which are the blood pressure thresholds beyond which cerebral hypoperfusion or hyperperfusion may occur. CBF tends to decrease when blood pressure falls below the LLA and increase when blood pressure exceeds the ULA.

Aims: The objective of this study was to evaluate and compare the intra- and postoperative LLA and ULA, along with the Time-Weighted Average (TWA) Mean Arterial Blood Pressure (MAP) below the LLA and above the ULA. Additionally, the study sought to identify factors related to these parameters during the perioperative period.

Methods: This was a sub-study within an ongoing single-center, prospective cohort study conducted from August 2021 to September 2023. It included adult patients scheduled for non-cardiac surgery exceeding 120 minutes, under general anesthesia, with invasive blood pressure monitoring, pre-existing anemia, or anticipated blood loss exceeding 500ml. CVA was measured through the correlation between MAP and regional cerebral oxygen saturation (rSO2) as detected by near-infrared spectroscopy (NIRS). Patients were assessed both intraoperatively and postoperatively. The LLA and ULA were determined using an automated curve-fitting algorithm as the MAP at which the cerebral oximetry index (COx) decreased from ≥ 0.3 to < 0.3 or increased from < 0.3 to ≥ 0.3, respectively, as MAP increased. The TWA-MAP below the LLA and above the ULA were calculated as areas between the MAP and the respective limit curves, normalized to the duration of CVA assessment. Multivariable linear regression models were used to analyze factors associated with the perioperative LLA, ULA, TWA-MAP below the LLA and TWA-MAP above the ULA.

Results: The final analysis included 423 patients. The median intraoperative LLA and ULA were 69.40 (63.94, 76.21) and 86.06 (79.42, 93.64) mmHg, respectively. The median postoperative LLA and ULA were 71.09 (62.94, 79.52) and 87.42 (77.07, 97.69) mmHg, respectively. The median intraoperative TWA-MAP below the LLA and above the ULA were 0.43 (0.11, 1.36) and 1.19 (0.43, 2.32) mmHg, respectively. The median postoperative TWA-MAP below the LLA and above the ULA were 0.14 (0.00, 0.74) and 0.293 (0.03, 0.86) mmHg, respectively. The differences in LLA and ULA between intra- and postoperative periods were not statistically significant (p=0.343 for LLA, p=0.322 for ULA). However, the intraoperative TWA-MAP below the LLA and above the ULA were significantly higher than their postoperative counterparts ($p < 0.001$ for both). Sex, the hemoglobin level before the surgery, and the occurrence of a blood transfusion during surgery were found to have a correlation with the intraoperative LLA; sex, BMI, the ASA physical status classification, and the use of sevoflurane anesthesia were determined to affect the intraoperative ULA; the change in hemoglobin levels from the preoperative period to the postoperative period was linked to the the postoperative LLA; sex and the duration of the surgery showed a relationship with the postoperative ULA; sex, Obstructive Sleep Apnea Syndrome (OSAS) status, blood transfusion during surgery, and preoperative hemoglobin levels were associated with the intraoperative TWA-MAP below the LLA; no variables were related to the intraoperative TWA-MAP above the ULA; age and OSAS status were correlated with the postoperative TWA-MAP below the LLA; sex, arterial hypertension, blood loss, and the amount of noradrenalin administered were in association with the postoperative TWA-MAP above the ULA.

Conclusion: Patients tend to have a higher TWA-MAP below the LLA and above the ULA during surgery than after surgery, indicating the need for tailored blood pressure management strategies in different perioperative phases. Multiple factors influence the perioperative limits of CVA and the TWA-MAP, with sex, hemoglobin level, and OSAS status being key determinants.

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11. Curriculum Vitae

Lebenslauf entfällt aus datenschutzrechtlichen Gründen.

12. Eidesstattliche Versicherung

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe, insbesondere ohne entgeltliche Hilfe von Vermittlungs- und Beratungsdiensten, 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. Das gilt insbesondere auch für alle Informationen aus Internetquellen.

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