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Cerebral autoregulation, spreading depolarization, and implications for targeted therapy in brain injury and ischemia

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Abstract: Cerebral autoregulation is an intrinsic myogenic response of cerebral vasculature that allows for preservation of stable cerebral blood flow levels in response to changing systemic blood pressure. It is effective across a broad range of blood pressure levels through precapillary vasoconstriction and dilation. Autoregulation is difficult to directly measure and methods to indirectly ascertain cerebral autoregulation status inherently require certain assumptions. Patients with impaired cerebral autoregulation may be at risk of brain ischemia. One of the central mechanisms of ischemia in patients with metabolically compromised states is likely the triggering of spreading depolarization (SD) events and ultimately, terminal (or anoxic) depolarization. Cerebral autoregulation and SD are therefore linked when considering the risk of ischemia. In this scoping review, we will discuss the range of methods to measure cerebral autoregulation, their theoretical strengths and weaknesses, and the available clinical evidence to support their utility. We will then discuss the emerging link between impaired cerebral autoregulation and the occurrence of SD events. Such an approach offers the opportunity to better understand an individual patient's physiology and provide targeted treatments.

Keywords: autoregulation; brain injury; cerebral physiology; cerebral blood flow; cerebral vasoreactivity; research network

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1 Cerebral blood flow and infarction

One of the main goals of brain physiology monitoring is to prevent ischemia of brain tissue. This may be done in an acute situation such as traumatic brain injury (TBI) or stroke where there is critically vulnerable brain, or in a chronic condition such as carotid occlusion, where patients are at risk of recurrent hemodynamic strokes. Monitoring is also relevant in patients with non-neurologic conditions who may be at risk for ischemia such as cardiac surgery. Tissue progression from ischemia to infarction is dependent on multiple factors. Quantifiable thresholds for permanent death and loss of electrical activity have been well-validated (Figure 1) (Astrup et al. 1981; Baron 2001; Symon et al. 1977). At the lowest cerebral blood flow (CBF) ranges (<6 cm^3/100 g/min), there is complete and irreversible terminal depolarization after only minutes of time (Heiss 1983; Morawetz et al. 1979). Electrical silence begins to occur at approximately 20 cm^3/100 g/min (Jones et al. 1981), which is reversible for the first few hours, but will progresses to infarction if there is not brain reperfusion (Yonas et al. 1989). Cerebral blood flow rates between 20 and 30 cm^3/100 g/min result in a vulnerable zone where the risk of infarction remains elevated during times of physiological stress (Jovin et al. 2003).

2 Cerebral autoregulation and the rationale for measurement

Vascular resistance is the strongest determinant of CBF based on Poiseuille's law, which in turn is primarily determined by vessel caliber. Due to the evolutionary need to maintain

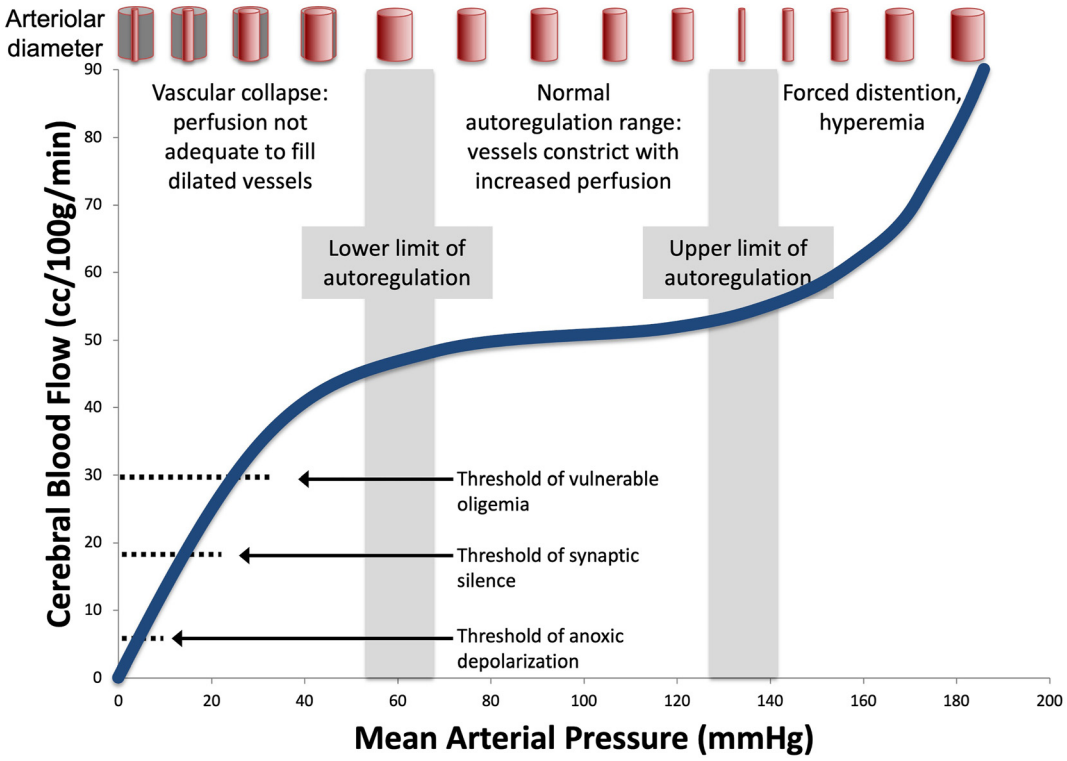

Figure 1: Standard model of cerebral autoregulation and quantitative thresholds for ischemia. With preserved myogenic control, precapillary arterioles dilate and constrict in response to changing perfusion pressure/blood pressure. The autoregulation thresholds are determined by the mechanical limitations of the arteriolar response. The property of autoregulation is not considering other regulators of cerebral blood flow such as pH or oxygen concentration.

consistent blood flow over a broad range of physiological blood pressures, a mechanism of pressure autoregulation exist to maintain a consistent CBF over a wide range of arterial blood pressures (Dirnagl and Pulsinelli 1990; Rapela and Green 1964; Rivera-Lara et al. 2017b). Separate from this pressure-dependent process, there are multiple mechanisms of CBF regulation that are affected by pH (Feletou et al. 2008; Kontos et al. 1977; Yoon et al. 2012) and $PaCO_2$ (Ainslie and Duffin 2009; Yoon et al. 2012), tissue oxygenation, and medications (Bouma et al. 1992). In addition, influence from the autonomic nervous system in CBF regulation may predominate in cases where the autoregulation capacity is exhausted (Koep et al. 2022; ter Laan et al. 2013).

With all of these mechanisms available, autoregulation is primarily dictated by an immediate intrinsic myogenic response of the pre-capillary arterioles (Vinall and Simeone 1981). (Note vessel diameter in Figure 1) The limits of autoregulatory capacity are therefore determined by the ability of the vessels to constrict (very high arterial pressure forces dilation above the autoregulatory limit (Vinall and Simeone 1981) and very low pressure leads to passive collapse below the autoregulatory limit). Autoregulation can be disturbed by chronic metabolic changes or acute injury. This can range from a loss of the stable zone CBF to hyperemia (rightward shift along the autoregulation curve) (Dirnagl and Pulsinelli 1990; RangeL-Castilla et al. 2008). In cases of chronic vaso-occlusive conditions such as carotid or vertebral stenosis and occlusion, brain regions may survive at or near the lower threshold of autoregulation. This makes such regions extremely susceptible to lower levels of blood flow variability such as transient drops in blood pressure (Nemoto et al. 2004). For these reasons, the range of blood pressure where CBF is preserved (horizontal axis in Figure 1) may dynamically change between patients based on individual pathology. Further, in patients with a focal lesion such as a stroke, there may be regionally impaired autoregulation.

In standard clinical practice, quantitative measurements of CBF with good spatial and temporal resolution are limited, and so various surrogate measurements of CBF have been developed. These include measurements such as brain tissue oxygenation (PbtO2), perfusion studies, and even intracranial pressure (ICP) as a surrogate measure for cerebral perfusion (using the cerebral perfusion pressure or CPP). CPP has been defined as mean arterial pressure (MAP) minus ICP, however it is not a direct measure of CBF.

These surrogate measures of CBF do not have a direct relationship to the quantitative thresholds of ischemia described in Section (1). This is where the utility of measurement of autoregulation may have the highest utility, therefore. By distinguishing whether a patient is on the "flat" part of the autoregulation curve as compared to the upper or lower limb, a clinician can estimate the risk for developing ischemia or hyperemia without a quantitative measurement of CBF. For example, if it can be concluded that a patient is on the left part of the autoregulation curve in Figure 1, then even minor decreases in blood pressure could potentially put the patient at risk of ischemia. Similarly, a patient on the right part of the curve may be at risk for hyperemia and hemorrhage.

Many techniques have been developed to measure autoregulation and its impairment. However, it is important to understand that there are strengths and weaknesses in all of these techniques (Riemann et al. 2020b; Rivera-Lara et al. 2017a). These may include weaknesses related to the actual measurement or gaps in the literature. Such information is relevant to adjusting different modifiers of an individual patient's physiology to improve CBF and thus decrease the risk of ischemia. For example, a patient with severely impaired autoregulation ipsilateral to an occlusive problem such as moyamoya disease may be considered for flow augmentation with an extracranial–intracranial bypass (Schubert et al. 2009). A patient with global loss of autoregulation with severely elevated intracranial pressure from hyperemia may be considered for moderate hyperventilation therapy to control $PaCO_2$ levels (and tissue acidosis) (Kelly et al. 1996). Finally, a patient with ischemic stroke may have a large oligemic region surrounding the ischemic core (i.e. penumbra) and would benefit from treatments to improve perfusion such as blood pressure augmentation (Bang et al. 2019) or even thrombectomy (Kobeissi et al. 2023). In sum, there are strong physiologic rationales to believe that patients across a variety of disease types could benefit from individualized treatment based on the state of autoregulation.

In this scoping review, we clarify technical and scientific strengths and weaknesses across the majority of approaches widely used to attempt to assess the state of autoregulation. We will also explore the relationship between impaired autoregulation, autoregulation directed therapy, spreading depolarizations, and ischemia.

3 Terminology

A brief note on nomenclature is needed. As various approaches to measure autoregulation have emerged, experienced centers have developed and used slight variations in nomenclature that can occasionally be confusing. For each index described below, we will describe common alternative notations or variations on the primarily used autoregulation index. Other terms such as "reserve" or "cerebrovascular reserve (Yonas et al. 1985)" are commonly used to indicate that a patient has vascular capacity for further vasodilation in order to respond to lower blood pressure, indicating a position on the "flat" part of the autoregulation curve. Similarly, "reactivity" testing is any test that assesses the capacity to respond to a vasodilating agent. Positive reactivity indicates a favorable position on the autoregulation curve (i.e. the "flat" part of the curve). Terms such as "misery perfusion" or "steal (Vorstrup et al. 1986a)" indicate that a brain region has exhausted capacity to respond with further vasodilation and is therefore on the left slope of the autoregulation curve. The phenomenon of "steal" represents a paradoxical decrease in flow in a region after a vasodilating challenge. This indicates that reserve is exhausted, the vessels are already maximally vasodilated, and the challenge test results in steal of blood flow to neighboring regions that remain capable of further vasodilation (Kuwabara et al. 1995; Tran Dinh et al. 1993). It should be noted that this review is not intended to discuss challenge tests that result in more localized changes in CBF (i.e., functional hyperemia), as these are more directly tied to understanding neurovascular coupling mechanisms, rather than disturbances in autoregulation per se.

4 Perfect measurement of autoregulation

All measurements of autoregulation are limited and inherently provide only partial information, which may be clouded by multiple confounding factors. A perfect technique would require a number of stipulations, which are currently technically impossible. (1) The technique would be required to measure *quantitative CBF* across all regions of the brain simultaneously. This is necessary because it is well established that different regions of the brain can have different autoregulation capacity. (2) The technique would need to be *continuously* available through bedside monitoring. This would be necessary as it is known that impairment of cerebral autoregulation can change with time, particularly after brain injuries and stroke (Aries et al. 2010). (3) The technique would need to assess accurate CBF *across all potential physiological blood pressure values*. For example, a patient with carotid occlusion may have adequate CBF at a mean arterial pressure (MAP) of 80 mmHg but have reduced CBF to ischemic levels at a MAP of 60 mmHg. An autoregulation

assessment that only evaluates the blood flow response over the range of 70–90 mmHg would therefore not detect impaired autoregulation at lower levels or higher levels.

Obviously, no technique can meet these requirements with available technology, but it is a useful thought experiment in order to critically consider the strengths and limitations of various techniques. At the most basic level, any measurement technique purporting to reflect aspects of cerebral autoregulation must meet two criteria: (1) the technique must ***measure CBF*** or some surrogate that can reasonably be expected to reflect CBF, and (2) there must be an ability to change an physiologic parameter (usually blood pressure) and "***challenge***" the measured CBF (or the surrogate) is measured, usually in conjunction with blood pressure, after changing a physiological parameter. As described in Section (2), a single measurement cannot determine if a patient has reserve or not. This is due to variability in the position of the curve with regard to blood pressure between patients and with different conditions. The necessary challenge test can be done in two main ways and Figure 2 shows a conceptual framework as to how such challenge tests would assess the state of cerebral autoregulation. The simplest and most direct method is to alter the blood pressure, either by pharmacologic intervention, or by measuring the effects of intrinsic blood pressure fluctuations. The CBF (or its surrogate) is then measured before and after this blood pressure challenge. If there is a change in blood pressure with no subsequent change in CBF, then one can conclude that autoregulation is preserved and there is adequate reserve. The second method is to give a vasodilating agent to evaluate if there is capacity for the cerebral vasculature to further dilate (resulting in increased CBF). In this challenge, the vasodilating agent is expected to "override" the myogenic control of vessel caliber. Specifically, if the vessels are already maximally dilated on the left slope of the autoregulatory curve, such a challenge would result in unchanged or even decreased CBF (steal phenomenon (Vorstrup et al. 1986a)). Such a vasodilatory challenge typically makes use of the separate mechanism of CO_2 acidification resulting in vasodilation. By increasing $PaCO_2$, either through breath holding or through inspired CO_2, a strong vasodilatory stimulus is induced, similar to with acetazolamide. Preserved CO_2 reactivity therefore would indicate a position on the flat, stable part of the autoregulatory curve. Similarly hyperventilation is expected to result in vasoconstriction, though should be used with caution due to the potential risk of inducing ischemia in patients with impaired reserve (Liu et al. 2019). As described in Section (2), due to variability in the position of the curve with regard to blood pressure

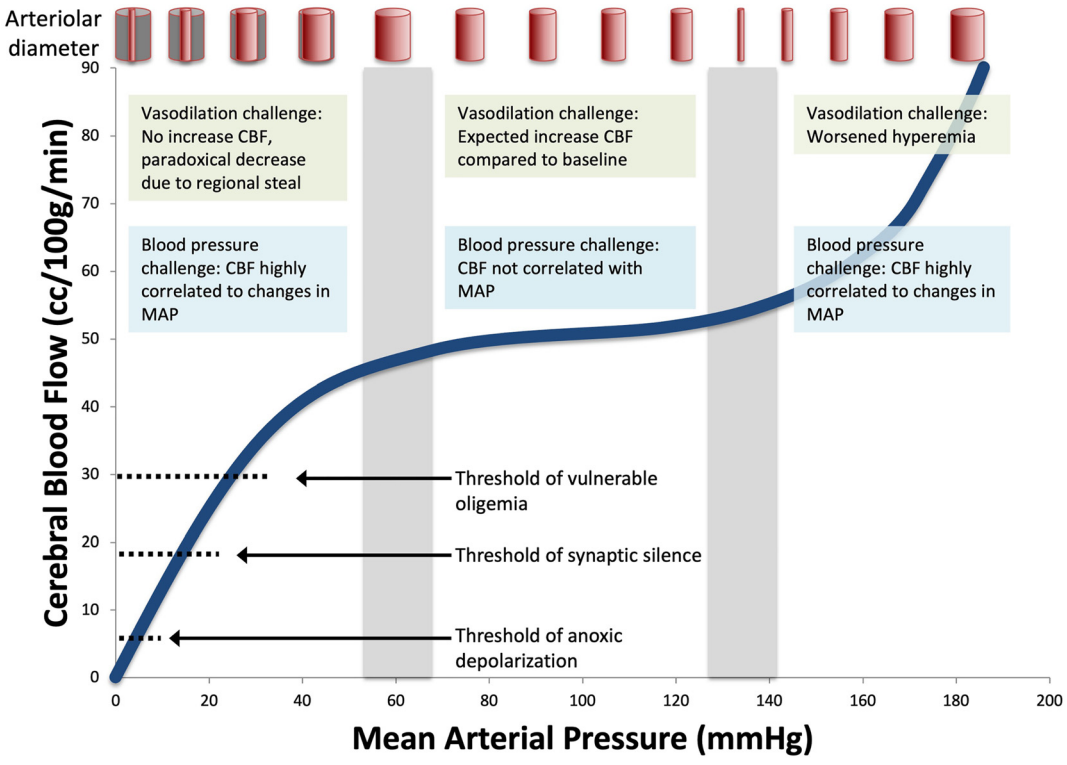

Figure 2: Challenge tests to assess cerebral autoregulation. The response to either blood pressure or vasodilatory challenge is noted in each "zone" of autoregulation. CBF, cerebral blood flow; MAP, mean arterial pressure.

between patients and with different conditions, a single measurement cannot determine if a patient has reserve (preserved autoregulation) or not.

Table 1 estimates most of the published approaches for assessment of cerebral autoregulation in terms of the strengths and limitations of spatial coverage, repeatability and the challenges commonly used. For example, imaging-based approaches may have good spatial coverage but because they are only "snapshots" in time, they are limited in their ability to continuously monitor changing autoregulatory states. The feasibility of performing a challenge test relies on the ability to repeat the test immediately after the challenge under similar physiologic conditions. For example, CT perfusion imaging cannot be repeated reliably until the contrast bolus has been eliminated. If there are changes in the patient's hematocrit, cardiac output, $PaCO_2$ or other variables, a follow-up test may or may not be measuring changes related to autoregulation. For continuous approaches such as reactivity indices, most are limited spatially to a relatively small region of brain but provide continuous measurements over many days. Most continuous measurement techniques take advantage of the intrinsic fluctuations

Table 1: Theoretical strengths and limitations of various approaches to autoregulation measurement. Number of "❍" from "❍" to "❍❍❍❍❍" corresponds to how well each autoregulation approach meets the criteria described.

Methodology	Spatial coverage	Temporal coverage	CBF measurement accuracy	Physiological challenge
Optimal (theoretical) test	Global, whole brain ❍❍❍❍	Continuous ❍❍❍❍❍	Quantitative, highly temporally resolved ❍❍❍❍❍	Response to MAP change over entire range of MAP ❍❍❍❍❍
Worst (theoretical) test	Tiny focal region ❍	Single measure only ❍	Poor correlation with quantitative CBF ❍	Limited range of MAP assessed or low reliability ❍
Xenon/CT CBF imaging with challenge	❍❍❍❍ Limited only by CT slice selection	❍❍ Can be repeated but requires coordination	❍❍❍❍❍ Gold standard CBF	❍❍❍ Limited to the range of challenge
MRI based approaches: global BOLD or quantitative large vessel flow with challenge	❍❍❍❍ Limited only by brain volume used	❍❍ Can be repeated but requires coordination	❍❍❍❍ BOLD signal highly correlated with CBF	❍❍❍ Limited to the range of challenge
PRx (moving correlation between ICP and MAP)	❍❍ ICP may reflect overall brain pathology	❍❍❍❍❍ Can be continued for days during high risk injury time	❍❍ ICP only theoretically correlated with CBF on a highly time resolved basis	❍ Intrinsic blood pressure fluctuations only. Other challenges of limited utility
ORx (moving correlation between PbtO2 and MAP)	❍ Point measurement at the tip of the probe only	❍❍❍❍❍ Can be continued for days during high risk injury time	❍❍❍❍ $PbtO_2$ highly correlated with CBF	❍❍ Can use both intrinsic fluctuations or discrete challenge
CBFRx (moving correlation coefficient between CBF and MAP)	❍ Point measurement at the tip of the probe only	❍❍❍❍ Can be continued for days during high risk injury time but frequent recalibrations	❍❍❍❍❍ Gold standard probe based CBF measurement	❍❍ Can use both intrinsic fluctuations or discrete challenge
OSRx (moving correlation coefficient between NIRS derived cerebral oxygen saturation and MAP)	❍❍❍ Provides regional coverage of several cm, typically bilaterally	❍❍❍❍ Can be continued for days during high risk injury time but limited if pads lose contact	❍❍❍ NIRS optical signal correlated with CBF	❍❍ Can use both intrinsic fluctuations or discrete challenge
TCD (either with challenge or as an intermittent continuous correlation with MAP- [Mx])	❍❍ Can insonate multiple proximal large vessels	❍❍❍ Can be repeated frequently	❍ Proximal flow velocity questionably associated with tissue CBF	❍❍ Can use both intrinsic fluctuations or discrete challenge
PET O15 CBF imaging with challenge	❍❍❍❍ Limited only by region imaged	❍ Difficult to coordinate, difficult to repeat	❍❍❍❍❍U Quantitative CBF, but using a non-diffusible tracer limits accuracy at low CBF values	❍❍❍ Limited to the range of challenge

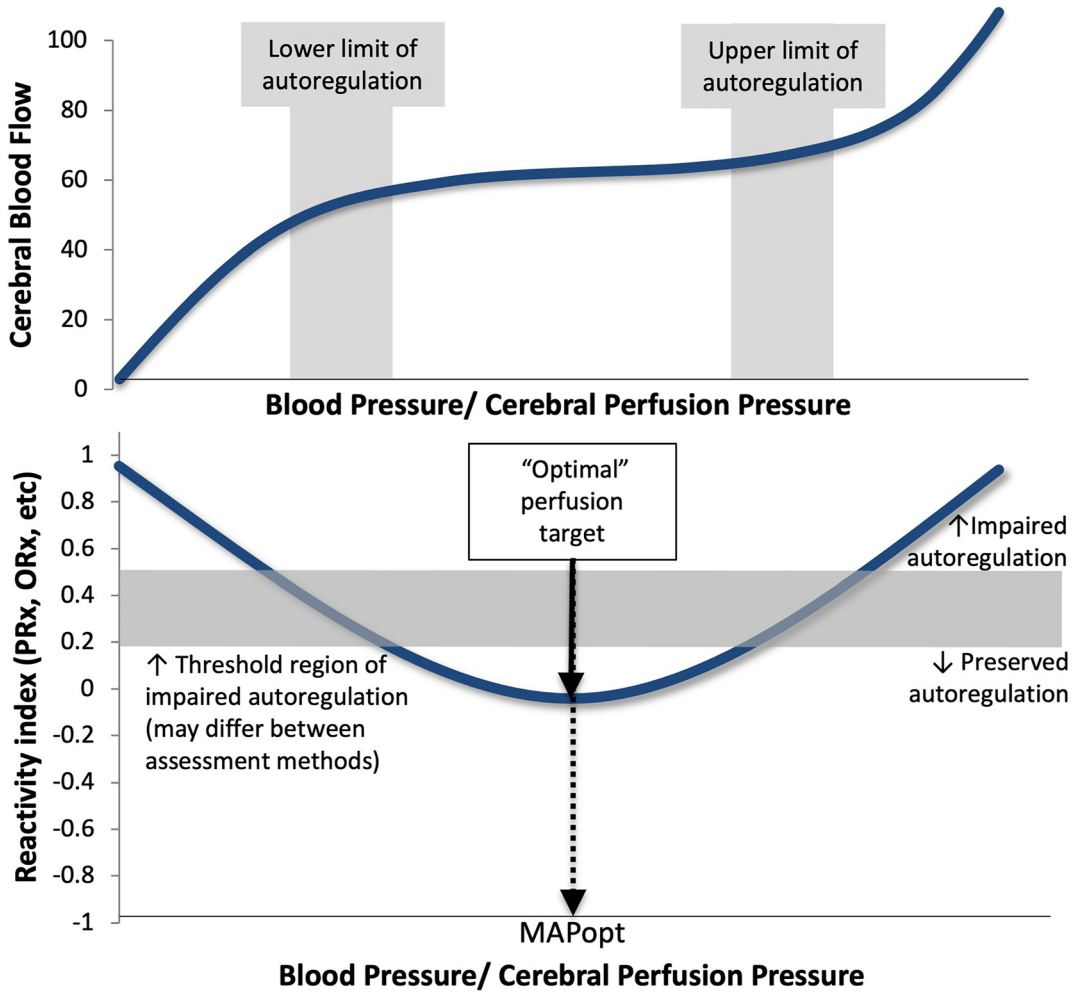

Figure 3: Rationale behind optimal MAP or CPP estimation. For a continuous index, the rolling correlation coefficient between blood pressure and CBF or its surrogate is calculated. The values are then plotted across the range of measured blood pressure in that patient during a given interval. When a characteristic "u shaped curve" can be calculated, the lowest point is assumed to be the blood pressure at which the patient is in the most "flat" part of the autoregulation curve, therefore serving as a potential therapeutic target.

in blood pressure to assess the autoregulation response. By plotting these associations across the patient's range of blood pressure variation, the blood pressure with the lowest association can be chosen as the "optimal" target to optimize autoregulation status (Zeiler et al. 2019a) (see Figure 3).

5 Assessing autoregulation measures: theory and evidence

Armed with the understanding that no test of autoregulation is perfect, we will assess the different approaches. We examine; underlying physiology in order to better understand the strengths and limitations of these techniques and then assess key features that can be used to evaluate the theoretical validity of the test. We emphasize spatial coverage (how much of the brain the test can resolve), temporal coverage (continuous versus intermittent measurements), the validity of the CBF measurement, and the validity of the physiological challenge procedure. We will also summarize published predictive literature for each measure.

5.1 Xenon/CT with acetazolamide (or other) challenge

5.1.1 Theory

Xenon/CT is a tomographic technique of CBF measurement which delivers quantitative values across each voxel of the

CT slice after several minutes of xenon inhalation (Carlson et al. 2011a). It is one of the most validated CBF measurement technologies and is often considered the "gold standard" for human CBF measurement (Olivot et al. 2009; Zaharchuk et al. 2011), despite the fact that it is not currently available in the United States. Xenon is a radio-opaque inert gas that is highly lipid soluble so can be used as a quantitative tracer by measuring both the arterial concentration and the arrival to the brain parenchyma with serial CT scans, fitting to the Kety-Schmidt model for flow (Carlson and Yonas 2010). The advantage of xenon/CT over many tomographic techniques is that after inhalation of xenon, it is rapidly eliminated by respiratory exchange (Johnson et al. 1991). This allows for immediate comparison with a challenge intervention (Carlson and Yonas 2010). This immediacy limits potential variability in hemoglobin levels, baseline blood pressure, hydration status, or other factors that could potentially affect CBF. Xenon^{133} is a related quantitative approach limiting assessments to regional or hemispheric values (Vorstrup et al. 1986b). As radioactive xenon^{133} is measured with single photon emission tomography, it has limited spatial resolution, limiting assessments to regional or hemispheric values (Vorstrup et al. 1986b).

The most commonly used autoregulation test with xenon/CT is a vasodilatory challenge. This is performed using a baseline xenon/CT followed by administration of a vasodilatory agent such as acetazolamide and immediate repeat xenon/CT study (Rogg et al. 1989). If CBF is increased, the clinician can conclude that the CBF is on the "flat" segment of the autoregulatory curve where there is further capacity for vasodilation (cerebrovascular reserve). If the CBF does not increase or even regionally decreases due to "steal" from marginally perfused brain to normal brain, the clinician can conclude that autoregulation is impaired either locally or globally (see Figure 4). Similar approaches can be performed with blood pressure challenges as well. If CBF does not change with blood pressure augmentation, the clinician can conclude that autoregulation is intact. Though xenon/CT has among the highest spatial coverage of all these techniques (only limited by the CT slices used), the temporal coverage is limited to the timing of the test. In addition, the test is limited to the state of autoregulation at the blood pressure at which the test was performed. See Figure 4 for example of this approach.

5.1.2 Evidence

Most of the evidence for the use of xenon for autoregulation assessment derives from studies assessing carotid occlusive pathology or ischemia after subarachnoid hemorrhage. Multiple anecdotal series have demonstrated the feasibility of measuring reactivity (preserved autoregulation) using xenon approaches with vasodilatory challenge in many conditions including stroke (Chollet et al. 1989; Vorstrup et al. 1986b), hemorrhage (Furuse et al. 2008; Kitahara et al. 1996), bypass and moyamoya disease (Batjer et al. 1988; Horowitz et al. 1995; Ishikawa et al. 1995; Patel et al. 2010; Touho et al. 1990; Vorstrup et al. 1986a; Yamashita et al. 1991, 1996), arteriovenous malformations (Tarr et al. 1990, 1991; Van Roost et al. 1996), normal pressure hydrocephalus (Tanaka et al. 1997), altitude sickness (Jensen et al. 1990), delayed cerebral

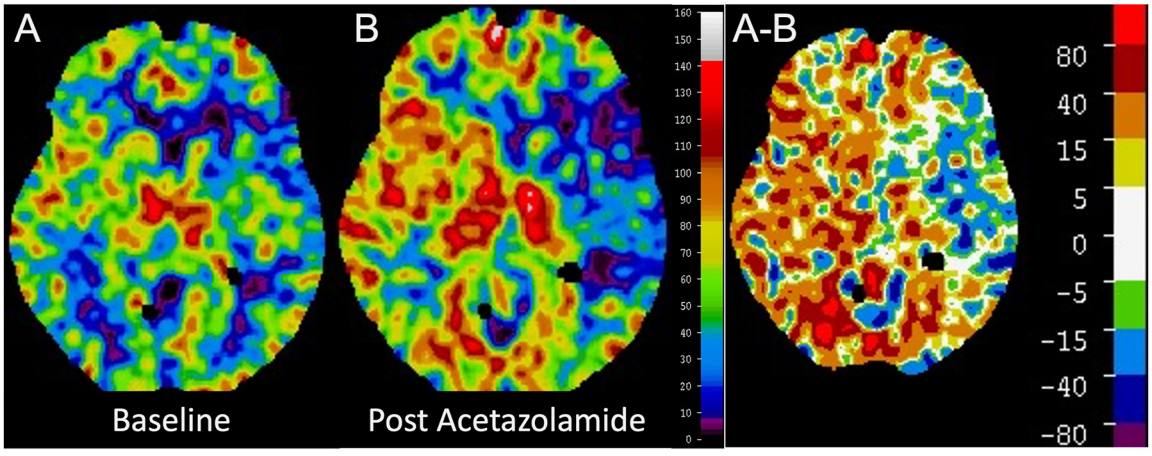

Figure 4: Example of steal in acetazolamide challenge test with xenon/CT: Patient with chronic left carotid occlusion. Baseline xenon/CT (A) demonstrates quantitative CBF for each CT voxel which correspond to the scale (center). After administration of acetazolamide (B), the CBF to the left middle cerebral artery (MCA) territory paradoxically decreases (steal). The difference between the two scans (A, B) is demonstrated, with increase flow (red) to most of the brain and decreased flow (blue) in the left MCA territory, demonstrating exhausted reserve. [In a previously published version of this article Figure 5 was placed at the position of Figure 4.]

ischemia/"vasospasm" in subarachnoid hemorrhage (Tran Dinh et al. 1993), and even in patients with diabetes (Rodriguez et al. 1993).

The prognostic value of xenon techniques with autoregulation/reactivity testing for stroke prediction has been validated across multiple centers. Yonas et al. (1993), found that in patients with carotid stenosis or occlusion, 6 month ipsilateral stroke rate in patients with impaired reactivity and low baseline CBF was 36 % compared to 4.4 % in those with normal reactivity. Similarly, Kuroda et al. (1993) stratified patients with carotid occlusion based on vascular reactivity for bypass and found that normalization of reactivity was associated with absence of subsequent stroke/TIA. Webster et al. (1995) likewise found an approximate 30 % stroke rate in patients with carotid stenosis or occlusion with impaired reactivity compared to a 2.3 % rate in those with normal reactivity. New strokes on MRI were also found more frequently during long term follow-up of asymptomatic patients with impaired reactivity compared to normal reactivity (Miyazawa et al. 2001). In a smaller group of patients with moyamoya disease, of the four patients with impaired reactivity assessed by xenon/CT, three had stroke in the interval awaiting reperfusion surgery, underscoring those at high risk in this group (McAuley et al. 2004). In a long-term study over five years, impaired reactivity was the only factor of multiple hemodynamic factors that was associated with risk of stroke (Ogasawara et al. 2002). In patients who underwent bypass for carotid occlusion, post-operative reactivity demonstrated improvement and a lower subsequent stroke risk compared to controls (Przybylski et al. 1998). Finally, in patients with aneurysmal subarachnoid hemorrhage, impaired autoregulation in the first four days of hemorrhage was significantly associated with worse outcome (Yoshida et al. 1996). Similarly, in acute stroke patients, impaired autoregulation was also associated strongly with poor clinical outcomes, despite similar raw quantitative CBF measurements (Kashiwagi et al. 2000).

Prediction of local tissue infarction is one of the key strengths of the xenon/CT method given the quantitative results provided, and the addition of autoregulation testing can strengthen this prediction ability. A threshold for tissue infarction after vasodilatory challenge of <15 cm^3/10 g/min has consistently emerged in both acute stroke (Kashiwagi et al. 2000) and subarachnoid hemorrhage (Tanaka et al. 1998).

In summary, autoregulation assessment with xenon/CT or xenon[133] has been historically widely used to aid in patient management. Those patient populations with impaired reactivity have been strongly associated with worse clinical outcomes and stroke. Though other intravascular contrast-based approaches with CT perfusion or MRI perfusion have become more widely available, these lack the ability to immediately repeat and compare the baseline with a physiologic challenge. Whether these techniques have the same predictive strength as xenon remains unknown.

5.2 MRI based autoregulation assessment

5.2.1 Theory

Highly localized functional hyperemia occurs following neurovascular coupling, which alters the ratio of oxy- and deoxyhemoglobin and forms the physiological basis of the blood-oxygen level dependent (BOLD) response used in functional MRI. Similarly, the BOLD response can also be used in conjunction with a vasodilatory challenge to isolate the vascular compartment of the neurovascular unit. While changes in the BOLD response are not a direct quantitative measurement of CBF, a key advantage of this approach is the reliance on an endogenous contrast agent rather than a potentially toxic substance (Kastrup et al. 2001). In addition to BOLD, arterial spin labeling (ASL) can be used as an MRI-based measure of CBF. This technique assesses brain perfusion by using magnetically labeled water in blood as a tracer, and directly measures any changes in CBF (Zhou et al. 2015). MRI can also be repeated in a relatively short interval for a challenge or reactivity test, with a much higher spatial resolution (typically 8 μL) relative to CT scans or even PET. Time to acquire MR imaging and other limitations generally restrict these tests to outpatient settings rather than in critical ICU patients.

5.2.2 Evidence

The most commonly used challenge tests to assess autoregulation are the breath holding test (which invokes a rise in CO_2 as a vasodilatory stimulus), external CO_2 administration (Mutch et al. 2012) and acetazolamide administration. In healthy volunteers, the breath holding test has been found to be very similar to CO_2 inhalation, but typically results in a higher degree of motion related artifact (Kastrup et al. 2001). While theoretically an attractive approach given the non-invasive nature and lack of need for contrast administration, there is a paucity of data relating these approaches to clinical outcomes, most likely secondary to cost and associated clinical logistics. Early stage studies have characterized reactivity changes that may occur in post concussive syndrome (Mutch et al. 2016) and stroke syndromes (Rodan et al. 2020). A recent study compared reactivity measurements using BOLD to those using functional NIRS in response to CO_2 challenge and found a close association

between the techniques as well as an association of impaired autoregulation in patients with chronic TBI (Amyot et al. 2020). Intrinsic CO_2 fluctuations have also been proposed as an adequate challenge test (Liu et al. 2017). While the magnitude of change is not as large as with a breath hold or CO_2 inhalation test, a strong correlation between such an approach and standard gas inhalation was observed in moyamoya patients (Liu et al. 2017). An impaired BOLD response to hypercapnia has been shown to be normalized in patients by carotid endarterectomy (Goode et al. 2009).

ASL provides a direct measure of arterial CBF, contrary to BOLD, which measures an aggregate of various neurophysiological signals related to venous factors more than arterial perfusion (Hall et al. 2016; Lee et al. 2001b; Zhou et al. 2015). A study comparing BOLD and ASL for measuring CVR has shown a stronger association of CVR between these techniques in the frontal and temporal areas relative to the parietal and occipital areas (Zhou et al. 2015). The authors suggest that this may be caused by the differences in vascular density between these regions, which influences the BOLD signal more than that of ASL. Furthermore, they highlight that in contrast to BOLD, ASL detects flow without information about the source, which forms a clinical limitation in patients with chronic vascular dysfunction with collateral vessels, obscuring hypoperfusion. Altogether, these current data suggest that BOLD and ASL can be used as complementary measures in autoregulation studies.

Quantitative MR angiography (NOVA: Noninvasive Optimal Vessel Analysis, VasSol, Inc., Chicago, IL, USA) offers an alternative approach for reactivity testing of the large vessels similar to TCD (transcranial Doppler ultrasound) approaches described in detail below. As opposed to TCD however, NOVA measures *quantitative* flow in the large vessels rather than flow *velocity*. This means that these measurements are standardizable across subjects. The technique also does not require contrast, allowing for repeat assessment after administration of acetazolamide (Carlson et al. 2012) or CO_2 (de Boorder et al. 2004). Since only large vessel flow is measured, the ability to predict stroke in the distal vascular bed is limited due to the possibility of direct or indirect (leptomeningeal) collateral flow. Nonetheless, appropriate reactivity to acetazolamide in a vessel distal to a proximal occlusive problem can be a reassuring measure of preserved autoregulation/reserve (Carlson et al. 2012).

While MRI-based techniques for measurement of cerebral autoregulation are attractive, particularly in the outpatient setting, further development with standardization of protocols and thresholds are needed.

5.3 Pressure reactivity index (PRx): moving correlation coefficient between intracranial pressure and mean arterial pressure

5.3.1 Theory

The pressure reactivity index (PRx) was initially developed and proposed in patients with severe TBI undergoing ICP monitoring. The measure is based on the hypothesis that ICP waveform data may be reflective of CBF changes on a highly time-resolved scale (Czosnyka et al. 1997b). It is calculated as a moving correlation coefficient between MAP and ICP. Though other related indices have also been proposed, PRx is well-described and strongly correlated with outcomes, particularly in TBI (Rivera-Lara et al. 2017a). The primary theoretical advantage of the PRx is that it provides continuous, time-resolved data during ICP monitoring. Intrinsic fluctuations in the patient's blood pressure are used as the "challenge" to assess autoregulatory capacity. These data can then be plotted as described in Section (2) (Figure 3) to hypothesize optimal targets for a patient's blood pressure. Minimizing the association between ICP and MAP changes theoretically indicates the patient is on the "flat" part of the autoregulatory curve at a given blood pressure (Aries et al. 2012b). The spatial resolution is somewhat limited if regional pathological disturbances in autoregulation are not reflected in ICP; however, since ICP is itself a generalized measure, there may be advantages over other focal probe-based measurements such as CBF probes and CBFRx (CBF reactivity). In other words, in patient with a large temporal contusion with surrounding edema and loss of autoregulation, there may be a reflection of these changes in ICP that are associated with MAP changes, that may not be reflected measured brain tissue oxygen tension ($PbtO_2$) or CBF in the remote frontal white matter. Intrinsic signal "noise" in PRx has also been noted, likely due to the same variables that also can affect ICP such as respiratory changes, artifact, hypertonic therapy, etc. (Rozanek et al. 2022). In addition, there are practical limitations in whether the assumptions of ICP as a reflection of CBF hold true in conditions such as post-hemicraniectomy or during active CSF drainage (Czosnyka et al. 2009).

5.3.2 Evidence

While most of the PRx literature is primarily related to TBI (Zeiler et al. 2017a), it has been applied across a relatively broad variety of disease states including aneurysmal subarachnoid hemorrhage (Owen et al. 2022; Sanchez-Porras et al. 2023; Sugimoto et al. 2016; Svedung Wettervik et al.

2021), intracerebral hemorrhage (ICH) (Diedler et al. 2010; Santos et al. 2011), normal pressure hydrocephalus (Czosnyka et al. 2005; Lalou et al. 2018), arteriovenous malformation rupture (Appavu et al. 2021), and post-cardiac arrest hypoxic-ischemic brain injury (Balu et al. 2021; Kirschen et al. 2022; Zipfel et al. 2022). The importance of impaired PRx has also been validated by performing xenon/CT CBF measurements while measuring PRx, and impaired PRx was associated with worse CBF (Johnson et al. 2016).

The goal of PRx measurement has been focused on defining an individual patient's optimal cerebral perfusion pressure (CPPopt) by plotting the PRx across the range of blood pressure and defining the nadir point where PRx is at its lowest (Aries et al. 2012b; Zweifel et al. 2008) (see Figure 3). This theoretically indicates the blood pressure (or CPP) where the patient is in flat part of the autoregulation curve. A generally accepted and validated threshold for impaired autoregulation as measured by PRx is >0.3 (Riemann et al. 2020b). Extensive retrospective and prospective data primarily in TBI have supported the hypothesis that worse PRx (>0.3) (Czosnyka et al. 2002) and farther derangements of actual CPP from CPPopt are associated with worse outcomes (Donnelly et al. 2018, 2019; Zeiler et al. 2019a; Zweifel et al. 2008). These data have in fact been compelling enough to support recent randomized trials testing CPPopt directed management, guided by PRx (Tas et al. 2021). A pilot study demonstrated feasibility of such an approach (Dias et al. 2015). A similar single arm study found that CPPopt-directed therapy had a larger influence on outcome in younger patients compared to older patients (Petkus et al. 2020). A larger multicenter study was therefore proposed in order to determine if this strategy could improve outcomes in severe TBI patients (Beqiri et al. 2019). The feasibility and safety results of this study of 60 subjects in 4 centers demonstrated feasibility in targeting CPPopt with no safety concerns (Tas et al. 2021).

In pediatric patients with TBI, PRx also seems to have predictive power regarding outcomes,; however the included numbers of patients is smaller (Abecasis et al. 2021; Brady et al. 2009; Gritti et al. 2023a; Hockel et al. 2017; Nagel et al. 2016; Zipfel et al. 2021). Recent larger studies have confirmed the ability to predict mortality and unfavorable outcomes (Velle et al. 2023) in pediatric patients with TBI using autoregulation with a proposed PRx threshold of 0.25 (Smith et al. 2023).

It is unclear if the worse outcomes associated with PRx in TBI patients can be extrapolated to include other types of cranial injury, such as in subarachnoid hemorrhage, where the association between MAP and ICP is less consistent (Eide et al. 2012; Kirkness et al. 2001; Rasulo et al. 2012). Some of this variation could be related to different practices in CSF drainage that may exist between injury types. Typically, CSF drainage is encouraged in SAH to treat hydrocephalus, whereas in TBI, often parenchymal ICP monitors are used and the amount of CSF drained is often with external ventricular catheters is less. Nonetheless, recent data support a similar association of poor outcome in SAH patients with impaired PRx (Svedung Wettervik et al. 2021); however, this association may only be in the delayed period when delayed cerebral ischemia (DCI) may occur and be related to impaired autoregulation (Chang et al. 2023). In patients with ICH, disturbed PRx (defined as >0.2) was found in nearly half of patients and was associated with worse outcomes (Diedler et al. 2014).

Finally, a variety of modifications to PRx have been proposed. These have been hypothesized to address some of the potential limitations of PRx. The "PAx" measurement uses ICP pulse amplitude instead of ICP alone to correlate with arterial blood pressure. This was found to have better discriminative power to detect mortality in TBI compared to PRx in patients with overall lower ICP (Aries et al. 2012a). The "RAC" uses correlation ["R"] between the ICP pulse amplitude ["A"] correlated with the CPP ["C"] instead of the blood pressure and may be a better predictor of outcomes (Zeiler et al. 2017b, 2019b). All of these modifications, however, may have different relevance and different critical thresholds to target so should not be considered interchangeable (Zeiler et al. 2018d).

The "long-PRx" was proposed as an alternative index in patients in whom ICP waveform data are not available for the usual waveform PRx calculation using 20-min bins (Sanchez-Porras et al. 2012). Similarly the "Low frequency autoregulatory index (LAx)" was proposed using 1 min bins (Depreitere et al. 2014). While these were both associated with outcomes (Sanchez-Porras et al. 2012), the higher resolution measurements appear to be superior (Lang et al. 2015, 2016; Riemann et al. 2020a,b). Recently, the "Ultra-Low frequency PRx" (UL-PRx) (Gritti et al. 2023a,b) has been proposed based on 0.0033 Hz sampling in 5-min bins, which was independently associated with poor outcome in adult and pediatric TBI patients. Other measures besides overall average PRx have also been proposed as potentially better measures of the overall burden of autoregulation impairment including the length of most severe impairment episodes (Preiksaitis et al. 2016) and intensity-duration plots (Svedung Wettervik et al. 2023).

In summary, PRx is the most standardized and well validated continuous measurement related to cerebral autoregulation, particularly in TBI. Additional studies are required to determine in which patients and which conditions it may be most relevant. In addition, it remains an open question as to whether or not goal directed therapy to target PRx (and the derived CPPopt) will result in better outcomes, or if it is a reflection of disease severity.

5.4 Oxygen reactivity index (ORx): moving correlation coefficient between brain tissue oxygen tension and mean arterial pressure

5.4.1 Theory

Brain tissue oxygen tension ($PbtO_2$) has emerged as a relatively reliable and accurate measurement in patients with brain injury that may represent an important complimentary method to ICP management alone (Fandino et al. 1999; Okonkwo et al. 2017). The probe measures diffusible oxygen resulting in a measurement of the partial pressure of brain oxygen ($PbtO_2$). To assess autoregulation status, a similar continuous correlation with MAP can be performed as with PRx resulting in the oxygen reactivity index (ORx). In addition, intermittent challenge tests with CO_2 or blood pressure changes can be used to qualitatively assess whether autoregulation is preserved. While this continuous oxygen related measurement may be a closer approximation of CBF as compared to ICP, there are significant limitations of this method. The probe only measures physiology in a small focal region, making it a poor reflection of overall brain physiology. The method is thus unable to detect an injury and impaired local autoregulation that is remote to the probe location (Hlatky et al. 2008; Rosenthal et al. 2008; Sarrafzadeh et al. 1998). Conversely, the temporal coverage, like the PRx, is excellent and can provide continuous assessment during the $PbtO_2$ monitoring time.

5.4.2 Evidence

The ORx as a continuous index was first reported in SAH (Jaeger et al. 2007) and then in TBI (Radolovich et al. 2009) patients. Though impaired ORx was associated with delayed infarcts in SAH, there is no correlation between ORx and the more established PRx in TBI patients. Further, "optimal" targets for CPP are not reliably determined using the ORx compared to the PRx based approach. Currently two different probes are available for measurement of $PbtO_2$ (Licox: Integra Neuroscience and Neurovent PTO: Raumedic), and while both have been validated. A study of patients with simultaneous measurements with both probes demonstrated some discordance in ORx measurement values (Dengler et al. 2013). In a systematic review of continuous approaches, 10 studies assessing ORx in TBI were found (Zeiler et al. 2017a), none of which directly assessed outcomes. More recent studies have suggested additional utility of the ORx, possibly as a complimentary measure to the PRx. Both measurements do not appear to be strongly correlated with each other, but both provide predictive roles regarding ischemia and outcome in SAH patients (Kastenholz et al. 2023; Owen et al. 2022). In a recent study of SAH patients with simultaneous multimodal autoregulation assessment including SD monitoring with ECoG, no association of ORx with clinical outcome was found; however, there did appear to be an association with the occurrence of SD (Owen et al. 2022).

5.5 CBFRx (cerebral blood flow reactivity index): moving correlation coefficient between cerebral blood flow and mean arterial pressure

5.5.1 Theory

Several invasive technologies exist to provide focal continuous measurement of quantitative cerebral blood flow (Dreier et al. 2009; Schroder and Muizelaar 1993). The two primary approaches involve either the use of a laser Doppler probe or a thermal diffusion probe (Vajkoczy et al. 2000). The most readily available of these is the Bowman thermal diffusion probe (Hemedex). These approaches have the advantage of providing quantitative CBF values and so absolute thresholds for ischemia can be used instead of relative values as described in Section (1). The primary limitation of these approaches is the focal rather than global nature of the assessment, similar to $PbtO_2$ probes discussed in the preceding section. In addition, these techniques are less stable and require frequent recalibration. These also have been noted to become inaccurate or lose monitoring ability after a relative short monitoring period (Kirkpatrick et al. 1994). In our data, we found that the thermal diffusion probe provided data in only approximately half of the measurements, as compared to data from $PbtO_2$ and ICP probes (Owen et al. 2022).

5.5.2 Evidence

The use of CBF probes to characterize either blood pressure responsive autoregulation or CO_2 reactivity has been described for over 30 years. As described in Section 4, increasing the $PaCO_2$ is a powerful vasodilator and so can be used to assess whether there is further vascular capacity along the autoregulatory curve. Tenjin et al. (1990) demonstrated that thermal diffusion probes can be used to assess the state of CO_2 reactivity in patients with brain injury, observing that impaired reactivity was associated with worse outcomes. Other studies have used intrinsic blood pressure variation as the challenge test, demonstrating a

strong association of impaired autoregulation with worse outcomes in patients with SAH (Lam et al. 1997) and other conditions (Dickman et al. 1991; Miller et al. 1998). Intraoperative assessment at the time of ruptured aneurysm clipping demonstrated that preserved autoregulation was associated with better outcomes (Cossu et al. 1999). Another study (Rosenthal et al. 2011) demonstrated the utility of assessment of both pressure reactivity and CO_2 reactivity with intermittent challenge tests in patients with TBI using thermal diffusion probes.

The use of continuous measurement of autoregulation indices based on intrinsic blood pressure fluctuations as an index (similar to the approaches described in Section 5.3) was pioneered by Czosnyka et al. (1997a). The "FRx", was developed and validated in the 2000s (Hecht et al. 2011). Given that other names for this index have been published, we have used CBFRx as a standard term. A similar moving correlation was described by Tackla et al. as the correlation between CPP and regional CBF ("rCBFx") in patients with TBI and was demonstrated to have utility as an approach to guide CPP management (Tackla et al. 2015) similar to PRx. More recently, CBFRx with laser doppler was compared to autoregulation measurements using PRx or transcranial doppler (TCD) (Zeiler et al. 2018c). The TCD-based reactivity measurements were found to be more closely associated with this gold standard approach compared to ICP derived indices such as PRx. This indicates that different nuances for the evaluation autoregulation may be conveyed by these different approaches based on the strengths and weaknesses described in Table 1. A systematic review in TBI found four studies using laser Doppler flow assessment and eight studies assessing thermal diffusion to assess autoregulation (Zeiler et al. 2017a). In the limited available data, the laser Doppler flow derived autoregulation measurement was associated with Glasgow outcome scale score at six months, while no outcome data were available for the studies using the thermal diffusion-based autoregulation assessment. We recently compared the CBFRx index to other autoregulation approaches in patients with simultaneous monitoring of PbtO2, scalp NIRS, ICP, and SD (spreading depolarization) in patients with SAH (Owen et al. 2022). In that study, as with the ORx in Section 5.4, CBFRx alone was not associated with clinical outcomes, though it did demonstrate a possible association with occurrence of SD events.

In summary, though CBF monitoring may be the "gold standard" to determine tissue perfusion, there are some limitations with stability of currently available implantable probes and the data is likely only reflective of a relatively small region of brain. Larger scale studies are needed to assess its relative value compared to other index measurements of autoregulation. Developing advances in non-invasive CBF approaches such as diffuse correlation spectroscopy (Baker et al. 2019) may represent future avenues with more global coverage that could be more relevant in assessment of regional autoregulation.

5.6 Oxygen saturation reactivity index (OSRx): moving correlation coefficient between cerebral oxygen saturation measured by near infrared spectroscopy and mean arterial pressure

5.6.1 Theory

Near infrared spectroscopy (NIRS) is a non-invasive approach that measures optical signals reflected through the skin, skull, and outer cortical surface using wavelengths sensitive to the relative concentrations of oxy- and deoxyhemoglobin. Regional cerebral oxygenation saturation (rSO_2) is calculated by subtracting the signal from the superficial layers and is posited to be related to CBF. For this reason, NIRS measurements, which are widely available clinically are an attractive surrogate for CBF in autoregulation assessment. Intermittent challenges with a CO_2 or blood pressure challenge can be used, however an index similar to the above continuous measurements (Sections 5.3 and 5.4) and can be generated using intrinsic blood pressure variations. This approach is attractive in that it does not require implanted monitoring devices and theoretically the detectors can be placed in any region of interest, however they are most typically placed bilaterally on the forehead. This increases the spatial coverage of this approach, and temporal utility is only limited by the time that the monitors are kept in place. The direct relationship between rSO_2 and CBF, however is unknown and the degree to which non-cerebral sources (such as scalp) may contribute to the measurements is also a significant potential limitation (Skov et al. 1991).

5.6.2 Evidence

As with other techniques, NIRS reactivity has been explored across a variety of conditions, but with most of the evidence and outcome assessments derived in the acute neurologic injury setting. Different notations for the index have been used, which reflect either different NIRS parameters or simply different notation. These include THx, COx, HVx, TOx, and OSRx. For the purposes of this review the OSRx terminology will be used. OSRx has been compared with PRx in

TBI patients, where they were found to be closely correlated (Zweifel et al. 2010a). Furthermore, a CPPopt curve (Figure 3) can be constructed and the resulting OSRx derived curves are closely correlated with the standard PRx curves (Dias et al. 2015). A vascular occlusion test has been proposed where the challenge used is a temporary manual carotid occlusion (reducing proximal perfusion pressure) (Donati et al. 2016). Impaired responses with NIRS to this test (decreased ipsilateral NIRS signal) were found to be associated with mortality in a variety of injury types (Donati et al. 2016). A systematic review of this approach, however found significant variability in values that were influenced by many non-physiologic factors, including medications (Niezen et al. 2022).

A majority of the TBI literature was initially focused on assessing the association between NIRS-derived autoregulation measures and existing measures such as PRx (Zeiler et al. 2017a). More recent data demonstrate a promising association between these measures and worse clinical outcomes in TBI; however, the data are generally found in smaller patient series and there are conflicting results based on a recent systematic review (Mathieu et al. 2020a). In subarachnoid hemorrhage patients, NIRS-based autoregulation impairment (higher reactivity to blood pressure changes) was found to be associated with worse functional outcomes (Silverman et al. 2019). In patients with carotid occlusion, lack of NIRS reactivity to CO_2 inhalation has been strongly associated with symptomatic status (Vernieri et al. 2006), and this impairment may be a predictor of subsequent stroke (Palazzo et al. 2010).

In patients with cardiac arrest, early impairment in OSRx was independently associated with increased mortality (Pham et al. 2015). Similarly, in a prospective study of patients in coma from a variety of insults, an OSRx threshold of >0.05 was found to be independently associated with mortality and disability (Rivera-Lara et al. 2020). Another prospective interventional trial in coma similarly found an association of higher OSRx in patients with worse outcomes (Laurikkala et al. 2021). In other non-neurologically injured critical care patients, a pilot feasibility study was attempted, however due to relatively low numbers with reliable autoregulation recordings, such a study was not thought to be feasible with that approach (Khan et al. 2021).

Intraoperative utility of assessing continuous autoregulatory response with NIRS during procedures such as cardiac surgery to direct optimal blood pressure has also been proposed (Montgomery et al. 2020). For example, elderly patients undergoing pelvic surgery were found to have worse autoregulatory capacity and a proposed higher optimal MAP target (Zhang et al. 2021).

Due to thin scalps and calvaria, the use of NIRS based approaches has a strong potential utility in infants (Cohen et al. 2019; Kooi et al. 2017; Massaro et al. 2015; Tian et al. 2016). Impaired autoregulation has been associated with poor outcomes in premature infants (Caicedo et al. 2011; Chock et al. 2020; De Smet et al. 2010; Hoffman et al. 2019). MAPopt values can also be calculated based on NIRS input and patients with lower deviations below the MAP opt have been shown to have worse outcomes a several injury types (Burton et al. 2015; Kirschen et al. 2021).

In summary, due to the non-invasive nature and high portability, NIRS-based autoregulation assessment represents an attractive physiology assessment tool across a wide variety of disease types. Additional data evaluating the association of NIRS with clinical outcomes or other physiologic derangements such as SD and infarct expansion may further pave the way to individualizing care across the longitudinal spectrum of care from acute injury to chronic recovery.

5.7 Transcranial Doppler (TCD) with CO_2 challenge and moving correlation coefficient of flow velocity and mean arterial pressure (Mx)

5.7.1 Theory

In practice, autoregulation assessment with TCD and various challenge stimuli is probably the most common method for assessing autoregulation due to the fact that it is non-invasive and relatively simple to perform. The technique can easily be used in either the outpatient setting or the ICU. TCD measures the flow *velocity* in the proximal large vessels around the circle of Willis. Flow velocity is a parameter that is indirectly related to CBF. Laser Doppler measurements of CBF as described in Section 5.5 are a different parameter compared to Doppler ultrasound (which measures only large vessel flow velocity), so the two should not be confused or conflated. Nonetheless, autoregulation assessment with TCD has been strongly associated with similar continuous measurement from laser Doppler CBF measurement (Zweifel et al. 2010b). The primary limitation of this technique is that there is reduced spatial coverage, as the collateral patterns to the cortex may be complicated by the presence of leptomeningeal collaterals. The response of proximal vessels may therefore not always reflect the state of parenchymal autoregulation in that territory. Variability in branching patterns of the

middle cerebral artery also can affect the reliability of results (Baumgartner et al. 1995). Finally, there is generally a need for a trained TCD technician to obtain the appropriate vascular windows to insonate the major vessels and maintain a consistent position before and after the challenge test or during the continuous index data acquisition, though automated systems have been developed that could facilitate longer term measurement (Mainali et al. 2022; Zeiler et al. 2018b).

5.7.2 Evidence

There have been numerous reports validating the utility of TCD assessment of autoregulation. Thus, TCD has been used across a variety of disease types ranging from acute brain injury (Lee et al. 2001a; Sorrentino et al. 2012), stroke (Chimowitz et al. 1993; Haubrich et al. 2005), hemorrhage (Minhas et al. 2019; Ratsep and Asser 2001) to various chronic conditions (Schweickert et al. 2009). In AVMs, the approach may be useful to assess the risk for reperfusion hyperemia during staged resection or embolization of an AVM (Kader et al. 1993). The specific challenge approach varies widely, including intrinsic fluctuations of blood pressure (Haubrich et al. 2005), breath holding, inhalation of CO_2, and acetazolamide administration (Lee et al. 1998; Schweickert et al. 2009). Comparative studies support a strong correlation between various methods (Provinciali et al. 1990).

Attempts to compare reactivity measurements using TCD with gold standard Xenon/CT, have shown mixed results (Ng et al. 2002; Pindzola et al. 2001). While intermittent challenge tests can be performed with TCD either using CO_2 or blood pressure challenge, correlation indices similar to the approach for PRx calculation have been developed. The most widely reported are the Mx (correlation between the *mean* TCD flow velocity and the CPP) and Sx (correlation between the *systolic* TCD flow velocity and CPP). Impairment in these indices has been correlated with outcomes after TBI (Czosnyka et al. 1996, 2001, 2002; Calviello et al. 2021; Schmidt et al. 2016). The Mx has also been used as a correlation of flow velocity with blood pressure only (rather than CPP) (Mxa) which eliminates the need for ICP monitoring to assess these data and seems to have similar predictive ability (Czosnyka et al. 2003; Lang et al. 2003) even though the measured values are not exactly equivalent (Lewis et al. 2007). Predictive thresholds indicating impaired autoregulation for the two measurements are both around 0.3 (Sorrentino et al. 2011). Newer TCD based approaches mirroring the Pax measurements have also been proposed using the pulse wave amplitude (nPRx and nPAx), and these were found to be associated both with the PRx, Mx, and clinical outcomes in TBI patients (Calviello et al. 2020; Radolovich et al. 2011). Measurements derived from the systolic flow velocity (Sx and Sxa) have been proposed to have a stronger association with outcomes than the mean derived versions (Budohoski et al. 2012b; Zeiler et al. 2018a). More complicated models based on "impulse response" and "transfer function" have also been proposed (Liu et al. 2015), though superiority either theoretically or in practice requires further assessment. The autoregulatory index (ARI) is an intermittent challenge approach where TCD is measured before and after a hypertensive challenge. Impaired ARI has been correlated with worse outcomes in pediatric TBI patients (Figaji et al. 2009; Vavilala et al. 2004). Pediatric patients likely have a different, more variable course of autoregulation impairment compared to adults, even in "mild" TBI (Lele et al. 2019; Thamjamrassri et al. 2022). In summary, the wide availability of TCD based approaches has led to a proliferation of approaches using different input functions and challenges. Further study is needed to better understand the optimum approach most associated with targetable physiologic dysfunction.

TCD based autoregulation assessment may also have prognostic and predictive ability in conditions other than TBI. One of the most feared complications of carotid endarterectomy or stenting is the cerebral hyperperfusion syndrome, which is thought to be a delayed normalization of the autoregulatory response due to chronic hypoperfusion (Li et al. 2024). The TCD "breath holding index" (TCD flow velocity before and after CO_2 challenge with breath holding) has been correlated with the occurrence of such events (Manojlovic et al. 2020; Sfyroeras et al. 2006, 2009).

Interestingly, impaired Mx did not seem to occur frequently in patients after early minor MCA stroke (Reinhard et al. 2005); however, it has been shown to worsen over four days after stroke (Reinhard et al. 2008). This later increase in Mx did seem to be correlated with infarct growth (Reinhard et al. 2012). Conversely, other groups have demonstrated association between the breath holding index after stroke and outcome (Troisi et al. 2012). There are many factors that could explain these discrepant results, including a notably different challenge stimulus, and different range of autoregulatory challenge assessment. In addition, stroke can be heterogeneous with different autoregulation responses between stroke subtypes (Guo et al. 2014) or severity (Salinet et al. 2019). Even after mechanical thrombectomy, there may be ongoing impaired autoregulation, arguing for the need for close targeted monitoring (Meyer et al. 2020). The most recent prospective data in ischemic stroke patients supports the association of impaired ipsilateral autoregulation measured by TCD with worse 3 and 12 month outcomes (Shen et al. 2022).

A meta-analysis demonstrated that in patients with ICH, impairment of autoregulation can be long lasting and associated with worse clinical status (Minhas et al. 2019). The autoregulation response may even worsen over the first five days after stroke (Reinhard et al. 2010). This derangement is likely long lasting and associated with worse clinical status (Minhas et al. 2019), however it may normalize by day 30 (Ma et al. 2016). A prospective feasibility study focused on autoregulation-directed therapy in such patients demonstrated improved autoregulatory status but no effect on clinical outcomes, though only 12 subjects were enrolled (Minhas et al. 2020).

In aneurysmal SAH, there also seems to be a strong association between Sxa and delayed cerebral ischemia (Budohoski et al. 2012a; Santos et al. 2016) as well as clinical outcomes (Budohoski et al. 2015). Other similar approaches using blood pressure and flow velocity correlations have supported these findings (Otite et al. 2014). An earlier prospective study in patients with aneurysmal SAH found that early impaired autoregulation as measured by TCD before and after brief carotid compression was strongly associated with poor outcomes (Rynkowski et al. 2019). Even early impairment, as measured by a transient hyperemic response challenge, was associated with worse outcomes (Rynkowski et al. 2019).

In carotid occlusive disease, impaired breath holding index or other CO_2 challenges have been associated with subsequent stroke (Bisschops et al. 2003; Reinhard et al. 2014; Silvestrini et al. 2000; Vernieri et al. 1999). These results have not been supported in larger long term follow-up studies (Jolink et al. 2014; Persoon et al. 2011). It has also been suggested that even in the absence of significant recurrent stroke, impaired reactivity may be associated with cognitive decline (Buratti et al. 2016) which improves with better reactivity after endarterectomy (Lattanzi et al. 2018; 2019).

A pilot prospective study of 37 patients in coma who underwent autoregulation assessment with TCD was found to have a high correlation between impaired autoregulation and mortality (Calviello et al. 2022). Medical therapies such as statins have also been demonstrated to improve TCD acetazolamide reactivity (Forteza et al. 2012; Sterzer et al. 2001; Tseng et al. 2005). In patients undergoing cardiopulmonary bypass, stroke, and delirium are common and a randomized trial using autoregulation directed blood pressure management demonstrated decreased delirium and improved cognitive outcomes (Hogue et al. 2021).

Despite all these promising data, it is important to remember that there are multiple strengths and weaknesses of both the TCD measurement technique and the associated challenges. A recent concerning study assessed autoregulation with the Mxa and transfer function analysis and found no distinguishing thresholds between normal volunteers and various injuries (sepsis, TBI, etc.) (Olsen et al. 2022). Certainly, these results do not discount the large preceding body of literature; however they do urge caution in how to incorporate these TCD based measurements into practice and the need to validate findings by other investigators.

5.8 PET CBF autoregulation assessment

Measurement of CBF with PET is accomplished by IV injection of H_2O^{15}, which is a rapidly degrading isotope. H_2O^{15} requires production at an onsite cyclotron, significantly limiting widespread use of this approach. Theoretically similar to the approach used to measure CBF with xenon/CT, the arrival of the tracer is imaged with PET and arterial concentrations are monitored with intermittent sampling to solve the Kety–Schmidt equation (Nariai 1996). Since the approach requires placement of an arterial line for quantitative measurements, qualitative measurements are often used, which does not require continuous blood pressure measurement. Without quantitative measures, the approach can thus only provide comparisons between hemispheres, without absolute CBF values. This approach may or may not have similar applicability to quantitative CBF measurements (Carlson et al. 2011b). Nonetheless, like with xenon/CT, challenge tests using either blood pressure, CO_2, or acetazolamide may all be used with PET imaging to assess the state of autoregulation. In a small study of patients with ischemic stroke, there was found to be no difference in autoregulation between hemispheres after a hypotensive challenge test with PET CBF imaging (Powers et al. 2009).

Overall, while PET CBF measurement is a powerful quantitative approach, the use of autoregulation testing is relatively limited both due to access and cost of the facilities as well as the fact that other PET approaches have the ability to obtain potentially more relevant variables related to hemodynamic compromise such as the oxygen extraction fraction (OEF) and the cerebral metabolic rate of oxygen consumption (CMRO2) (Kuroda et al. 2006; Nemoto et al. 2007; Yamauchi et al. 2004). Assessing the OEF response to acetazolamide has been proposed as a potential tool to assess the autoregulation response indirectly (Nemoto et al. 2007)

6 Autoregulation and spreading depolarization (SD)

Spreading depolarization (SD) has emerged as a central mechanism of ischemic injury progression across a variety

of neurological injuries and ultimately SD represents a final mechanism of brain death (Carlson et al. 2018; Dreier et al. 2018). Recurring SD and ultimately, terminal SD (anoxic depolarization) in some cases, occur in the ischemic penumbra of stroke and probably contribute to brain death, particularly in very low flow, compromised regions (Carlson et al. 2018; Dreier et al. 2009, 2017, 2018). Such a mechanism may account for the time dependency of ischemic thresholds between 6 cm^3/100 g/min and 30 cm^3/100 g/min, where the added metabolic and ischemic stress of recurrent SD progressively pushes expanding windows of tissue oligemia into the zone of irreversible ischemia (Dreier et al. 2018; Hartings et al. 2017; Luckl et al. 2018) over hours to days or longer.

While SD has been recognized in laboratory conditions for many years, the ability to record SD in human brain has been limited for a number of reasons (Dreier et al. 2017; Drenckhahn et al. 2012; Hartings et al. 2014; Hund et al. 2022). First, the DC shifts are very low frequency events, which are typically filtered in standard scalp or subdural recordings. Second, the time scale used evaluates events that occur over many minutes rather than the short time scale used to monitor standard ECoG activity. Third, these events occur spatially along gyri and so scalp recordings may be limited using wider electrode spacing to see these temporal events. Finally, the capacitance of the skull and scalp may limit the transmission of these low frequency signals.

The occurrence of these events therefore remained a mystery until pioneering work in traumatic brain injury documented the definite occurrence of SD after brain injury using subdural electrodes placed at the time of surgery (Strong et al. 2002). Since then patients with a variety of conditions that require neurosurgical intervention have undergone SD monitoring with a similar approach of placing a temporary subdural electrode at the time of surgery (Dreier et al. 2017). Attempts to use depth electrodes placed using a bedside bolt have been attempted but are less reliable for recording and cover a much smaller region (Jeffcote et al. 2014). Recent reports have reinvigorated the idea that scalp recordings may be able to be used to detect SD, however further validation is needed (Chamanzar et al. 2023).

The ability to definitively monitor SD in patients with brain injury and stroke for several days after surgery during the most high risk times for secondary injury has therefore been a notable advance in the past decade. Multiple sources of both preclinical and clinical data have suggested that lower CBF can trigger secondary SD after ischemia, which in turn can cause additional damage (Hartings et al. 2017; von Bornstadt et al. 2015) due to the large metabolic load. Monitoring SD may therefore be a complimentary approach to understand if there is focal or regional ischemia/metabolic instability, leading to onset of these unusually large pathophysiological events. Importantly, evidence that SD is associated with impaired autoregulation has been proposed by several groups. When the probability of SD is plotted against blood pressure, an interesting trend has emerged in preliminary assessments in TBI (Hartings et al. 2009), SAH (Owen et al. 2022), and malignant hemispheric stroke (Chau et al. 2022). It was found that the probability of SD is relatively stable across a middle range of blood pressure but increases notably at the lower ranges and decreases at the upper ranges (Figure 5). This pattern suggested a possible reflection of the autoregulation curve as the underlying mechanism for these SD probability curves. It makes physiologic sense that lower cerebral blood flow would be

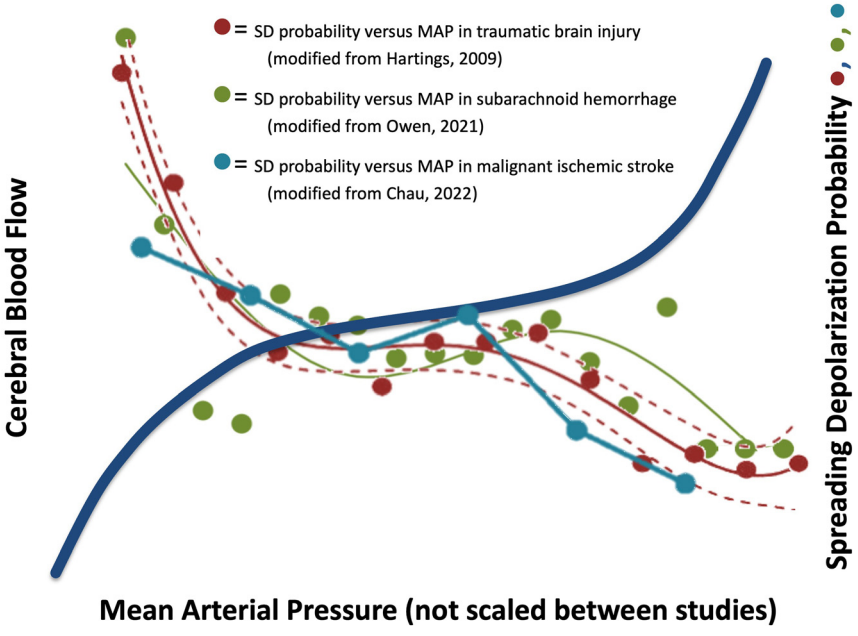

Figure 5: Proposed relationship of SD probability and cerebral autoregulation. The standard autoregulation curve is overlayed on the probability of SD versus MAP observed in multiple studies. Scales for SD probability and MAP thresholds vary between studies and are scaled to emphasize the potential qualitative association with increased SD possibility in the zone where autoregulation is impaired coupled with a potential protective effect with hyperperfusion. [In a previously published version of this article Figure 4 was placed at the position of Figure 5.]

associated with increased risk of SD. One the other hand, these curves also raise the possibility that vulnerable tissue could be protected from SD with hypertension at the upper part of the curve. The association between SD and impaired autoregulation was directly assessed and showed that SD was associated with impaired autoregulation as measured by PRx, ORx, and potentially OSRx (Owen et al. 2022; Sanchez-Porras et al. 2023). A different group similarly assessed the relationship between long PRx with SD, noting a significant association, particularly with clusters of SD (Sanchez-Porras et al. 2023).

A separate but related concept is that impaired autoregulation could also be associated with decreased tissue responses to SD. Sugimoto et al. demonstrated parallel worsening duration of SD and elevation of PRx prior to a clinical episode of DCI after SAH (Sugimoto et al. 2016). The role of impaired autoregulation may also have a relevant relationship with the hemodynamic response to each SD even beyond the overall relationship between incidence of SD. In a study with parallel monitoring of SD and CBF probes adjacent to ECoG electrode leads, the local CBF response to SD was described. When autoregulation appeared to be

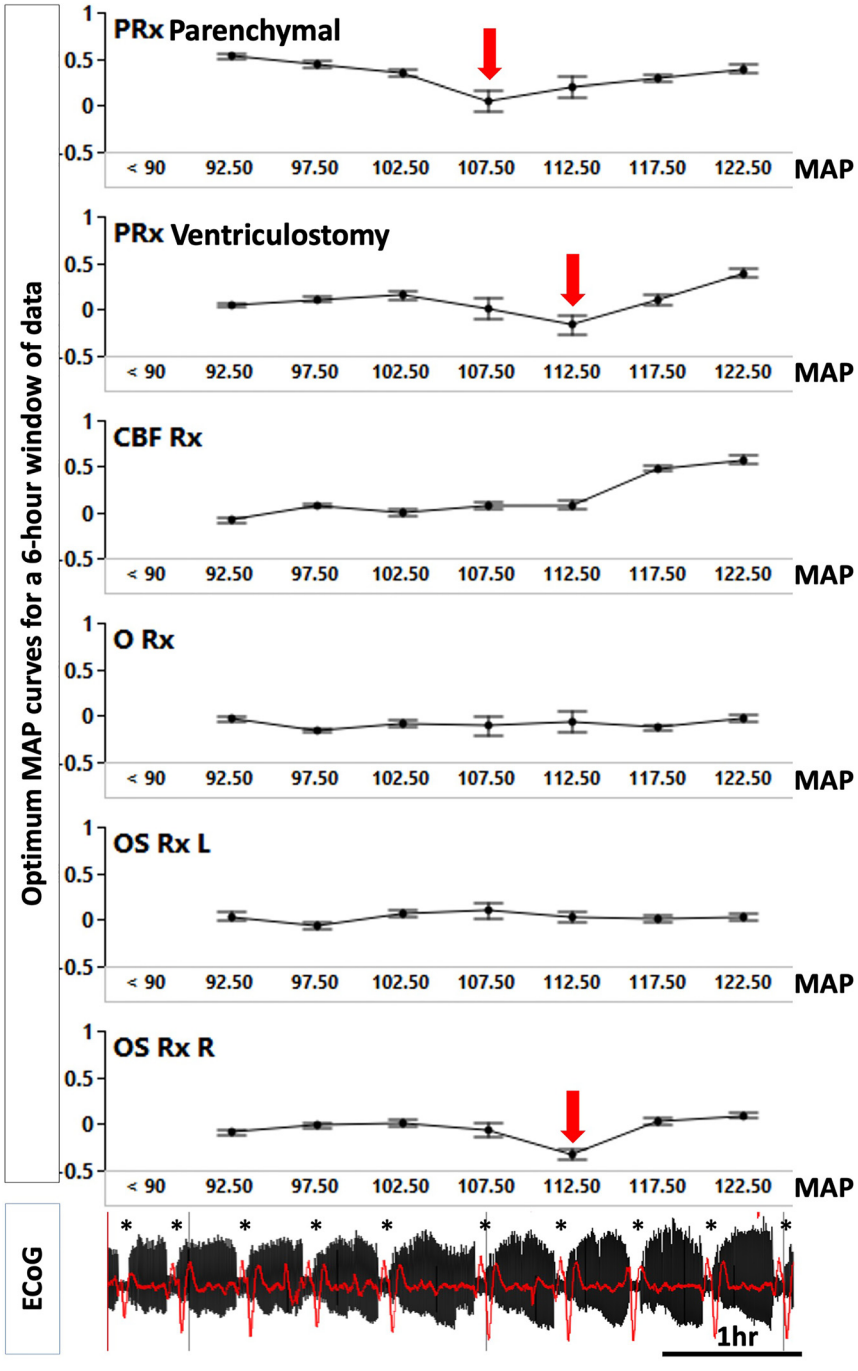

Figure 6: Continuous multimodal autoregulation indices assessed with proposed optimal MAP for each index over a 6-h window coupled with subdural SD monitoring data in a patient with right sided delayed cerebral ischemia/vasospasm. "*" represent SD occurrence in the same 6-h window. The recurring clusters of SD indicate that there is likely vulnerable brain at risk of ischemia. The autoregulation indices may then be used to determine the hypothetical optimal MAP for this patient and then assess if this decreases the frequency of SD events in the next monitoring window. In this case it appears that the MAPopt is between 107 and 112 (red arrows) based on multimodal assessment using ICP and scalp NIRS.

intact, SD resulted in a local hyperemic response. This is physiologically expected local response of healthy tissue to SD. In contrast, impaired autoregulation was associated with a progressively "inverse" hemodynamic response to SD (Hinzman et al. 2014). The importance of the hemodynamic response to SD is critical. Due to its large metabolic demand, a transient increase in blood flow should typically accompany SD whereas in metabolically compromised tissue (or states of impaired autoregulation) this inverse hemodynamic response leads to a wave of ischemia, which can result in infarct expansion (Dreier 2011) and edema formation (Mestre et al. 2020). This is supported indirectly by the fact that the progression of peri-contusional edema was strongly associated with impaired autoregulation as measured by PRx and PAx in TBI (Mathieu et al. 2020b).

Non-invasive measures of cerebral autoregulation could have important implications for management of patients with "mild" traumatic brain injuries or other conditions where SD monitoring may not be available. For example, SD has recently been proposed in preclinical models to be the pathophysiologic event that leads to the clinical concussion syndrome (Bouley et al. 2019; Carlson and Shuttleworth 2021; Pacheco et al. 2019). Since impaired autoregulation as measured by TCD has been observed in some patients with minor head injury (Junger et al. 1997; Len et al. 2011), it is plausible that this could secondary reflect SD occurrence and could have implications for recovery, therapy, and return to play.

In patients with large hemispheric strokes, SD has been strongly associated with infarct expansion and worse outcomes (Dohmen et al. 2008; Nakamura et al. 2010). Recent data have suggested that SD that occurs in large strokes for days after the initial insult could be triggered by metabolic challenges and even by clinical stimulation (Carlson et al. 2023; von Bornstadt et al. 2015). Impaired autoregulation in the penumbral region could be one of these triggering events that allows minor blood pressure changes to result in ischemic, SD triggering events (Chau et al. 2022). Non-invasive measurement of autoregulation in such patients either with NIRS (OSRx) or TCD (Mx) may therefore be an attractive surrogate way to monitor either the risk or consequences of recurring SD in such patients. Several studies using TCD based autoregulation assessment demonstrated a delayed worsening of autoregulation as measured by the Mx which was also associated with worse outcomes and larger strokes (Reinhard et al. 2012). This observation could plausibly correspond to this secondary, harmful phase of SD occurrence, thought to lead to secondary stroke expansion and edema formation (Mestre et al. 2020).

These observations provide additional insight into the role of autoregulation monitoring and targeted therapy. Specifically, the observed impaired autoregulation in acute neurologic injuries, which has been associated with worse clinical outcomes may be related to the risk of inducing secondary SD and worsened hemodynamic response to SD. A strategy of optimized blood pressure management based on autoregulation assessment coupled with SD monitoring as a feedback mechanism to assess metabolic compromise may therefore provide powerful insight to the ongoing risk of ischemia in such patients. See Figure 6 for an example of multimodal autoregulation monitoring coupled with SD monitoring in a patient with subarachnoid hemorrhage. Advances in minimally invasive and non-invasive approaches for SD monitoring could greatly facilitate such a strategy.

7 Conclusions

Advances in understanding of the physiology of ischemia as it relates to clinical monitoring in the ICU have the potential to change the paradigm of targeted therapies for acute neurologic injuries. Using available and emerging monitoring strategies, the risk of ischemia as measured by impaired cerebral autoregulation can already be incorporated into care using existing technologies and bedside analysis. As these techniques become more widely available, the potentially complimentary nature of different approaches to assess autoregulation needs to be explored. Determining the optimal input functions and challenge tests can help further refine the best strategies to individualize blood pressure or cerebral perfusion pressure management in a given patient. In conditions such as stroke and hemorrhage, where blood pressure management is guided by broad generalized recommendations from clinical trials, there is an enormous opportunity to develop protocols based on an individual patient's physiology at a specific stage of their disease. Finally, understanding how secondary, triggered SD relates to this process of ischemia and injury progression is critical and may offer additional strategies to monitor for ongoing compromise and responses to intervention. The first clinical trials assessing such individualized care strategies based on autoregulation assessment (COGiTATE (Tas et al. 2021)) and occurrence of SD (INDICT (Hartings et al. 2023)) are already underway and will pave the path in the future for translational studies focused on patient specific physiology optimization.

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