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Why and how to assess cerebral autoregulation?

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Around the turn of the century, a better understanding of the complex physiology of cerebral blood flow (CBF) regulation has emerged. It is now acknowledged that cerebral autoregulation is much more complicated than we previously thought it was, with the shape of the autoregulation curve and limits of autoregulation that may vary enormously and unpredictably, both within and between patients. The consequence is that to safeguard the cerebral circulation, the dogma that an empirically chosen blood pressure guarantees adequate CBF in any individual patient has to be abandoned. Integration of cerebral autoregulation monitoring in daily perioperative patient care offers the opportunity to guide blood pressure management to the individual patient's need. The most common approach tests the effect of changes in blood pressure on an estimate of CBF. However, a “gold standard” to assess cerebral autoregulation is not yet available, and the literature shows considerable disparity of methods and criteria.

Introduction

Cerebral autoregulation is defined as the ability of the cerebral vasculature to maintain a constant cerebral blood flow (CBF) despite changes in perfusion pressure. This immense complexity of vascular reactivity, determined by a variety of different regulation mechanisms, has been simplified into one single concept, the autoregulation concept (Fig. 1). The three key elements in the autoregulation concept are the autoregulation plateau, the lower limit of autoregulation (LLA), and the upper limit of autoregulation (ULA). The autoregulation plateau, wherein CBF remains constant, lies within the mean

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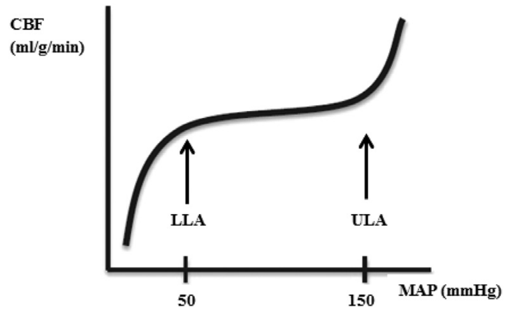

Fig. 1. Classic depiction of cerebral autoregulation, with autoregulation plateau, lower limit of autoregulation (LLA), and upper limit of autoregulation (ULA). CBF: cerebral blood flow; MAP: mean arterial blood pressure.

arterial blood pressure (MAP) range of 50–150 mmHg. The plateau is owed to the active myogenic control of small cerebral arteries and arterioles. If blood pressure decreases, cerebral blood vessels dilate, and if blood pressure increases, they constrict, hereby maintaining a constant blood flow. At the limits of autoregulation, myogenic vasoactivity capacities are exhausted, and the CBF becomes “pressure passive”: CBF decreases when blood pressure moves below the LLA and increases when blood pressure exceeds the ULA.

The autoregulation concept dates from 1959 [1] and has instantly been widely accepted; therefore, even currently, most caregivers feel confident with a blood pressure within the presumed autoregulation range. However, already in 1997, the validity of this concept was criticized [2], and it is now acknowledged that CBF regulation is much more complicated than we previously thought it was.

New insight #1: the limits of autoregulation may vary

Joshi et al. demonstrated that the limits of autoregulation vary enormously and unpredictably between patients [3]. In their study in more than 200 patients undergoing cardiac surgery, the LLA varied between a MAP of 40 mmHg to more than 90 mmHg. Therefore, for some patients, a MAP of 40 mmHg is enough to maintain CBF, whereas some patients need 90 mmHg. If in these patients MAP is lower than 90 mmHg, CBF will inevitably drop. Joshi also demonstrated that the LLA cannot be predicted based on demographic and disease-specific information. No relationship was found between the preoperative MAP and the LLA, nor was there an association between the MAP at LLA and the presence of diabetes, hypertension, or prior cerebrovascular events.

New insight #2: regulation of CBF is much more complex than just pressure regulation

The second new insight is that regulation of CBF is determined by much more factors than just blood pressure, as we previously thought it was. Many mechanisms are involved in the regulation of cerebral circulation and pressure regulation is integrated within these other mechanisms. We refer the interested reader to the excellent overview of Meng et al. [4].

For instance, it is now recognized that changes in cardiac output will induce changes in CBF [4]. If cardiac output increases, the autoregulation curve shifts upward, and hence, CBF will increase. In contrast, if cardiac output decreases, the curve is shifted downward and CBF will also decrease. It is assumed that the autoregulation mechanism itself remains unaffected, but actually, this is still unknown.

Another important factor in the regulation of CBF is carbon dioxide (CO_2). For an extensive review of the effects of CO_2 on cerebral autoregulation, we refer the reader again to the work of Meng et al. [5]. Hypercapnia induces cerebral vasodilation, thus inducing an upward shift of the autoregulation curve, a shift of the LLA to the right, and a shift of the ULA to the left. The more severe the hypercapnia, the more extended the changes in the autoregulation curve will be. The same mechanism applies to all agents that affect cerebral vasoreactivity. For instance, inhalation anesthetics may also induce cerebral vasodilation, and therefore, these agents will have a similar effect on the cerebral autoregulation curve as that of CO_2 [6].

New insight #3: position and shape of the autoregulation curve may change

Medical science has begun to acknowledge that the classical autoregulation curve is an idealized one and that the position and the shape of the autoregulation curve may be changed by a myriad of factors. Therefore, instead of having a classical autoregulation curve as shown in Fig. 1, our patients might as well have a curve like the one shown in Fig. 2.

New insight #4: there might be optimal blood pressure

But even with an impaired autoregulation curve, there might be an optimal blood pressure in the middle of the autoregulation curve at which the autoregulatory function is most robust (Fig. 3, indicated with a square). Identifying the range of optimal cerebral autoregulation offers the potential for individualization of blood pressure targets, and integrating the "optimal MAP" in daily critical care management might shift the current clinical paradigm of "one size fits all" care to individualized, physiology-based blood pressure management [7,8].

How to assess cerebral autoregulation?

To construct a metric of autoregulation, three elements are needed:

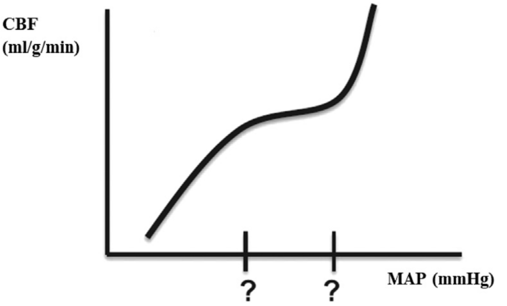

Fig. 2. Actual autoregulation curve, with unknown limits of autoregulation (question marks). CBF: cerebral blood flow; MAP: mean arterial blood pressure.

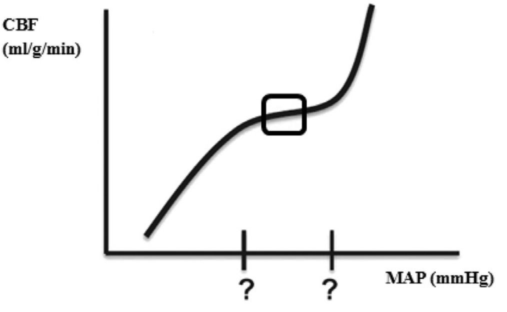

Fig. 3. Autoregulation curve with "optimal blood pressure" (indicated with a square) where the autoregulatory function is most robust. CBF: cerebral blood flow; MAP: mean arterial blood pressure.

1. A change in cerebral perfusion pressure (CPP)
2. A measure of CBF
3. A mathematical estimation of the relationship between CPP and CBF

Metric #1: change in CPP

Measurement of CPP

Although theoretically CPP should be plotted, this requires invasive monitoring of intracranial pressure (ICP) (CPP = MAP − ICP). Therefore, in cases where ICP is unavailable or when a low ICP is assumed, arterial blood pressure (ABP) is considered a valid substitute for CPP. However, it has to be acknowledged that in any condition where an elevated ICP is expected, such as in traumatic head injury or neurosurgery, ICP measurement is essential for the correct estimation of CPP.

The most correct method to obtain ABP is through invasive monitoring, as noninvasive methods may lack accuracy and precision. As expected, the availability of noninvasive, continuous, and accurate measurement of ABP would facilitate the incorporation of autoregulation testing into routine clinical practice.

Changes in ABP and CPP

In addition to a continuous measurement of ABP, pressure changes are also necessary. These pressure changes can be induced, for instance, by acute blood volume displacement (head up tilting, lower body negative pressure, Valsalva maneuver) or by administration of vasoactive agents. These methods are often used in research, but they are less practical and potentially harmful in the clinical setting. In addition, it has been demonstrated that CBF dynamics are driven by the rate of change in blood pressure rather than absolute pressure per se; therefore, the precipitous change in ABP might elicit autoregulatory reactions that would not be seen with gradual changes in pressure [9,10]. Another major limitation of these methods is that large changes in ABP might affect other physiological variables, which could also have an influence on CBF (sympathetic activation, baroreceptor reflex, etc.).

A valid alternative is to rely on the spontaneous cardiovascular oscillations that are present in most individuals [11]. Whereas the autoregulation system acts as a high-pass filter, buffering against hemodynamic changes in the 0.01–0.4 Hz range (sometimes referred to as “static” autoregulation), it has been shown that when arterial pressure fluctuations are relatively fast (faster than 0.1 Hz, e.g., due to the cardiac cycle), changes in arterial pressure and CBF occur almost synchronously. These oscillations of the sympathetic vasomotor tone can be used for assessment of cerebral autoregulation (often referred to as “dynamic” autoregulation). A disadvantage of this method is that the magnitude of such natural blood pressure variations may not be strong enough to challenge CBF. Furthermore, some variations in CBF may be due to other uncontrolled confounding influences such as sympathetic activation, effects of drugs, and changes in CO_2 or brain metabolism, decreasing the accuracy of this method.

Metric #2: measure of CBF

To assess cerebral autoregulation, changes in CBF are plotted over a wide range of blood pressures. Therefore, the second metric is a real-time measure of CBF. However, no convenient means of measuring actual CBF currently exists. Hence, estimates of CBF are being used.

Estimates of CBF

Finding appropriate methods to estimate CBF is challenging owing to the myriad of physiological variables that influence CBF. The most common bedside techniques adopted for estimating CBF are related to flow, volume, or oxygenation. However, each technique has its particular drawbacks, and it has to be remembered that none of them provides a direct measurement of CBF and that no single method can be regarded as a “gold standard” at the present stage.

Estimates of CBF related to flow

- Transcranial Doppler (TCD) ultrasound measures CBF velocity in the proximal portion of large intracranial arteries. The drawback is that changes in CBF velocity will reflect only changes in CBF if the diameter of the insonated artery remains constant. However, it is criticized that the diameter of large cerebral vessels can change due to sympathetic stimulation or infusion of vasoactive drugs. Another drawback is that it is technically challenging to apply TCD continuously; therefore, it is usually limited to intermittent measurements.

Estimates of CBF related to volume

Cerebral blood volume is considered to indirectly reflect the radius of the cerebral blood vessels and hence CBF.

- ICP indirectly reflects cerebral blood volume. Changes in ABP lead to changes in vasomotor tone, which causes changes in intracranial blood volume, and thus changes in ICP. However, ICP monitoring is an invasive technique that restricts its use to neurocritical care settings.
- Total hemoglobin measured with near-infrared spectroscopy (NIRS). Some NIRS devices are able to calculate total cerebral hemoglobin, which is thought to reflect total cerebral blood volume.
- Ultrasonic time-of-flight measurements. The operating principle is based on the time taken by the ultrasonic wave to travel the distance from the transmitter to the receiver (the time of flight).

Estimates of CBF related to oxygenation

These estimates rely on the equation: rate of cerebral oxygen consumption ($CMRO_2$) = CBF x arteriovenous O_2 difference. It is assumed that $CMRO_2$ and arterial oxygen content remain constant throughout the measurement period, and therefore, CBF is estimated solely based on measurements of cerebral venous oxygen saturation.

- Brain tissue oxygen monitoring is an invasive technique with restricted use.
- Jugular bulb oximetry is also an invasive technique that limits its widespread clinical use.
- Cerebral oxygen saturation measured with NIRS. For use in the clinical setting, NIRS seems to be the most promising tool thus far [12]. Based on a similar principle as that of pulse oximetry, it allows continuous, noninvasive, real-time monitoring of cerebral oxygen saturation (S_cO_2) in a small sample of the frontal cortex [13]. However, the use of NIRS as an estimate of CBF entails some considerable assumptions. The interrogated tissue sample contains all the different vascular components, and hence, S_cO_2 values represent a mixture of arterial, capillary, and venous oxygen saturations. Therefore, all factors that influence the cerebral oxygen balance and/or cerebrovascular reactivity will affect S_cO_2: arterial blood oxygen content, cerebral oxygen consumption, oxygen-tissue diffusivity, CO_2, and CBF. It has been assumed that over a brief time period, all these variables remain constant, and therefore, changes in S_cO_2 are due to changes in CBF, indicating that these two variables can be interchanged.

Another important aspect to consider is that NIRS technology is based on sending near-infrared light through the tissues, where it is attenuated because of a combination of absorption and scattering. It is a prerequisite that the quantity of light scattering remains constant during the measurements and that changes in attenuation result solely from changes in absorption [14]. However, in conditions of brain injury, tissue composition may vary substantially over time (contusions, hemorrhages, and brain swelling), resulting in changes in light absorption and scattering. Accurate quantification of S_cO_2 and data quality could therefore be questioned in the setting of neurosurgery and neurointensive care [15].

Metric #3: mathematical estimation of the relationship between CPP and CBF

Different analyses have been used to estimate the relationship between blood pressure and CBF. The most common and simplest method is to calculate the correlation coefficient between MAP and the estimate of CBF. However, it could be argued that cerebral autoregulation is a complex physiological system and that simple correlation analysis does not cope with the complex interplay and the time-varying aspects of the different physiological mechanisms [16]. Caicedo and coworkers analyzed four different measurement models used for cerebral autoregulation assessment (correlation, coherence, modified coherence, and transfer function). Although transfer function gain was proposed as the most robust method when used for cerebral autoregulation studies, correlation was also considered as a robust method, despite some time delay-related restrictions [17].

By plotting the estimate of CBF over blood pressure, an index of autoregulatory vasoreactivity is generated. A multitude of autoregulation indexes has been determined depending on the method to estimate CBF. The cerebral oximetry index (COx) [18], the total hemoglobin reactivity index (THx) [19], and the hemoglobin volume index (HVx) [20] are the correlation coefficients between ABP and, respectively, S_cO_2 or total hemoglobin, all measured with NIRS. The pressure reactivity index (PRx) is the correlation coefficient between perfusion pressure and ICP (measured invasively) [21]. The mean flow index (Mx) is the correlation coefficient between ABP and CBF velocity measured with TCD [22], whereas the volumetric reactivity index (VRx) is the correlation coefficient between ABP and ultrasonic measurements [23]. For a detailed description of existing cerebral autoregulation indices, we refer the interested reader to some excellent reviews [24,25].

Blood pressure in the autoregulation range is indicated by a correlation coefficient that approaches zero, i.e., there is no correlation between the estimate of CBF and MAP. A correlation coefficient approaching one indicates a strong correlation between the two signals and has to be interpreted as either impaired autoregulation or MAP, being beyond the limits of autoregulation.

Varying definitions to decide between intact and impaired autoregulation are found in literature. Generally, a correlation coefficient <0.3 is considered consistent with intact autoregulation and the MAP with the lowest correlation is considered the “optimal MAP.” However, noise on the data may impede identification of intact and impaired regions. A further impediment for assessment of autoregulation is that due to interpatient variability, no specific threshold will apply to everyone. Moreover, it has been postulated that the flat part of the autoregulation curve is never really horizontal but slightly tilted [26]. So autoregulation is not an on–off phenomenon, with correlations between CBF and MAP jumping from zero (intact autoregulation) to one (impaired autoregulation), which makes interpretation of autoregulation data rather cumbersome.

Current clinical applications of cerebral autoregulation monitoring

Studies that evaluate cerebral autoregulation have been expanding during the past few years. Especially in neonatology [27,28], cardiac surgery [9,29–34], and neurocritical care [35–42], cerebral autoregulation has been extensively investigated owing to the high incidence of brain injury in these domains. Recently, interest has been broadened to the area of septic shock [43–45], out of hospital cardiac arrest [46–48], and noncardiac surgery [49,50]. In all these areas, an association between impaired cerebral autoregulation and adverse outcomes has been demonstrated.

Impaired cerebral autoregulation has been demonstrated in 35% of patients undergoing cardiac surgery [9]. Consequently, in the case of an empirically chosen MAP target, patients may spend varying amounts of time with MAP outside the autoregulation range. In some recent studies, it has been demonstrated that MAP variations outside the autoregulatory range, not the absolute MAP values, were associated with adverse outcomes [29–34]. In patients with acute kidney injury after cardiac surgery, the time and magnitude spent for MAP below the LLA were significantly higher than those for patients without acute kidney injury, although absolute blood pressure values were equal between the two groups [29]. A significant association was also found between blood pressure excursions below the LLA and major morbidity (for example, renal failure, duration of mechanical lung ventilation, and low cardiac output syndrome) [30]. A recent study demonstrated that a blood pressure below the optimal MAP based on COx monitoring was associated with an increase in postoperative plasma GFAP (glial fibrillary acidic protein), which is a brain-specific injury biomarker [31]. However, on the other hand, increase in blood pressure above the ULA might predispose the patient to cerebral injury. Excursions of blood pressure above the ULA were associated with increased risk for delirium in patients undergoing cardiac surgery [32,33].

Patients with brain injuries constitute another population at high risk of impaired autoregulation. A consensus statement from the Neurocritical Care Society and the European Society of Intensive Care Medicine suggested that continuous monitoring of cerebral autoregulation might help guide ABP and CPP targets to "optimal" levels in patients with traumatic brain injury and might contribute to prognostication [35]. Management at or close to the "optimal CPP" has been shown to be associated with better outcomes in patients with brain injury [51,52]. There are ample excellent reviews in the domain of neurocritical care, which we would like to refer to [38–42].

Clinical relevance of cerebral autoregulation monitoring

Based on the classical concept of cerebral autoregulation, maintaining a "normal blood pressure" to ensure adequate perfusion of the brain has been emphasized in critical care management. Hence, often medications are given to increase blood pressure to improve cerebral perfusion. However, as discussed before, the position and the shape of the autoregulation curve may have shifted away, with LLA and ULA varying considerably and unpredictably [3] and an autoregulation plateau that may be very narrow [53]. The clinical implication is that CBF might become pressure-dependent, meaning that CBF changes in parallel with blood pressure changes. This exposes the patient to the risk of decreased cerebral flow and potential ischemia when blood pressure is relatively too low and conversely to the risk of increased cerebral flow and increased ICP when blood pressure is relatively too high. As the individual limits of autoregulation are unknown, it is likely that empiric blood pressure management will result in patients having a MAP outside the autoregulatory range for at least part of surgery or stay in intensive care. The practice of applying a fixed blood pressure threshold in an individual patient is therefore risky, and tighter pressure control is needed [54]. If autoregulation monitoring can individualize blood pressure targets, it could provide a more effective means for preventing cerebral hypoperfusion and hyperperfusion than the current standard of care.

Perspectives

Currently, most cerebral autoregulation assessments are performed offline. With the sophistication of signal processing and online analysis software, the future challenge lies in the successful integration of autoregulation monitoring and "optimal MAP" assessment into patient care management. A promising analysis tool in this regard is the ICM+® technology (Cambridge Enterprise Ltd, Cambridge, United Kingdom, http://www.neurosurg.cam.ac.uk/icmplus), that enables real-time multimodal assessment of cerebral autoregulation and determination of the "optimal" perfusion pressure.

Conclusion

To date, blood pressure targets remain mostly empirically chosen during clinical care management. However, progress in perioperative and critical care might depend on moving away from "one-size-fits-all" assumptions. Routine assessment of cerebral autoregulation and identification of the range of "optimal" blood pressures might in the future offer the potential for individualization of blood pressure targets and better patient care. However, clinical application of cerebral autoregulation monitoring has been hindered by substantial difficulties. First, there still is an incomplete understanding of the complex cerebral autoregulation physiology. Second, different approaches to conceptualize the cerebral autoregulation phenomenon have been applied, but none of them has been validated against a criterion standard because there simply is no "gold standard."

Practice points

- The immense complexity of all different physiological mechanisms that contribute to cerebral autoregulation has been simplified to one single concept.
- In the near future, real-time assessment of cerebral autoregulation is a feasible option, making autoregulation-guided treatment a plausible management strategy.
- Evidence shows a close relationship between impaired cerebral autoregulation and adverse outcomes.
- The literature on methods to assess cerebral autoregulation shows high diversity regarding key methodological aspects.

Research agenda

- Much of the cerebral physiology remains incompletely understood.
- The future challenge lies in the successful integration of autoregulation monitoring and "optimal MAP" assessment into daily patient care management.
- There is a great need to standardize cerebral autoregulation measurement.
- Clinical benefits await reproducible prospective evidence.
- "Optimal" blood pressure management has been recommended but remains to be firmly established.

Conflicts of interest

A. Moerman has received lecture fees from Medtronic (INVOS) and Sorin (NIRO). S. De Hert has no conflicts of interest.

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