Cerebral autoregulation and anesthesia
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Purpose of review
This review will examine the recent literature on anesthesia and monitoring techniques in relation to cerebral autoregulation. We will discuss the effect of physiologic and pharmacological factors on cerebral autoregulation alongside its clinical relevance with the help of new evidence.

Recent findings
Intravenous anesthesia, such as combination of propofol and remifentanil, provides best preservation of autoregulation. Among inhaled agents sevoflurane appears to preserve autoregulation at all doses, whereas with other agents autoregulation is impaired in a dose-related manner.

Summary
Intraoperative cerebral autoregulation monitoring is an important consideration for the patients with neurologic disease. Transcranial Doppler based static autoregulation measurements appears to be the most robust bedside method for this purpose.

Keywords
anesthetics, cerebral autoregulation, cerebral blood flow, cerebral blood flow velocity, cerebral perfusion pressure, transcranial Doppler

Introduction
The brain is a metabolically active organ that requires a continuous supply of energy. This requirement is met by a constant delivery of oxygen and nutrients via the cerebral circulation despite variations in its perfusion pressure. This homeostatic mechanism was first demonstrated by Fog (1939) in cats but it was not accepted until 1959 when Lassen described the concept of cerebrovascular autoregulation [1]. Even today, half a century later, we only have a limited understanding how this mechanism works at the molecular level.

Lassen illustrated this phenomenon using the triphasic autoregulation curve, which was constructed from cerebral blood flow measurements in several different human studies using Kety and Schmidt’s nitrous oxide method. He stated that cerebral blood flow autoregulation is the intrinsic ability of the cerebral vasculature to provide constant cerebral blood flow (CBF) despite changes in cerebral perfusion pressure (CPP).

The limits of autoregulation identified between 50 and 150 mmHg of perfusion pressure are not precise points but, rather, inflection points at which the gradient of the pressure/flow relationship starts to change significantly and indicates that outside of these limits the protective autoregulatory response is lost [1–3]. Myogenic, neurogenic, and metabolic factors have been hypothesized as mechanisms responsible for control of this intrinsic function. The actual mechanism, however, may require more than a single factor. Via cerebrovascular autoregulation as well as flow metabolism coupling the brain can match its metabolic demand under a variety of situations from normal daily activities to some pathologic processes (e.g., seizures), whereas this may be impaired in others (e.g., severe traumatic brain injury) [2–8].

In this review we will discuss the factors affecting the cerebral autoregulation and its determination in acute and operating room environments.

Clinical implications of impaired cerebrovascular autoregulation in brain injury
There are multifactorial injury mechanisms that can be attributed to the release of excitatory mediators (cytokines, free radicals), hyperglycemia, hyperthermia, and hypoxemia. Elevated intracranial pressure (ICP) may result in cerebral ischemia due to cerebral hyperperfusion, whereas cerebral hyperperfusion with increased intravascular hydrostatic pressure may lead to the development of cerebral edema [9]. The loss of cerebrovascular autoregulation will exacerbate these mechanisms that promote secondary brain injury.
Factors affecting cerebrovascular autoregulation under anesthesia

A variety of physiologic and pharmacological factors can affect cerebrovascular autoregulation.

Physiologic factors

There is a wide range of individual variation regarding the lower and upper limits of cerebrovascular autoregulation in health and disease. Although mean arterial pressures of 50 and 150 mmHg are often described as the standard autoregulatory range, in reality, published figures in humans vary considerably. Drugs including anesthetics further affect the values of these limits [10*,11].

Change in PaCO₂ exerts a profound effect on cerebral perfusion with 3–4% change in CBF for every 1-mmHg change in PaCO₂. In addition, this change in cerebrovascular resistance (CVR) with change in PaCO₂ also impacts cerebrovascular autoregulation. Previously conducted studies revealed that hypercapnia impairs dynamic cerebrovascular autoregulation (dCA), as measured using the thigh cuff deflation method as well as by transfer-function analysis of flow velocity changes with spontaneously fluctuating blood pressure [12,13*,14**,15*]. Hypocapnia, on the contrary, increases CVR, improves vascular tone, and augments cerebrovascular autoregulation while decreasing CBF. Ainslie et al. [15*] recently published their findings suggesting changes in ventilation and intrathoracic pressure rather than PaCO₂ may be the primary cause of the observed changes in dCA as measured by transfer-function analysis. These observations are in conflict with an understanding of interaction between PaCO₂ and cerebrovascular autoregulation and indirectly suggest that 'dynamic autoregulation' as measured by phase-shift and transfer-function analysis, perhaps is not a reliable method of quantifying cerebral autoregulation.

Todd [16] has published the effects of anemia on animal cerebrovascular autoregulation. Hemodilution reduces viscosity and vascular resistance resulting in an increase in CBF. This decrease in vascular tone conceivably can decrease autoregulatory capacity. Indeed the lower limit of autoregulation has been shown to increase with anemia [17]. Moreover, Ogawa et al. [18] recently reported that in healthy human volunteers, dCA is impaired as a result of hypervolemic hemodilution. This area clearly needs further high-quality studies to determine the effect of anemia on autoregulation in patients with cerebral disease.

Although the changes are small, mild hypothermia may decrease, whereas hyperthermia can enhance dynamic cerebrovascular autoregulation [19].

Drug-related factors

Although retrospective studies generally fail to demonstrate a difference in outcome between intravenous and inhaled anesthetic agents in patients with traumatic brain injury there are fundamental differences in the influence of anesthetic agents on cerebrovascular autoregulation [20*].

Compared to inhaled anesthetics, which generally have a dose-related depressive effect on autoregulation (except sevoflurane), propofol preserves autoregulation both at high and low doses in healthy individuals [21]. However, high doses of propofol have been shown to impair cerebrovascular autoregulation in head-injured patients; this aspect needs to be verified in larger studies [20*]. In patients with increased intracranial elastance, elevated ICP or in which complex surgical approaches require intraoperative electrophysiological monitoring, propofol-based intravenous anesthesia remains the first choice [22,23].

When remifentanil is used together with propofol, it induces a dose-dependent metabolism-coupled reduction in CBF with preserved cerebrovascular autoregulation. The combined use of propofol and remifentanil anesthesia has been shown to preserve CVR and cerebrovascular autoregulation [22].

Compared to other inhaled agents, sevoflurane in clinically relevant doses does not increase CBF, although propofol at comparable doses results in more profound cerebral vasoconstriction [24], and it does not impair cerebrovascular autoregulation [25,26]. Schluenzen et al. [27] demonstrated that although there are regional alterations on CBF with inhalational anesthetic agents, global CBF remains unaffected.

Dexmedetomidine is a pure α₂ agonist that is increasingly utilized in intensive care units as a sedative agent to create a state of 'conscious sedation' associated with minimal respiratory depression and some analgesia. These desirable characteristics facilitate intermittent neurologic evaluations and weaning from mechanical ventilators. With regards to neuroanaesthesia, it may create an ideal sedation state to facilitate procedures including awake craniotomy, carotid endarterectomy under regional anesthesia, carotid angioplasty and stenting, and other neuro-interventional procedures. Its effects on cerebrovascular autoregulation in injured brains still need to be determined [28*]. Although it has little effect on static cerebrovascular autoregulation (sCA) in healthy volunteers (unpublished observation) it may weaken the dCA and delays restoration of CBF velocity to normal with reduction in blood pressure [29**].

Interaction between CO₂ and anesthetic agents

Hypercapnia impairs cerebrovascular autoregulation and there is an interactive effect between hypercapnia and
anesthetic agents. Thus propofol can preserve cerebrovascular autoregulation in patients with PaCO₂ as high as 55 mmHg, whereas a similar level of hypercapnia would abolish cerebrovascular autoregulation in the same conditions under sevoflurane anesthesia [30]. At the same time, hypocapnia can reverse isoflurane-induced cerebrovascular autoregulation impairment [31].

Vasodilators
Glyceryl trinitrate (GTN) is a potent vasodilator of the middle cerebral artery (MCA) and leads to reduced flow velocities but maintained or increased CBF secondary to intracranial vasodilatation. Moppet et al. [32] recently demonstrated in healthy volunteers that, similar to the effects of hypercapnia, GTN increases the effective CPP by reduction in cerebral vessel tone without impairment in cerebrovascular autoregulation.

Quantification of autoregulation under anesthesia
Measurement of cerebrovascular autoregulation is a complicated process due to the fact that there are many physiologic variables that can affect the CBF either directly or through metabolic coupling. There are also technical limitations to each measurement method that requires certain assumptions to be made.

To be clinically relevant and provide useful feedback to the clinician, the measurement method of cerebrovascular autoregulation must be noninvasive, robust, repeatable, inexpensive, and should have a steep learning curve with good temporal resolution. Currently available methods will be discussed within this context.

Fundamental elements of autoregulation determination
(1) CBF measurement or a CBF surrogate. Autoregulation measurement essentially assesses the corresponding change in CBF in response to change in blood pressure while maintained other physiologic variables constant, notably PaCO₂ and cerebral metabolism. Thus an essential element is measurement of CBF or its surrogate. Transcranial Doppler (TCD) has superior advantages in acute settings, particularly in the operating room environment, as a measurement method for cerebrovascular autoregulation [33]. TCD measures cerebral blood flow velocity as a surrogate of CBF [12]. Validity of this approach has been previously published and accepted [34,35].

(2) Perfusion pressure measurement. To be accurate, changes in CBF should be measured against a change in CPP. However, the latter is only available if ICP monitoring is present (CPP = MAP – ICP). Otherwise systemic arterial blood pressure is substituted. This would introduce an element of inaccuracy if ICP changes with changes in blood pressure.

(3) Ideally stimulus should be provided to trigger a change in blood pressure. This stimulus can be spontaneous as in spontaneous variation in blood pressure or evoked as in pharmacological or nonpharmacological alteration in blood pressure. The direction of blood pressure change may also be important but the discussion is beyond the scope of this article.

Cerebrovascular autoregulation can be thought of as comprising both fast and slow components in terms of the changes in cerebral vascular resistance (CVR) in response to changes in pulsatile and mean cerebral perfusion pressures, respectively [36,37].

The gold standard for testing of cerebrovascular autoregulation is the static method measuring CBF changes with changes in blood pressure or CPP. More recently, ‘dynamic’ autoregulation testing has been introduced. Dynamic autoregulation, while testing the fast component of cerebrovascular autoregulation, tends to be affected earlier than static autoregulation and is more vulnerable to a variety of insults. Static autoregulation, however, preferentially assesses the slow components of cerebrovascular autoregulation [36,38,39,40].

Applicability of technology in the operative room
Autoregulation measurements based on the waveform analysis and phase shift during spontaneous fluctuations in blood pressure are not suitable for the intraoperative assessment of disturbed cerebrovascular autoregulation, but are easier to perform. Not surprisingly, the majority of publications related to the use of these methodologies are focused on patients in the intensive care unit. To clarify and contrast the advantages and limitations of different methods, we will classify them into two broad categories: spontaneous and evoked measurement techniques. Evoked methods describe the observations of blood flow changes to a variety of blood pressure perturbations, whereas the spontaneous methods rely on the changes in blood flow in relationship to spontaneous fluctuation of blood pressure. These could be further divided into pharmacological and nonpharmacological methods as summarized in Table 1.

Static cerebrovascular autoregulation measurements
Static measurements evaluate the change in CVR in response to the manipulation of MAP allowing sufficient time for the flow and pressure to plateau. In other words,
Table 1 Measurement modalities of cerebral autoregulation

<table>
<thead>
<tr>
<th>Category</th>
<th>Type of stimulus</th>
<th>Method of stimulus</th>
<th>Measurement of CBF or CBF surrogate</th>
</tr>
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<tbody>
<tr>
<td>Evoked</td>
<td>Static CA</td>
<td>Pharmacologic&lt;br&gt;Vasopressor: phenylephrine, norepinephrine angiotensin&lt;br&gt;Vaso depressor: Nitroprusside, trimetaphan</td>
<td>Indicator dilution ((^{133})Xe, (^{85})Kr, (N_2O))&lt;br&gt;Xenon-CT&lt;br&gt;CT perfusion&lt;br&gt;Transcranial Doppler&lt;br&gt;Arterio-venous (O_2) difference&lt;br&gt;Near-infrared spectroscopy&lt;br&gt;Transcranial Doppler&lt;br&gt;Arterio-venous (O_2) difference&lt;br&gt;Transcranial Doppler, Carotid artery occlusion 5–7 s</td>
</tr>
<tr>
<td>Nonpharmacologic Body tilt</td>
<td>Full table tilt</td>
<td>Thigh cuffs inflated (&gt;200) mmHg for 3 min followed by sudden deflation&lt;br&gt;Valsalva maneuver&lt;br&gt;Carotid artery occlusion 5–7 s</td>
<td>Transcranial Doppler</td>
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<tr>
<td>Dynamic CA</td>
<td>Nonpharmacologic</td>
<td>Dynamic variation of blood pressure during periods of rest</td>
<td>Transcranial Doppler</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>Dynamic CA</td>
<td>Nonpharmacologic&lt;br&gt;Spontaneous variation of blood pressure during periods of rest</td>
<td>Transcranial Doppler</td>
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CA, cerebral autoregulation; CBF, cerebral blood flow.

these studies assess the outcome of cerebrovascular autoregulation rather than the process of cerebrovascular autoregulation itself. If CVR does not change with change in MAP, autoregulation is said to be impaired. As cerebrovascular autoregulation is not a perfect homeostatic mechanism, the percentage change in CVR generally is less than the percentage change in blood pressure. The slope of this autoregulatory response can be quantified using the autoregulatory index (ARI) which can be calculated from the percentage change in CVR over the percentage change in CPP resulting in a dimensionless number between 0 and 1 [40].

\[
ARI = \frac{\%\Delta CVR}{\%\Delta CPP}
\]

Using TCD, CVR can be derived from MAP/flow velocity.

Autoregulatory index can be determined over a period of 10 min and can be repeated with minimal risk. A value of 0 means completely absent autoregulation, whereas a value of 1 means perfect autoregulation. The normal value is 0.7 ± 0.2. Generally an ARI greater than 0.4 is regarded to represent preserved autoregulation [12,21,41].

**Dynamic cerebrovascular autoregulation measurements**

In 1989, Aaslid et al. [12] introduced the thigh cuff method to produce sudden drops in ABP as a standard stimulus to study the temporal evolution of the CBF response and described the term of dCA. During this study, the transient (6–7 s) decrease in blood pressure (15–20 mmHg) was induced by rapidly deflating thigh blood pressure cuffs following a 2-min inflation at 100 mmHg above systolic blood pressure. Arterial blood pressure was measured continuously either invasively or noninvasively, whereas TCD monitoring of MCA blood flow velocity changes were recorded. Autoregulation was quantified by examining the changes in CVR during the transient decrease in blood pressure.

As such the results of dynamic methods of cerebrovascular autoregulation determination are influenced by both the latency and the capacity of the autoregulatory response to the changes in MAP.

Although in general there is good concordance between static and dynamic cerebrovascular autoregulation testing [40] sCA is more robust than dCA as the former is not affected by latency changes. Thus low-dose inhaled anesthetics affect dCA but not sCA. For studies of dCA, a pharmacological intervention is not required, and the method is entirely noninvasive.

**Spontaneous dynamic cerebrovascular autoregulation measurements**

For the measurement of dCA several new methods based on waveform analysis are proposed [42].

Mean velocity index (Mx) is based on the assumption that, if autoregulation is intact, the change in blood flow velocity in the MCA will be out of phase with the change in CPP (Mx ≤0), whereas if autoregulation is absent they would be in phase (Mx > 0). These measurements are based on hourly simultaneous recordings of MCA flow velocity and invasive blood pressure during quiet periods in an unstimulated patient [43,44,45**].

Index of pressure reactivity (PRx) is calculated from the analysis of spontaneous slow waves of MAP and ICP. Possible values therefore range from –1 to 1. Negative or zero values indicate intact pressure reactivity; positive values indicate disturbed pressure reactivity and impaired autoregulation [46–53].
Recently the tissue oxygenation index (Tox) has been described using near-infrared spectroscopy (NIRS) to monitor cerebrovascular autoregulation. This method compares the changes in tissue oxygenation over short periods of time in response to changes in arterial pressure, under the assumed stable arterial saturation, stable metabolism, and probably stable diffusion potential [54*].

The criticism of these methods includes

1. Compared to evoked measurements, the signal-to-noise ratio is considerably small.
2. These are hourly trend measurements with off-line analysis, and therefore they deliver delayed feedback.
3. The results are confounded by flow-metabolism coupled changes, for example if the patient is stimulated resulting in both increase in blood pressure and cerebral blood flow, this would be interpreted as impaired autoregulation.

Similarly carotid artery compression method provides qualitative rather than quantitative assessment. It is only applicable in patients with good collateral circulation and carries an inherent risk of carotid artery embolism [55–60].

**Clinical applications of autoregulation testing**

From the above discussion it would be apparent that at the present time sophisticated cerebrovascular autoregulation determination has limited clinical application, and is perhaps most useful in the management of patients with traumatic brain injury in the intensive care unit. On the contrary, static and dynamic autoregulation using TCD may be useful with management of neurologic patients in the operating room.

The potential clinical applications include

1. Optimization of blood pressure management in the patients with traumatic brain injury undergoing nonneurosurgical procedures
2. Goal-directed blood pressure support in the patients with critical carotid artery stenosis
3. Perioperative management of patients undergoing carotid endarterectomy
4. Blood pressure management in uncontrolled hypertensive patients

**Conclusion**

The introduction of TCD technology has made it possible to determine cerebrovascular autoregulation at the bedside, both in the intensive care unit and in the operating room. There are inherent strengths and weaknesses as well as limitations to the various methods outlined in this review. The sCA testing appears to be the most robust and reproducible method. The challenge is for the anesthesiologist to identify the clinical scenario in which this information can benefit the patient and improve outcome.

**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest
** of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 688–689).

16. Heat stress does not impair the ability to control cerebral perfusion after a rapid reduction in perfusion pressure, whereas reduced transfer function gain and coherence in the very-low-frequency range during heat stress suggest that dynamic cerebral autoregulation is improved during spontaneous oscillations in blood pressure within this frequency range.
18. It seems that hyperventilation, rather than PetCO2, has an important influence on dynamic cerebrovascular autoregulation.
autoregulation during isoflurane, desflurane, and propofol anesthesia. Anesthesiology 1995; 83:66–76.


33 Norepinephrine, despite increasing arterial pressure, did not increase the eCVP. The eCPP increased significantly with GTN, despite decreased MAP. Cerebral vascular tone is an important determinant of CPP during pharmacologically induced changes in arterial pressure.


39 Panerai RB. Transcranial Doppler for evaluation of cerebral autoregulation. Clin Auton Res 2009 (in press). Combined with the availability of non invasive devices for continuous measurement of arterial blood pressure, the relatively low cost, ease of use, and excellent temporal resolution of TCD have stimulated the development of new techniques to assess cerebral autoregulation in the laboratory or bedside using a dynamic approach, instead of the more classical ‘static’ method.