

*Deborah J. Culley, M.D., Editor*

# Cerebral Autoregulation-oriented Therapy at the Bedside

## A Comprehensive Review

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### ABSTRACT

This comprehensive review summarizes the evidence regarding use of cerebral autoregulation-directed therapy at the bedside and provides an evaluation of its impact on optimizing cerebral perfusion and associated functional outcomes. Multiple studies in adults and several in children have shown the feasibility of individualizing mean arterial blood pressure and cerebral perfusion pressure goals by using cerebral autoregulation monitoring to calculate optimal levels. Nine of these studies examined the association between cerebral perfusion pressure or mean arterial blood pressure being above or below their optimal levels and functional outcomes. Six of these nine studies (66%) showed that patients for whom median cerebral perfusion pressure or mean arterial blood pressure differed significantly from the optimum, defined by cerebral autoregulation monitoring, were more likely to have an unfavorable outcome. The evidence indicates that monitoring of continuous cerebral autoregulation at the bedside is feasible and has the potential to be used to direct blood pressure management in acutely ill patients. (ANESTHESIOLOGY 2017; 126:1187-99)

**M**ORE than half a century has passed since the concept of cerebral autoregulation was first described by Lassen,<sup>1</sup> who found optimal and constant cerebral blood flow within a cerebral perfusion pressure range of 50 to 150 mmHg. This broad, “safe cerebral perfusion pressure” range was subsequently adopted as doctrine for the management of mean arterial blood pressure (MAP) in healthy human individuals,<sup>2-6</sup> based primarily on animal experiments.<sup>7-11</sup> Advances in technology now offer the ability to collect data through cerebral autoregulation monitoring and refine decades-old guidelines, thus potentially improving outcomes by individualizing cerebral perfusion pressure. Recently, a much narrower cerebral perfusion pressure autoregulatory plateau of 80 to 120 mmHg was reported by using bedside cerebral autoregulation monitoring in adults with acute subarachnoid hemorrhage.<sup>12</sup> Additionally, the lower limit of autoregulation ranged from a MAP of 43 to 90 mmHg in individuals undergoing cardiac surgery.<sup>13</sup>

Cerebral autoregulation can be assessed clinically at the bedside by measuring changes in cerebral blood flow, or its

surrogates, in relation to cerebral perfusion pressure.<sup>14,15</sup> The newest and most innovative application of cerebral autoregulation monitoring is the determination of individualized optimal MAP and optimal cerebral perfusion pressure with the delineation of individual autoregulatory ranges. After reviewing the literature in major databases (PubMed/MEDLINE, Embase, and Google Scholar) from 1990 through 2016 using combinations of the keywords “cerebral autoregulation,” “optimal arterial pressure,” “optimal cerebral perfusion pressure,” “cerebral oximetry,” “transcranial Doppler,” and “intracranial cerebral pressure,” we found 12 observational studies over the last 6 yr that have determined the feasibility of using cerebral autoregulation monitoring to delineate optimal MAP or optimal cerebral perfusion pressure at the bedside in adults undergoing cardiopulmonary bypass; adults with acute traumatic brain injury, intracerebral hemorrhage, or subarachnoid hemorrhage; neonates with hypoxic-ischemic encephalopathy; and children with moyamoya syndrome.<sup>16-25</sup> Of these studies, 66% (6 of 9) showed that patients in whom

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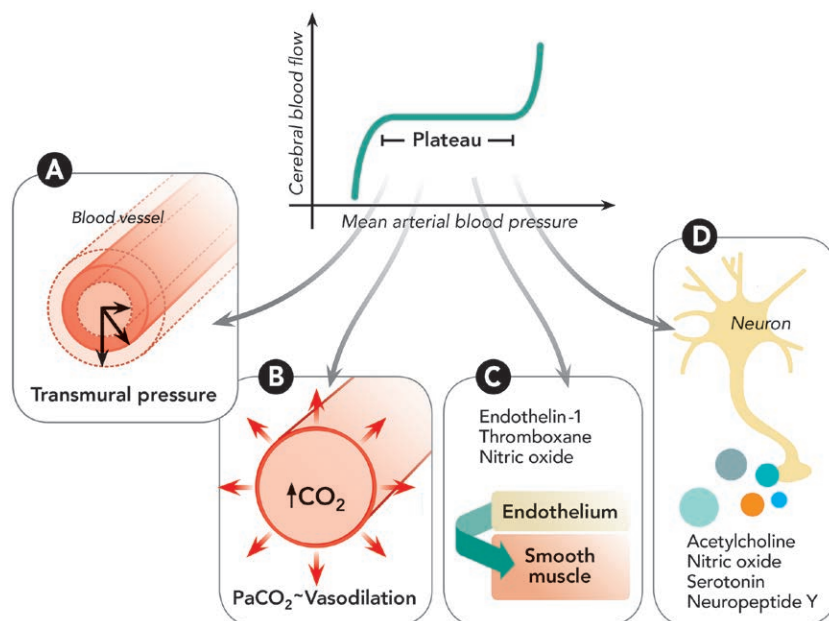
actual MAP or cerebral perfusion pressure was widely different from optimal MAP or optimal cerebral perfusion pressure were more likely to have an unfavorable outcome.<sup>16–20</sup> The strength of these data prompted the Brain Trauma Foundation to recommend cerebral autoregulation monitoring as an option to optimize cerebral perfusion pressure in patients with acute traumatic brain injury.<sup>26</sup> Nonetheless, the guidelines for arterial blood pressure management still recommend a single target blood pressure for critically ill patients and those with acute stroke: the International Guidelines for Management of Sepsis<sup>27</sup> recommend a MAP of at least 65 mmHg; the American Heart Association/American Stroke Association guidelines recommend a systolic blood pressure of less than 140 mmHg after acute intracerebral hemorrhage<sup>28</sup> and aneurysmal subarachnoid hemorrhage before aneurysm clipping or coiling<sup>29</sup> and a systolic blood pressure of less than 180 mmHg after intravenous recombinant tissue plasminogen activator for acute ischemic stroke.<sup>30</sup> Other societies now recognize that patients with a history of hypertension may have a cerebral autoregulation curve that is shifted to the right and require a higher MAP. For example, the European Society of Intensive Care Medicine<sup>31</sup> recommends an initial target MAP of at least 65 mmHg (level 1 evidence; quality of experience, low) and a higher MAP in septic patients with history of hypertension and in patients who show clinical improvement with higher blood pressure (level 2 evidence; quality of experience, moderate). These guidelines do not currently recommend cerebral autoregulation-guided therapy and leave many unanswered questions: What is the optimal MAP target in patients with a history of long-standing hypertension? Do patients with acute

brain injury and elevated intracranial pressure (ICP) have different lower and upper limits of cerebral perfusion pressure than patients without intracranial injury?

The purpose of this comprehensive review is to summarize the evidence regarding use of cerebral autoregulation-directed therapy at the bedside to optimize and individualize cerebral perfusion pressure and to assess whether doing so can improve functional outcomes. We start by describing the physiology and methods used to measure cerebral autoregulation and then discuss validation of different cerebral autoregulation indices with a principal focus on evaluating the evidence behind the determination of optimal MAP/optimal cerebral perfusion pressure and its ability to accurately predict outcomes.

### Physiology of Cerebral Autoregulation

Cerebral autoregulation protects the brain against hypoperfusion caused by hypotension, as well as against hypertension-induced hyperemia.<sup>32</sup> Four mechanisms regulate cerebral blood flow, including myogenic, neurogenic, endothelial, and metabolic responses (fig. 1). Myogenic tone is generated when the smooth muscle of small arteries and arterioles contracts in response to increased pressure and relaxes in response to decreased pressure.<sup>33</sup> A rapid change in transmural pressure ( $\Delta_p = 10$  to 25 mmHg/s) triggers immediate changes in vessel diameter.<sup>34</sup> The latency between the onset of transmural stimulation and the beginning of the vessel's mechanical response is usually less than 250 ms.<sup>35</sup> The neurogenic mechanism, also called “neurovascular coupling,” is less well elucidated and involves the control of moderate- and small-diameter vessels.



**Fig. 1.** Illustration of the mechanisms of cerebral autoregulation. (A) In the myogenic mechanism, changes in the transmural pressure influence changes in arterial diameter through contraction or relaxation of the smooth muscle. (B) In the metabolic mechanism, the concentration of carbon dioxide ( $\text{CO}_2$ ) produced in the oxidative phosphorylation process affects small artery diameter. (C) The endothelial mechanism is based on the paracrine secretion of substances (nitric oxide and vasoconstrictors like endothelin-1 and thromboxane A<sub>2</sub>) that stimulate the smooth muscle. (D) In the neurogenic mechanism, neuroglial cells contribute to the control of moderate- and small-diameter vessels by secreting different neurotransmitters with vasoactive properties.

Neurons secrete different neurotransmitters with vasoactive properties, such as acetylcholine or nitric oxide, which cause vasodilatation, and serotonin and neuropeptide Y, which stimulate vasoconstriction.<sup>36</sup> By using infrared videomicroscopy of interneurons and adjacent microvessels in rats, Cauli *et al.*<sup>37</sup> showed that microvessels constrict in response to interneuronal depolarization. The metabolic mechanism occurs in smaller vessels that are subject to changes in the local microenvironment that alter vasomotor responses.<sup>38</sup> For example, hypotension below the lower limit of autoregulation leads to low cerebral blood flow and a consequent accumulation of carbon dioxide. For every 1-mmHg increase in  $P_{aCO_2}$ , there is an approximately 4% increase in cerebral blood flow caused by vessel vasodilatation. Conversely, hypertension above the upper limit of autoregulation results in hyperperfusion and a drop in carbon dioxide. For every 1-mmHg decrease in  $P_{aCO_2}$ , vessel vasoconstriction will cause a 4% decrease in cerebral blood flow.<sup>38</sup> This reactivity has been attributed to the response of cerebral vessel smooth muscle to  $H^+$ .<sup>39</sup> Last, the endothelium generates a variety of signals that influence cerebrovascular tone under normal conditions and during disease as well. The endothelium secretes vasodilators such as nitric oxide and vasoconstrictors like endothelin-1 and thromboxane A<sub>2</sub>.<sup>40</sup> One of the benefits of statins is their ability to upregulate nitric-oxide synthase, causing cerebral artery dilation and increased cerebral blood flow.<sup>41</sup>

### Methods to Measure Cerebral Autoregulation and Cerebrovascular Reactivity

Cerebrovascular reactivity is the ability of vascular smooth muscle to change basal tone in response to variations of physiologic parameters, such as arterial blood pressure, and metabolic factors, such as cerebral carbon dioxide and oxygen levels.<sup>15</sup> When cerebrovascular reactivity is exhausted, cerebral blood flow becomes dependent on systemic arterial blood pressure. Cerebral autoregulation is one aspect of cerebrovascular reactivity that involves vascular tone changes in response to fluctuations in arterial blood pressure. Vessels may still demonstrate responses to further changes in carbon dioxide concentration.<sup>42,43</sup> These vascular responses that continue to occur outside the MAP range of stable cerebral blood flow are also part of the cerebral autoregulatory mechanism (metabolic, endothelial, among others) that protects the brain.<sup>42</sup> Therefore, the terms cerebral autoregulation and cerebrovascular reactivity should not be used synonymously, as vasodilatation reaches its maximum at arterial pressures below the lower threshold for constant cerebral blood flow.<sup>44,45</sup>

Regulation of the brain vasculature's ability to maintain constant cerebral blood flow can be assessed by two modalities: static and dynamic autoregulation.<sup>46</sup> Static autoregulation describes the extent to which the cerebrovascular bed can constrict or dilate when cerebral perfusion pressure varies. Dynamic autoregulation also incorporates information

on the rate at which such adaptive changes in cerebrovascular resistance occur.<sup>47</sup> Only dynamic cerebral autoregulation allows for continuous measurement of cerebral autoregulation and therefore determination of optimal MAP and optimal cerebral perfusion pressure, the most novel application of cerebral autoregulation monitoring.

### Technology for Cerebral Autoregulation Monitoring

The technology used to calculate cerebral autoregulation and cerebrovascular reactivity in the clinical setting includes transcranial Doppler, which measures cerebral blood flow velocity; near-infrared spectroscopy, which measures regional cerebral oxygen saturation; the brain tissue oxygen monitor, which measures tissue oxygen partial pressure; ICP monitors; and, more recently, ultrasound-tagged near-infrared spectroscopy, which measures cerebral blood flow velocity (table 1). All these measurements are used as surrogates for the gold standard of cerebral blood flow, which no currently available device can quantify.<sup>48</sup> Figure 2 shows the devices that are frequently used to measure cerebral autoregulation or cerebrovascular reactivity.

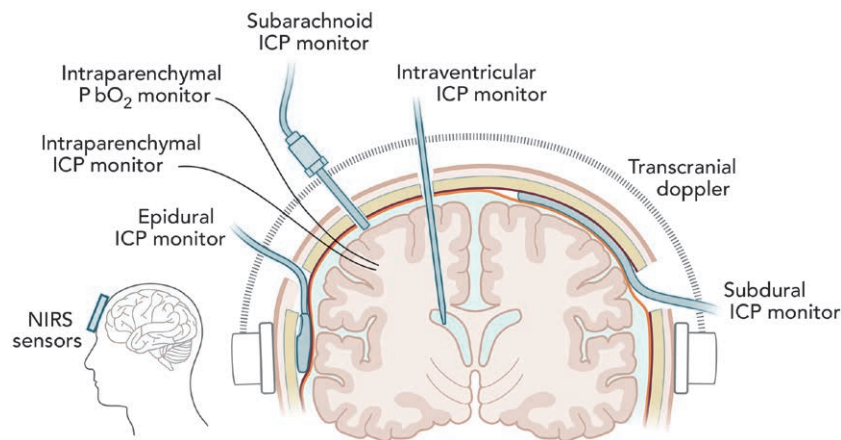
Transcranial Doppler is an accepted noninvasive tool for continuous monitoring of cerebral blood flow velocity and is a well-validated method to assess cerebral autoregulation.<sup>49,50</sup> Cerebral autoregulation testing with transcranial Doppler measures cerebral blood flow velocity from the middle cerebral arteries. Because measurement of middle cerebral artery diameter is not standard, transcranial Doppler provides only a surrogate for cerebral blood flow based on the assumption that middle cerebral artery diameter changes minimally with changes in MAP.<sup>51</sup> As cerebral blood flow velocity is a pulsatile phenomenon, it can be monitored in a time domain that relies only on spontaneous changes of MAP or cerebral perfusion pressure. A moving correlation coefficient can then be calculated between cerebral blood flow velocity and MAP or cerebral perfusion pressure; this coefficient is called the mean velocity index.<sup>52</sup>

Near-infrared spectroscopy is also a noninvasive device that measures regional cerebral oxygen saturation. Near-infrared light is transmitted from a source embedded in a sensor attached to the forehead and directed toward the frontal lobe. Light in the near-infrared spectrum (700 to 950 nm) can traverse biologic tissue because of the relative transparency of tissue to light at these wavelengths. Several biologic molecules, termed chromophores, have distinct absorption spectra in the near infrared.<sup>53</sup> Oxyhemoglobin, deoxyhemoglobin, and cytochrome  $aa_3$  (a complex protein present in the mitochondria that is involved in the oxidative phosphorylation process) are the most abundant chromophores that absorb near-infrared light between 700 and 1,000 nm.<sup>53,54</sup> The amount of light detected by sensors positioned at set distances from the light source is a function of reflectance from the light-tissue angle, scattering from body tissues, and absorption by chromophores.<sup>53,55</sup> This technology makes the following assumptions: cytochrome  $aa_3$  and bilirubin are minimal, and the hemoglobin measured

**Table 1.** Cerebral Autoregulation Indices with Their Cutoffs to Define Impaired Autoregulation

Surrogate of CBF	Device or Monitor	Cerebral Autoregulation Index	Correlation Between	Cutoff for Impaired CA	Reference No.
Regional cerebral oxygenation	NIRS	Cerebral oximetry index	Regional cerebral oxygenation and MAP	>0.3	58
Total hemoglobin volume	NIRS	Hemoglobin volume index	Total hemoglobin volume and MAP	>0.3	81
Regional cerebral oxygenation	NIRO	Tissue oxygen index	Regional cerebral oxygenation and MAP	>0.1 >0.13	82 12
Tissue hemoglobin	NIRO	Tissue hemoglobin index	Oxygenated and deoxygenated hemoglobin and MAP	NA	—
CBF velocity	UT-NIRS	CBF velocity index	CBF velocity and MAP	NA	—
CBF velocity	TCD	Dynamic autoregulatory index	CBF velocity and MAP	<4	83
CBF velocity	TCD	Systolic flow velocity index	Systolic CBF velocity and MAP	>0.1 >0.05	82 12
CBF velocity	TCD	Mean flow velocity index	Mean CBF velocity and MAP	>0.3 >0.46	52 84
CBF velocity	TCD	Mean flow velocity index	Mean CBF velocity and cerebral perfusion pressure	>0.3	49,71,72
Tissue oxygen pressure	Brain tissue oxygen monitor	Brain tissue oxygen pressure reactivity index	Tissue oxygen pressure and cerebral perfusion pressure	>0.4	85
ICP	ICP monitor	Pressure reactivity index	5- to 10-s mean ICP and MAP	>0.3	52
ICP	ICP monitor	Diastolic coefficient index	Diastolic CBF velocity and diastolic MAP	>0.24	84
ICP	ICP monitor	Low-frequency autoregulation index	Minute-by-minute mean ICP and MAP	NA	—
ICP	ICP monitor	Low-frequency sample pressure reactivity index	20-min averages of ICP and MAP	>0.2	86

CA = cerebral autoregulation; CBF = cerebral blood flow; ICP = intracranial pressure; MAP = mean arterial blood pressure; NA = not described yet; NIRO = near-infrared oxygenation monitor; NIRS = near-infrared spectroscopy; TCD = transcranial Doppler; UT-NIRS = ultrasound-tagged near-infrared spectroscopy.



**Fig. 2.** Principal devices used to measure cerebral autoregulation and cerebrovascular reactivity and their positioning. ICP = intracranial pressure; NIRS = near-infrared spectroscopy.

is contained in a fixed mixture of vessels that are approximately 70 to 75% venous and 25 to 30% arterial blood volume.<sup>56,57</sup> Equations used to account for variability in venous:arterial ratios are manufacturer specific; therefore, regional cerebral oxygen saturations derived from different machines are not equivalent.<sup>55,56</sup> The cerebral oximetry index is derived from the correlation between regional cerebral oxygen saturation from near-infrared spectroscopy and MAP or cerebral perfusion pressure.<sup>58</sup>

An innovative new hybrid device, CerOx (Ornim Medical Ltd., Israel), uses a single, noninvasive probe to provide a brain oximeter and blood flow monitor that utilizes a combination of near-infrared light and a localized low-power ultrasound. The ultrasound signal is a sequence of phase-modulated waves with a central frequency at 1 MHz, which is similar to the frequency (2 MHz) of transcranial Doppler.<sup>59</sup> This ultrasound-tagged near-infrared spectroscopy estimates changes in microcirculatory blood flow within the



interrogated volume of  $1 \text{ cm}^3$ .<sup>59,60</sup> The cerebral blood flow velocity index is derived from the correlation between cerebral blood flow velocity from ultrasound-tagged near-infrared spectroscopy and MAP or cerebral perfusion pressure.<sup>61</sup>

Other methods estimate cerebrovascular reactivity by measuring changes in ICP with ICP monitors. Normally, the cerebral blood volume and ICP vary inversely with arterial blood pressure.<sup>62</sup> Therefore, if cerebrovascular reactivity is intact, a significant increase in MAP will produce vasoconstriction, a decrease in cerebral blood volume, and a decrease in ICP.<sup>15,39,63,64</sup> If vessels are nonreactive, an increase in MAP would cause an increase in the cerebral blood volume and, thereby, ICP.<sup>15</sup> The pressure reactivity index is the most commonly used index to measure cerebrovascular reactivity in patients with traumatic brain injury and is derived from the correlation between ICP and MAP.<sup>15</sup>

The disadvantages of some older cerebral autoregulation detection methods are that they require a hemodynamic stimulus to induce a change in MAP, such as thigh cuff release,<sup>65</sup> increase in arterial partial pressure of carbon dioxide,<sup>66</sup> tilt table declination,<sup>67</sup> application of negative body pressure,<sup>68</sup> carotid artery compression,<sup>69</sup> or vasoactive drug administration.<sup>70</sup> The safety of such manipulations in compromised patients prone to organ injury from alterations in MAP is of concern. Thus, newer methods of cerebral autoregulation monitoring are based on cerebral blood flow responses to spontaneous changes in cerebral perfusion pressure or MAP that may occur over time and slow-wave oscillations in cerebral blood volume and cerebral blood flow—lasting from 30 s to a few minutes—secondary to normal physiologic functions such as breathing.<sup>3,49,52,71–75</sup>

The advantage of using transcranial Doppler- and near-infrared spectroscopy-derived cerebral autoregulation indices is that they are noninvasive, whereas ICP and tissue oxygen partial pressure monitors require intracranial catheters that carry risks for hemorrhage, meningitis, and ventriculitis.<sup>76</sup> The principal disadvantage of transcranial Doppler is the requirement for a trained technician, which restricts widespread applicability. The use of transcranial Doppler is also hampered by the 10 to 15% rate of inadequate acoustic windows prevalent in African Americans, Asians, and elderly women.<sup>77</sup>

Limitations to these devices must be acknowledged. Near-infrared spectroscopy measures regional cerebral oxygen saturation through sensors that are placed on the forehead. Therefore, the cerebral autoregulation calculations are limited to regional cerebral oxygen saturation from the frontal lobes, with some contamination from the external carotid artery.<sup>78</sup> The brain tissue oxygen monitor is also a local measure and may not reflect global oxygenation and metabolism, especially in patients suffering from focal injuries. Moreover, there is an active debate on the most appropriate location to place monitoring probes.<sup>79</sup> ICP monitors are a global measure and may not reflect local changes. Studying

the effect of arteriolar vasoconstriction and vasodilation through their effect on ICP will inevitably include a dampening effect.<sup>21</sup> Finally, transcranial Doppler can provide only an estimation of cerebral blood flow when the diameter of the sampled artery does not change throughout the examination. Magnetic resonance imaging can be used to test this assumption.<sup>80</sup>

### Cerebral Autoregulation Indices

There are more than 21 cerebral autoregulation indices. Some measure cerebral autoregulation (cerebral oximetry index, tissue oxygen index, cerebral blood flow velocity index, systolic flow velocity index, mean flow velocity index, and brain tissue oxygen pressure reactivity index), whereas others measure cerebrovascular reactivity (pressure reactivity index, hemoglobin volume index, tissue hemoglobin index, and dynamic autoregulatory index). Table 1 provides definitions of all of the cerebral autoregulation indices and descriptions of how to measure and calculate them. Generally, when cerebral autoregulation is lost, the cerebral autoregulation indices approximate to 1, indicating pressure passivity; a negative index or one that approaches 0 indicates intact pressure reactivity. Despite this general principle, each index has a different cutoff to define impaired autoregulation, with a range from 0.069 to 0.46.<sup>12,49,52,58,71,72,81–86</sup> This wide variability in cutoff values depends on the different devices used as surrogates of cerebral blood flow measurements and the population studied. The dynamic autoregulatory index is the only one that uses a different scale than the ones mentioned above, and it ranges from 0 (absent cerebral autoregulation) to 9 (most efficient cerebral autoregulation).<sup>87</sup>

### Validation of Invasive versus Noninvasive Cerebral Autoregulation Methods

Multiple new cerebral autoregulation indices have been validated against long-standing ones during the past couple of decades. This approach makes it easy to start using newer and possibly superior methods to measure cerebral autoregulation or cerebrovascular reactivity clinically. More importantly, noninvasive methods can be compared to invasive ones. A detailed description of the validation studies is presented in table 2. One of the noninvasive cerebral autoregulation indices most often used at the bedside is mean flow velocity index based on MAP. The mean flow velocity index based on MAP is derived from the correlation between cerebral blood flow velocity and MAP, and numerous studies have validated it against mean velocity index based on cerebral perfusion pressure<sup>52,72,88</sup> in patients with intracranial injury ( $R = 0.789$ ,  $P < 0.001$ ). Mean flow velocity index based on MAP has also shown good agreement in validations against dynamic autoregulatory index and pressure reactivity index:  $R = -0.38$ ,  $P < 0.001$ <sup>89</sup>;  $R = 0.58$ ,  $P < 0.001$ <sup>90</sup>;

**Table 2.** Validation Studies of Cerebral Autoregulation Indices

Comparison	R Value	P Value
Studies in patients with intracranial injury		
Mean flow velocity index based on cerebral perfusion pressure vs. mean flow velocity index based on MAP <sup>52</sup>	0.566	<0.01
Mean flow velocity index based on cerebral perfusion pressure vs. mean flow velocity index based on MAP <sup>72</sup>	0.789	<0.001
Mean flow velocity index based on cerebral perfusion pressure vs. mean flow velocity index based on MAP <sup>88</sup>	0.755	<0.001
Mean flow velocity index based on cerebral perfusion pressure vs. dynamic autoregulatory index <sup>91</sup>	-0.62	0.0001
Mean flow velocity index based on MAP vs. tissue oxygen index <sup>92</sup>	0.61	0.004
Mean flow velocity index based on MAP vs. systolic flow velocity index <sup>98</sup>	0.89	<0.001
Mean flow velocity index vs. dynamic autoregulatory index <sup>89</sup>	-0.38	<0.001
Mean flow velocity index vs. tissue hemoglobin index <sup>92</sup>	0.26	0.28
Pressure reactivity index vs. mean flow velocity index based on cerebral perfusion pressure <sup>100</sup>	0.58	<0.001
Pressure reactivity index vs. low-frequency sample pressure reactivity index <sup>17</sup>	0.7	<0.00001
Pressure reactivity index vs. low-frequency sample pressure reactivity index <sup>97</sup>	0.846	<0.001
Pressure reactivity index vs. brain tissue oxygen pressure reactivity index <sup>96</sup>	0.851	<0.04354
Pressure reactivity index vs. tissue oxygen index <sup>92</sup>	0.40	0.04
Pressure reactivity index vs. tissue hemoglobin index <sup>92</sup>	0.63	<0.001
Pressure reactivity index vs. tissue hemoglobin index <sup>101</sup>	0.56	0.0002
Studies in patients with no intracranial injury		
Mean flow velocity index based on MAP vs. cerebral oximetry index <sup>93</sup>	0.51	<0.001
Mean flow velocity index based on MAP vs. cerebral oximetry index <sup>95</sup>	0.55	<0.0001
Mean flow velocity index based on MAP vs. tissue oxygen index <sup>94</sup>	0.81	<0.0001
Cerebral blood flow velocity index vs. mean flow velocity index based on MAP <sup>61</sup>	0.39	<0.001
Mean flow velocity index based on cerebral perfusion pressure vs. hemoglobin volume index <sup>81</sup>	0.5915	<0.001

MAP = mean arterial blood pressure.

and  $R = -0.62$ ,  $P < 0.0001$ .<sup>91</sup> Other noninvasive cerebral autoregulation methods that use the near-infrared oxygenation (NIRO-200) monitor have been validated against invasive methods. For example, the tissue oximetry index and tissue hemoglobin index each showed good agreement with the pressure reactivity index ( $R = 0.40$ ,  $P = 0.04$ ;  $R = 0.63$ ,  $P < 0.001$ , respectively).<sup>92</sup> In patients without intracranial injury, cerebral oximetry index (derived from near-infrared spectroscopy, INVOS monitor [Medtronic/Covidien, Ireland];  $R = 0.51$ ,  $P < 0.001$ )<sup>93</sup> and tissue oxygen index ( $R = 0.81$ ,  $P < 0.0001$ )<sup>94</sup> have each been validated against mean flow velocity index based on MAP. The hemoglobin volume index, derived from near-infrared spectroscopy (INVOS monitor), has also been validated against mean flow velocity index based on cerebral perfusion pressure in patients without intracranial injury ( $R = 0.5915$ ,  $P < 0.0001$ ).<sup>81</sup> All of these significant correlations between the invasive and noninvasive methods and others are described in table 2.<sup>17,61,95-101</sup> These results support the accuracy of noninvasive methods and their potential utility in cerebral autoregulation and cerebrovascular reactivity monitoring.

### Measurement of Optimal Cerebral Perfusion Pressure and Optimal MAP in Individual Patients

Over the last decade, several advances in determining optimal cerebral perfusion pressure and optimal MAP have been made. The cerebral autoregulation indices that have been used

to determine the optimal values are validated (*i.e.*, pressure reactivity index, cerebral oximetry index, tissue hemoglobin index) and have demonstrated significant ability to predict outcomes.<sup>74,90,100,102</sup> We will describe the methodology used to determine optimal cerebral perfusion pressure and optimal MAP; a summary of these study results is shown in table 3.

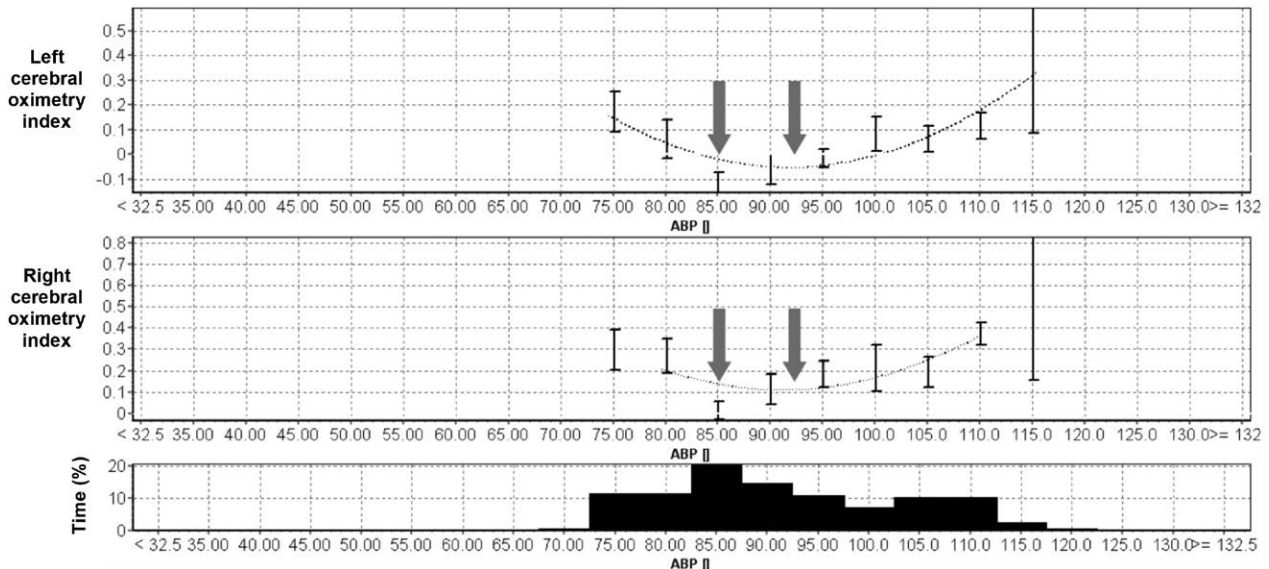
#### Second-order Polynomial Formula (U-shaped Curve)

This method has been used most frequently in studies of traumatic brain injury in which optimal cerebral perfusion pressure is calculated by fitting a U-shaped curve over 4-h periods of monitoring (table 3). That curve, also known as the U-shaped parabola, is supposed to represent the real plot of cerebral autoregulation indices *versus* cerebral perfusion pressure or MAP; as a result, the optimal cerebral perfusion pressure or optimal MAP is logically assumed to be the X-vertex of the curve modeled by the parabolic formula ( $Ax^2 + Bx + C$ ). The estimation of the optimal cerebral perfusion pressure by this method is thought to be exact because it represents an exact MAP or cerebral perfusion pressure point that reflects the real lowest magnitude of the cerebral autoregulation index used. Despite the accuracy assumed of this method, several limitations are worth noting. First, this method does not identify optimal pressures in all monitored patients, only in up to 55% of the monitor recordings.<sup>16,23</sup> Second, this formula does not take into consideration the percentage of time in each bin recorded; therefore the calculated optimal pressure can be biased by outliers. Figure 3 shows a clear typical error of the second-order polynomial

**Table 3.** Summary of the Reported Optimal Cerebral Perfusion Pressure and Optimal Mean Arterial Blood Pressure Sorted by the Population Studied

Patient Population	Optimal Pressure Studied	Autoregulation Index Used (Time Window)	Sample Size	Proportion of Time CPP <sub>OPT</sub> or MAP <sub>OPT</sub> Identified	Method	Mean ± SD or Median [IQR] of the Optimal Pressure (mmHg)	Association with Poor Outcome	Reference No.
Traumatic brain injury	CPP <sub>OPT</sub>	Pressure reactivity index (4h)	307	55%	U-shaped curve	74.7 ± 8.2	Below and above CPP <sub>OPT</sub>	16
		Low-frequency autoregulation index (1–24 h)	55	97%	DATA CAR	70.8 ± 11.4	Below and above CPP <sub>OPT</sub>	21
	CPP <sub>OPT</sub>	Pressure reactivity index (4h)	30*	NA	U-shaped curve	68.87 ± 9.73† 63.6 ± 7.9‡	Only below CPP <sub>OPT</sub>	18
		Pressure reactivity index (4h)	18	NA	U-shaped curve	88 ± 7	Only below CPP <sub>OPT</sub>	19
		Low-frequency sample pressure reactivity index (4h)	307	NA	U-shaped curve	76.9 ± 10.1	No statistically significant associations with outcome	17
Intracerebral hemorrhage	CPP <sub>OPT</sub>	Pressure reactivity index (4h)	55	44%	U-shaped curve	72.5 ± 7.6	No statistically significant associations with outcome	21
		Pressure reactivity index (4 days)	48	72%	U-shaped curve	78.6 ± 12.2	NP	22
		Cerebral oximetry index (4h)	18	NA	U-shaped curve	88 ± 7	NP	19
		Brain tissue oxygen pressure reactivity index (4h)	18	NA	U-shaped curve	85 ± 6	NP	19
		Cerebral blood flow velocity index (4h)	18	NA	U-shaped curve	85 ± 6	NP	19
	CPP <sub>OPT</sub>	Pressure reactivity index (48h)	38	84%	Lowest CA index	76.25 ± 9.67	NP	23
		Pressure reactivity index (NA)	38	57%	U-shaped curve	83 ± 7.06	No statistically significant associations with outcome	24
		Pressure reactivity index (NA)	25	NA	Lowest CA index	78 ± 2.6§ 98 ± 3.6	No statistically significant associations with mortality	25
		Cerebral oximetry index (NA)	121	NA	Lowest CA index	78 ± 12.8	Below the MAP <sub>OPT</sub> (for brain injury as outcome)	20
		Cerebral blood flow velocity index (1.85h)	69	NA	Lowest CA index	71 ± 12	NP	61
Subarachnoid hemorrhage	CPP <sub>OPT</sub>	Mean flow velocity index based on MAP (1.85h)	69	NA	Lowest CA index	74 ± 12	NP	61
		Mean flow velocity index based on MAP (1.48h)	109	87%	Lowest CA index	75 ± 11	NP	81
Cardiac surgery	MAP <sub>OPT</sub>	Hemoglobin volume index (1.48h)	109	100%	Lowest CA index	74 ± 13	NP	81
		Hemoglobin volume index (6h)#	14	NA	Lowest CA index	50 [45–55]	Only below MAP <sub>OPT</sub>	104
		Hemoglobin volume index (6.5h)**	17	NA	Lowest CA index	45 [45–50]		
Hypoxic-ischemic encephalopathy (neonates)	MAP <sub>OPT</sub>	Hemoglobin volume index (30.5h)††	NA	NA	Lowest CA index	45 [45–55]		
		Cerebral oximetry index (NA)	7	86%	Lowest CA index	70 [60–95]‡‡ 90 [85–90]§§	NP	103
Pediatric unilateral and bilateral vasculopathy	MAP <sub>OPT</sub>	Hemoglobin volume index (NA)	7	86%	Lowest CA index	70 [60–95]‡‡ 80 [75–85]§§	NP	103

\*Children between 1 and 15 yr old. †In patients with unfavorable outcome. ‡In patients with favorable outcome. §During baseline. ¶During vasospasm. \*\*During normothermia. ††During hypothermia. ‡‡Intraoperative data. §§Postoperative data. CA = cerebral autoregulation; CPP<sub>OPT</sub> = optimal cerebral perfusion pressure; DATA CAR = dynamic adaptive target of active cerebral autoregulation; IQR = interquartile range; MAP = mean arterial blood pressure; MAP<sub>OPT</sub> = optimal mean arterial blood pressure; NA = not available; NP = not performed.



**Fig. 3.** A representative 4-h monitoring period shows a difference of more than 5 mmHg between the optimal mean arterial blood pressures (MAPs), defined by the U-shaped curve, and the lowest cerebral autoregulation index. This patient presented with an intracerebral hemorrhage and was continuously monitored with near-infrared spectroscopy. The *top* graph shows the left cerebral oximetry index, the *middle* graph shows the right cerebral oximetry index, and the *bottom* graph shows the histogram of monitoring time in each bin. The first arrow (at 85 mmHg) represents the optimal mean arterial blood pressure defined by the U-shaped curve method, and the second arrow (at 93 mmHg) represents the optimal mean arterial blood pressure determined by the lowest cerebral autoregulation index method.

formula that could be resolved by adjusting or weighting the curve to time or excluding bins with a monitoring time of less than 3% (fig. 3, bottom).

Recently, a study described the factors associated with such limitations in detail and concluded that the absence of slow arterial blood pressure waves, higher pressure reactivity index values, lower doses of sedative-analgesic drugs, higher vasoactive medication doses, no administration of maintenance neuromuscular blockers, and the presence of decompressive craniectomy were independently associated with the absence of a U-shaped curve.<sup>22</sup>

#### Lowest Cerebral Autoregulation Index (Nadir)

Most of the studies on cardiac surgery and pediatrics and only one study on head injury have used the lowest cerebral autoregulation index as the absolute intact cerebral autoregulation. This method is based on the nadir value of the cerebral autoregulation index during the monitoring period, which could be a positive or negative value but should not be greater than the cutoff value established for the corresponding cerebral autoregulation index used. This method has the advantage of determining optimal pressures in most patients regardless of the time window for monitoring. However, it is limited by the fact that it is less objective than the polynomial derivation method and can have greater variability when more than one negative value of similar magnitude is observed at different MAPs (for example, two negative values at MAPs of 70 and 90 mmHg). It is important to recognize that no study has yet compared the last two methods discussed.

#### Dynamic Adaptive Target of Active Cerebral Autoregulation

Only one study has used the dynamic adaptive target of active cerebral autoregulation (DATACAR) technique, which appears to be more accurate for determining an exact and individualized optimal cerebral perfusion pressure. This method uses the same formula as the conventional U-shaped curve but additionally takes into account different time windows (*i.e.*, 1, 2, 4, 6, 8, 12, and 24 h) and assigns a weight factor to optimal cerebral perfusion pressure based on the goodness of fit of their respective U-shaped curves and the lower value of the cerebral autoregulation index of the optimal cerebral perfusion pressure. When compared with the conventional U-shaped method, this method allows optimal cerebral perfusion pressure identification in a greater number of patients and shows better accuracy for predicting outcome.<sup>21</sup>

#### Summary of the Evidence Regarding Optimal Cerebral Perfusion Pressure and Optimal MAP

Researchers have conducted multiple observational studies in adults and several in children to optimize arterial blood pressure in hospitalized patients by defining the patients' own physiologic cerebral autoregulation curve instead of using a nonindividualized target pressure recommended by guidelines. The primary objective was to provide optimum perfusion to the brain and potentially other organs (table 3). These studies calculated the optimal cerebral perfusion pressure and optimal



MAP in different populations and determined the feasibility of delineating them with cerebral autoregulation monitoring at the bedside.<sup>16,21–24,81,103</sup> Four studies investigated the association of hypotension and/or hypertension based on autoregulation monitoring in adult patients with acute traumatic brain injury and functional outcomes as follows. In a large retrospective study with prospectively collected data from 327 patients in whom the pressure reactivity index was used to define optimal cerebral perfusion pressure, cerebral perfusion pressure below the optimal level increased the incidence of fatal outcome, whereas excessively high cerebral perfusion pressure levels were associated with an increased proportion of severe disability.<sup>16</sup> Similar findings were reported in a cohort of 55 patients in whom a low-frequency autoregulation index was used to determine optimal cerebral perfusion pressure. The authors reported that having actual cerebral perfusion pressure close to the low-frequency autoregulation index—based optimal cerebral perfusion pressure was associated with increased survival.<sup>21</sup> In a multivariate model, the average absolute difference between actual cerebral perfusion pressure and optimal cerebral perfusion pressure was independently associated with increased mortality. In another smaller cohort of 18 patients that used the pressure reactivity index to calculate optimal cerebral perfusion pressure, patients with a larger discrepancy (more than 10 mmHg) between actual cerebral perfusion pressure and optimal cerebral perfusion pressure were more likely to have an adverse outcome defined as a Glasgow outcome scale value equal to or greater than 3 ( $P = 0.04$ ).<sup>19</sup> Contrary to the aforementioned studies, one study did not find an association between optimal cerebral perfusion pressure and death or severe disability when using a new index called the low-frequency sample pressure reactivity index; however, this index has been found to have a poor predictive value for outcome by itself and also for calculation of optimal cerebral perfusion pressure.<sup>17</sup>

Only two small studies have included patients with aneurysmal subarachnoid hemorrhage ( $n = 38$ ) and intracerebral hemorrhage ( $n = 25$ ).<sup>24,25</sup> Neither found a significant association between optimal cerebral perfusion pressure and functional outcome using the pressure reactivity index. One observational study of 121 patients undergoing cardiac surgery reported that hypotension defined with cerebral autoregulation monitoring based on the cerebral oximetry index leads to brain cellular injury characterized by elevations in serum levels of the brain-specific injury biomarker glial fibrillary acidic protein.<sup>20</sup>

Several observational studies in children have calculated optimal MAP with bedside cerebral autoregulation monitoring.<sup>18,103,104</sup> One study of 28 neonates with hypoxic-ischemic encephalopathy used the hemoglobin volume index to evaluate the association between blood pressure below the optimal MAP and poor outcome defined as motor and cognitive impairments at 21 to 32 months of age. The authors found that neonates with greater blood pressure deviation below optimal MAP during rewarming after therapeutic hypothermia had poor outcome.<sup>104</sup> Similar results were reported in a cohort of 30 children

with traumatic brain injury who were 6 months to 16 yr old. The authors reported that both the duration and the magnitude of negative deviations in the difference between cerebral perfusion pressure and optimal cerebral perfusion pressure were associated with unfavorable outcome defined as a Glasgow outcome scale value equal to or greater than 4.<sup>18</sup>

It is interesting to note that the mean or median calculated optimal MAP or optimal cerebral perfusion pressure differs across populations and possibly patient comorbidities. For example, patients with intracerebral hemorrhage had a higher mean optimal cerebral perfusion pressure than did patients with traumatic brain injury: 85 mmHg *versus* 75 mmHg, respectively. In addition, patients with aneurysmal subarachnoid hemorrhage and vasospasm had a higher optimal cerebral perfusion pressure than did those without vasospasm (98 mmHg *vs.* 78 mmHg, respectively). Furthermore, in some populations of patients with traumatic brain injury, the excess or deficit of cerebral perfusion pressure or MAP, based on their respective optimal values, has been associated with severe disability, whereas in patients who have undergone cardiac surgery, for example, only the deficit of MAP was associated with brain cellular injury. These differences may be explained in part by the detrimental effects of excess cerebral perfusion pressure in patients with severe acute brain injury, ICP elevation, and poor brain compliance, who may, *via* hydrostatic forces, suffer worsening cerebral edema and further rise in ICP.<sup>16</sup> More importantly, most of the calculated mean and median optimal cerebral perfusion pressures and optimal MAPs summarized in table 3 are different from the targets recommended for blood pressure control in the current guidelines, illustrating the importance of individualizing MAP and cerebral perfusion pressure goals to achieve better outcomes.

### Barriers to Adopting These Techniques into Clinical Practice

The calculation of optimal cerebral perfusion pressure and optimal MAP appears to be a useful application of cerebral autoregulation and may help clinicians individualize MAP and cerebral perfusion pressure goals to promote optimal patient management. Nevertheless, this novel technology lacks randomized controlled trial data to determine the clinical effectiveness of interventions based on optimal cerebral perfusion pressure and optimal MAP. Moreover, this technology is expensive and can be time consuming. For dynamic cerebral autoregulation monitoring and optimal cerebral perfusion pressure or optimal MAP determination, software such as ICM+ (University of Cambridge, Cambridge, United Kingdom)<sup>105</sup> is required to calculate instantaneously the correlation between the surrogate of cerebral blood flow used and MAP or cerebral perfusion pressure. Therefore, before this technology is adopted into widespread clinical practice, evidence-based data from randomized controlled trials are needed to support the premise that individualizing MAP or cerebral perfusion pressure goals based on cerebral autoregulation monitoring improves patient outcomes.

## Conclusions

Monitoring of cerebral autoregulation has the potential to be used at the bedside to direct and individualize blood pressure management in the acutely ill patient. This review summarizes the evidence behind this new application of cerebral autoregulation monitoring, which has demonstrated large interindividual variability in the lower and upper limits of autoregulation, autoregulatory plateau, and optimal MAP. Cerebral autoregulation monitoring might allow clinicians to individualize management in acutely ill adults and children and thereby optimize their cerebral perfusion. Autoregulation-directed therapy should be evaluated by prospective, large-scale, randomized controlled trials in the near future.

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## Competing Interests

The authors declare no competing interests.

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