Optimal Hemodynamic Parameters for Brain-injured Patients in the Clinical Setting: A Narrative Review of the Evidence

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Abstract: Defining optimal hemodynamic targets for brain-injured patients is a challenging undertaking. The physiological interference observed in various intracranial pathologies can have varying effects on cerebral physiology at different time points. This narrative review provides an overview of cerebral autoregulatory physiology and common misconceptions, and examines the physiological considerations and clinical evidence for determining optimal hemodynamic parameters in acutely brain-injured patients with relevance to modern neuroanesthesia and neurocritical care practice.

Key Words: blood pressure, cerebrovascular circulation, acute brain injury, neuroanesthesia, neurocritical care, perioperative care

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Systemic blood pressure management that is tailored and appropriate to "real-time" cerebrovascular physiology is a cornerstone of neuroanesthesia and neurocritical care practice. Defining and establishing an "optimal" cerebral perfusion pressure (CPP) so as to avoid cerebral ischemia or hyperemia can be particularly challenging in brain-injured patients, because of both the intervariability that exists among individuals' baseline cerebral autoregulatory status and the complex pathophysiological disturbances to "normal" cerebral hemodynamics associated with various intracranial pathologies. The purpose of this narrative review is to summarize the mechanisms by which cerebral autoregulation acts to maintain cerebral perfusion and to comprehensively examine the clinical evidence for defining optimal hemodynamic parameters in patients with traumatic brain injury (TBI), spontaneous intracerebral hemorrhage (ICH), aneurysmal subarachnoid hemorrhage (aSAH), and acute ischemic stroke (AIS).

CEREBRAL AUTOREGULATION, DYSAUTOREGULATION, AND COMMON MISCONCEPTIONS

Cerebral autoregulation describes the adaptive relationship between cerebral blood flow (CBF) and CPP, which acts to maintain a constant CBF across CPP fluctuations between the lower-limit of autoregulation (LLA) and the upper-limit of autoregulation (ULA). This adaptive response is accomplished by cerebral vessel dilation and constriction (Fig. 1).[1–3] When CPP falls below the LLA or exceeds the ULA, CBF becomes "pressure-passive," whereby further systemic hypotension results in decreased CBF and cerebral ischemia, and further systemic hypertension results in increased CBF and cerebral hyperemia and/or edema (Fig. 2).

However, the classic understanding summarized above, and largely dictated by the seminal work of Lassen in 1959,[2] may not offer a full explanation of cerebral autoregulation.[2,4] First, the LLA and ULA on the cerebral autoregulatory curve are not sharp inflection points (they appear as such because they are the result of logistic regression that represents population-based data), but rather they are "rounded shoulders."[5] These "rounded shoulders" more accurately depict cerebral physiology as it occurs in an individual patient, with a slow and gradual decline of CBF as CPP approaches the LLA. Second, the CBF plateau between the LLA and the ULA is actually at a slight incline or upward slope, as opposed to the level plateau that is often represented in standard physiological descriptions, that is, CBF increases slightly as CPP increases from the LLA toward the ULA, albeit much less dramatically than what is observed during pressure-passive flow below the LLA or beyond the ULA.[6] Third, cerebral autoregulation, as classically described, is a representation of neurophysiology in healthy, unanesthetized patients, and this "idealized" cerebral autoregulatory relationship is frequently impaired by anesthetic agents, vasoactive medications, long-standing or acute physiological changes, and various intracranial (cerebrovascular and noncerebrovascular) pathologies.[7–9] The intricacy and interdependency of multiple physiological and

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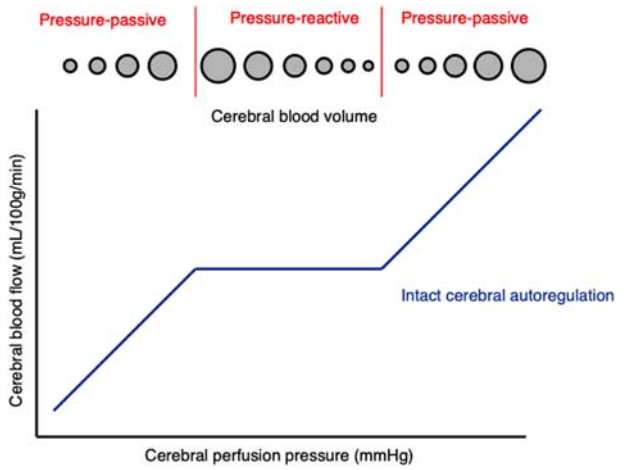

FIGURE 1. Normal cerebral autoregulation. Under normal cerebral physiology, the cerebral blood flow (CBF) remains relatively constant when the cerebral perfusion pressure (CPP) fluctuates between the lower-limit and the upper-limit of autoregulation. This is accomplished by cerebral vasodilation when the CPP falls and by cerebral vasoconstriction when the CPP rises. This part of the cerebral autoregulatory curve is "pressure-reactive." When the CPP falls below the lower-limit of autoregulation, the vasodilatory ability of the arteriolar bed is exhausted and the cerebral vessels collapse because of passive recoil, thereby resulting in a decrease in CBF. Similarly, when the CPP rises above the upper-limit of autoregulation, the vasoconstrictive ability of the arteriolar bed is exhausted and the cerebral vessels expand, thereby resulting in a rise in CBF. These parts of the cerebral autoregulatory curve are "pressure-passive." full color online

pathological factors on "normal" cerebral autoregulation may explain, at least in part, why a "one-size-fits-all" approach of targeting a predefined hemodynamic goal may not be feasible for brain-injured patients. Fourth, the placement of the LLA at a CPP of 50 mm Hg, as depicted in Lassen's original work in 1959,[2] and in most subsequent physiological descriptions, represents an averaged value for a heterogenous population; in fact, significant variability in the LLA exists amongst individuals.[5,10] It is now well-accepted that the assignment of the LLA at 50 mm Hg is, in most cases, a significant underestimation, and that the LLA can be "moveable," permanently shifted, and in some cases lost completely in brain-injured patients (Fig. 2). Finally, cerebral autoregulation, while prone to impairment in an injured brain region, may remain largely intact in nonimpaired areas. In this regard, "optimizing" global cerebral perfusion may in fact be harmful to injured brain regions because of heterogenous dysautoregulation in injured areas and intact autoregulation in uninjured areas.[11]

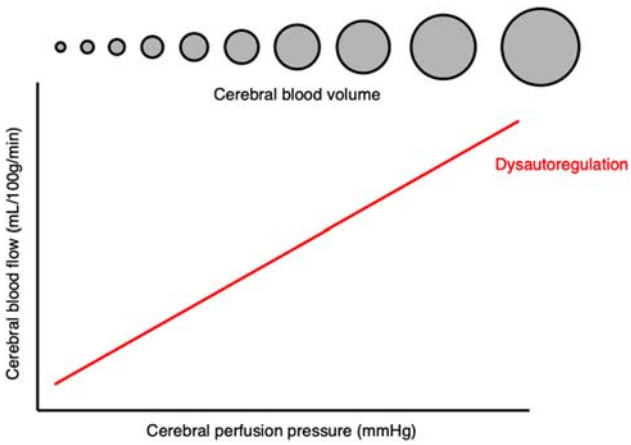

FIGURE 2. Cerebral dysautoregulation. With impaired cerebral physiology, the cerebral blood flow (CBF) becomes "pressure-passive" across a wide range of cerebral perfusion pressures (CPP). When CPP falls, the CBF subsequently falls and the brain thus becomes at risk for ischemia. When CPP rises, the CBF subsequently rises and the brain thus becomes at risk for edema, hyperemia, and/or hemorrhage. full color online

Studies have demonstrated the feasibility of determining static cerebral autoregulation (the relationship between CBF and CPP at steady-state), and dynamic cerebral autoregulation (the rate of CBF change in response to rapid fluctuations of CPP), with the use of transcranial Doppler ultrasonography.[12,13] Other neuromonitoring modalities, including near-infrared spectroscopy, have also been used for determining cerebral autoregulation noninvasively.[14] A closely related but distinct entity from cerebral autoregulation is the Pressure Reactivity Index (PRx)—a measure of cerebrovascular reactivity as determined by the continuous measurement of intracranial pressure (ICP), CPP, and mean arterial pressure (MAP) over a prespecified timeframe. A comprehensive description of these advanced neuromonitoring modalities for assessment of autoregulatory state is beyond the scope of this narrative review, and more details can be found elsewhere.[4,15] These considerations, and the subtleties in our understanding of individual cerebral autoregulatory physiology, are, in large part, the reason why it is has historically been difficult for clinicians to determine optimal hemodynamic parameters for both brain "healthy" and brain-injured patients in various clinical settings.

TBI

TBI affects ~69 million people worldwide each year, and is a disease with a wide spectrum of severities, etiologies, and outcomes.[16,17] The complex and still evolving understanding of the pathophysiology of TBI, as it progresses from primary brain injury through insult from subsequent cascades of secondary brain injury, combined with the concomitant individual intervariability in cerebral autoregulatory capacity, truly makes it difficult to establish a "one-size-fits-all" systemic blood pressure target that ensures optimal cerebral perfusion. For obvious ethical reasons, active blood pressure manipulation to identify the effects of systemic hypotension on TBI outcomes has not been studied in prospective randomized controlled trials (RCTs).[18,19] Nonetheless, observational studies over the past 30 years have consistently identified systemic hypotension as a predictor of poor outcomes in TBI patients.[19–21] In the setting of intact cerebral autoregulation, the detrimental effect of hypotension may be related to cerebral vasodilation and a

subsequent increase in ICP, while in the setting of impaired autoregulation, systemic hypotension is believed to exert its adverse effect primarily through a failure to increase CBF as it becomes pressure dependent. The sequela of both purported mechanisms of injury is decreased cerebral perfusion and, ultimately, cerebral ischemia, which certainly has a role in the secondary brain injury cascade.

On the basis of traditional definitions of hypotension and the available observational data at the time, the Brain Trauma Foundation (BTF) published its "Guidelines for the Management of Severe TBI, third edition" in 2007 with a level II recommendation to avoid systemic hypotension, as defined by systolic blood pressure (SBP) <90 mm Hg.[19] Emerging observational data have since challenged this traditional definition of hypotension.[22–26] A prespecified observational study embedded within the Excellence in Prehospital Injury Care (EPIC) TBI Study, encompassing a cohort of 3844 TBI patients with a median age of 35 years, found a decreased adjusted odds ratio (OR) for death for every 10 mm Hg increase in the lowest prehospital SBP (adjusted OR: 0.81; 95% confidence interval [CI]: 0.75-0.88; $P < 0.001$) across a SBP range of 40 to 120 mm Hg.[25] An interesting finding of the study was the linear association observed between SBP and mortality across a wide range of blood pressure, suggesting that the historical cut-off value for hypotension (SBP 90 mm Hg) may be inaccurate and, also, that there may not be a meaningful "safe" SBP threshold for TBI patients. The subsequent revised edition of the BTF guideline (2017)[18] was greatly influenced by a retrospective observational study by Berry et al[26] After stratifying 15,777 TBI patients into 3 age groups, these authors sequentially applied ten multivariate logistic regression models for the probability of death for each admission SBP between 60 and 150 mm Hg at 10 mm Hg increments, and identified the "optimal threshold of hypotension" associated with increased mortality by choosing the regression model with the best statistical fit and optimal discriminatory power. The adjusted ORs for mortality were then calculated for the defined optimal threshold of hypotension for each age group. As a result, Berry et al[26] concluded that a SBP higher than that given as the traditional definition of hypotension was required in TBI patients; the optimal threshold for hypotension was SBP 110 mm Hg for patients aged 15 to 49 years old (adjusted OR: 1.98; 95% CI: 1.65-2.39; $P < 0.0001$), SBP 100 mm Hg for patients aged 50 to 69 years old (adjusted OR: 2.20; 95% CI: 1.46-3.31; $P = 0.0002$), and SBP 110 mm Hg for patients aged 70 years and older (adjusted OR: 1.92; 95% CI: 1.35-2.74; $P = 0.0003$). Importantly, clinicians should be cognizant that the observational design of these studies allows only determination of associations, not causations. Nonetheless, in light of this new evidence, the BTF subsequently revised its target blood pressure recommendation in the fourth edition of the TBI guideline published in 2017,[18] giving a Level III recommendation to maintain SBP $\geq$100 mm Hg for patients aged 50 to 69 years and SBP $\geq$110 mm Hg for patients aged 15 to 49 years and over 70 years (Table 1).

While current guidelines emphasize the importance of avoiding systemic hypotension in TBI patients, what remains elusive is whether systemic hypertension should also be avoided. TBI patients often remain in a state of catecholamine excess following a severe injury to brain parenchyma, and the resulting hypertension (in the setting of impaired cerebral autoregulation) may lead to new or worsening intracranial hemorrhage, cerebral hyperemia, and/or cerebral edema.[27–29] Such hypertension may in fact also play a role in the secondary brain injury cascade which follows the initial cerebral insult. Observational studies have consistently demonstrated a U-shaped relationship between SBP and TBI-related mortality, with increased mortality being observed in patients with either systemic hypotension or hypertension (hypertension being defined variably as SBP >140, >150, or >160 mm Hg in most observational studies).[23,30,31] Further supporting the notion that catecholamine excess and the resultant hypertension may be harmful is a 2017 systematic review and meta-analysis of nine observational studies, encompassing 2005 TBI patients who received beta-blockers and 6240 patients who did not, that demonstrated a mortality benefit associated with beta-blocker exposure following TBI.[32] The evidence available to date, though circumstantial at best, suggests that hypertension may in fact be harmful in the setting of TBI. Certainly, the question of what the optimal upper-limit of blood pressure is, and when this target should be sought, in TBI patients warrants further study.

It is essential to be aware that SBP should not be used as the sole hemodynamic target of therapy in TBI. As stated by the BTF, "the interrelationship between SBP, MAP, and CPP should be kept in mind as one considers threshold recommendations in these guidelines."[18] Furthermore, one needs to be cognizant that our understanding of cerebral perfusion and autoregulation is based on population data and, given the variability in premorbid conditions and degree of cerebral autoregulation impairment that is present, the blood pressure threshold for optimal perfusion is expectedly different for every TBI patient. Indeed, the evidence suggests that dynamic autoregulation is often impaired in TBI patients.[33] Retrospective studies have shown that an optimal CPP can be determined by the continuous measurement of ICP, CPP and MAP and calculation of the PRx.[34,35] While ongoing research aims to determine whether this individualized, autoregulation-guided, approach to optimizing cerebral hemodynamics may improve clinical outcomes, there is currently insufficient evidence to guide clinicians on how to translate the information derived from these advanced neuromonitoring modalities of autoregulatory state directly into clinical practice.[18,36]

SPONTANEOUS ICH

Spontaneous nontraumatic ICH, with an overall incidence of 24.6 per 100,000 person-years, has been associated with significant short-term and long-term mortality worldwide.[37,38] Patients with ICH often present with systemic hypertension, a phenomenon postulated to be

TABLE 1. Guideline-based Blood Pressure Targets for Neurosurgical and Brain-injured Patients

	Guideline	Recommendation	
Traumatic brain injury	BTF 4th edition	50-69 y-old	SBP > 100 mm Hg
		15-49 y-old	SBP > 110 mm Hg
		≥ 70 y-old	
Intracerebral hemorrhage	AHA/ASA 2015	SBP <140 mm Hg	
	ESO 2014/2018	SBP 110-140 mm Hg	
		Avoid SBP reduction > 90 mm Hg from baseline	
Aneurysmal subarachnoid hemorrhage	AHA/ASA 2012	Before securing aneurysm	SBP <160 mm Hg
	NCS 2011		SBP <160 mm Hg
			MAP <110 mm Hg
	ESO 2013		SBP <180 mm Hg
			MAP > 90 mm Hg
	AHA/ASA 2012	Therapy for DCI	Induced hypertension
	NCS 2011		No BP target
Acute ischemic stroke	AHA/ASA 2018	No reperfusion strategy	BP <220/120 mm Hg
	ESO 2018	Before tPA	BP <185/110 mm Hg
		After tPA	BP <180/105 mm Hg ×24 h
	AHA/ASA 2018	EVT	Before EVT:
			BP <185/110 mm Hg
	SNACC 2014		During EVT:
			SBP 140-180 mm Hg
			DBP <105 mm Hg
	ESO 2019		During EVT:
			BP <180/105 mm Hg
			After EVT:
			BP <180/105 mm Hg ×24 h

AHA indicates American Heart Association; AIS, acute ischemic stroke; ASA, American Stroke Association; BP, blood pressure; BTF, Brain Trauma Foundation; DBP, diastolic blood pressure; DCI, delayed cerebral ischemia; ESO, European Stroke Organization; EVT, endovascular thrombectomy; MAP, mean arterial pressure; NCS, Neurocritical Care Society; SBP, systolic blood pressure; SNACC, Society for Neuroscience in Anesthesiology and Critical Care; tPA, tissue plasminogen activator.

caused either by a neuroendocrine stress response and resultant catecholamine excess consequent to the primary brain injury, as a reflexive response to an elevated ICP from the mass effect of the parenchymal hematoma, or a combination thereof.[39] This hypertension, though potentially a neuroprotective response acting to preserve CPP in the presence of a local mass effect, may in theory worsen the brain injury by both expanding the size of the hematoma and causing cerebral hyperemia and brain edema in the setting of impaired autoregulation.[7,40–43] Indeed, the literature consistently demonstrates an association between systemic hypertension and poor outcomes in patients with ICH.[44] This finding, along with the observation that an ischemic penumbra surrounding the ICH core does not exist, provided the scientific rationale behind the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial 2 (INTERACT-2).[45,46]

The INTERACT-2 study was an international, multicenter, prospective, randomized, assessor-blinded trial involving 2794 patients with spontaneous ICH.[46] Within 6-hour of ICH onset, study participants were randomized either to an intensive blood pressure reduction group (target SBP <140 mm Hg within 1 h of randomization and maintained for 7 d) or a guideline-therapy group (target of SBP <180 mm Hg and maintained for 7 d). While the primary outcome (death or major disability at 90 d) was not significantly different between the intensive blood pressure reduction group and the guideline-therapy group (52.0% vs. 55.6%, respectively; adjusted OR: 0.87; 95% CI: 0.75-1.01; $P = 0.06$), the prespecified ordinal analysis demonstrated a shift toward lower 90-day modified Rankin score (mRS) in the intensive blood pressure reduction group (pooled OR for shift to higher mRS: 0.87; 95% CI: 0.77-1.00; $P = 0.04$). In addition, patients in the intensive blood pressure reduction group reported better overall health-related quality of life at 90 days. Interestingly, there was no significant difference in hematoma size growth between the 2 groups, suggesting that a distinct mechanism unrelated to the degree of hematoma expansion may have been responsible for the improved functional outcomes in the intensive blood pressure reduction group.

In light of the findings of INTERACT-2, the American Heart Association (AHA)/American Stroke Association (ASA) revised their recommendation in the 2015 ICH guidelines, which state that acute blood pressure reduction to SBP <140 mm Hg is safe (Class I recommendation; Level of Evidence A) and is potentially effective at improving functional outcomes (Class IIa recommendation; Level of Evidence C) in ICH patients who present with SBP 150 to 220 mm Hg[47] (Table 1). Similarly, the European Stroke Organization (ESO) published recommendations in its 2014 guidelines and in a 2018 update that "intensive blood pressure reduction (systolic target <140 mm Hg in <1 h) is safe and may be superior to a systolic target <180 mm Hg" for ICH patients, and, furthermore, that blood pressure should be lowered "as soon and as fast as possible" because of the risk of hematoma expansion, while keeping SBP > 110 mm Hg and avoiding SBP reduction > 90 mm Hg from "baseline" for concerns related to acute kidney injury.[48,49] The recommendation to avoid excessive SBP reduction stemmed

from a prospective observational cohort examined by Burgess et al[50] who identified, by logistic regression analysis of 448 patients with ICH, that a SBP reduction >90 mm Hg from admission SBP was associated with increased risk of developing acute kidney injury (OR: 2.08; 95% CI: 1.19-3.62; $P=0.010$). The benefits of blood pressure control also extend beyond the acute phase of ICH, as the evidence suggests that long-term antihypertensive therapy should be used for secondary prevention of ICH.[47,51–53]

Controversy on this topic arose following the publication of the Antihypertensive Treatment of Acute Cerebral Hemorrhage II (ATACH-II) Trial in 2016.[54] ATACH-II was a multicenter RCT that compared intensive blood pressure therapy (SBP target 110 to 139 mm Hg for 24 h after randomization) with standard therapy (SBP target 140 to 179 mm Hg for 24 h after randomization) within 4.5 hour of ICH onset. The trial was halted at 1000 patients for futility, when an interim analysis revealed no significant difference in death or major disability between the intensive blood pressure therapy group and the standard therapy group (38.7% vs. 37.7%, respectively; adjusted relative risk 1.04; 95% CI: 0.85-1.27; $P=0.72$). In fact, there was evidence of harm with aggressive blood pressure reduction, which was associated with increased 7-day renal adverse events (9% vs. 4%; $P=0.002$).

Though the findings of the ATACH-II trial contradict those of the INTERACT-2 trial at first glance, the discordant results between these 2 well-conducted RCTs may be explained by differences in study design. First, the potentially therapeutic effect of acute blood pressure reduction in ATACH-II may have been diminished or eliminated by the relatively shorter duration of therapy prescribed (SBP <140 mm Hg for 24 h) as compared with INTERACT-2 (SBP <140 mm Hg for 7 d). Second, in the ATACH-II trial the mean SBP at 2 hours was 130 mm Hg in the intensive therapy group and 141 mm Hg in the standard therapy group, while in INTERACT-2 the mean SBP at 1 hour was 150 mm Hg in the intensive therapy group and 164 mm Hg in the standard therapy group. The relatively greater blood pressure reduction observed in the ATACH-II trial as compared with INTERACT-2 may account for the lack of therapeutic effect of intensive blood pressure reduction in ATACH-II, as overly aggressive blood pressure reduction following ICH may potentially be detrimental to the injured brain. In fact, a post hoc analysis of the INTERACT-2 data identified (with the use of proportional odds and logistic regression models) an increased OR for death or major disability associated with both SBP <130 mm Hg and >139 mm Hg in the 7 days following ICH, suggesting the possibility that there is a "sweet spot" for the blood pressure target in ICH patients.[55] This U-shape relationship between blood pressure and mortality was similarly reported in previous observational studies.[56]

Complicating the matter further is emerging evidence demonstrating an association between blood pressure variability following ICH and worsened clinical outcomes, suggesting that how we achieve the blood pressure target might be as equally important as the absolute blood pressure target itself.[57–59] The association of blood pressure variability with poor outcome may be related to the fact that dynamic autoregulation can be impaired in the setting of ICH. Research is ongoing to determine whether therapeutic measures aimed to improve cerebral autoregulation after ICH may in turn improve clinical outcomes.[60,61]

aSAH

With a global incidence of 7.9 per 100,000 person-years, aSAH is a devastating neurological event with a reported 90-day mortality of 30%.[62,63] Among patients with aSAH who survive to hospital admission, the risk of early rebleeding, which carries a mortality as high as 60%, has been reported to be in the range of 8% to 23%.[64] Thus, the initial goal in the management of aSAH patients, along with cerebrospinal fluid diversion to preserve cerebral perfusion in the context of hydrocephalus and management of other associated medical complications, is to prevent rebleeding through modest systemic blood pressure reduction, with the intention of protecting the weakened wall of a ruptured, unsecured aneurysm from excessive transmural pressure.[10,65]

An early retrospective studies by Wijdicks et al[66] reported that aSAH patients who received antihypertensive treatments had a lower incidence of rebleeding as compared with those who did not receive antihypertensives. Similarly, in a retrospective observational study of 273 aSAH patients, Ohkuma et al[67] compared the various admission SBPs between the rebleed and the nonrebleed cohorts, calculating ORs for rebleeding at various admission SBP cut-off points between 120 and 180 mm Hg using logistic regression analysis; SBP >160 mm Hg was identified as a potential risk factor for rebleeding (OR: 3.1; 95% CI: 1.5-6.8; $P=0.0016$) in this retrospective series. However, BP reduction is not without potential harm after aSAH. In the study by Wijdicks et al,[66] there was a higher incidence of cerebral infarction (43% vs. 22%; $P=0.03$) among those who received antihypertensives, thereby highlighting the importance of striking a balance between prevention of rebleeding and avoidance of secondary cerebral ischemia.[66]

Indeed, from a physiological standpoint, the transmural pressure (calculated as the MAP–ICP) is equivalent to the CPP, and ICP is often elevated because of the mass effect from a concomitant obstructive hydrocephalus, cerebral edema, parenchymal hematoma, or subdural hemorrhage that may occur in the context of aSAH.[10] Thus, targeting a standard or fixed SBP goal to prevent rebleeding without consideration of the contributory role of ICP to the transmural pressure and CPP may potentially place cerebral tissue, which is already subject to impaired autoregulation, at risk for secondary injury. Furthermore, since CBF is normally continuous throughout the cardiac cycle, and transmural pressure is determined by MAP and not SBP, establishing a MAP target rather than a SBP target may perhaps be more sensible in the prevention of rebleeding.[68]

In light of the available evidence and in the absence of RCTs, the 2012 AHA/ASA guideline for management of aSAH patients recommended a SBP target <160 mm Hg to prevent rebleeding (Class IIa recommendation; Level of Evidence C) while "balancing the risk of stroke, hypertension-related rebleeding, and maintenance of cerebral perfusion

pressure" (Class I recommendation; Level of Evidence B)[65] (Table 1). Likewise, the Neurocritical Care Society recommended targeting SBP <160 mm Hg and MAP <110 mm Hg in patients with unsecured ruptured aneurysms (Low Quality Evidence; Strong Recommendation) in its 2011 consensus guideline.[69] The ESO published similar recommendation in 2013, but with a less stringent SBP target of <180 mm Hg, while maintaining MAP > 90 mm Hg until the aneurysm is secured.[70]

Up to 30% of aSAH patients who survive the initial insult may suffer from delayed cerebral ischemia (DCI), a complex pathophysiological phenomenon that includes arterial and arteriole vasospasm, cortical spreading ischemia, and microcirculatory vasoconstriction and thrombosis.[71] DCI is a common late complication of aSAH (3 to 21 days postinsult) that contributes significantly to overall morbidity and mortality. While classic "triple-H" therapy (hypertension, hemodilution, and hypervolemia) has fallen out of favor in recent years, induced hypertension, a maneuver intended to improve CBF and ultimately oxygen delivery to brain regions with angiographic vasospasm and/or hypoperfusion, has remained the mainstay of treatment for DCI since its benefit was first reported > 4 decades ago.[72] This is supported by observations that aSAH patients had worse outcomes following surgical clipping when CPP fell below 70 mm Hg.[73,74] Several noncontrolled studies have also demonstrated improvement of CBF to hypoperfused brain regions and reduction in poor clinical outcomes following vasopressor-induced hypertension in aSAH patients with DCI.[75–77]

On the basis of available data, the AHA/ASA recommends the use of induced hypertension for aSAH patients with DCI, unless the blood pressure is already elevated at baseline or if cardiac status precludes such intervention (Class I; Level of Evidence B).[65] The Neurocritical Care Society similarly recommends induced hypertension as first-line therapy for DCI, while emphasizing the importance of augmenting blood pressure "in a stepwise fashion with assessment of neurologic function at each MAP level to determine if a higher blood pressure target is appropriate."[69]

The Hypertension Induction in the Management of AneurysmaL subArachnoid hemorrhage with secondary IschaemiA (HIMALAIA) trial was a prospective, multicenter, single-blinded RCT that aimed to examine the effect of induced hypertension on clinical outcomes in aSAH patients with DCI.[78] In this trial, patients within 3 hours of symptomatic onset of DCI were randomized to either a treatment group, which received vasopressors and intravenous fluid to induce hypertension until improvement of neurological deficits (with a maximum MAP of 130 mm Hg or SBP of 230 mm Hg), or a control group, which had a minimal MAP target of 80 mm Hg regardless of neurological symptoms. With the intention of recruiting 240 patients, the trial was unfortunately terminated prematurely in 2015 because of slow recruitment and an apparent lack of effect of CPP augmentation in the treatment arm.[79] On the basis of the analysis of the 41 patients recruited to the trial, there was no statistical difference in the incidence of poor neurological outcome, as defined by mRS > 3 at 3 months, between the treatment and control groups (57% vs. 40%, respectively; adjusted OR: 1.0; 95% CI: 0.6-1.8;). However, the lack of clinical effect of hypertensive therapy in this study may have been the result of limited power because of incomplete recruitment and small differences in MAP between the 2 groups during the intervention period; MAP difference was 11.1 and 5.7 mm Hg between the 2 groups at 24 and 72 hours, respectively.

Thus, at the present time, there is no evidence from controlled studies supporting the practice of induced hypertension for DCI, and likewise there is no evidence to support a specific blood pressure target or an appropriate duration of induced hypertension before de-escalation of therapy.[70] Following the premature termination of the HIMALAIA study, it was assumed that, because of clinical equipoise, similar RCTs to examine the efficacy of induced hypertension for DCI are unlikely ever to be conducted again.[80] With evidence suggesting that the dynamic autoregulatory index is often impaired in aSAH patients, and that the degree of impairment may be correlated with poor neurological outcome, further research is needed to determine whether an autoregulatory-oriented approach should be undertaken for the management of DCI.[81]

AIS

Cerebrovascular disease is estimated to be responsible for 10% of all deaths worldwide each year, and AIS accounts for roughly 87% of all strokes.[82,83] Blood pressure elevation is a common observation during the acute phase after AIS, and moderate hypertension has been hypothesized to be a protective physiological response to improve regional CBF to the ischemic penumbra that is distal to the obstructed vessel and dependent on collateral circulation for perfusion.[84] On the basis of this physiological assumption, arterial hypotension would be detrimental for AIS patients. Interestingly, however, observational studies have not consistently demonstrated an association between hypotension and poor outcomes following AIS, and no randomized studies have been conducted to examine the effects of hypotension and blood pressure manipulation on AIS outcomes because of ethical reasons.[85–87] Nonetheless, the AHA/ASA 2018 guideline for the management of AIS patients recommended correction of hypovolemia and hypotension to support organ perfusion (Class I recommendation; Level of Evidence C), though no specific blood pressure target is provided, and with the stipulation that the definition of hypotension should be individualized based on premorbid conditions.[88]

At the opposite end of the spectrum, extreme systemic hypertension (aside from concerns for multisystem end-organ damage) may lead to cerebral hyperemia and hemorrhagic transformation of infarcted brain tissue where cerebral autoregulation is impaired in the setting of AIS.[89] In particular, patients receiving recombinant tissue plasminogen activator (tPA) following AIS are at elevated risk for ICH. The landmark trial by the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group in 1995 created the precedent for all subsequent studies that examined the effect of blood pressure

manipulation in AIS patients.[90] However, randomized studies examining the effects of blood pressure reduction in AIS patients have yielded mostly either neutral or negative results. This may be partially explained by the fact that some of the studies either achieved statistically but not clinically significant differences in blood pressure between the reduced blood pressure groups and control groups, or examined a heterogeneous patient population in terms of stroke subtypes and reperfusion strategies.[91–100] The only "positive" trial in this regard was the Efficacy of Nitric Oxide, with or without continuing antihypertensive treatment, for management of high blood pressure in acute Stroke (ENOS) trial, an international, multicenter RCT that examined the effect of a glyceryl trinitrate dermal patch on neurological outcomes following AIS.[101] In the prespecified subgroup analysis of the ENOS trial (denoted as the ENOS-early study), including 273 patients who were randomized within 6 hours of stroke onset to receive either 5 mg glyceryl trinitrate patch or placebo, patients in the treatment group had improved functional outcomes as represented by a lower mRS at 90 days (adjusted OR: 0.51; CI: 0.32-0.80; $P = 0.004$). However, the interpretation of this result requires extreme caution as the findings of such subgroup analysis can be spurious owing to the small and heterogeneous study population.

On the basis of the available evidence, the AHA/ASA recommends that, while there is uncertain benefit to blood pressure reduction below 220/120 mm Hg within the first 48 to 72 hours of symptom onset, it may be reasonable to lower blood pressure by 15% during the first 24 hours after AIS if the blood pressure is greater than 220/120 mm Hg when no reperfusion strategy is planned and where there are no comorbid conditions mandating immediate antihypertensive treatment (Class IIb recommendation; Level of Evidence C).[88] The ESO similarly recommends against lowering systemic blood pressure unless it is very high (> 220/120 mm Hg) in AIS patients who are not receiving recanalization therapy.[49] The blood pressure "limit" of 220/120 mm Hg was derived from the exclusion criteria of the RCTs that examined the effects of blood pressure reduction in patients with AIS.[97,100,102,103] Thus, despite these recommendations, there is in fact no clinical evidence to support the lowering of blood pressure below 220/120 mm Hg in the absence of hypertension-related comorbid conditions. With regard to drug-induced hypertension in the setting of AIS, the AHA/ASA recommended that it should not be performed outside of a clinical trial setting (Class IIb recommendation; Level of Evidence C) because the literature has not consistently demonstrated its efficacy.[88,104] In contrast, the ESO recommendation reflects a more favorable approach to drug-induced hypertension, stating "In patients with large vessel occlusion, fluctuating symptoms, and low systolic blood pressure who are ineligible for recanalization therapy, it is reasonable to consider systolic blood pressure elevation to prevent early neurological deterioration" (Grade C).[49]

The optimal blood pressure target in AIS patients, perhaps, lies somewhere between both extremes. In the post hoc analysis of 17,398 AIS patients included in the International Stroke Trial (a multicenter RCT examining the effect of aspirin and subcutaneous heparin on AIS outcomes), a U-shape relationship between admission SBP and 14-day mortality was identified using a logistic regression model.[105] The SBP nadir with the lowest frequency of poor outcome was identified to be 150 mm Hg, and every 10 mm Hg decrease in SBP below 150 mm Hg was associated with an adjusted OR for 14-day mortality of 1.155 (95% CI: 1.095-1.216; $P < 0.0001$), while every 10 mm Hg increase in SBP above 150 mm Hg was associated with an adjusted OR for 14-day mortality of 1.048 (95% CI: 1.012-1.079; $P = 0.016$). Other observational cohorts have similarly identified a U-shape association between systemic blood pressure and poor neurological outcomes following AIS, thereby supporting the notion that either extreme of blood pressure may be detrimental.[106,107]

In the setting in which tPA administration is planned in AIS patients, the AHA/ASA recommends targeting a blood pressure <185/110 mm Hg before tPA initiation and BP <180/105 mm Hg for 24 hours after tPA administration (Class I recommendation; Level of Evidence B).[88] Similar recommendations were also made by the ESO.[49] This blood pressure target was derived from the exclusion criteria in RCTs that examined the effects of thrombolytics in AIS patients, and, while several observational studies have similarly demonstrated an association between elevated systemic blood pressure and hemorrhagic conversion and/or worsened neurological outcomes following tPA, the exact upper-limit blood pressure target remains unclear.[90,108–112]

Anderson et al[113] attempted to address this question in the Enhanced Control of Hypertension and Thrombolysis Stroke (ENCHANTED) study. The ENCHANTED trial was an international, multicenter, prospective RCT in which 2196 alteplase-eligible AIS patients within 6 hours of stroke onset were randomized to either an intensive blood pressure-lowering group (SBP 130 to 140 mm Hg within 1 h) or a guideline treatment group (SBP <180 mm Hg) for 72 hours following tPA administration.[113] While there was no statistically significant difference in the primary outcome (mRS at 90 d) between the 2 groups, there was a lower incidence of ICH in the intensive blood pressure-lowering group compared with the guideline treatment group (14.8% vs. 18.7%, respectively; OR: 0.75; 95% CI: 0.60-0.94, $P = 0.0137$). A few important caveats to this study require clinicians to interpret its results with caution. First, the difference in mean SBP at 1 hour and 24 hours between treatment and guideline groups was 6.4 and 5.3 mm Hg, respectively, begging the question of whether this clinically negligible difference in SBP was responsible for the purported positive outcome. Second, the SBP target of 130 to 140 mm Hg in the intervention arm may have been too low, potentially jeopardizing perfusion to the ischemic penumbrae where cerebral autoregulation was yet to be restored.[111] Hence, the SBP target of 130 to 140 mm Hg in the ENCHANTED trial may indeed cause harm and thereby have neutralized any potentially favorable outcome because of a reduced incidence of ICH.[114] Indeed, a retrospective analysis of 11,080 patients who received thrombolysis after AIS in the Safe Implementation of

Thrombolysis in Stroke–International Stroke Thrombolysis Register (SITS-ISTR) identified that SBP 141 to 150 mm Hg was associated with the most favorable outcome at 3 months.[111] Lastly, the study population may have presented with a heterogeneous degree of reperfusion following tPA administration, and cerebral perfusion may in fact have been compromised if blood pressure was lowered when the occluded cerebral vessel was not completely recanalized.[115,116]

In the setting in which mechanical endovascular thrombectomy (EVT) is planned, the AHA/ASA guideline recommends blood pressure <185/110 mm Hg before EVT, though no postprocedural blood pressure target is provided. In its 2014 guideline, the Society for Neuroscience in Anesthesiology and Critical Care recommended to maintain SBP 140 to 180 mm Hg and diastolic blood pressure <105 mm Hg during EVT (Class IIa recommendation; Level of Evidence B), while considering adjustment to a lower blood pressure target following successful recanalization of occluded vessels in order to minimize the risk of hyperperfusion and hemorrhagic conversion (Class IIb recommendation; Level of evidence C).[117] The ESO similarly recommended a target blood pressure <180/105 mm Hg during and for 24 hours following EVT, to avoid hypotension during EVT (but without providing a LLA blood pressure), and to take into account the degree of reperfusion achieved when choosing a postprocedural blood pressure target (ie, a lower blood pressure target if complete reperfusion is achieved).[118] The blood pressure target of <185/105 mm Hg was derived from the exclusion criteria from multiple RCTs examining the effects of EVT in AIS patients.[119–121] While there have not been any prospective trials examining periprocedural hemodynamic management of EVT, other observational studies have consistently identified the association between postprocedural hypertension and poor neurological outcome. In the retrospective analysis of 365 patients from three RCTs comparing general anesthesia with sedation for EVT, every 10-minute increase in cumulative time with MAP <70 mm Hg and MAP >90 mm Hg was associated with a shift toward higher mRS scores at 90 days, with an adjusted OR of 1.30 (95% CI: 1.03-1.65; $P = 0.03$) and an adjusted OR of 1.08 (95% CI: 1.04-1.11; $P < 0.001$), respectively.[122] In the post hoc analysis of the 500 patients included in the Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial, a U-shape association between blood pressure and neurological outcome was identified, with the nadir SBP at ~120 mm Hg.[123] Similarly, in a multicenter retrospective cohort of 1245 patients who received EVT for AIS, higher blood pressure was associated with an increased likelihood of ICH and mortality.[124]

It is likely that the optimal systemic blood pressure range in AIS patients varies on an individual basis, and that this range is furthermore very likely dependent upon and fluctuates with the time point along the course of AIS and treatment, the choice of reperfusion strategy, degree of reperfusion following tPA or mechanical EVT, and stroke subtypes and patient-specific comorbidities.[104] The varying degree of impairment in dynamic cerebral autoregulation amongst AIS patients likely plays an important role in explaining why a "one-size-fits-all" approach to optimizing cerebral perfusion is often inadequate in this setting.[125,126]

CONCLUSION

While defining an optimal systemic blood pressure target for neurosurgical and brain-injured patients remains elusive, and is complicated by both pathology and patient characteristics, it is evident that a "one-size-fits-all" approach is not advisable. Guidelines, at best, provide a general approach towards managing a patient population with regards to a specific parameter or parameters, but do not speak to the subset of patients who may benefit from physiologically directed alterations to the proposed recommendations. In regard to the patient populations discussed above, further complication is introduced by the nature of the heterogeneous pattern of brain injuries that exist and the varying degrees of cerebral autoregulatory reserve present, even within the same patient but affecting different areas of the brain. Furthermore, when considering the evidence presented above, the use of different vasoactive agents, while targeting a predefined blood pressure endpoint, may have differing effects on cerebral hemodynamics at the microcirculatory level.

In addition to the inherent variability in cerebral physiology among different patients with different intracranial pathologies, the optimal blood pressure target may change, and frequently does, within the same patient at different time points of treatment because of the ever-evolving nature of these brain injuries. Indeed, the trials mentioned above with "positive" results, such as ENOS-early, INTERACT-2, and ENCHANTED, are those that tend to institute blood pressure interventions in the acute phase of the cerebral event, while other trials with relatively delayed interventions have shown mostly "neutral" or "negative" results.[127]

Limitations to even the "high level" of evidence presented above do exist, as in the case of the TBI guidelines in which level-1 evidence supporting the guideline recommendations is lacking because it would not be ethically justifiable to conduct a randomized study that assigns patients to potentially harmful interventions (ie, blood pressure targets that deviate significantly from the accepted standards of care).[128] In relative comparisons, the evidence supporting the hemodynamic management for AIS and ICH patients is more compelling than that for TBI and aSAH patients.

It is, therefore, essential for neuroanesthesiologists and neurointensivists to appreciate the pathophysiological factors that may impact the "idealized" cerebral autoregulation curve, to understand clearly the evidence upon which various guideline recommendations for blood pressure management are based, and to individualize the "optimal" hemodynamic parameter for each neurosurgical and brain-injured patient for which they care.

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