Blood Pressure Management After Central Nervous System Injury

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Fred Rincon, Jack C. Rose, and Stephan A. Mayer

Contents

Abstract

Uncontrolled hypertension is often encountered after brain injury. The mechanisms surrounding this physiopathological response are related to autoregulatory responses aimed at preserving the cerebral blood flow in injured areas. The initial hypertensive response may precipitate further injury. Conversely, aggressive blood pressure reduction may be associated with ischemia. Despite the clear role of blood pressure as a modulator of acute brain injury, there is considerable controversy and a lack of high-quality data regarding the demographics, outcomes, and optimal management of high blood pressure in acute brain-injured patients. Recognition of the autoregulatory abnormalities seen after brain injury and careful control of blood pressure are necessary for the optimal management of these patients.

Keywords

Hypertensive emergency • Hypertension • Stroke • Cerebral edema

Introduction

Central nervous system (CNS) injury is a common precipitant of hypertensive crisis and a contributor to end-organ damage. Acute ischemic stroke (AIS), intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), traumatic brain injury (TBI), and several other CNS insults can precipitate a "pressor" response that may lead to aggravation of primary brain injury. Extremes of blood pressure, both high and low, are associated with higher morbidity and mortality in all subtypes of hemorrhagic and ischemic strokes [1–5], TBI [6], and other CNS insults such as cardiac arrest [7].

Because extreme levels of blood pressure may be detrimental to these patients, optimal practice involves admission to an intensive care unit (ICU) or at least to an intermediate level of care (IMC) where narrow targets of blood pressure can be maintained using intermittent or

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continuous intravenous antihypertensive or vasoactive medications. However, there are no studies that have evaluated the effects on short- or long-term outcomes from this aggressive approach, particularly in hypertensive crisis.

Despite the clear role of blood pressure as a modulator of acute brain injury, there is considerable controversy and a lack of high-quality data regarding the demographics, outcomes, and optimal management of high blood pressure in acute brain-injured patients. Recent data from small epidemiological studies and the results of phase II clinical trials have helped us to understand the implication of the problem, implications of medical therapies, and the implementation of alternatives for the management of hypertension during neurological emergencies.

Epidemiology of Hypertensive Crisis

The majority of prehospital emergency medical services (EMS) are not permitted to deliver intravenous antihypertensive medications, and not all agencies that use intravenous medications use the same one for a similar indication. In some areas of the USA, advanced level EMS personnel are permitted to give intravenous antihypertensives under strict medical control orders. Most EMS systems are instructed to maintain infusions during transfers, but infusions must be initiated by a physician at the referring institution prior to transport and maintained under direct or telecommunicated physician supervision. In this environment, acute severe hypertension is seen frequently in the emergency department (ED) particularly in the context of life-threatening neurological conditions.

The incidence of hypertensive emergency is disproportionately higher in the elderly, male, and African American populations [8], and approximately 1–2 % of all patients with hypertension are estimated to have hypertensive emergencies [9, 10]. One study of ED admissions found that hypertensive crises accounted for 28 % of all medical emergencies and urgencies, with 77 % having history of chronic hypertension [11].

In the Study of Treatment of Acute Hypertension (STAT) [12], nearly 30 % of 1,566 patients presenting to an ED with acute hypertension had a CNS insult. The most common diagnoses were SAH (38 %), ICH (31 %), and AIS (18 %), followed by TBI (8 %), hypertensive encephalopathy (4 %), and status epilepticus (1 %). The mortality rate of patients with CNS insults was four times as higher than hypertensive patients with no CNS involvement (24 % vs. 6 %, $p<0.0001$). Among hypertensive neurological patients, median initial blood pressure was 183/95 mmHg and did not differ between survivors and non-survivors. There was also no difference in maximal levels of systolic or diastolic blood pressure. However, non-survivors had significantly *lower* minimum systolic and diastolic blood pressures during the course of treatment (103/45 vs. 118/55 mmHg, $p<0.0001$), with the highest risk of hypotension within the first 6 h of admission (Fig. 12.1). The most commonly used first antihypertensive was labetalol (48 %), followed by nicardipine (15 %), hydralazine (15 %), and sodium nitroprusside (13 %) (Table 12.1). Mortality was also associated with an increased risk of neurological deterioration (32 % vs. 10 %, $p<0.0001$).

The STAT registry suggests that blood pressure overtreatment may be a significant contributor to poor outcome in patients with stroke and other forms of severe brain injury. This may be due to secondary ischemic injury in the setting of impaired cerebral autoregulation. Strategies aimed at emphasizing rapid and precise blood pressure control while avoiding overtreatment are needed [12].

Physiology and Pathophysiology

Neural Mechanisms of Blood Pressure Control

The brain plays an important role in setting and modulating blood pressure. Results of experiments have demonstrated the importance of the baroreceptor reflex, brainstem pressor and depressor centers, and the interaction between bulbospinal pressor and medullary depressor pathways [13]. Activation or dysfunction of these structures during acute neurological disease is thought to be triggered by direct injury or by neurohumoral stimulation as a protective response against further cellular damage [14]. The peripheral mechanisms of blood pressure dynamics are better understood (Fig. 12.2). Blood pressure is equal to the product of cardiac output (CO itself is a product of stroke volume times heart rate) and the systemic vascular resistance (SVR, $BP = CO \times SVR$). Most significant blood pressure derangements in the setting of neurological injury reflect changes in SVR, with circulating and local factors acting on endothelium and vascular smooth muscle [14]. Triggers of acute changes in peripheral vasomotor tone include excess catecholamines, angiotensin II, vasopressin-ADH, aldosterone, thromboxane, endothelin, prostaglandins, and nitric oxide [15]. Vascular smooth muscle contraction is calcium dependent, involving L-type calcium channel opening and intracellular storage release.

Autoregulation

Cerebral perfusion pressure (CPP) is calculated from the mean arterial pressure (MAP) minus the intracranial pressure (ICP). In healthy individuals ICP is approximately 5 mmHg; CPP is therefore effectively equal to MAP. Cerebrovascular autoregulation refers to the brain's ability to

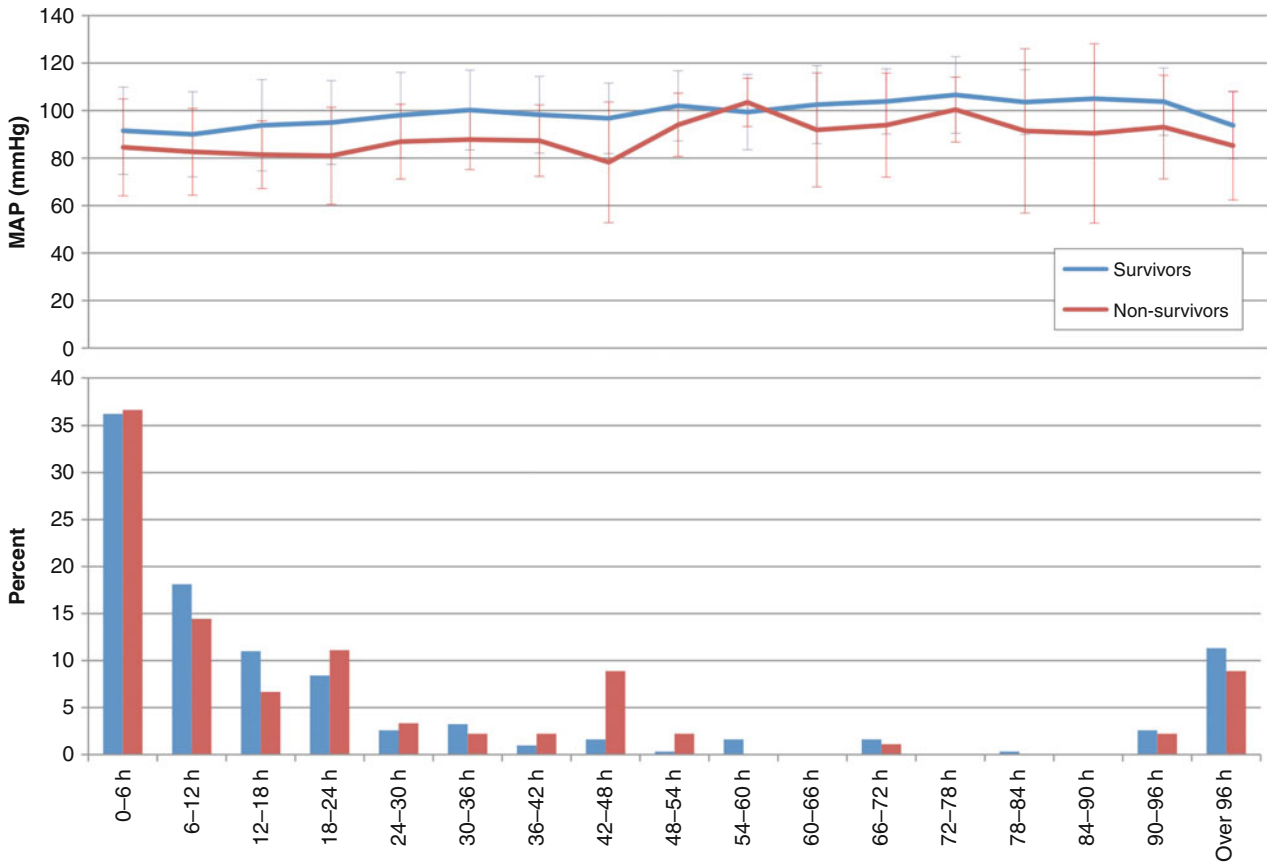

Fig. 12.1 Level and timing of lowest-recorded mean arterial blood pressure (*MAP*) in neurological patients with hypertensive crisis. Regardless of mortality status, lowest-recorded blood pressure occurred most frequently within 6 h of admission. "Percent" in *bottom* panel refers to timing of lowest-recorded BP among dead and alive patients (Reprinted with permission from Mayer et al. [12])

maintain a constant CBF despite large changes in CPP (see the extended plateau segment of Fig. 12.3) [14]. This typically holds for CPP levels between 50 and 150 mmHg [16] and is accomplished by neuro-myogenic modification of the diameter of precapillary arterioles—the key determinant of cerebral vascular resistance. Beyond the upper and lower limits of autoregulation, CBF passively follows changes in CPP in a linear fashion; these limits are shifted to the right in patients with chronic hypertension (Fig. 12.3) [16]. Acute neurological diseases such as ischemic stroke, severe TBI, and SAH associated with vasospasm can impair cerebrovascular autoregulation in zones of injury so that CBF becomes entirely pressure passive (Fig. 12.3).

Stage 1 cerebral hemodynamic failure refers to situations in which autoregulation and collateral recruitment adequately maintain CBF [14]. Normal CBF averages 50 ml/100 g/min; the human ischemic threshold is approximately 20 ml/100 g/min but varies with the degree of coexisting pathology and the location and duration of ischemia [17]. PET studies have shown that coupling of CBF to cerebral metabolic activity can be altered in cases of moderate ischemia so that metabolism is maintained by increasing the fraction of oxygen extracted (OEF) from the blood [17]. This process is called Stage 2 cerebral hemodynamic failure [14]. When both stages are exhausted, frank cerebral energy failure and cellular death ensue (Fig. 12.3).

CPP and ICP

When intracranial compliance is reduced as a result of an intracranial mass lesion or brain edema, autoregulation-triggered vasodilation increases cerebral blood volume (CBV) and can therefore raise ICP. Patients with increased ICP are especially vulnerable to decreases in MAP since CPP (by definition) is reduced when ICP is high, and vasodilatory compensation only aggravates the situation. Failure of autoregulation at the extremes of CPP and the relationship between ICP and CBF are shown in Fig. 12.3. Beyond the lower limit of autoregulation, passive vessel collapse occurs and ischemic damage predominates; above the upper limit, autoregulatory breakthrough leads to increased intravascular pressure and volume, hyperperfusion injury, and vasogenic edema [14].

Table 12.1 Parenteral vasoactive agents in neurological emergencies: preferred antihypertensives and vasopressors

Drug	Mechanism	Dose	Onset	Duration	Common adverse effects	Cautions
Antihypertensives						
Labetalol	α1, β1, β2 antagonist	20–80 mg bolus every 10 min, up to max 300 mg; 0.5–2 mg/min infusion	5–10 min	3–6 h	Bradycardia (heart block), dizziness, nausea, vomiting, scalp tingling, bronchospasm, orthostatic hypotension, orthostatic hypotension, hepatic injury	Asthma, COPD, LV failure, second or third degree AV block
Esmolol COPD	β1 antagonist	500 μg/kg bolus, 50–300 μg/kg/min infusion	1–2 min	10–30 min	Bradycardia (heart block), hypotension, nausea, bronchospasm	Asthma, LV failure, second or third degree AV block
Nicardipine	L-type CCB (dihydropyridine)	5–15 mg/h infusion	5–10 min	30 min–4 h	Reflex tachycardia, headache, nausea, flushing, local phlebitis	LV failure, severe AS, cardiac ischemia
Enalaprilat	ACE inhibitor	0.625 mg bolus, then 1.25–5 mg every 6 h	15–30 min	6–12 h	Variable response, precipitous fall in BP in high-renin states, headache, cough	Acute MI, h/o hypersensitivity
Fenoldopam	DA-1 agonist	0.1–0.3 μg/kg/min infusion	5–15 min	30 min–4 h	Tachycardia, headache, nausea, dizziness, flushing	Glaucoma, liver disease (cirrhosis with portal HTN)
Clevidipine	L-type CCB (dihydropyridine)	1–2 mg/h infusion	2–4 min	5–15 min	Headache, nausea, vomit	Soybean allergy
Nitroprusside[a]	Nitrovasodilator (arterial and venous)	0.25–10 μg/kg/min infusion	Immediate	1–4 min	Nausea, vomiting, muscle twitching, sweating, thiocyanate and cyanide intoxication	Coronary artery disease, elevated ICP
Vasopressors and inotropes						
Phenylephrine	α1 agonist	40–180 μg/min	Immediate	20–40 min	Headache, myocardial ischemia, tachycardia, nausea, dyspnea	Tachyarrhythmias, CAD, thyroid disease
Dopamine	DA-1 agonist α1, DA-1 agonist α1, β1, DA-1 agonist	1–2.5 μg/kg/min 2.5–10 μg/kg/min >10 μg/kg/min	1–2 min	<10 min	Headache, tachycardia, nausea, chest pain, dyspnea, ischemic limb necrosis	Tachyarrhythmias, CAD, sulfa hypersensitivity
Norepinephrine	α1, β1 agonist	2–40 μg/min	Immediate	<10 min	Tachycardia, infusion site necrosis, limb ischemia	Myocardial ischemia, sulfa hypersensitivity
Epinephrine	α1, β1 agonist	2–0 μg/min	Immediate	<10 min	Tachycardia, infusion site necrosis, limb ischemia	Myocardial ischemia, sulfa hypersensitivity
Dobutamine[b]	β1, β2 agonist	2–20 μg/kg/min	1–2 min	10–15 min	Headache, tachycardia, nausea, dyspnea, cardiac ectopy	Tachyarrhythmias, myocardial ischemia, severe hypotension, obstructive HCM
Vasopressin	V1a, V2 agonist	0.01–0.03 units/min	Immediate	10–15 min	Rebound hypotension	Ischemic skin intestinal ischemia Decreased cardiac output and hepato-splanchnic flow

Adapted with kind permission of Springer Science + Business Media from Rose and Mayer [14]

Abbreviations: *COPD* chronic obstructive pulmonary disease, *LV* left ventricle, *AV* atrioventricular, *CCB* calcium channel blocker, *ACE* angiotensin-converting enzyme, *MI* myocardial infarction, *CAD* coronary artery disease, *PVC* premature ventricular contraction, *HCM* hypertrophic cardiomyopathy

[a]Nitroprusside is becoming less favored for use in neurological emergencies (see text)

[b]Dobutamine primarily augments cardiac output and has a minimal pressor effect

Blood Pressure Management in Specific Neurological Emergencies

Severe hypertension without acute end-organ damage is referred to as a hypertensive urgency. These patients may be treated with an oral antihypertensive within 24 h to several days in a closely monitored inpatient or outpatient setting [18]. Hypertensive emergencies refer to conditions in which BP elevation occurs in the setting of acute end-organ damage involving the brain, heart, kidneys, or retina. In the case of neurological hypertensive emergencies, brain injury can both cause and result from blood pressure elevation. Hypertensive emergencies require intensive blood pressure control with intravenous antihypertensive agents, usually within 1 h of occurrence [19].

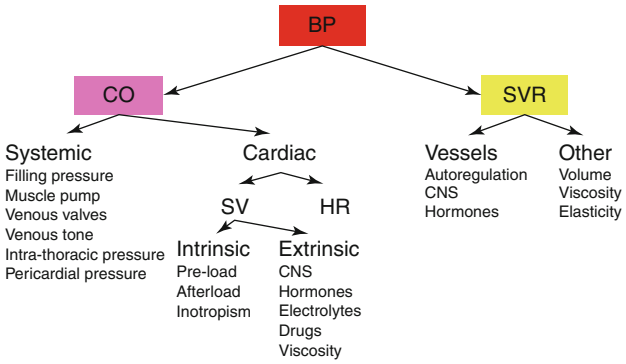

Fig. 12.2 Determinants of blood pressure (*BP* blood pressure, *CO* cardiac output, *SVR* systemic vascular resistances, *SV* stroke volume, *HR* heart rate, *CNS* central nervous system)

Choice of Agent

Intravenous antihypertensive agents available for the management of hypertensive crises fall into the broad categories of arterial vasodilators (hydralazine, fenoldopam, nicardipine, and enalaprilat), venous vasodilators (nitroglycerin), mixed venous and arterial vasodilators (sodium nitroprusside), negative inotropic/chronotropic agents with (labetalol) or without vasodilator properties (esmolol), and α-adrenergic receptor blockers for increased sympathetic activity (phentolamine) [20]. Intermittent intravenous labetalol is most often selected as the initial intravenous antihypertensive for stroke patients with acute severe hypertension (50 %), followed by nicardipine (15 %), hydralazine (15 %), and sodium nitroprusside (13 %) [12]. Nicardipine is more often administered initially for patients with acute hemorrhagic stroke than for patients with AIS [20]. Clevidipine, an ultrashort-acting dihydropyridine L-type calcium channel blocker with rapid onset and offset of action, has also recently been approved for the reduction of blood pressure [21]. Comparative studies have demonstrated that clevidipine is as safe and effective as nitroglycerin, sodium nitroprusside, or nicardipine for reducing blood pressure but has greater ability to maintain a given target range [22–24] (Table 12.1).

Intracerebral Hemorrhage

Blood pressure is frequently elevated in patients with acute ICH, and these elevations are often the highest encountered in the practice of medicine [25]. Causes of this extreme vasopressor response include upregulation of the sympathetic

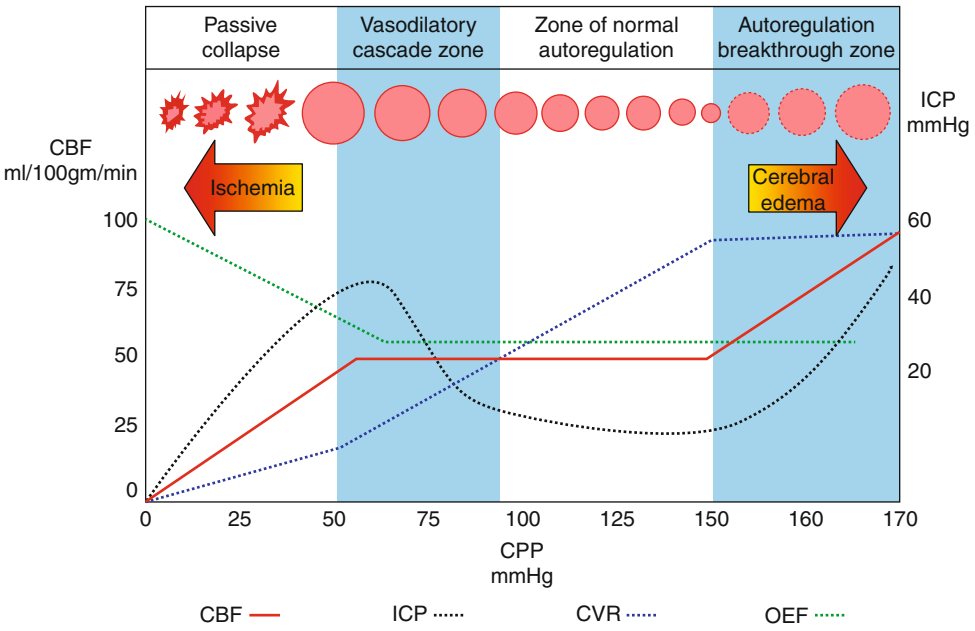

Fig. 12.3 Cerebrovascular autoregulation and its failure, relationships between cerebral blood flow (*CBF*), cerebral vascular resistances (*CVR*), and oxygen extraction fraction (*OEF*) across different levels of cerebral perfusion pressure (*CPP*). The curve depicting intracranial pressure (*ICP*) applies only to pathological conditions of reduced intracranial compliance (Adapted with kind permission of Springer Science+Business Media from Rose and Mayer [14])

nervous system, renin-angiotensin axis, and pituitary-adrenal axis [14]. The presence or degree of acute hypertension may affect the outcome after ICH. Single-center studies and a systematic review have reported an increased risk of deterioration, death, or dependency with extremely high or low admission blood pressure after ICH [3–5, 26–28]. In the majority of cases, elevated admission blood pressure is the primary issue in acute ICH.

Uncontrolled hypertension could theoretically contribute to acute expansion of the hematoma within the first 3–4 h of onset and later aggravate peri-hematoma edema and ICP, both of which may translate into adverse outcomes after ICH. Hematoma size is an important determinant of mortality after ICH, and early hematoma growth (Fig. 12.4) has been consistently associated with poor clinical outcomes [29–33]. An expanding hematoma may result from persistent bleeding and or rebleeding from a single arteriolar rupture. Some studies have reported evidence of hematoma growth from bleeding into an ischemic penumbra zone surrounding the hematoma [34, 35], but other reports have not confirmed the existence of ischemia at the hypoperfused area in the periphery of the hematoma. In a classic study by Brott and colleagues [29], no association was demonstrated between hematoma growth and levels of blood pressure, but the use of antihypertensive agents may have negatively confounded this association. Similarly, initial blood pressure levels were not associated with hematoma growth in the Recombinant Activated Factor VII ICH Trial [36].

Despite the conflicting evidence, it is generally agreed that extreme hypertension after ICH should be carefully treated. Controversy exists regarding the optimal threshold for treatment and target level, however. Overly aggressive blood pressure reduction in setting of impaired autoregulation might predispose to ischemia in peri-hematoma brain tissue, whereas intact autoregulation might result in reflex vasodilation and increases in ICP. In a pilot trial of blood pressure reduction after ICH, 14 patients with supratentorial ICH were randomized to receive either labetalol or nicardipine within 22 h after ictus to lower the MAP by 15 %. Cerebral blood flow (CBF) studies were performed before and after treatment with positron emission tomography and [15O] water. No changes in global or peri-hematoma CBF were observed [37]. Two early studies demonstrated that a controlled, pharmacologically based reduction in blood pressure had no adverse effects on cerebral blood flow in humans or animals [38, 39].

The results of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT) were published in 2008 [40]. This study was an open-label trial of 403 patients randomized to a target systolic blood pressure of <180 or <140 mmHg within 6 h of onset. The study showed a trend toward lower relative and absolute growth in hematoma from baseline to 24 h in the intensive treatment group compared with the control group. In addition, there was no excess of neurological deterioration or other adverse events related to intensive blood pressure lowering, nor were there any differences across several measures of clinical outcome, including disability and quality of life between groups, although the trial was not powered to detect such outcomes. INTERACT provides important preliminary data that early and intensive blood pressure reduction can reduce ongoing bleeding in acute ICH; the data are insufficient to recommend a definitive policy.

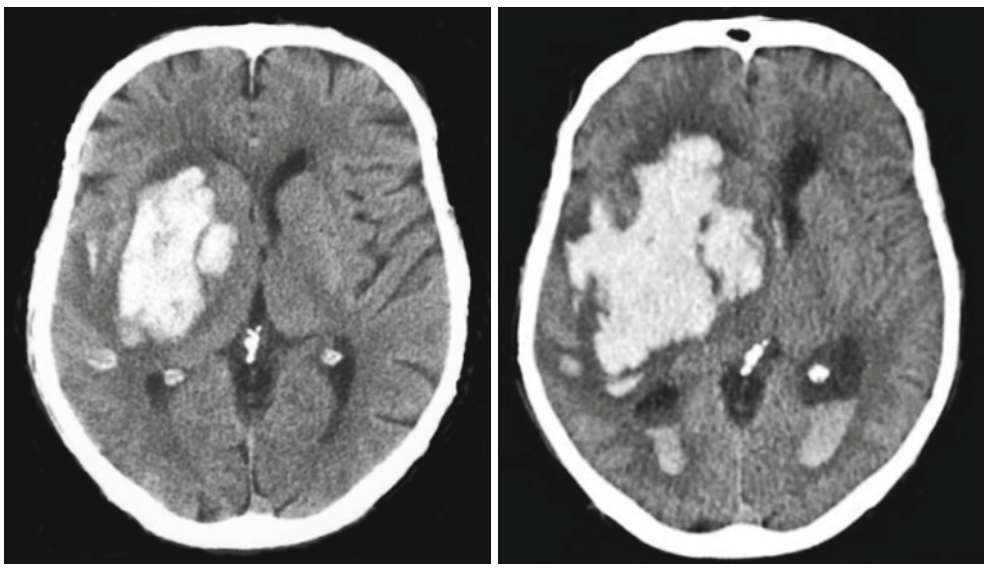

Fig. 12.4 Hematoma growth (Reprinted with permission from Mayer et al. [90])

The Antihypertensive Treatment in Acute Cerebral Hemorrhage (ATACH) trial [41, 42] also confirmed the feasibility and safety of early rapid blood pressure reduction in ICH. This study employed a dose escalation scheme using intravenous nicardipine for blood pressure reduction in 80 patients with ICH, with an eventual systolic target of <140 mmHg. No effect was seen on outcome or neurological worsening. Both INTERACT and ATACH have shown that while early and intensive blood pressure lowering is clinically feasible, whether such treatment improves clinical outcomes remains unclear.

Current ICH guidelines from the American Heart Association indicate systolic blood pressure should be maintained below 180 mmHg and mean arterial pressure below 130 mmHg with *continuous* infusion agent (Table 12.1) during the acute phase of ICH [43]. In addition, in patients who have larger hemorrhages (generally >30 ml) who are at risk for intracranial hypertension, ICP monitoring should be considered to ensure that CPP is maintained above 60 mmHg. A more recent study of 18 comatose ICH patients using brain multimodality monitoring showed that CPP levels >80 mmHg were associated with a reduced risk of critical brain tissue hypoxia, which in turn was associated with increased mortality [44]. Preferred agents are beta-blockers and calcium channel blockers (Table 12.1). The use of nitroprusside has drawbacks since this agent is associated with higher rate of medical complications [45] and may exacerbate cerebral edema and intracranial pressure [46]. Oral and sublingual agents are not preferred, because of the need for immediate and precise blood pressure control. Though no prospective study has addressed the timing of conversion from IV to oral antihypertensive management, this process can generally be started between 24 and 72 h, as long as the patient's critical condition has been stabilized [47].

Acute Ischemic Stroke

Much controversy exists regarding the management of blood pressure during the acute and subacute phases of ischemic stroke [48]. Current American Stroke Association (ASA) guidelines [49] recommend withholding antihypertensive therapy for AIS unless there is planned thrombolysis and evidence of concomitant non-cerebral hypertensive organ damage (e.g., acute myocardial ischemia, aortic dissection, pulmonary edema, or renal failure) or if the blood pressure is excessively high—arbitrarily chosen to be SBP >220 or DBP >120 mmHg based on the upper limit of normal cerebral autoregulation [49] (Table 12.2).

Some facts regarding blood pressure and AIS are undisputed. The vast majority (usually estimated at 80 %) of patients with cerebral ischemia present with acutely elevated blood pressure regardless of etiologic subtype or preexisting hypertension, and this dramatic blood pressure elevation spontaneously attenuates over time, starting within the first 24 h and continuing to decline steadily for the next 7–10 days [50, 51]. An ischemic penumbra exists for up to 3–6 h after the onset of ischemia and plays an important role in modifiable tissue injury [16]. Cerebral ischemia impairs autoregulation and probably leads to focal pressure-passive CBF [16, 52], which in turn may be aggravated by significant pharmacological lowering of the blood pressure [53]. Case reports and small series have shown short-term clinical improvement from pharmacological blood pressure *elevation* among certain AIS patients [54], but this intervention is not supported by improvements in long-term clinical outcomes and may be associated with more cardiac and pulmonary dysfunction at expense of temporal neurological improvement [49].

It remains unclear whether acute hypertension is causally associated with increased stroke morbidity and mortality. Retrospective studies have reported conflicting data: some reports have found an association between elevated admission blood pressure and both poor outcome [55, 56] and good outcome [57]. More recent studies have reported a U-shaped relationship where poor outcome was associated with especially low or high admission blood pressure [2, 53]. Some studies have found that a spontaneous decline in blood pressure within the first 4–48 h after stroke is associated with improved outcome [58], whereas others have found a higher risk of poor outcome with early and steep reductions in blood pressure [59]. These contradictions may be explained in part by active blood pressure lowering with antihypertensive medication, which was not carefully controlled for in these observational studies [48].

Subarachnoid Hemorrhage

Prevention of Rebleeding

Aneurysmal SAH carries a high rate of mortality and morbidity, much of which is related to the direct effects of hemorrhage and aneurysm rebleeding. Left untreated, the cumulative risk of rebleeding is 20 % at 2 weeks and 30 % at 1 month after initial rupture. However, there is little evidence that uncontrolled hypertension definitively increases the risk of rebleeding [60]. Nonetheless, most centers actively control elevated blood pressure to a SBP of ≤160 mmHg or lower prior to open surgical or endovascular treatment of the ruptured aneurysm. One recent study reported a positive linear correlation between very early rebleeding and increasing SBP ≥160 mmHg [61], but one could find fault with their criteria for rebleeding. A more recent study of 574 SAH patients found that admission Hunt and Hess grade and large aneurysm size, but not admission blood pressure, were independent risk factors for rebleeding, which occurred in nearly 7 % of

Table 12.2 Summary of BP management in selected neurological emergencies

Condition	Target (mmHg)	Recommended medications	Level of evidence[a]
Acute ischemic stroke			
Outside t-PA window			
Most cases[b]	BP ≤ 220/120	Labetalol, esmolol, or nicardipine IV	II
		Candesartan PO	I
Fluctuating deficit or large DWI-PWI mismatch	Consider induced hypertensionup to 20–25 % baseline MAP elevation	Phenylephrine, Levophed, or dopamine IV, follow with midodrine or fludrocortisone PO	III
IV thrombolysis	BP ≤185/110 before and ≤180/105 after t-PA	Labetalol, esmolol, or nicardipine IV	II
Intracerebral hemorrhage			
Acute phase	MAP ≤ 130	Labetalol, esmolol, or nicardipine IV	III
Post-craniotomy	MAP ≤ 100	Labetalol, esmolol, or nicardipine IV	III
Comatose with ICP monitor	CPP > 80	Labetalol, esmolol, or nicardipine IV	III
Subarachnoid hemorrhage			
All cases for 21 days	Avoid SBP ≤100	Nimodipine 60 mg PO every 4 h	I
Pre-repair	SBP ≤ 160	Labetalol, esmolol, or nicardipine IV	III
Symptomatic vasospasm	Raise SBP to maximum 200–220	Phenylephrine, dopamine, or norepinephrine IV	II
Poor grade with ICP monitor	CPP > 70	Phenylephrine, dopamine, or norepinephrine IV	III
Severe traumatic brain injury			
Acute phase (pre-ICP monitor)	SBP ≥ 90	Phenylephrine, dopamine, or norepinephrine IV	II
ICU phase (post-ICP monitor)	CPP 50–70	Phenylephrine, dopamine, or norepinephrine IV	I
Traumatic spinal cord injury			
For the first 7 days	SBP ≥ 90	Phenylephrine, dopamine, or norepinephrine IV	II
Spinal cord infarction			
Within several hours of onset	MAP ≥95 and lumbar drain to maintain CSF pressure ≤10 cm	Phenylephrine, dopamine, or norepinephrine IV	III
Hypertensive encephalopathy			
Within 1 h	Lower MAP by 20–25 % or DBP to ≤110 (whichever is higher)	Labetalol, esmolol, or nicardipine IV	II
Eclampsia			
All cases	Maintain MAP 105–125	$MgSO_4$ 2 g/h IV	I
		Labetalol, esmolol, or nicardipine IV	III

Adapted with kind permission of Springer Science + Business Media from Rose and Mayer [14]
Abbreviations: *t-PA* tissue plasminogen activator, *DWI* diffusion weighted imaging, *PWI* perfusion weighted imaging
[a]*Class I* based on one or more high-quality randomized controlled trials, *Class II* based on two or more high-quality prospective or retrospective cohort studies, *Class III* case reports and series, expert opinion
[b]Requires absence of acute hypertensive non-cerebral organ injury

patients [62]. Extremes of blood pressure on admission (MAP >130 or <70 mmHg) have also been associated with poor outcome after SAH [63].

The specific blood pressure target and agents used to treat acute hypertension in acute SAH vary between centers and clinicians. Some experts advocate not treating unless the MAP is greater than 140 mmHg, whereas others aggressively maintain SBP less than or equal to 120 or 160 mmHg [64]. Current AHA management guidelines reflect the uncertainty that comes from the lack of definitive data, noting that while antihypertensive therapy alone is not recommended to prevent rebleeding, it is frequently used in combination with monitored bed rest [60]. If elevated blood pressure is treated, an arterial catheter is generally indicated, and a short-acting parenteral agent that has minimal adverse cardiovascular and ICP effects is desirable; labetalol, esmolol, and nicardipine best meet these criteria (Table 12.1).

Poor-Grade SAH

In poor-grade SAH patients (Hunt-Hess grade 4 or 5), as in severe TBI, the overriding concern is the maintenance of adequate CPP in the face of ICP elevation [64, 65]. Aggressive volume resuscitation with isotonic crystalloid is also indicated to minimize hypovolemia from excessive natriuresis. Pain and agitation may also contribute to arterial hypertension, which may respond to analgesics and sedation with agents such as propofol, fentanyl, and dexmedetomidine. Nimodipine (60 mg PO every 6 h) can significantly lower blood pressure, leading some clinicians to give reduced doses on a sliding scale based on systolic blood pressure; we

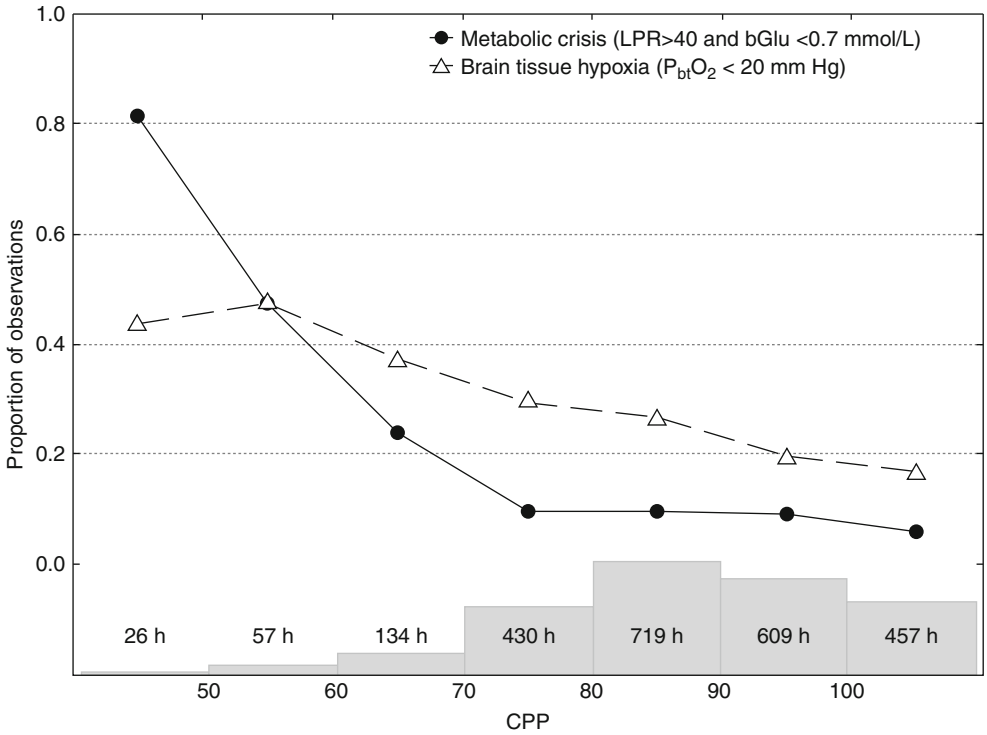

Fig. 12.5 Risk of brain tissue hypoxia and metabolic crisis, reflecting energy failure and secondary ischemia, as a function of cerebral perfusion pressure (*CPP*) level in 30 poor-grade SAH patients. *LPR* lactate/pyruvate ratio, *bGlu* brain glucose concentration (Reprinted with permission from Schmidt et al. [66])

give 30 mg PO for SBP 120–140 mmHg and hold nimodipine for SBP <120 mmHg [64] (Table 12.2).

In poor-grade patients (Hunt-Hess 4 and 5), aggressive blood pressure reduction must be weighed against the risk of cerebral ischemia or reflex vasodilation and ICP elevation. A recent study in a cohort of poor-grade SAH patients studied with brain multimodality monitoring after aneurysm repair found that CPP >70 mmHg was associated with a lower risk of brain tissue hypoxia and oxidative metabolic crisis (Fig. 12.5) [66]. This study suggests that a CPP of 70 mmHg may be the low "safe threshold" for these patients and demonstrates the feasibility of using multimodality monitoring to optimize CPP targets in individual patients.

Hypertensive Normovolemic Therapy

Delayed cerebral ischemia (DCI) from vasospasm occurs in 20–30 % of SAH patients and causes significant morbidity and mortality. Untreated, nearly half of all poor outcomes are attributed to this complication [67, 68]. Historically, most institutions started rescue therapy for symptomatic vasospasm with "triple-H" therapy: hypervolemia, hypertension, and hemodilution achieved by aggressive colloid and crystalloid infusion (target central venous pressure ≥8 or pulmonary diastolic pressure >14 mmHg) and vasopressor administration (Tables 12.1 and 12.3). Triple-H therapy was recommended based on uncontrolled case series demonstrating deficit resolution and improved outcomes; controlled trials demonstrating unequivocal safety and efficacy have not been reported [64]. Most intensivists elevate blood pressure until resolution of the neurological deficit, up to a maximal SBP of 200–220 mmHg. Prophylactic use of triple-H therapy following aneurysm treatment has not been shown to reduce the frequency DCI [69]. Inducing hypertension can be challenging, especially in patients with cardiac and renal dysfunction. Congestive heart failure and myocardial ischemia are the most common complications; aneurysm rebleeding was rare with triple-H therapy after surgical or endovascular aneurysm repair [69]. Hypertensive normovolemic therapy should be performed in an ICU with capabilities for arterial blood pressure and central venous or pulmonary artery catheter measurements and frequent chest x-ray, fluid balance, electrolyte, electrocardiogram, and cardiac enzyme assessments. Phenylephrine is used most often as a first-line agent because tachycardia often complicates the use of dopamine or norepinephrine. The inotropes dobutamine or milrinone can then be added to maintain for cardiac index augmentation (optimally >4.0 L/min/m^2) in the face of medically refractory spasm [69] or when left ventricular performance is reduced [70]. Recent published guidelines from the Neurocritical Care Society warn against the induction of hypervolemia based on higher risk of pulmonary complications [71].

Table 12.3 Hemodynamic effects of vasopressors on cerebral circulation

Drug	CBF	ICP	$CMRO_2$	$PbtO_2$
Phenylephrine	⇑	⇑	⇔	⇔
Norepinephrine	⇑	⇔	⇔	⇑
Epinephrine	⇑	N/A	⇑	N/A
Dopamine	⇑	⇔	⇔	⇔
Vasopressin	⇑	N/A	⇔	⇑

Adapted with kind permission of Springer Science + Business Media from Muzevich and Voils [91]
CBF cerebral blood flow, *ICP* intracranial pressure, *$CMRO_2$* cerebral metabolic rate of oxygen, *$PbtO_2$* brain tissue oxygen tension

Traumatic Brain and Spinal Cord Injury

Hypertension is much less common than hypotension in trauma patients for a variety of reasons including exsanguination, vasodilation due to neurogenic mechanisms or the systemic inflammatory response syndrome, pneumothorax, and neurogenic stunned myocardium. In the Study of Treatment of Acute Hypertension (STAT) [12], only 8 % of 432 neurological patients presenting to an emergency department (ED) with acute hypertension had TBI. Conversely, acute hypotension (SBP < 90 mmHg) is an important factor associated with poor outcome in TBI [6, 65]. Multiple clinical studies of severe TBI have reported improved outcome versus historical controls with intensive resuscitation protocols focusing on including blood pressure or CPP support [65]. The goal of fluid resuscitation in the prehospital and hospital setting is to optimize cardiac output, cerebral blood flow, and brain tissue perfusion to prevent secondary ischemic brain injury. A landmark study by Cooper and colleagues [6] demonstrated that a regimen of hypertonic saline was not superior to conventional crystalloid therapy for resuscitation after in hypotensive TBI patients with Glasgow Coma Scale scores of 3–8.

The pathophysiology of traumatic CNS injury is thought to involve both primary and secondary insults: primary injury such as diffuse axonal damage is sustained immediately, whereas secondary injury begins shortly after the traumatic event and involves complex cellular and molecular processes. Ischemia has traditionally been considered a major component of the secondary injury process. This premise has led investigators to focus on CPP and ICP optimization after severe TBI to avoid or prevent irreversible ischemic CNS damage. Both regional and global hemispheric CBF reductions occur immediately after TBI [72, 73]. More recent studies suggest that concomitant early metabolic suppression (perhaps related to mitochondrial dysfunction) may mitigate the development of ischemia at low CBF levels [74]. The extent to which TBI impairs cerebrovascular autoregulation is another important area of uncertainty. Current opinion favors a spectrum of autoregulatory dysfunction—ranging from no clinical dysfunction in some patients to significant pressure passivity and/or rightward shifting of the curve in others. A triphasic hemodynamic response to severe TBI has been described, with an initial period of hypoperfusion on day 0, followed by hyperemia on days 1–3 and relative vasospasm from days 4–15 [75].

CPP Monitoring and Therapy

The traditional management approach to severe TBI has focused on treating reducing ICP and brain edema, as significant ICP elevations have been strongly associated with increased morbidity and mortality. Measures such as aggressive hyperventilation and osmodiuresis to maintain ICP below 20 mmHg at all times and at all costs were employed without attention to the potentially detrimental effects that these measures might have on CBF. More recently, two alternative strategies have more been articulated: CPP-targeted therapy and intracranial volume minimization. The first, sometimes described as "the Rosner approach" (based on the neurosurgeon who developed and popularized it) by maintaining relatively high CPP levels [76–78] at the expense of added cardiopulmonary stress.

This CPP augmentation strategy has been shown to minimize the frequency of ICP elevation and result in better outcomes versus historical controls treated with traditional ICP reduction strategies [78]. The only randomized trial comparing this approach to traditional ICP strategies found a reduction in the number of jugular venous desaturations with the higher CPP target [79]. At the same time, clinical outcomes were no different, and a significant increase in the risk of acute respiratory distress syndrome was found in the high CPP group. A recent study has found that norepinephrine is more predictable and effective than dopamine for raising blood pressure and transcranial Doppler flow velocities after severe TBI [80].

An alternate approach, developed by and named after investigators in Lund, Sweden, employs measures including the judicious use of antihypertensives to minimize intravascular hydrostatic pressure and cerebral blood volume. The "Lund concept" assumes a disruption of the blood–brain barrier and recommends manipulations to decrease the hydrostatic forces and increase osmotic pressures to

minimize cerebral blood volume and vasogenic edema [81]. This is achieved in theory by maintaining relatively low CPP levels of 50–70 mmHg while ensuring a euvolemic state with normal hemoglobin, pCO_2, and plasma protein concentrations [82].

Invasive brain multimodality monitoring of CBF, brain tissue oxygen tension, jugular venous oxygen saturation, and microdialysis has shown promise as a means of which therapeutic strategy might be most useful in a particular patient. Computerized bedside graphical displays (ICU Pilot®, CMA Microdialysis, Solna, Sweden) can allow clinicians to identify whether ICP and MAP are positively correlated, in which a low CPP would be preferable, or negatively correlated, in which the a higher CPP would be desirable. Clinical trials are needed to determine whether goal-directed CPP therapy based on individualized multimodality monitoring targets can improve outcome after TBI [83, 84]. Until further data is available, the Brain Trauma Foundation guidelines recommending a CPP target 50–70 mmHg [65] (Table 12.2).

Spinal Cord Injury (SCI)

The management of BP in acute SCI is less complex than in severe TBI, despite the belief that the spinal cord has vascular autoregulation similar to the brain. There are two syndromes that can present with markedly abnormal blood pressure unique to SCI: neurogenic shock, due to acute inhibition of resting sympathetic peripheral vasomotor tone, and autonomic dysreflexia, in which blood pressure is labile and extreme hypertension can be triggered by minor physical stimulation below the level of injury [85]. Both syndromes occur primarily after cervical or upper thoracic cord injury.

Inferred from TBI and animal SCI data, systemic hypotension is thought to contribute to increased secondary CNS injury as well as to non-neurological (especially cardiac) morbidity and mortality. Consistent with this hypothesis are several small, uncontrolled series that report improved outcomes in SCI patients from aggressive medical intensive care with attention to maximizing physiological parameters, including blood pressure. Most of these studies deliberately maintained MAP >90 mmHg for 1 week with vasopressors and volume resuscitation. Current guidelines suggest that hypotension (SBP <90 mmHg) be scrupulously avoided after acute SCI and that MAP be maintained at or above 90 mmHg during the first week after injury (Table 12.2).

Spinal Cord Infarction

For the treatment of acute spinal cord infarction, induced hypertension combined with aggressive lumbar CSF drainage to maximize spinal perfusion pressure is a preferred treatment. Most experience with this technique has come from patients with delayed spinal ischemia after thoracoabdominal aortic aneurysm repair. Lumbar drainage to maintain CSF pressure <10 cm H_2O, with or without vasoactive drugs to maintain MAP >95 mmHg, has been reported to result in marked clinical improvement when instituted within several hours of the onset of symptoms [86] (Table 12.2). More experience with this type of intervention and the role of novel techniques for neuroprotection such as mild to moderate induced hypothermia is needed before it can be widely recommended.

Hypertensive Encephalopathy

Hypertensive encephalopathy (HE) arises from systemic blood pressure elevation sufficient to regionally overwhelm the upper limit of cerebrovascular autoregulation (Fig. 12.3). Pressure and volume overload of the cerebral circulation classically leads to endothelial dysfunction, blood–brain barrier disruption, hydrostatic vasogenic edema, petechial hemorrhages, and a characteristic pattern of edema on magnetic resonance imaging, which primarily involves the posterior circulation (posterior reversible encephalopathy syndrome). This anatomic predilection is felt to be due to the scarcity of sympathetic innervation of distal posterior circulation vessels. Papilledema and intracranial hypertension may be present, particularly when global brain edema is present. The blood pressure may be extremely high (exceeding 250/150 mmHg), but the rate of rise and the baseline blood pressure may be just as important determinants of disease severity than the peak blood pressure that is reached.

Untreated, hypertensive encephalopathy can lead to seizures, cortical blindness, frank hemorrhage, coma, and death. Despite a lack of randomized clinical trial data, treatment is generally directed toward decreasing the MAP by 20–25 % or the DBP to 100 mmHg (whichever is higher) within 1 h (Table 12.2). Comatose patients should have an ICP monitor placed; ICP should be maintained below 20 mmHg and CPP within a tight range of 70–90 mmHg. Short-acting parenteral antihypertensives (such as labetalol, nicardipine, or enalaprilat) should be given initially, and drugs such as nitroprusside that can cause cerebral vasodilation or increased ICP are best avoided. Fenoldopam may be the favored therapy in the setting of acute renal insufficiency.

Eclampsia

This condition refers to a particular form of hypertensive encephalopathy that occurs in the setting of pregnancy-induced hypertension. Because of its association with

microvascular and endothelial damage, neurological manifestations of HE can occur at much lower blood pressures in eclamptic patients than in patients with essential hypertension [87]. Blood pressure management is significantly more complicated than essential hypertension-related encephalopathy. In eclampsia, the physiology of pregnancy can alter drug metabolism, there are two circulations to consider, and certain antihypertensives are strictly contraindicated based on adverse fetal effects (namely, ACE inhibitors and angiotensin receptor blockers). Based on consensus opinion and small numbers of randomized trials, MAP in eclampsia is targeted between 105 and 125 mmHg [87]. Magnesium sulfate (2 g/h IV) reduces the risk of recurrent seizures and lowers blood pressure [88]; it should be administered to all preeclamptic and eclamptic patients. As in other neurological emergencies, initial control of blood pressure with a fast-acting easily titratable agent such as labetalol or nicardipine is advised [87–89].

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