Part I

Acute Management of Neurological Emergencies
Hypertensive Emergency

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Introduction

Hypertension and neurologic disease coexist frequently, either as a cause or consequence of the underlying neurologic disease. In addition, the management of elevated blood pressures in this setting has significant impact on outcomes. Hypertension is defined as systolic blood pressure greater than 140 mmHg or diastolic blood pressure greater than 90 mmHg. The National Health and Nutrition Survey (NHANES) is conducted by the Centers for Disease Control and Prevention obtaining data from US household individuals regarding health and nutrition for the purpose of improving the US health through policy. The NHANES 2005 to 2006 data reported that 29% of the United States population 18 years and older are diagnosed with hypertension. Of the population with treated hypertension, greater than 64% has controlled hypertension. Men have a higher rate of hypertension until the age of 45 when the incidence of hypertension equalizes between men and women.

In 2006 the mortality from hypertension was reported in 56,561 individuals. Both the prevalence from hypertension and mortality has increased from the late 1990s to the 2000s. The estimated direct and indirect cost of hypertension for the year 2010 was 76.6 billion US dollars.

The sequelae of hypertension include strokes, myocardial ischemia, aortic dissection, and renal insufficiency. The remaining text of the chapter will focus on the management of blood pressure in the specified acute neurologic diseases.

Hypertensive crisis is defined as an abrupt elevation of blood pressure, to a point that the blood vessels are unable to maintain constant blood flow in the setting of increasing perfusion pressures to specific organs, also known as disruption of autoregulation. The end result leads to end-organ damage from ischemia or hemorrhage. The end result leads to end-organ damage from ischemia or hemorrhage.

Patients with blood pressure elevations greater than 180/110 mmHg are categorized into the following diagnoses:

1. Severe hypertension: no to mild symptoms and no acute end-organ damage
2. Hypertensive urgency: significant symptoms and mild acute end-organ damage. Mild end-organ damage is defined as dyspnea and headaches.
3. Hypertensive emergency: severe symptoms with life-threatening end-organ damage

Life-threatening end-organ damage is defined as acute ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, acute aortic dissection, myocardial infarction, acute heart failure, eclampsia, renal insufficiency, and acute
pulmonary edema, to name a few. The first instinct when dealt with this situation as a practitioner is to acutely correct the problem. However, there are some considerations prior to acutely correcting the blood pressure in a hypertensive crisis. The remainder of the chapter will discuss these considerations in relation to neurologic emergencies.

Hypertensive urgencies include 25% of ED medical visits, while hypertensive emergencies are one-third of the cases. CNS complications are the most frequent of the hypertensive emergencies. The hypertensive emergent patient with neurologic sequelae needs urgent attention, with hourly blood pressure monitoring and neurologic examination in an intensive care unit. Prior to discussing blood pressure management, a discussion of cerebral autoregulation and the parental antihypertensive agents will be reviewed.

**Cerebral Autoregulation**

Cerebral blood flow (CBF) is tightly controlled under the normal conditions, with cerebral perfusion pressures (CPP) ranging from 50 to 150 mmHg. Cerebral perfusion pressures can be calculated from mean arterial pressure (MAP) minus jugular vein pressure (JVP). Intracranial pressure (ICP) is substituted for JVP under conditions where the ICP is greater than the JVP. Cerebral autoregulation involves arteriole caliber changes in response to changes in the blood pressure; however, there are upper and lower limits that lead to a disruption of this system with resultant ischemia or cerebral edema (Figure 1.1).

The underlying mechanisms of autoregulation that allow for vessel caliber changes are myogenic and metabolic. When the MAP decreases, the arterioles constrict to increase the CBF; however, if hypotension persists beyond the lower limit threshold, resultant cerebral ischemia exists. If the blood pressure continues to increase above the higher limit threshold, the result is hyperemia and cerebral edema. However, in brain dysfunction, the blood–brain barrier and cerebral endothelium is disrupted, leading to leaky blood vessels with subsequent fibrinoid deposition into the cerebral vasculature. This results in vascular narrowing, with compensatory vasodilation. In these circumstances the autoregulation curve follows a more linear pattern with the CBF being dependent on perfusion pressures.

Normal CBF is 50 mL/100 g brain tissue per minute. Reversible injury, occurs at 15–20 mL/100 g/min, and irreversible injury is less than 15 mL/100 g/min. The occurrence of cell death is based on the product of the degree and length of time of ischemia. The ischemic penumbra is vulnerable tissue with impaired autoregulation and low blood flow despite high oxygen extraction. Therefore the tissue is salvageable but has a high risk of becoming ischemic if the blood flow is not recovered in a short period of time.

![Figure 1.1](image_url)

**Figure 1.1.** Autoregulation maintains cerebral blood flow relatively constant between 50 and 150 mmHg mean arterial pressure. The range is right shifted in chronically hypertensive patients. (Reproduced from Ruland and Aiyagari. *Hypertension* 2007; 49: 978, with permission from Wolters Kluwer Health.)
An EEG is a useful tool for monitoring seizures, but also for detecting cerebral blood flow. In the operation room, older studies have shown that EEG can detect real-time ischemia. When cerebral blood flow reaches 25–30 mL/100 g/min, an EEG demonstrates a change in morphology, amplitude, and frequency. When the CBF decreases to less than 15 mL/1006/min, the EEG becomes isoelectric. The neurons that produce the excitatory post-synaptic potential (EPSP) and inhibitory post-synaptic potential (IPSP) for the electrodes are the same neurons (pyramidal neurons) that are sensitive to hypoxia.

Antihypertensive Agents

Hypertensive emergency can be fatal, and needs prompt treatment. The initial treatment is blood pressure control, in a reliable and controlled fashion, therefore oftentimes, requiring parental agents and arterial blood pressure monitoring. There are multiple classes of antihypertensives one has to choose from; however, there are also many factors to consider prior to administration. The most important factor to consider in neurologic damage is increased intracranial pressure. A few class of antihypertensive agents work via vasodilatory mechanisms, which can lead to further increases in intracranial pressure and potentially further worsening of neurologic injury. Another factor is the onset and duration of action. Rapid fluctuations of hypotension and hypertension can lead to worsening cerebral injury. An agent that can be turned off and out of the system quickly is more desirable in case of an acute hypotensive episode.

Preferred Agents for Hypertensive Emergencies with Brain Dysfunction

Beta Blockers

Labetalol is a selective alpha-1 and nonselective beta antagonist. The onset of action is 2–5 minutes with a peak effect seen in 5–15 minutes. The hypertensive effect can last for 2–4 hours. Beta action does cause a decrease in heart rate but maintains the cardiac output. Similarly, cerebral perfusion is maintained with the use of beta blockers.

Start with a loading dose of 20 mg, increasing subsequent doses from 20 to 80 mg every 10 minutes to the desired effect. In the author’s institution, if repeat labetalol boluses do not result in the desired effect, an infusion is initiated starting at 1–2 mg/min.

Esmolol is a short-acting beta antagonist, with no direct effect on the peripheral vasculature. Decreased blood pressure is secondary by decreasing cardiac output. The onset of action is 60 seconds, with a duration of action of 10–20 minutes. Esmolol has a unique metabolic profile, being metabolized by red blood cell (RBC) esterases. In the setting of anemia, Esmolol can have a prolonged effect. Due to its pure beta action, caution should be used in patients with COPD. Similarly it should be avoided in patients in decompensated heart failure, due to compromising myocardial function.

Start with a loading dose of 500–1000 μg/kg, with a continuous infusion at 50 μg/kg/min to a maximum of 300 μg/kg/min.

TIPS & TRICKS

Beta blocker toxicity can present with bradycardia, hypotension, bronchospasm, and hypoglycemia. An ECG can be helpful with detecting PR prolongation. QT prolongation can sometimes be detected. It should be treated with atropine for bradycardia, intravenous fluids and vaspressors for hypotension. Glucagon is a well-known antedote for the treatment of beta blocker toxicity.

Calcium Channel Blockers

Three types of calcium channel blocker exist: dihydropyridines, phenylalkylamines, and benzothiapines. The two types of calcium channels that exist in the vasculature are L-type and T-type.
The action of calcium channel blockers on L-type channels decrease calcium influx, resulting in elevated GMP levels. The elevated GMP levels lead to vascular smooth muscle relaxation, vasodilation and decrease systolic blood pressure.

Nicardipine and clevidipine are the preferred parental calcium blocker agents for cerebrovascular hypertensive emergencies. Nicardipine crosses the blood brain barrier, leading to vasodilation of the small-resistance arterioles, with little to no increases in intracranial pressure. The infusion rate starts at 5 mg/h, with incremental increases 2.5 mg/h every 5 minutes for a maximum infusion 30 mg/h. The onset of action is 5–15 minutes, with duration of action 4 to 6 hours.

Of note, nicardipine has other properties that make it attractive in neurological diseases. It has a high affinity to ischemic cerebral tissue due to the acidic pH of ischemic tissue. Once in the cell, it is transformed to its active form, which may lead to a direct neuroprotective effect.

The effect of nicardipine on intracranial pressure has been studied. Narotam et al. (2008) performed a prospective case-control study of 30 patients with hypertensive emergencies in acute brain disease. Nicardipine was the first-line antihypertensive agent. The results supported the ability to maintain cerebral perfusion pressures above 70 with no increase in ICP and increased parenchymal brain tissue oxygenation.

Clevidipine is a third-generation dihydropyridine calcium channel blocker, recently used in a trial of blood pressure management in acute intracerebral hemorrhage. The drug acts by arteriole dilation, with an onset of action 2–4 minutes and a duration of action 5–15 minutes. It is metabolized by red blood cell esterases. Clevidipine has antioxidative properties as a free-radical scavenger. Continuous infusions start at 1–2 mg/h, and is increased every 90 seconds until blood pressure goals are attained. However, there are a few less attractive features of the drug: 1) infused in a lipid emulsion, requiring triglyceride monitoring during infusion, 2) contraindicated in patients with allergies to soy and egg products, and patients with lipid metabolism disorders, and 3) can develop microbial growth in solution.

### Other Agents Used for Hypertensive Emergencies
#### Nitric Oxide Vasodilators
Sodium nitroprusside is a potent arterial and venous vasodilator, leading to significant preload and afterload reductions. However, ICP elevations can occur in patients with neurologic injury. The first studies were performed on neurosurgical patients under anesthesia revealing vasodilation of large-capacitance vessels leading to vasodilation and increased intracranial pressure. Another negative consequence is cyanide toxicity. Sodium nitroprusside contains 44% of cyanide, which is further metabolized to thiocyanate by the liver, and eliminated by the kidneys. There is an increased risk for cyanide toxicity in patients with liver and kidney dysfunction. Cyanide toxicity leads to cellular hypoxia with neurologic consequences and cardiac arrest. The neurologic consequences include encephalopathy, seizures, and coma. Thus, the use of sodium nitroprusside and other nitric oxide drugs are discouraged due to the potential for worsening intracranial pressures.

Diuretics have no role in the acute management of hypertensive emergencies in neurological and nonneurological disorders due to the increased frequency of volume depletion. Specifically in the neurological patient, altered mental status and dysphagia can further exacerbate volume depletion, leading to increased fluid administration in the acute setting to prevent further dehydration and kidney injury.

A list of medications used to treat acute hypertensive emergencies and the doses used are listed in Table 1.1.

### Acute Ischemic Stroke
Blood pressure management in acute ischemic stroke is complex; lowering blood pressure could potentially worsen the infarct size and cause neurologic deterioration, while allowing blood pressures to remain elevated could lead to hemorrhagic transformation and worsening brain edema. If the patient is a thrombolytic candidate or received thrombolytics, pressures excessively elevated can also lead to hemorrhagic transformation. Retrospective analysis of outcomes post-thrombolysis has also shown a worse outcome in
<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Dosage</th>
<th>Onset</th>
<th>Duration</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labetalol</td>
<td>$\alpha_1\beta$ antagonist</td>
<td>Loading doses 20 mg with repeated boluses every 10 min Infusion rates 1–2 mg/min for target blood pressure</td>
<td>2–5 min</td>
<td>2–4 h</td>
<td>Reactive airway disease COPD Decompensated heart failure Bradycardia Second or third degree heart block</td>
</tr>
<tr>
<td>Esmolol</td>
<td>$\beta_1$ antagonist</td>
<td>Loading dose 0.5–1.0 mg/kg Infusion rates 50 ug/kg/min to max 300 ug/kg/min</td>
<td>60 s</td>
<td>10–20 min</td>
<td>Reactive airway disease COPD Decompensated heart failure Bradycardia Second or third degree heart block</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>Dihydropyridine calcium channel antagonist</td>
<td>Initial infusion 5 mg/h, increasing 2.5 mg/h every 5 min. Maximum 15 mg/h</td>
<td>5–15 min</td>
<td>4–6 h</td>
<td>Severe aortic stenosis</td>
</tr>
<tr>
<td>Clevidipine</td>
<td>Dihydropyridine calcium channel antagonist</td>
<td>Initial infusion 1–2 mg/h, increasing the dose x2 every 90 s to max 32 mg/h</td>
<td>6 min</td>
<td></td>
<td>Defective lipid metabolism disorders</td>
</tr>
<tr>
<td>Enalaprilat</td>
<td>ACE inhibitor</td>
<td>Initial dose of 0.625 with repeated doses 1.25 mg every 6 h</td>
<td>15 min</td>
<td>12–24 h</td>
<td>Acute renal failure Acute MI Bilateral renal artery stenosis Pregnancy hyperkalemia</td>
</tr>
<tr>
<td>Sodium nitroprusside</td>
<td>Nitric oxide donor leading to vascular smooth muscle relaxation via intracellular second messenger systems</td>
<td>Initial dose of 0.3–0.5 $\mu$g/kg/min, increasing 0.5 $\mu$g/kg/min for desired effect, max dose 2 $\mu$g/kg/min.</td>
<td>1–3 min</td>
<td>1–3 min</td>
<td>Increased intracranial pressures Acute MI Hepatic or renal failure due to increase risk for cyanide toxicity</td>
</tr>
</tbody>
</table>
patients with a history of hypertension, despite the administration of thrombolysis. Studies focusing on blood pressure management in acute ischemic stroke have shown that patients with lower blood pressure on admission had poor outcomes. Vemmos and colleagues examined the mortality at 1 month and 12 months after ischemic and hemorrhagic strokes in relation to admission blood pressures. Their findings concluded that patients with ischemic strokes had the best outcomes with an admission systolic blood pressure of 120–140 mmHg, and patients with an admission systolic blood pressure less than 101 mmHg or greater than 220 mmHg had the highest mortality rates. Therefore, current guidelines recommend maintaining systolic blood pressure less than 220 mmHg and diastolic blood pressure less than 120 mmHg. The majority of patients will reset to normotensive days after their stroke.

In regards to blood pressure augmentation during an acute stroke, there are no good studies to date to support artificially raising blood pressures in an acute stroke. Current recommendations are to discontinue home blood pressure medications and allow the blood pressures to rise to their specific targets irrespective of thrombolysis. If thrombolytics have been instituted, patients need monitoring in an intensive care unit, preferably a neurocritical care unit, with the use of short-acting parental antihypertensives if patients’ blood pressures are raised outside their specific targets.

**Intracerebral Hemorrhage**

Intracerebral hemorrhages represent 15% of all strokes. Despite more sophisticated medical interventions, neurological outcome and mortality continue to significantly impact patients with intracerebral hemorrhages. More specifically, patients with a decrease in the neurologic examination prior to hospital admission have a significantly greater mortality. The initial neurologic deterioration is frequently due to rebleeding of the initial hemorrhage.

There has been poor evidence for guiding blood pressure goals in intracerebral hemorrhages; however, the 2010 Stroke Guidelines has a new recommendation based on two clinical trials: INTERACT and ATACH. The new guidelines state that it is “probably safe” to lower systolic blood pressures less than 140 mmHg if presenting systolic blood pressures are less than 220 mmHg. However, there is insufficient data for a defined blood pressure target.

Kazui et al. (1997) examined the risk factors for hematoma enlargement. 83% of the subjects had a pre-existing diagnosis of hypertension and 76% of the hemorrhages were in classical, hypertensive locations. In their study population, Kazui et al. (1997) noted that admission systolic blood pressure greater than 200 mmHg was significantly associated with hematoma enlargement.

The INTERACT trial randomized 404 patients to intensive blood pressure control of systolic blood pressure less than 140 mmHg or guideline-based blood pressure control of systolic blood pressure less than 180 mmHg for the first 24 hours to 7 days after stroke onset. 296 patients had all CT scans available for full statistical analysis. Patients in the intensive blood pressure lowering group showed reduced hematoma volumes, 3.15 cc and 2.45 cc at 24 and 72 hours, respectively. However, the results have been questioned due to enrollment bias with patients with smaller hemorrhage volumes than previous trials, less acuity based on NIHSS and GCS: NIHSS ranged from 5 to 15 and GCS ranged 13 to 15. The patient population was more diverse due to hospitals located in Australia, China, and South Korea, with possible different etiologies and pathophysiologies involved.

The ATACH trial enrolled 60 patients to one of three tiers of blood pressure goals within 6 hours of symptom onset. The primary outcomes included neurologic deterioration and serious adverse events. They did not analyze hematoma growth or perihematoma edema. The most serious adverse events and neurologic deterioration occurred in the most intensive tier, systolic blood pressure less than 140 mmHg. There was no difference in mortality between the groups. The ATACH trial produced opposite results to the INTERACT trial, showing more negative outcomes in patients with systolic blood pressures less than 140 mmHg after stroke onset. However, as pointed out, ATACH did not analyze the hematoma volumes and both studies had different patient populations.

There is still no correct answer for the low end of systolic blood pressure in intracerebral
hemorrhage, or if patients have a worse outcome with high or low blood pressure. We still need high-powered studies to assist with this fundamental management of intracerebral hemorrhage in the acute setting.

**TIPS & TRICKS**

Elevated blood pressures in intracerebral hemorrhage are frequently seen. However, persistent elevated blood pressures hours after the initial insult can be an indicator of rebleeding or worsening edema. If blood pressures are not responding to antihypertensives, a dose of mannitol or hypertonic saline can be given with close blood pressure monitoring. If blood pressures decrease, the persistent hypertension is an indicator of a worsening edema.

### Blood Pressure and Aneurysmal SAH

Subarachnoid hemorrhage is a devastating disease, with a high mortality depending on the severity of the hemorrhage. The risk factors for aneurysmal subarachnoid hemorrhage include hypertension, alcohol use, tobacco use, Adult Polycystic Kidney Disease, and connective tissue disorders. 30-day mortality from subarachnoid hemorrhage has been reported as high as 50% in the AHA guidelines, with the amount of blood, medical comorbidities, and time to treatment being important factors affecting the outcome. However, the goal of this chapter is to discuss blood pressure management in subarachnoid hemorrhage. Blood pressure goals depend on the state of the aneurysm – unsecured or secured.

Many factors are thought to contribute to the risk of rebleeding in the unsecured aneurysm and the literature is currently unsure of the role of blood pressure and rebleeding risk. However, most centers in America will maintain a systolic blood pressure of less than 160 mmHg. The current stroke guidelines do not give an absolute value for blood pressure control; however, they recommend that the blood pressure should be controlled. For blood pressure management, the use of short-acting parental antihypertensive agents should be instituted.

After securing the aneurysm, the goal of blood pressure focuses on vasospasm management. Vasospasm is the arterial narrowing secondary to inflammatory changes from blood products from the initial subarachnoid hemorrhage. Vasospasm can lead to neurologic deficits by reduced blood flow and ischemic brain tissue, collectively termed “delayed cerebral ischemia.” Nimodipine, a calcium channel blocker, is the only proven drug that improves the outcomes in patients with cerebral vasospasm in the context of subarachnoid hemorrhage. Detecting cerebral vasospasm will be discussed in another chapter of this textbook, and the hypertensive management of vasospasm will be discussed only briefly here.

The goal of management of vasospasm is optimizing oxygenation to the brain. During the management of vasospasm, patients require intensive care monitoring for arterial catheterization and triple lumen catheters. This is performed by reducing cerebral metabolism and intracerebral pressures, and optimizing cerebral perfusion. Blood pressure management is paramount in optimizing cerebral perfusion pressures, which is achieved through the use of hemodynamic augmentation. Considerable controversy exists as to the best method to achieve increased cerebral blood flow in the patient with severe vasospasm. However, it is known that during the acute period of vasospasm cerebral autoregulation is disturbed. Methods to induce hypertension or increased cardiac output have been advocated and may require additional intravascular monitoring. When these measures have not resulted in reversal of delayed cerebral ischemia, patients are referred for intra-arterial opening of the vessels.

### Dysautonomia in Guillain–Barre Syndrome (GBS)

Dysautonomia is now one of the leading causes of increased mortality in GBS. It is a very common phenomenon in GBS, with increased risk when patients present with respiratory failure, tetraplegia, or bulbar involvement. It is defined as overactivity or underactivity of the sympathetic
system, causing either extreme hypertension and tachycardia and/or extreme hypotension and bradycardia.

Cortelli et al. (1990) have found pathological lesions in the intermediolateral horns of the spinal cord, sympathetic chains of white rami, and involvement of glossopharyngeal and vagus nerves in patients with dysautonomia from GBS. Durocher et al. (1980) examined the catecholamine levels of patients with dysautonomia, resulting in the high urinary catecholamine secretion of VMA, HVA, and 5 HIA; high CSF dopamine and serotonin levels; and normal serum serotonin levels.

These studies provide evidence for the underlying sympathetic pathology presenting with the signs of dysautonomia; however, the literature is scarce in the management of dysautonomia. Due to concerns for hypotension, it has been recommended to allow patients to maintain elevated blood pressures unless end-organ failure proceeds. When patients do progress to hypotension, pressors are indicated, and with severe bradycardia, transcutaneous pacing may be indicated.

**Hypertensive Encephalopathy**

Hypertensive encephalopathy is an entity seen in patients with acute blood pressure elevations in the setting of many clinical scenarios. A later chapter will be dedicated to hypertensive encephalopathy, however, to initiate the discussion on blood pressure management, it should be understood that the parietal-occipital lobes are preferably involved due to the lack of sympathetic innervation in the posterior circulation. Acute blood pressure elevations lead to hyperperfusion and blood–brain barrier dysfunction, with protein and fluid extravasation leading to vasogenic edema and, sometimes, intracerebral hemorrhage.

The clinical effects of hypertensive encephalopathy include, but are not limited to, headache, altered mental status, visual changes, seizures, and coma.

Blood pressure management needs careful attention, with acute lowering of the MAP by 25% of admission MAP or diastolic less than 100 mmHg within 1 hour, to prevent seizures and intracranial hemorrhage. Short-acting agents are a better choice for tighter blood pressure control.

**Bibliography**


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