CHAPTER 100
Acute Hypertension Management in the ICU
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INTRODUCTION
Hypertension is extraordinarily common, with over 1 billion individuals affected worldwide in 2000, 26% of the worldwide population in 2010, and projections of 29% of the population by 2025 (1,2). Between 1% and 2% of persons with chronic hypertension have hospital admissions related to cardiovascular disease (3,4). Because hypertension is so common, and because such a wide variety of conditions can be categorized as hypertensive emergencies, acutely elevated blood pressure is still a factor in a substantial number of medical visits to emergency departments and a frequent problem in the intensive care unit (ICU) (Table 100.1) (5,6).

Hypertensive crisis (Table 100.2) is defined as a systolic blood pressure greater than 180 mmHg or a diastolic blood pressure greater than 120 mmHg (7). Hypertensive crises may then be divided into two categories: hypertensive emergency and hypertensive urgency. Hypertensive emergency is now defined by the above elevated blood pressure measurements along with impending or continued organ dysfunction (7). This means the blood pressure elevation itself does not need to be directly responsible for causing end-organ damage, as it was previously defined. For example, acute hypertension is usually the result of, rather than the immediate cause of, an acute ischemic stroke. If the patient is to be treated with thrombolytics, it becomes imperative to maintain the blood pressure within certain narrow limits to minimize the risk of hemorrhagic transformation while at the same time not compromising cerebral blood flow. Thus, in this chapter, we define a hypertensive emergency as being associated with impending or continued organ dysfunction. Although the term malignant hypertension has been discouraged by some, it is still widely used in the literature to describe the syndrome where organ dysfunction is a direct consequence of the elevated blood pressure, rather than an epiphenomenon. The presence of papilledema is not necessarily required for the diagnosis of malignant hypertension to be made (3,8).

In contrast, a hypertensive urgency is defined as a condition with severe blood pressure elevation and no target-organ damage, such that the blood pressure can be decreased more gradually over the course of several hours, often with oral medications. It is therefore the presence or absence of organ dysfunction, rather than the absolute degree of blood pressure elevation, which determines whether a patient is classified as having a hypertensive emergency or urgency. It is not always clear how clinicians distinguish between hypertensive urgencies and the situation where a patient simply has severe, poorly controlled, chronic hypertension.

We will discuss the pathophysiology, diagnosis, and treatment of acute hypertension in the ICU both in a general manner and when pertaining to specific end-organ disease state.

PATHOPHYSIOLOGY OF HYPERTENSION-INDUCED END-ORGAN DYSFUNCTION
Blood flow to organs is kept relatively constant despite variations in blood pressure. This process is called autoregulation, and its limits are usually between mean arterial pressure (MAP) values of about 50 and 150 mmHg. Increases in blood pressure induce arteriolar smooth muscle contraction and vasoconstriction, while reductions lead to vasodilatation. Extreme hypertension exceeding the upper range of autoregulation causes edema, hemorrhage, and organ dysfunction, while reductions in blood pressure beyond the lower limits of autoregulation result in tissue hypoperfusion and ischemia (Fig. 100.1). In addition to a widespread, systemic myogenic response, there are also more organ-specific vascular regulatory mechanisms to protect against the effects of acute hypertension. The likelihood of end-organ damage increases not only with the absolute degree of blood pressure elevation, but also with the rate at which this occurs (8). With chronic hypertension, there is hypertrophy in the walls of small arteries and arterioles, and the autoregulatory curve is shifted to the right, such that blood flow can be maintained constant, even at unusually high blood pressures. Conversely, ischemia may occur when blood pressure falls to levels that would otherwise be well tolerated. In the setting of neurologic injury, autoregulation is often impaired, and cerebral blood flow becomes directly dependent on blood pressure (Fig. 100.1).

Normal endothelial function is necessary for the regulation of vascular tone, blood pressure, and regional blood flow (Fig. 100.2). The endothelium is involved in maintaining a delicate balance between vasodilating substances (e.g., nitric oxide, bradykinin, prostacyclin) and vasoconstrictors (e.g., endothelin), as well as between coagulation and fibrinolysis. Elevations in humoral vasoconstrictors leads to acute elevation in systemic vascular resistance and could trigger a hypertensive crisis (9–11). Thrombotic microangiopathy (TMA), endothelial dysfunction, elevated thrombin generation, and platelet activation, with enhanced fibrinolysis, have been associated with hypertensive crisis and ischemic complications (12). Platelet activation in particular has been found in both hypertensive emergency and urgency, and may be an early finding of hypertensive crisis (12). When blood pressure is elevated, natriuretic peptides are released from the endothelium, which in turn induce sodium and water loss, with decreased intravascular volume (8). Excessive activation of the renin-angiotensin system causes vasoconstriction and inflammation, and has been demonstrated to cause hypertensive emergencies in animal models, an effect that can be inhibited with the use of angiotensin-converting enzyme (ACE) inhibitors (13,14). Angiotensin II levels are elevated in most cases of malignant hypertension, particularly when the
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etiology is a renal condition (15). Increased risk of hypertensive emergency has been associated with the presence of the DD genotype of the ACE gene (16). As the blood pressure rises dramatically, endothelial compensatory mechanisms fail, and injury ensues with subsequent fibrinoid necrosis, increased permeability, and inflammation. Therefore, paradoxically, both hyperemia and TMA and ischemia develop during a hypertensive crisis (12) (Fig. 100.2).

DIAGNOSIS, ETIOLOGY, AND MANIFESTATION

Malignant Hypertension

The peak incidence of malignant hypertension occurs between the ages of 40 and 50, with risk factors including poor long-term blood pressure control, lack of a primary care physician, noncompliance with antihypertensive medications, male gender, African-American ethnicity, illicit drug use, and lower socioeconomic status (17–20). Prior to the availability of effective antihypertensive therapy, the mortality of malignant hypertension was very high, with approximately 80% of patients dying within a year; hence, the term malignant (21).

At least 90% to 95% of patients with chronically elevated blood pressure can be classified as having “essential” hypertension, meaning that the underlying cause is multifactorial and not specifically known. A small proportion of patients have “secondary” hypertension, where there is an identifiable and sometimes treatable condition that is responsible for raising blood pressure (22). In contrast, among patients who present with malignant hypertension, as many as 50% to 80% may have a secondary etiology (23). Other clues that should alert clinicians to the possibility of secondary hypertension include a history of blood pressure that is resistant to medical therapy, sudden worsening in a previously well-controlled patient, and the onset of hypertension at an unusually young or old age (24).

Renovascular disease, the most common cause of secondary hypertension, may be present in as many as 45% of patients...
with severe or malignant hypertension, although the proportion is higher in Caucasians than African Americans (25). Features that suggest renovascular hypertension include atherosclerotic vascular disease in other organ systems, systolic-diastolic abdominal bruits, a history of deterioration in renal function with exposure to ACE inhibitors or angiotensin II receptor blockers (ARBs), recurrent flash pulmonary edema, and small kidneys (determined by ultrasound or other imaging).

Hypertension is almost universally present in patients with acute or chronic kidney disease, especially when the etiology is a glomerulonephropathy (26). Hypertension is a common manifestation of obstructive sleep apnea, and can be improved by the administration of noninvasive positive airway pressure (27). Various and rare endocrinologic causes, including primary aldosteronism, Cushing syndrome, hypercalcemia, hyperthyroidism or hypothyroidism, and pheochromocytoma, are also responsible for a small proportion of cases. Several illicit drugs can cause malignant hypertension in addition to other hypertensive emergencies. Sympathomimetics, such as cocaine and methamphetamine, have been implicated in causing intracerebral and subarachnoid hemorrhage (SAH), ischemic stroke, and aortic dissection (28–30). However, various drugs used in clinical practice have also been reported to cause severe hypertension, or even hypertensive emergencies. The most commonly implicated are erythropoietin and various immunosuppressants, most notably cyclosporine, tacrolimus, interferon, and high-dose corticosteroids, although it is sometimes difficult to separate the hypertension-inducing effects of these drugs from the complications of the diseases they are intended to treat (31,32). A careful history, physical examination, and appropriate diagnostic testing to exclude causes of secondary hypertension are indicated during the hypertensive emergency and after it has resolved (Table 100.3).

**Retinopathy**

Endothelial damage and leakage of plasma proteins into the retina lead to edema and the formation of hard exudates. Focal areas of ischemia and infarction within the nerve fiber layer cause white areas, called *cotton wool spots*, to appear. Breakdown of the blood-retinal barrier results in the emergence of flame-shaped hemorrhages within the retina. The development of papilledema has historically been used to differentiate “accelerated” from “malignant” hypertension. However, the presence or absence of papilledema has little impact on the natural history and prognosis of hypertensive emergencies, nor should it significantly alter management (33). The mechanism of papilledema may include elevated intracranial pressure (ICP), which is known to be present in some patients with hypertensive encephalopathy, as well as ischemia of the optic nerve.

**TABLE 100.3 Etiologies of Malignant Hypertension**

<table>
<thead>
<tr>
<th>Category</th>
<th>Etiologies</th>
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<tbody>
<tr>
<td>Essential hypertension</td>
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<tr>
<td>Secondary hypertension</td>
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<td>Renovascular disease</td>
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<td>Atherosclerosis, thrombosis</td>
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<td>Fibromuscular dysplasia</td>
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<td>Medium and large vessel vasculitis</td>
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<td>Glomerular disease</td>
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<td>Glomerulonephritis</td>
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<td>Small vessel vasculitis</td>
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<td>Microangiopathies</td>
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<td>Scleroderma</td>
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<tr>
<td>Renal parenchymal disease</td>
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<td>Polycystic kidney disease (and others)</td>
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<td>Renin-producing tumors</td>
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<td>Endocrine causes</td>
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<td>Pheochromocytoma</td>
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<td>Primary hyperaldosteronism</td>
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<td>Cushing syndrome</td>
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<td>Hypercalcemia</td>
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<tr>
<td>Aortic coarctation</td>
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<tr>
<td>Medications (e.g., cyclosporine, tacrolimus, erythropoietin)</td>
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<tr>
<td>Sympathomimetic drugs (e.g., cocaine, amphetamines)</td>
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nerve head (34). It should be noted that ophthalmoscopic examination for hypertensive retinopathy has relatively high rates of inter- and intraobserver variability, particularly among nonophthalmologists (35).

**Nephropathy and Microangiopathy**

Certain conditions causing acute renal failure may cause hypertensive emergencies, but severely elevated blood pressure can also cause renal dysfunction, a condition called *malignant nephrosclerosis*. Renal biopsies reveal fibrinoid necrosis, hyperplastic arteriolitis, neutrophilic infiltration, and thrombosis of glomerular capillaries (12). The histologic appearance can be difficult to distinguish from other microangiopathies, such as hemolytic-uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) (36). It is therefore not surprising that more than a quarter of patients with malignant hypertension, especially those with acute renal failure, have typical clinical features of microangiopathy, including thrombocytopenia, elevated lactate dehydrogenase, and schistocytes on blood smear (12,37). Impaired renal perfusion leads to greater activation of the renin–angiotensin system, which further augments vasoconstriction, fluid retention, and blood pressure elevation. The earliest evidence of renal involvement is the presence of abnormal urine sediment, with proteinuria, hematuria, and the appearance of red and white blood cell casts. This is followed by the development of acute renal failure, which is sometimes severe enough for patients to require dialysis, and occasionally results in end-stage renal disease.

**Neurologic Hypertensive Emergencies**

**Stroke**

Acute stroke is one of the most common indications for which emergent blood pressure control may be necessary, and often the most frequent form of end-organ damage in a consecutive series of patients with hypertensive emergencies (5). Stroke is the second leading cause of death worldwide, and is also a major reason for long-term disability. Cerebral ischemia is responsible for 70% to 80% of strokes, while intracerebral hemorrhage (ICH) and SAH account for 5% to 20%, and 1% to 7%, respectively (38,39).

Hypertensive ICH is thought to be due to long-standing hypertension. The shear forces at the point of acute angles from large vessels to smaller perforating vessels and chronic hypertension cause atherosclerosis, fibroblast proliferation, lipid deposits in the vessel wall, and collagen replacing smooth muscle cells over prolonged periods of time. All of this weakens the vessels and decreases their compliance, thereby putting them at risk for rupture (Fig. 100.3) (40–43). In 1868, Charcot and Bouchard described microaneurysms as the cause of bleeding; these microaneurysms have since been found to be subadventitial hemorrhages and extravascular clots (42,43). Most often ruptures occur in the lenticulostriate vessels, causing hemorrhage into the basal ganglia; the thalamostriate vessels, causing hemorrhage into the thalamus; the pontine perforators, causing pontine hemorrhage; cerebellar vessels and, less often, the small vessels in the cortex causing hemorrhage in the parenchyma. ICH can also be due to hemorrhage in an intraparenchymal lesion such as in tumor, either primary or metastatic, or amyloid angiopathy (39).

Overall, more than 80% of patients with ischemic or hemorrhagic strokes are initially hypertensive to some degree (39,44). Even without treatment, the blood pressure usually declines gradually over the first several hours or days in-hospital; however, most patients with acute ICH are treated for acute hypertension (45). For instance, in the recent INTERACT 2 trial, 42.9% of 1,430 patients in the conservative arm were treated to keep SBP less than 180 mmHg, and 90.1% of 1,399 patients were treated in the aggressive arm to keep SBP less than 140 mmHg (46). In addition, in the well-known National Institute of Neurological Disorders and Stroke (NINDS) trial...
evaluating recombinant tissue plasminogen activator (rt-PA) for the management of acute ischemic stroke, 19% of patients had an initial blood pressure of more than 185/110 mmHg, and 60% had a blood pressure of more than 180/105 mmHg during the first 24 hours in-hospital (47). Whether or not it is appropriate (see Treatment section), more than half of these patients receive antihypertensive medications during the first few days of hospitalization (48). The incidence of hypertension with SAH is somewhat lower, but aggressive treatment is often advocated in order to minimize the initial risk of rebleeding from the aneurysm (49,50).

**Posterior Reversible Encephalopathy Syndrome**

The clinical manifestations of posterior reversible encephalopathy syndrome (PRES) in the setting of acute blood pressure elevation are collectively described by the term “hypertensive encephalopathy” characterized by the subacute development of neurologic signs and symptoms and may include headache, altered mental status, seizures, and visual disturbances (51). Headaches are usually generalized, severe, and poorly responsive to analgesics and improve rapidly with treatment of hypertension (52). Altered mental status can range from lethargy and confusion to stupor and coma, although the latter is unusual. The posterior predominance of PRES is reflected by the frequent occurrence of unilateral or bilateral visual disturbances, including hemianopsia, visual neglect, cortical blindness, Anton syndrome (patient is not aware of blindness), and visual hallucinations. Focal seizures originating in the occipital regions have also been described, although they most often generalize, and may be recurrent (53).

The characteristic clinical features and magnetic resonance imaging (MRI) findings of vasogenic edema in posterior white matter led to the description of a clinical radiologic syndrome, now most commonly termed posterior reversible encephalopathy syndrome (PRES), but previously known as reversible posterior leukoencephalopathy syndrome (RPLS) and hypertensive encephalopathy syndrome (HTE) (51,54). Although cerebral edema can sometimes be seen on computed tomography (CT) scans, PRES is best visualized using T2 and fluid-attenuated inversion recovery (FLAIR) MRI sequences. Diffusion-weighted image (DWI) MRI has confirmed that vasogenic edema is much more prominent than cytotoxic edema and, although PRES is usually “reversible,” some patients do develop ischemic strokes (55). Interestingly, lesions with increased diffusion-weighted and decreased apparent diffusion coefficient (ADC) values, which normally correspond to ischemic stroke, later have completely reversed on MRI (51).

Many patients do not adhere perfectly to the typical patterns of PRES: gray matter involvement of the cerebral cortex and basal ganglia, as well as edema occurring in the frontal lobes, posterior fossa, and brainstem are found in 10% to 30% of cases (51); it is rare for only one vascular territory to be involved (Fig. 100.4A–C).

The pathophysiology of PRES is both not completely understood and controversial. The older hypothesis is hypertension can lead to vasoconstriction by autoregulation and subsequent hypoperfusion, ischemia, and cerebral edema (51). The newer hypothesis is severe elevations in blood pressure eventually cause a breakdown of the blood–brain barrier, with subsequent development of vasogenic cerebral edema. White matter is less tightly packed than the overlying cerebral cortex thereby making it more vulnerable to the spread of edema. Although occurring most commonly in association with severe hypertension, there are other conditions that may at least predispose to, if not directly cause, the development of PRES, perhaps because they induce endothelial toxicity. PRES has been described in association with certain medications—most notably cyclosporine (32,51)—and other immunosuppressive agents, as well as in the setting of microangiopathies, connective tissue diseases, vasculitis, and preeclampsia (56). Endothelial injury, therefore, seems to be a common link between these conditions (51). Because of the importance of endothelium in autoregulation, injury may lead to an inability to vasodilate, leading to hypoperfusion, thereby arguing for the older hypothesis of pathogenesis. As to why PRES most often occurs posteriorly is up to some debate. Based on a histofluorescence study from the 1970s, showing a greater concentration of sympathetic fibers around arterioles in the anterior brain, it is thought this allows greater vasoconstriction and relative protection against the effects of severe hypertension (57). A more...
Recent study looking into quantifying perivascular nerve fibers in human cerebral arteries has shown a greater concentration of sympathetic fibers around the posterior cerebral arteries and posterior communicating arteries. This then lends itself to the hypothesis that greater sympathetic innervation leads to vasoconstriction and possibly hyperperfusion, endothelial injury, and cerebral edema (51,58). This further leads to controversy and questions into the exact pathophysiology of PRES.

**Cardiovascular Hypertensive Emergencies**

Approximately 20% of patients with malignant hypertension present with cardiac complications, which may include myocardial ischemia or pulmonary edema (59). Many patients have a pre-existing history of chronic hypertension with already existing left ventricular hypertrophy and diastolic dysfunction, while a smaller subset also has impaired systolic function. Left ventricular hypertrophy increases myocardial oxygen requirements while also outstripping vascular supply and compressing coronary arterioles. The increased afterload associated with severe hypertension further increases myocardial wall stress and oxygen demand, such that ischemia occurs, especially if there is also concomitant coronary artery disease. Increased wall thickness and changes to the extramyocardial collagen network impair myocardial relaxation, and cause pressure within the left ventricle to rise at relatively lower volumes during diastole. As a result, even small increases in intravascular volume and afterload can produce pulmonary edema (60).

**Acute Heart Failure**

Acute heart failure is responsible for 5% to 10% of hospital admissions, with hospital mortality of about 4%, increasing to more than 50% at 1 year. In a large American registry, 73% of patients had a history of chronic hypertension, and 50% were hypertensive at admission (61). In patients presenting with flash pulmonary edema, acute hypertension is particularly common, and is likely to be both a consequence and contributing cause. Patients suspected of having acute heart failure should have a chest x-ray, echocardiogram, electrocardiogram, oxygen saturation, blood chemistry, full blood counts, and natriuretic peptide measurements (62). If the measured NT-pro-BNP or BNP level is less than the cut-off points of, respectively, 300 pg/mL and 100 pg/mL, acute heart failure can be ruled out (62). These tests have the goal of determining if ventilation and oxygenation are adequate, if the patient is hypotensive or in shock, has life-threatening tachy- or bradydysrhythmias, acute valvular disease, or acute coronary syndrome (ACS). The patient may need noninvasive or invasive ventilation, cardioversion, pacing, inotrope infusion, mechanical circulatory support, or coronary reperfusion (62). A history of chronic hypertension exists in 40% to 70% of patients with ACSs, and about 30% have an elevated blood pressure when initially assessed (63,64). Severe uncontrolled hypertension at admission (>180/110 mmHg) is a relative contraindication to thrombolysis for ST-elevation myocardial infarction (STEMI) (65). ACS is diagnosed by clinical symptoms of chest pain and ST changes on electrocardiogram, but troponin biomarkers have the most utility, approaching 100% sensitivity (66,67). In fact, chest pain syndromes without troponin biomarker elevation are excluded from the definition of ACS and, instead, are classified as a subtype of severe stable coronary artery disease (66).

**Aortic Dissection**

Aortic dissection is a relatively rare condition, with an annual incidence of between 3 and 6 cases/100,000 persons/year, with about two-thirds being Stanford type A (involving the ascending aorta or the arch) and one-third being type B (involving the descending aorta) (68,69). With modern medical and surgical therapy, the mortality has decreased from as high as 90% to approximately 47% for type A who survive to admission, and 13% for type B (69). About 65% to 70% of patients have a history of chronic hypertension and, in one study, 46% of patients had documented systolic blood pressure of greater than 180 mmHg in the prior 5 years before dissection. Most patients (70%) with type B dissection have an admission systolic pressure of more than 150 mmHg, compared with just over a third of those with type A dissections, of whom approximately 25% actually present with hypertension or in frank shock (68). The pathophysiology and mechanism by which hypertension predisposes to aortic dissection is still under investigation. Current postulates stem from decreased flow in the vasa vasorum; when this flow is decreased, there is inadequate oxygen delivery to the entire thickness of the aortic wall. This leads to ischemic outer media, decreased smooth muscle cells, and changes in the elastic laminae, leading to stiffness of the outer media. Interlaminal shear forces occur between the healthy inner layer and stiff outer layer, which eventually lead to aortic dissection (70,71).

**Perioperative Hypertension**

Preoperative hypertension is thought to be a perioperative risk factor for mortality, major morbidity, prolonged length of stay, and readmission (72), although this is questioned. Classically, operative cases have been canceled for hypertension greater than 180/110 mmHg. However, a study of 989 hypertensive patients who had a diastolic pressure of greater than 100 mmHg just prior to surgery were either treated with intranasal nifedipine and immediate surgery, or surgery was delayed with slower lowering of the blood pressure over a course of days; delaying surgery did not improve outcomes (73). Increased pulse pressure—the systolic pressure minus diastolic pressure—has been shown to yield increased risk for perioperative cerebral events and mortality in patients having cardiac surgery (74). The American Heart Association now recommends weighing the risk of delaying nonemergent surgery to control severely elevated blood pressure—greater than 180/100 mmHg—versus proceeding (75).

Intraoperative blood pressure elevations of greater than 20% of baseline blood pressures are considered to be a hypertensive emergency (76). Intraoperative hypertension has the highest incidence during carotid, abdominal aortic, peripheral vascular, abdominal, and intrathoracic operations. Depending upon the patient population, type of surgery, and how hypertension is defined, 3% to 34% of operative interventions are complicated by postoperative hypertension in the recovery room or ICU, with the most important risk factors being inadequately controlled pain and a pre-existing history of hypertension, especially if antihypertensives were withdrawn in the preoperative period (77,78). Elevations in blood pressure...
occur most often during the initial 30 to 60 minutes after surgery, may last for several hours, and have been associated with higher rates of postoperative hemorrhage and myocardial ischemia in certain patient populations (77). Hypertension is particularly frequent following neurosurgical and cardiovascular procedures, occurring in, respectively, 54% to 91% and 30% to 80% of patients undergoing craniotomy and coronary artery bypass grafting (79–81). The elevation in blood pressure is postulated to be due to increases in sympathetic tone and vascular resistance (77,82).

**Pregnancy-Induced Hypertension**

Hypertension complicates approximately 6% to 8% of pregnancies, and is responsible for 18% of maternal deaths in the United States, 26% of maternal deaths in Latin America and the Caribbean, and 9% of the deaths in Africa and Asia (83). Pregnancy-induced hypertension (PIH) encompasses gestational hypertension, preeclampsia, and eclampsia. Gestational hypertension is defined as blood pressure elevation, greater than 140/90 mmHg beginning after 20 weeks gestation and resolving by 12 weeks postpartum. Eclampsia is defined as gestational hypertension with proteinuria, greater than or equal to 300 mg in 24 hours, or as proteinuria in women with known hypertension but who previously did not have proteinuria prior to 20 weeks gestation. Preeclampsia is associated with vasoconstriction, endothelial dysfunction, platelet aggregation, and increased coagulation (83). Preeclampsia occurs in 2% to 8% of pregnancies with important risk factors including nulliparity, antiphospholipid antibodies, diabetes mellitus, obesity, family history, multiple (twin) pregnancies, maternal age over 40, and a previous history during other pregnancies. Maternal complications can include progression to eclampsia, pulmonary edema, microangiopathy, renal failure, and placental abruption. The most common neonatal complications are prematurity and intrauterine growth restriction. Most cases of PIH do not present until after 36 weeks of gestation. Recently, a multicenter, randomized control trial looked at the induction of labor versus expectant monitoring for gestational hypertension or mild preeclampsia after 36 weeks’ gestation (HYPITAT) (84). This study found induction of labor resulted in a lower incidence of poor maternal outcome and therefore recommend for inducing labor (84). Eclampsia is defined as the development of severe neurologic manifestations, including seizures and a depressed level of consciousness, in women with preeclampsia, which is not attributed to another cause. It complicates 1% to 2% of severe preeclampsia and 79% of cases have signs and symptoms in the week prior to the event: headache in 56%, hypertension in 48%, proteinuria in 46%, visual disturbances in 23%, and epigastric pain in 17% (83).

**TREATMENT**

**Pharmacologic Agents**

An ideal pharmacologic agent (Table 100.4) for treatment of hypertensive emergencies should have a rapid onset in order to immediately reduce the progression of organ failure, but should also be short acting and easy to titrate to avoid excessively lowering the blood pressure below the range of auto-regulation of cerebral, coronary, and renal arterial systems. Because of this, intravenous agents should be used, rather than ones requiring the sublingual or intramuscular routes (85). The following agents are the most commonly used.

**β-Blockers**

Labetalol is the most commonly used intravenous β-blocker (and α-blocker) for the management of hypertensive emergencies. One of its unique properties is that when given intravenously, it blocks both α- and β-receptors, although the nonselective β-blocking effect is more prominent at a ratio of 1:7 (85). Labetalol is usually administered as 10- to 20-mg boluses, which can be repeated every 15 minutes until the desired effect is achieved. Blood pressure lowering begins within 2 to 5 minutes, with maximal effect after about 5 to 15 minutes and elimination half-life of around 5.5 hours (85). Labetalol can also be delivered as an infusion, beginning at a dose of 1 to 2 mg/min. It has been demonstrated to be safe and effective in the management of severe hypertension, with advantages that it does not cause reflex tachycardia, has little effect on cerebral blood flow or ICP, and does not decrease cardiac output (85,86). Because of its lipophilic nature, labetalol does not cross the placenta well, and there is extensive

| TABLE 100.4 Intravenous Pharmacologic Agents for Management of Hypertensive Emergencies |
|-----------------|-----------------|-----------------|-----------------|
| **Drug** | **Dose** | **Onset** | **Duration** | **Precautions** |
| Labetalol | 10–20 mg boluses | 5–15 min | 2–4 hrs | Bradycardia, heart block; LV dysfunction; asthma |
| Esmolol | 0.5 mg/kg load, 50–200 μg/kg/min | 5 min | 10–30 min | Bradycardia, heart block; LV dysfunction; asthma |
| Nicardipine | 3–15 mg/min | 5–15 min | 30–60 min | Rebound tachycardia |
| Clevidipine | 2–32 mg/h | 2–6 min | 2–10 min | Reflexive tachycardia; rebound hypertension; each 100 mg vial has 20 g of soya bean oil |
| Fenoldopam | 0.1–1.6 μg/kg/min | 5–15 min | 20–60 min | Glaucoma |
| Nitroprusside | 0.25–10 μg/kg/min (ideally less than 2 μg/kg/min) | Immediate | 1–10 min | Cyanide toxicity with prolonged infusions; coronary steal; ↑ ICP |
| Nitroglycerin | 10–200 μg/min | Immediate | 3–10 min | Severe hypotension in hypovolemic patients; ↑ ICP; contraindicated if on PDE-5 inhibitors |
| Enalaprilat | 0.625–2.5-mg bolus, every 6 hrs | 15 min | 4–6 hrs | Renal failure; hyperkalemia |
| Hydralazine | 10–20 mg every 4–6 hrs | 5–20 min | 2–6 hrs | Reflex tachycardia; ischemic heart disease |

ICP: Intracranial pressure; LV, left ventricular; PDE-5, phosphodiesterase-5.
experience using it in pregnancy, making it one of the preferred agents in the management of preeclampsia and eclampsia (83).

Esmolol is an extremely short-acting, relatively cardioselective β-blocker, with onset within less than a minute, and a unique metabolism by red blood cell esterases such that its duration of action is only 10 to 20 minutes; in anemic patients the half-life can be increased. A loading dose of 0.5 mg/kg is administered over 1 minute, followed by an infusion of 50 μg/kg/min, which can be adjusted as often as every 5 minutes to a maximum dose of 200 μg/kg/min. This maximum dose is due to the toxicities of the solvent, propylene glycol: renal toxicity, elevated osmolar gap, metabolic acidosis, cardiac arrhythmias, seizures, and hemolysis (87). Esmolol is a useful agent when blood pressure is elevated and cardiac output is preserved, especially when there are concerns about myocardial ischemia. Because it decreases heart rate as well as myocardial contractility, cardiac output is lowered. It may also cause bronchospasm and, therefore, should be used in caution in patients with low cardiac output or chronic obstructive pulmonary disease (83).

Nicardipine

Nicardipine is a second-generation dihydropyridine calcium channel blocker (CCB) that inhibits calcium influx through L-type channels, thereby preventing smooth muscle contraction, particularly in vascular smooth muscle, rather than cardiac myocytes. Thus, nicardipine causes arterial vasodilation, with minimal venodilation or change in cardiac output. It increases stroke volume and coronary blood flow leading to a favorable oxygen consumption versus supply ratio (85). It is most often administered as an intravenous infusion, beginning at 3 to 5 mg/hr, to a maximum of 15 mg/hr, but it can also be given as 0.5- to 3-mg boluses, and dosing has been reported up to 30 to 45 mg/hr. Because of a distribution half-life of less than 3 minutes and an intermediate elimination half-life of less than 45 minutes, nicardipine has a relatively rapid onset and offset (88). It has compared favorably with sodium nitroprusside (NTP) in clinical trials, with therapeutic targets achieved in a similar amount of time, fewer episodes of severe hypotension, and less frequent dose adjustment (88,89).

Nicardipine has been used in a variety of settings, including malignant hypertension, perioperative hypertension, hemorrhagic stroke, preeclampsia, and acute heart failure. It is generally well tolerated, with few adverse effects when used with caution. Given that nicardipine may increase cerebral blood flow, one might expect that it would raise ICP. Although this has been reported, it does not appear to be a major concern in most studies (85,90).

Clevidipine

Clevidipine is a third-generation, intravenous, dihydropyridine calcium channel antagonist. It selectively inhibits L-type channels, which inhibits the influx of calcium leading to smooth muscle relaxation. This equates to potent arterial vasodilatory properties with little effect on myocardial inotropy and venous capacitance. It has been shown to significantly increase stroke volume and cardiac output (91). Clevidipine has a rapid onset of about 2 minutes, with goal blood pressure being reached within 6 minutes and steady state reached in 15 minutes. It is metabolized by red blood cell esterases and has a half-life of around 2 minutes. It also has numerous antioxidative properties, increases NO concentrations, and decreases intracellular calcium concentration (85,91). Initial infusion rate is recommended at 2 mg/hr and may be doubled every 90 seconds to reach target blood pressure. The US guidelines recommend using a lower dose increase and at 5- to 10-minute intervals as the target blood pressure is nearied. The maximum dose is 32 mg/hr, with a maximum of 1,000 mL/24-hour period and maximum infusion period of 72 hours (91). Clevidipine has been shown to be safe in treatment of acute ICH, acute ischemic stroke, SAH, perioperative hypertension, acute heart failure, and patients with renal dysfunction and severe hypertension. It is available in many European countries for blood pressure control in the perioperative setting and in the United States when oral therapy is not feasible (91).

Fenoldopam

Fenoldopam is a selective dopamine-1 (DA-1)-receptor agonist, which produces peripheral, renal, splanchnic, and, to a lesser degree, coronary vasodilatation. Stimulation of DA-1 receptors also promotes natriuresis. Unlike dopamine, fenoldopam does not have any effect on DA-2 receptors, nor does it act at the α- or β-adrenergic receptor level. It does not cross the blood–brain barrier, and therefore has no effect on intraparenchymal dopamine receptors. There are cranial endothelial DA-1 receptors and, therefore, fenoldopam causes some cerebral vasodilatation. It is typically administered in doses of 0.025 to 1 μg/kg/min, and begins to lower blood pressure after as little as 2 minutes, although the maximal effect is not seen for at least 20 to 30 minutes or more; with discontinuation of an infusion, the elimination half-life is less than 10 minutes. Reflex tachycardia, related to activation of the baroreflex, may occur and can be attenuated with concomitant use of a β-blocker (92). A theoretical advantage of fenoldopam is improved renal blood flow, but clinical trials have shown conflicting results in decreases in renal replacement therapy or death (93–96). Fenoldopam has been demonstrated to be effective at controlling blood pressure in hypertensive emergencies, with efficacy similar to nitroprusside, but has shown no clear improvement in outcomes; it has also been considerably more expensive than NTP (97), although this may be changing with the upheaval of the US generic drug market. Overall, fenoldopam seems to have few adverse effects. It does raise intraocular pressure, and should therefore probably be avoided in patients with a known history of glaucoma (98,99).

Sodium Nitroprusside

NTP has been used in the management of hypertensive emergencies for over 40 years, and continues to be used, largely because of its rapid onset, short duration of action, affordability—although the upheavals in the US generic drug market may be changing this—familiarity, and efficacy (8,100). Sodium nitroprusside is a potent arterial and venous vasodilator, which has an onset within less than 30 seconds and a duration of action of only 2 to 3 minutes, such that cessation of the infusion allows blood pressure to rise back to previous levels within 1 to 10 minutes. Cardiac output is either preserved or increased, and cardiac filling pressures decrease (85). The mechanism of action involves the release of NO into the bloodstream, activation of guanylate cyclase, and subsequent
conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP) in vascular smooth muscle, which in turn inhibits the intracellular movement of calcium. The usual starting dose of sodium nitroprusside is 0.25 to 0.5 μg/kg/min, and it is increased in increments of 0.5 μg/kg/min every 5 to 10 minutes until the goal blood pressure is achieved.

Sodium nitroprusside has the potential for several serious, life-threatening complications. First, despite lowering preload and afterload, sodium nitroprusside may induce coronary steal, whereby excessive vasodilatation of coronary arterioles shunts blood away from ischemic regions (85). This effect may help explain the findings of a large clinical trial in which patients with acute myocardial infarction and high left ventricular filling pressures had worse outcomes when treated with nitroprusside within the first 8 hours, but improved outcomes thereafter (101).

Second, NTP is often avoided in neurologic emergencies because of the observation that it vasodilates cerebral vasculature, increases cerebral blood volume, and therefore raises ICP (85,102). The demonstration of this phenomenon is not entirely consistent in the literature, and it may be advisable with a somewhat slower administration (103).

Third, each nitroprusside molecule has five cyanide moieties, such that cyanide makes up 44% of the drug’s molecular weight (85). Cyanide is metabolized by transulfuration in the liver to thiocyanate, which is 100 times less toxic than cyanide, and is cleared in the urine and stool; when this pathway is overwhelmed, cyanide accumulates and causes toxicity. Patients receiving sodium nitroprusside are particularly vulnerable when treated with prolonged, high-dose infusions, especially if hepatic and renal function are impaired, or if sulfur stores are depleted because of malnutrition (100). Cyanide blocks oxidative phosphorylation and essentially causes tissue anoxia and lactic acidosis despite adequate oxygen delivery, leading to high venous oxygen saturation levels. Manifestations of cyanide poisoning include depressed mental status, seizures, and, eventually, bradycardia and hemodynamic collapse. Cyanide levels are not easily monitored, and the development of lactic acidosis is a late finding. The development of tachyphylaxis to nitroprusside, with consequent increasing dose requirements, may be a harbinger of toxicity (100).

Treatment of cyanide poisoning consists of discontinuation of sodium nitroprusside, supportive care with the delivery of 100% oxygen, and the administration of sodium nitrite (300 mg IV), followed by sodium thiosulfate (12.5 gm IV). The use of sodium nitrite is controversial, as it actually causes the production of methemoglobin, which, although also potentially toxic, binds avidly to cyanide. Sodium thiosulfate acts as a sulfur donor to promote the formation of thiocyanate, and has been used effectively as monotherapy. Hydroxycobalamin combines with cyanide to form cyanocobalamin, and may provide synergy with sodium thiosulfate. Both agents have been used prophylactically with infusions of nitroprusside to prevent cyanide accumulation. Accumulation of thiocyanate, although far less toxic than cyanide, may also cause complications (104). The coadministration of thiosulfate infusions in patients receiving nitroprusside infusions, in the 4 to 10 μg/kg/min range, has been advocated.

Because of these concerns, and despite sodium nitroprusside’s extensive track record, it should be administered at as low a dose as possible, and for as short a duration as possible. It has been argued sodium nitroprusside should only be used in patients with normal renal and hepatic function and only after newer, alternative agents have failed (85).

Nitroglycerin
Because nitroglycerin produces more venous, than arterial, dilatation, it is usually not used as first-line therapy for hypertensive emergencies, unless there is concurrent pulmonary edema or myocardial ischemia. When either of these are the case, it is usually started at 5 to 10 μg/min, and can be titrated up every 5 to 10 minutes to doses as high as 200 to 300 μg/min. Particular caution must be exercised in the setting of hypovolemia (85). Patients using drugs for erectile dysfunction should not be given nitroglycerin or nitroprusside, as this may induce profound hypotension (80). As with nitroprusside, there are case reports of nitroglycerin increasing ICP, such that it should be used with caution in brain-injured patients (105).

Enalaprilat
Enalaprilat is an ACE inhibitor in intravenous form. Its effect is not seen for about 15 minutes, takes an hour to reach peak effect, and lasts for up to 6 hours. As with all ACE inhibitors, patients who have decreased renal perfusion are at risk for acute renal injury and hyperkalemia if given this drug (85).

TREATMENT FOR SPECIFIC HYPERTENSIVE EMERGENCIES

Malignant Hypertension
Because of the shift in the autoregulatory curve that occurs with prolonged hypertension, rapid reductions in blood pressure may cause organ ischemia (106). With hypertensive urgencies, the blood pressure should therefore be reduced carefully and gradually with oral medications over the course of several days. It is not precisely known how long it takes for the autoregulatory curve to recover and shift back toward the left, thus, the initial goal should never be normal blood pressure.

With hypertensive emergencies, the blood pressure must be reduced immediately, with an initial goal of no more than a 15% reduction. Specific treatment goals should be individualized to ensure that the pressure is reduced sufficiently for organ failure to resolve without compromising perfusion. To facilitate keeping blood pressure within a narrow range, placement of an arterial catheter and careful observation in the ICU are recommended.

Neurologic
Acute Ischemic Stroke
Although acute hypertension is common in patients with ischemic stroke, optimal treatment remains uncertain. The greatest priority in these patients is to preserve as much of the ischemic penumbra as possible and to avoid hemorrhagic conversion and malignant cerebral edema. Because autoregulation is usually impaired within the penumbra, pressure reductions may cause blood flow to fall, which in turn may increase infarct size (107). However, several older observational studies have
inconsistent results, demonstrating lowering blood pressure may cause worsened, better, or no change in clinical outcome (108–111). Preliminary pilot studies have suggested that transcranial Doppler middle cerebral artery (MCA) flow velocities, cerebral perfusion as determined by MRI, and neurologic examination may improve with supranormal augmentation of blood pressure using a vasopressor (112). The International Stroke Trial of more than 17,000 patients found a U-shaped relationship, where the best outcomes occurred in patients with a presenting systolic blood pressure of about 150 mmHg (113). The 2013 American Stroke Association guidelines currently recommend not treating hypertension unless the systolic pressure exceeds 220 mmHg, the diastolic pressure exceeds 120 mmHg, or there is another medical condition which would benefit from lowering the blood pressure (111). Finally, in a large, multicenter, randomized and controlled study in which patients were randomized to reduction of blood pressure by 25% within 24 hours and to less than 140/90 mmHg within 7 days versus discontinuing all antihypertensive medications, there was no difference in death or major disability at 14 days, at hospital discharge, or at 3-month follow-up (114).

The exception to this rule is if the patient is a candidate for intravenous or, possibly, intra-arterial thrombosis. Of patients who receive intravenous rt-PA for treatment of acute ischemic stroke, 5% to 6% will develop ICH (115). Whether lowering blood pressure helps to limit this risk is not certain. However, patients in whom systolic and diastolic pressure could not easily be lowered to, respectively, less than 185 mmHg and 110 mmHg, were excluded from the definitive clinical trial (116). Patients who did receive thrombolysis had a goal blood pressure of less than 180/105 mmHg. Approximately 10% of patients require intravenous antihypertensive therapy prior to receiving thrombolysis, while 25% to 30% require treatment in the 24 hours after thrombolysis (47).

**Intracerebral Hemorrhage**

Good neurologic recovery is very uncommon if the volume of ICH exceeds 30 to 60 mL. Hematoma growth is a dynamic process that occurs over several hours, with a significant proportion of patients having detectable expansion even within the first few hours after presentation to the ED or ICU (117). Patients with early hematoma enlargement have substantially worse outcomes, and it is likely that therapy that can limit this early growth will improve outcomes. Numerous studies have suggested that patients with higher blood pressure at presentation are more likely to develop hematoma expansion and have a higher mortality (118,119). The main reason for previous concern for lowering the blood pressure has been the observation that there is reduced blood flow around areas of ICH and the belief that this represents an ischemic penumbra that could be compromised with lower blood pressure. However, studies using positive emission tomography and MRI have suggested that there is reduced blood flow around areas of ICH and the corresponding reduction in cerebral metabolic rate (120). Furthermore, cerebral blood flow autoregulation in this region appears to be preserved, so that lowering blood pressure does not adversely impact regional blood flow (121).

Based on these data, the INTensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT) 1 and 2, and Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) I and II were undertaken (46,122). The INTERACT 2 trial reported results in the Spring of 2013, demonstrating that intensive lowering of systolic blood pressure to less than 140 mmHg within 6 hours of onset did not result in a change in rate of death or severe disability. However, ordinal analysis of modified Rankin scores did show improvement in functional outcomes with intensive blood pressure control (46). ATACH II is an ongoing, multicenter, 5-year, randomized, controlled, phase-III trial to determine if intensive blood pressure lowering within 3 hours of onset and for 24 hours by intravenous nicardipine decreases the likelihood of death or disability by 10% at 3 months, compared to conservative treatment (122). The current American Heart Association guidelines from 2010 were promulgated prior to completion of these studies, and state that for patients with systolic blood pressure of 150 to 220 mmHg, its acute lowering to 140 mmHg is probably safe (39).

**Subarachnoid Hemorrhage**

Nontraumatic SAH results from a ruptured intracranial aneurysm in more than 80% of cases (49). The risk of recurrent hemorrhage from the aneurysm is 4% to 13.6% within the first 24 hours (50). Risk factors associated with rebleeding include longer time to securing of the aneurysm, worse admission neurologic examination, previous sentinel headaches, larger aneurysm size, and systolic blood pressure greater than 160 mmHg. Many centers attempt to decrease the risk of recurrent hemorrhage by reducing blood pressure prior to securing the aneurysm, with review articles often citing goal systolic pressures of less than 140 to 180 mmHg (49). However, the efficacy of this practice remains uncertain, with conflicting results from observational studies. Particular caution should be exercised when treating patients with high-grade SAH who are stuporous or comatose, because these patients may have a raised ICP, and excessive reduction in blood pressure may compromise cerebral perfusion and promote ischemia. Current American Heart Association guidelines recognize the lack of evidence on how intensely to control the blood pressure, but state that decreasing the systolic blood pressure to less than 160 mmHg is reasonable (50).

After the aneurysm has been treated, the most concerning complication is the development of cerebral vasospasm and delayed ischemic neurologic deficits (DINDs), which occur in approximately 20% to 40% of patients, with maximum risk between days 7 and 10 after the event, resolving by post bleed day 21 (50). Hypertension should not routinely be treated during this time, even at relatively high levels, since this practice increases the risk of DIND. If clinical vasospasm develops, first-line therapy actually involves hemodynamic augmentation, using vasopressors to raise blood pressure in order to increase cerebral blood flow and improve cerebral perfusion in conjunction with endovascular treatments such as intra-arterial vasodilator infusions and balloon angioplasty (50).

**CARDIOVASCULAR HYPERTENSIVE EMERGENCIES**

**Acute Heart Failure and Pulmonary Edema**

Acute hypertension exists in the majority of patients presenting with flash pulmonary edema, and is likely to be both a consequence and contributing cause (61,123). The venodilating properties of nitroglycerin make it an excellent initial choice
as an antihypertensive in both normotensive and hypertensive patients, especially if there is failure to improve after administration of a loop diuretic. In titrating the dose of intravenous nitroglycerin, clinicians should be aware that relatively large doses, often in excess of 100 μg/min, may be required to significantly lower cardiac filling pressures and improve symptoms (124). Patients who benefit from aggressive afterload reduction, such as those with acute aortic or mitral regurgitation (if not hypotensive), may require a more potent arterial vasodilator than nitroglycerin, such as nitroprusside or nicardipine.

Although ACE inhibitors are standard care for chronic heart failure, there is little evidence of benefit for acute decompensated heart failure. The only intravenous preparation, enalaprilat, was potentially harmful when routinely administered to patients within the first 24 hours following STEMI, and is therefore not recommended (125). Considerable caution must be exercised when intubating hypertensive patients with acute pulmonary edema, since it is very common for blood pressure to drop precipitously with sedation and positive pressure ventilation. Noninvasive ventilation should be considered in dyspneic patients with pulmonary edema but, again, may reduce blood pressure with initiation and should be used in caution in patients in shock (62). Another agent that has been proposed for use in acute heart failure is nesiritide (recombinant human brain natriuretic peptide). However, it has not been demonstrated to improve clinically important outcomes when compared with standard therapy (126), may worsen renal function (127), and has been linked to a possible increased risk of short-term death (128). In a trial comparing low-dose dopamine or low-dose nesiritide in addition to diuretic therapy in patients in acute heart failure with renal dysfunction, neither drug improved congestion or renal function (129). In a recent international, multicenter, randomized controlled trial, clevidipine was demonstrated to be faster and more effective in reducing blood pressure into the target range, and in reducing dyspnea symptoms when compared to standard of care intravenous blood pressure lowering agents (130).

**Acute Coronary Syndromes**

Although definitive therapy for ACSs involves antithrombotic agents and revascularization, other steps can be taken to decrease oxygen consumption. Oxygen consumption is increased by increases in heart rate, contractility, and wall stress. Wall stress is estimated by Laplace’s equation:

\[
\text{Stress} = \frac{\text{pressure} \times \text{radius}}{(2 \times \text{wall thickness})}
\]

- β-Blockers decrease heart rate, contractility, and blood pressure, and are recommended for all ACS patients without a contraindication. β-blockers have been shown to decrease mortality by 28% to 34%, decrease the reinfarction rate by 18%, and cardiac arrest by 15% (131). Intravenous β-blockers must be used with caution in patients with reduced left ventricular systolic function and in those in whom there is concern about impaired cardiac conduction (e.g., inferior myocardial infarction). A large clinical trial of early intravenous, followed by oral, β-blockade in patients with STEMI demonstrated an increased risk of cardiogenic shock, mostly in high-risk patients: age greater than 70, systolic blood pressure less than 120 mmHg, and heart rate greater than 110 beats/min (131). ACE inhibitors decrease afterload and oxygen consumption; captopril, ramipril, andtrandolapril have all been shown to reduce mortality in patients with heart failure and after myocardial infarction (131). ACE inhibitors should be given within 24 hours of myocardial infarction in patients with a left ventricular ejection fraction of less than 40% or heart failure (131). If the blood pressure remains significantly elevated, especially with ongoing chest pain or pulmonary edema, then nitroglycerin should be used. In addition to reducing oxygen consumption by decreasing preload and left ventricular end-diastolic volume, nitrates also vasodilate coronary arteries, especially at the site of plaque disruption. If three sublingual tablets (0.4 mg over 5 minutes) are ineffective, then an intravenous infusion should be started and adjusted to alleviate chest pain and reduce blood pressure (10% reduction in normotensive patients, 30% reduction in hypertensive patients) (65). Use of nitroglycerin in combination with phosphodiesterase inhibitors can cause profound hypotension and, therefore, nitrates should be avoided in patients who have taken sildenafil and tadalafil. The aldosterone receptor antagonist, eplerenone, has been shown to further reduce mortality in patients with acute myocardial infarction with heart failure who have already been treated with a β-blocker or ACE inhibitor. CCBs should only be used in patients for augmented hemodynamic support, not as routine primary agents. Caution must be taken with dihydropyridine CCBs, nifedipine and amlodipine, as they can cause reflex tachycardia, and caution must be taken with nondihydropyridine CCBs, verapamil and diltiazem, in patients with heart failure and pulmonary edema due to their negative inotropic effects (131). Preconditioning strategies such as remote upper limb transient ischemia by suprainfarction of blood pressure cuff have been shown to reduce all-cause mortality in comparison to standard care. Cyclosporine administration for postconditioning to prevent reperfusion injury is currently being studied in Europe in the larger Cyclosporine and Prognosis in Acute MI Patients (CIRCUS; NCT01502774) trial.

**Aortic Dissection**

The purpose of emergently lowering blood pressure in aortic dissection is to decrease shear stress on the aorta and limit propagation of the intimal tear and false lumen. In order to concomitantly reduce both blood pressure and the force of left ventricular contraction, first-line therapy consists of a β-blocker or, if contraindicated, a CCB with negative inotropic and chronotropic properties (e.g., diltiazem or verapamil). Pure vasodilators should not be used in isolation. If possible, the heart rate should be lowered to less than 60 beats/min, and the blood pressure reduced as much as can be tolerated, ideally below a systolic pressure of 120 mmHg. Because patients often have substantial chest discomfort, the use of opiates to ameliorate pain may greatly reduce antihypertensive requirements. If the blood pressure remains elevated despite adequate β-blockade, a vasodilator can be added. There is extensive experience with nitroprusside in this setting, although other agents have also been used (88,132).

**Perioperative Hypertension**

Perioperative hypertension is a common phenomenon, as previously mentioned, especially after vascular surgery, neurosurgery, intrathoracic surgery, and abdominal surgery. Almost all of the agents previously mentioned have been studied and the choice of agent should depend upon the patient’s specific comorbidities and operation.
Hypertension occurs in the setting of craniotomy more often than with any other type of surgery (79). Neurosurgery results in the release of large amounts of vasoactive substances that raise blood pressure, including catecholamines, endothelin, and renin (133). Importantly, severe hypertension occurring intraoperatively or during the first 12 postoperative hours has been associated with a higher risk of intracranial hemorrhage complicated craniotomy (79). Recently a clinical trial found nicardipine to be superior to esmolol in the treatment of emergence hypertension after intracranial tumor resection (81).

Mild intraoperative hypotension is sometimes used for vascular neurosurgical procedures, such as microsurgical excision or endovascular obliteration of arteriovenous malformations (AVMs) in order to reduce the risk of hemorrhage. With AVM, the sudden “repressurization” of previously hypotensive arterioles may contribute to the development of regional hyperemia, edema, and bleeding, a condition sometimes referred to as “normal perfusion pressure breakthrough.” Consequently, hypertension should be avoided in the immediate postoperative period; indeed, systolic blood pressure is frequently kept between 90 and 110 mmHg in the immediate postoperative period. Conversely, the sacrifice of vascular branches during the procedure, or vassospasm from surgical manipulation and retraction, may also create areas of relative underperfusion, such that hypotension would also be deleterious (134).

There are certain neurosurgical procedures where tight postoperative blood pressure control is particularly important. In most patients undergoing carotid stenting or endarterectomy, the sudden resolution of carotid stenosis results in a sudden, asymptomatic, 20% to 40% increase in ipsilateral cerebral blood flow. However, in some patients, the increase can be much more profound, to the degree that it overcomes the autoregulatory capacity of the corresponding, previously hypoperfused territory. The resulting cerebral hyperperfusion syndrome (CHS) is characterized by the presence of vasogenic edema, which resembles PRES in that there is a posterior predilection. Patients who are most vulnerable are those with relatively severe carotid stenosis and poor collateral circulation, but postoperative hypertension is also an important risk factor. CHS is treated with tight blood pressure control, but agents that cause cerebral vasodilatation, including nitroprusside ideally should be avoided (135).

**Preeclampsia and Eclampsia**

Although hypertensive encephalopathy and eclampsia have largely been considered separate entities, they have a similar pathophysiology and essentially the same MRI findings, PRES (136). Definitive treatment for severe preeclampsia and eclampsia is delivery, but careful intravenous blood pressure control is frequently also necessary.

Treatment of hypertension in severe preeclampsia has not been shown to improve perinatal outcomes, and may actually contribute to a decrease in neonatal birth weight (137). Thus, pharmacologic therapy is not recommended unless the degree of blood pressure elevation is severe (defined as SBP exceeding 160 mmHg or DBP exceeding 105 to 110 mmHg) or there are end-organ complications. Oral medications, with a systolic goal pressure of 140 to 155 mmHg and a diastolic goal of 90 to 105 mmHg, may be sufficient in the absence of organ dysfunction, but more rapid and tighter control is necessary for severe preeclampsia and eclampsia. Although there has been extensive experience with intravenous hydralazine (5 to 10 mg every 15–20 minutes to a maximum dose of 30 mg), this agent has a relatively slow onset, has not commonly been used as an infusion, may overshoot blood pressure goals, and has recently been linked to worse outcomes, including more placental abruption, adverse effects on fetal heart rate, lower Apgar scores, and a greater need for cesarean section (138). Other intravenous agents that have been successfully and safely used include labetalol and nicardipine (88,139). In addition, magnesium sulfate should be given to prevent the development of seizures in patients with severe preeclampsia, and should be used to prevent further seizures should eclampsia occurs (140).

**SUMMARY**

Treatment of acute hypertension and hypertensive crisis is common in the ICU. Determining the underlying cause, and how it is affecting end organs, is paramount in selecting the best treatment options. Manifestations in the course of a hypertensive emergency may impact all organs, but especially the cardiovascular system and brain, and this greatly affects therapeutic options and goals. With few exceptions from the rule (aortic dissection or severe pulmonary edema), the patient’s blood pressure should be reduced in a stepwise approach, and with precision, by intravenous medications rapidly delivered, while monitoring the cardiovascular and central nervous systems. The selection of the ideal antihypertensive agent depends on both the cause and the end-organ dysfunction as detailed in this chapter.

**Key Points**

- Extreme hypertension exceeding the upper range of autoregulation causes edema, hemorrhage, and organ dysfunction, while reductions in blood pressure beyond the lower limits of autoregulation result in tissue hypoperfusion and ischemia.
- Normal endothelial function is necessary for the regulation of vascular tone, blood pressure, and regional blood flow.
- Ideal pharmacologic agents for treatment of hypertensive emergencies have a rapid onset, are short-acting and are easy to titrate.

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