CHAPTER 126 ■ ACUTE HYPERTENSION MANAGEMENT IN THE ICU

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DEFINITIONS

Acute hypertension is a common issue in the intensive care unit (ICU). The settings in which blood pressure elevation occur are highly variable, and optimal care must be tailored to the pathophysiology of the specific circumstances in which it is encountered. The terminology used in the literature to classify this heterogeneous group of disorders has been somewhat inconsistent and confusing (Table 126.1). The terms, hypertensive emergency or hypertensive crisis, are commonly defined as a marked increase in blood pressure associated with target-organ damage, implying that the blood pressure should be lowered emergently.

Some authors have reserved the definition of hypertensive emergency for the situation where blood pressure elevation itself is directly responsible for causing end-organ damage. However, clinicians more often need to rapidly lower blood pressure in situations where hypertension, although not necessarily directly responsible for causing the condition, may contribute to deterioration. 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 broadly—as any condition in which blood pressure should be lowered immediately. 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 this diagnosis to be made.

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, that 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. The most recent Joint National Committee Guidelines (JNC 7) classify patients with hypertension into stage 1 (systolic blood pressure [SBP] 140-159 mm Hg or diastolic blood pressure [DBP] 90-99 mm Hg) and stage 2 (SBP exceeding 160 mm Hg or DBP exceeding 100 mm Hg). The previously used category of “stage 3 hypertension” (SBP exceeding 180 mm Hg or DBP exceeding 110 mm Hg) has been combined with stage 2 (3).

EPIDEMIOLOGY AND ETIOLOGY

Hypertension is extraordinarily common, with over 1 billion individuals affected worldwide, and only a minority of these having adequate blood pressure control (4). The incidence of hypertensive emergencies and urgencies has not been assessed in population-based studies. Less than 1% of persons with chronic hypertension ever present in this fashion (2). Nevertheless, because hypertension is so common, and because such a wide variety of conditions other than malignant hypertension 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 ICU (5,6) (Table 126.2).

Malignant Hypertension

The peak incidence of malignant hypertension occurs between the ages of 40 and 50, and risk factors include 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 class (7–10). 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) (11).

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 (3). In contrast, among patients who present with malignant hypertension, as many as 50% to 80% may have a secondary etiology (12). 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 (13). 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...
A syndrome in which:

- Hypertensive emergency: Subarachnoid hemorrhage, Acute myocardial infarction, Microangiopathy, Retinopathy and papilledema
- Any condition where Malignant nephrosclerosis and acute renal failure, Normal perfusion pressure breakthrough (post-AVM resection), Cardiovascular Disease and Dysfunction

Malignant hypertension:

- Acute intracerebral hemorrhage, Acute heart failure

Hypertensive urgency:

- Aortic dissection, October 25, 2008 15:11
- Hypertensive encephalopathy/RPLS, Cerebral hyperperfusion syndrome (postendarterectomy), Severe hypertension following cardiovascular surgery

ETIOLOGIES OF MALIGNANT HYPERTENSION

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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>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>Renal parenchymal disease</td>
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<td>Renin-producing tumors</td>
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<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, amphetamine)</td>
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MALIGNANT HYPERTENSION

- Hyperensive encephalopathy/RPLS
- Retinopathy and papilledema
- Acute heart failure
- Myocardial ischemia
- Malignant nephrosclerosis and acute renal failure
- Microangiopathy

NEUROCITICAL CARE EMERGENCIES

- Acute ischemic stroke requiring thrombolysis
- Acute intracerebral hemorrhage
- Subarachnoid hemorrhage
- Severe hypertension following craniotomy
- Cerebral hyperperfusion syndrome (postendarterectomy or stenting)
- Normal perfusion pressure breakthrough (post-AVM resection)

CARDIOVASCULAR EMERGENCIES

- Acute myocardial infarction
- Acute heart failure
- Aortic dissection
- Severe hypertension following cardiovascular surgery

PRE-ECLAMPSIA/ ECLAMPSIA

- AVM, arteriovenous malformation, RPLS, reversible posterior leukoencephalopathy syndrome

The proportion is higher in Caucasians than African Americans (14). 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 angiotensin-converting enzyme (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 (15). Hypertension is a common manifestation of obstructive sleep apnea, and can be improved by the administration of noninvasive positive airway pressure (16). Various rare endocrine causes, including primary aldosteronism, Cushing syndrome, hypercalcemia, hypothyradism, 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, ischemic stroke, and aortic dissection (17–19). 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 (20,21). 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 126.3).
recombinant tissue plasminogen activator (rt-PA) for the management of acute ischemic stroke. An echocardiogram should be obtained to screen for valvular disease or infective endocarditis. An MRI of the brain is indicated if there is suspicion of hemorrhage, especially in the setting of anticoagulation. Acute hypertension complicates approximately 12% of pregnancies, and is responsible for 18% of maternal deaths in the United States. When blood pressure elevation occurs prior to 20 weeks’ gestation, it is considered chronic hypertension. If it occurs without complication after 20 weeks, it is referred to as gestational hypertension. In contrast, pre-eclampsia is a form of pregnancy-induced hypertension that is associated with vascular endothelial dysfunction, platelet aggregation, and increased coagulation. Although it is usually defined by the consistent presence of hypertension and proteinuria (more than 300 mg of protein per 24 hours), some patients can develop severe symptoms in the absence of proteinuria. Pre-eclampsia occurs in 2% to 10% 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, and renal failure. The most common neonatal complications are prematurity and growth restriction. Eclampsia is defined as the development of severe neurologic manifestations, including seizures and a depressed level of consciousness, in women with pre-eclampsia (37,38).

Cardiovascular Hypertensive Emergencies

Acute heart failure is responsible for 5% to 10% of hospital admissions. Hospital mortality is about 4%, but increases to more than 50% by 1 year. In a large American registry, 73% of patients had a history of chronic hypertension, and 50% were hypertensive at admission (39). In patients presenting with flash pulmonary edema, acute hypertension is particularly common, and is likely to be both a consequence and contributing cause. A history of chronic hypertension exists in about 40% to 70% of patients with acute coronary syndromes, and about 30% have an elevated blood pressure when initially assessed (40,41). Severe uncontrolled hypertension at admission (greater than 180/110 mm Hg) is a relative contraindication to thrombolysis for STElevation myocardial infarction (STEMI) (42).

Aortic dissection is a relatively rare condition, with an annual incidence of about 3 to 4 cases per 100,000 persons per year. With modern medical and surgical therapy, the mortality has decreased from as high as 90% to about 20%–35%. More than 70% of patients have a history of chronic hypertension, but blood pressure can be highly variable at presentation. Most patients (70%) with type B dissections (descending aorta) have an admission systolic pressure of more than 150 mm Hg compared with just over a third of those with type A dissections (ascending aorta), of whom approximately 25% actually present with hypertension or in frank shock (43).

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 60 and 150 mm Hg. Increases in blood pressure induce arteriolar smooth muscle contraction and vasconstriction, while reductions in blood pressure beyond the lower limits of autoregulation result in tissue hypoperfusion and ischemia (Fig. 126.1). 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. For example, increased delivery of filtrate to the distal nephron stimulates a tubuloglomerular feedback system that promotes afferent arteriolar vasodilation (44). 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 (1). With chronic hypertension, there is hypertrophy in the walls of small arteries and arterioles, and the autoregulation 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. 126.1).

Normal endothelial function is necessary for the regulation of vascular tone, blood pressure, and regional blood flow. 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. When blood pressure is elevated, vasoactive peptides are released from the endothelium, which in turn induce sodium and water loss, with decreased intravascular volume (1). 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 ACE inhibitors (45). Angiotensin II levels are elevated in most cases of malignant hypertension, particularly when the etiology is a renal condition (46). Increased wall stress and prolonged vasoconstriction in the face of severe hypertension eventually causes endothelial compensatory mechanisms to fail, such that a vicious cycle ensues, with consequent hyperemia, increased permeability, inflammation (endoarteritis), platelet aggregation, coagulation, and thrombosis. Transmural necrosis and the entry of blood components into the vessel wall lead to obliteration of the lumen and replacement of smooth muscle with fibrous tissue, a process called fibrinoid necrosis (47). Patients with malignant hypertension may therefore paradoxically develop both hyperemia (due to endothelial dysfunction and loss of autoregulation) and ischemia (due to thrombosis and fibrinoid necrosis) (Fig. 126.2).

**Manifestations**

**Hypertensive Encephalopathy/Reversible Posterior Leukoencephalopathy Syndrome**

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, making it more vulnerable to the spread of edema (48). Swelling occurs predominantly, but not exclusively, in the posterior regions of the brain. This is thought to be due to a larger concentration of sympathetic fibers around arterioles in the anterior brain, which results in a greater degree of vasoconstriction and relative protection against the effects of severe hypertension (49). 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 *reversible posterior leukoencephalopathy syndrome* (RPLS) or *posterior reversible encephalopathy syndrome* (PRES) (50). 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 RPLS, perhaps because they induce endothelial toxicity. RPLS has been described in association with certain medications—notably cyclosporine (21)—and other immunosuppressive agents, as well as in the setting of microangiopathies (51), connective tissue diseases, vasculitis, and pre-eclampsia (52). Although cerebral edema can sometimes be seen on computed tomography (CT) scans, RPLS is best visualized using T2 and fluid-attenuated inversion recovery (FLAIR) MRI sequences. Diffusion-weighted MRI has confirmed that vasogenic edema is much more prominent than cytotoxic edema and, although RPLS is usually “reversible,” some patients do develop ischemic strokes (53). Many patients do not adhere perfectly to the typical patterns of RPLS; gray matter involvement of the cerebral cortex and basal ganglia, as well as edema occurring in the frontal lobes, posterior fossa, and brainstem have all been described. It is rare for only one vascular territory to be involved (Fig. 126.3).

The clinical manifestations of RPLS in the setting of acute blood pressure elevation are collectively described by the term, *hypertensive encephalopathy*, which is characterized by the subacute development of neurologic signs and symptoms and may include headache, altered mental status, seizures, and visual disturbances (54,55). Headaches are usually generalized, severe, and poorly responsive to analgesics and improve rapidly with treatment of hypertension (56). Altered mental status can
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Vasoparalysis:
Catecholamines
Angiotensin II
Endothelin I
Thromboxane
Vasopressin

Vasodilation:
Nitric oxide
Prostacycline

Endothelial compensation exhausted
Inflammation

Autoregulation breakthrough
Hyperemia
Increased endothelial permeability

Increased inflammation
Platelet degranulation/aggregation
Thrombosis
Fibrinoid necrosis

Edema
Ischemia

Retinopathy
Endothelial damage and leakage of plasma proteins into the retina lead to edema and the formation of hard exudates (Fig. 126.4). 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 (58). The mechanism of papilledema may include raised intracranial pressure (ICP), which is known to be present in some patients with hypertensive encephalopathy (59), as well as ischemia of the optic nerve head (60). It should be noted that ophthalmoscopic examination for hypertensive retinopathy has relatively high rates of inter- and intraobserver variability, particularly among nonophthalmologists (61).

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. The histologic appearance can


FIGURE 126.3. Fluid-attenuated inversion recovery magnetic resonance imaging sequences of a 15-year-old patient with a history of Wegener granulomatosis presenting with seizures and altered mental status. The findings are consistent with reversible posterior leukoencephalopathy syndrome (RPLS). Although vasogenic edema is seen predominantly posteriorly, anterior changes are also present.
Section XII: Cardiovascular Disease and Dysfunction

FIGURE 126.4. Severe hypertensive retinopathy with evidence of disc swelling (DS, papilledema), cotton wool spots (CWS), and flame-shaped hemorrhage (FH). (From Wong T, Mitchell P. The eye in hypertension. Lancet. 2007;369:425–435, used with permission.)

be difficult to distinguish from other microangiopathies, like hemolytic uremic syndrome and thrombotic thrombocytopenic purpura (62). 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 (63). 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. In one series, more than 20% of patients with malignant hypertension required dialysis (64), but this is more common when the etiology is secondary rather than essential hypertension, particularly with renal causes (12). The degree of renal dysfunction is an important prognostic variable (64).

Cardiovascular Complications

Approximately 20% of patients with malignant hypertension present with cardiac complications, which may include myocardial ischemia or pulmonary edema (65). Many patients have a pre-existing history of chronic hypertension, and already have 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 (66) and compressing coronary arteries. 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 (67).

Treatment

Pharmacologic Agents

An ideal pharmacologic agent (Table 126.4) 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

<table>
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<th>TABLE 126.4</th>
<th>INTRAVENOUS PHARMACOLOGIC AGENTS FOR MANAGEMENT OF HYPERTENSIVE EMERGENCIES</th>
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<tbody>
<tr>
<td>Drug</td>
<td>Dose</td>
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<tr>
<td>Nitropusside</td>
<td>0.25–10 μg/kg/min (ideally &lt;2 μg/kg/min)</td>
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<tr>
<td>Nitroglycerin</td>
<td>10–200 μg/min</td>
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<tr>
<td>Labetalol</td>
<td>10–40 mg boluses, 1–4 mg/min infusion</td>
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<tr>
<td>Esmolol</td>
<td>0.5 mg/kg load, 50–200 μg/kg/min</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>3–15 mg/min</td>
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<tr>
<td>Fenoldopam</td>
<td>0.1–1.6 μg/kg/min</td>
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<tr>
<td>Enalaprilat</td>
<td>0.625–2.5 mg bolus, every 6 h</td>
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<tr>
<td>Hydralazine</td>
<td>10–20 mg every 4–6 h</td>
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ICP, intracranial pressure; LV, left ventricular; PDE-5, phosphodiesterase-5.
excessively lowering the blood pressure for long periods of time. The following agents are the most commonly used.

**Sodium Nitroprusside.** Sodium nitroprusside (NTP) has been used in the management of hypertensive emergencies for over 40 years, and continues to be considered first-line therapy, largely because of its rapid onset, short duration of action, affordability, familiarity, and efficacy (1,68). NTP is a par- enterally administered, 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 (69,70). The mechanism of action involves the release of nitric oxide 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 NTP is 0.25 to 0.5 μg/kg/minute, and it is increased in increments of 0.5 μg/kg/minute every 5 to 10 minutes until the goal blood pressure is achieved. NTP has the potential for several serious, life-threatening complications. First, despite lowering preload and afterload, NTP may induce coronary steal, whereby excessive vasodilatation of coronary arterioles shunts blood away from ischemic regions. 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 a worse outcome when treated with nitroprusside within the first 8 hours but improved outcomes thereafter (71).

Second, NTP is often avoided in neurologic emergencies because of the observation in several studies that it vasodilates cerebral vessels, increases cerebral blood volume, and therefore raises ICP (72). The demonstration of this phenomenon is not entirely consistent in the literature (73), and it may be avoidable with a somewhat slower administration (74).

Third, each nitroprusside molecule has five cyanide moieties, such that cyanide makes up 44% of its molecular weight. 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 over- whelmed, cyanide accumulates and causes toxicity. Patients receiving NTP 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 (68,75). Cyanide blocks oxidative phosphorylation and essentially causes tissue anoxia and lactic acidosis despite adequate oxygen delivery and 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 mon- itored, 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 (68,76).

Treatment of cyanide poisoning consists of discontinuation of nitroprusside, supportive care with the delivery of 100% oxygen, and the administration of sodium nitrite (300 mg IV), followed by sodium thiosulfate (12.5 g 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 cyanothriucobalamin, and may pro- vide synergy with sodium thiosulfate (77). Both agents have been used prophylactically with infusions of nitroprusside to prevent cyanide accumulation (78,79). Accumulation of thio- cyanate, although far less toxic than cyanide, may also cause complications (68,79).

Despite these concerns, NTP has an extensive track record, and many prospective studies have not found evidence of clini- cal toxicity even after using it for several days. Still, NTP should be administered as low a dose as possible, and for as short a duration as possible. Newer, alternative agents are increas- ingly being used as they become available, largely because of concerns about cyanide toxicity with NTP.

**Nitroglycerin.** Because nitroglycerin produces more venous than arterial vasodilatation, it is usually not used as first-line therapy for hypertensive emergencies, unless there is concur- rent pulmonary edema or myocardial ischemia. It is usually started at 5 to 10 μg/minute, and can be titrated up every 5 to 10 minutes to doses as high as 200 to 300 μg/minute. Partic- ular caution must be exercised in the setting of hypovolemia. Patients using drugs for erectile dysfunction should not be given nitroglycerin or nitroprusside, as this may induce profound hy- potsension (80). With nitroprusside, there are case reports of nitroglycerin increasing ICP, such that it should be used with caution in brain-injured patients (81).

**β-Blockers.** Labetalol is the most commonly used intravenous β-blocker for the management of hypertensive emergencies. One of its unique properties is that it blocks both α and β receptors, although the β-blocking effect is more prominent (82). Labetalol is usually administered as 10- to 20-mg bo- luses, 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 10 to 15 minutes. Labetalol can also be delivered as an infusion, beginning at a dose of 1 to 2 mg/minute. It has been demonstrated to be safe and effective in the management of severe hypertension, with advantages including that it does not cause reflex tachycardia, and has little effect on cerebral blood flow or ICP (83). La- betalol does not cross the placenta well, and there is extensive experience using it in pregnancy, making it one of the preferred agents in the management of pre-eclampsia and eclampsia (94).

Esmolol is an extremely short-acting, relatively cardiacselective β-blocker, with an onset within less than a minute, and is uniquely metabolized by red blood cell esterases, such that its duration of action is only 10 to 20 minutes. A loading dose of 0.5 mg/kg is administered over 1 minute, followed by an infusion of 50 μg/kg/minute, which can be adjusted as often as every 5 minutes to a maximum dose of 200 μg/kg/minute (85). It is a useful agent when blood pressure is elevated and cardiac output is preserved, especially when there are concerns about myocardial ischemia.

**Nicardipine.** Nicardipine is a dihydropyridine calcium channel blocker 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 vasodilatation, with minimal ven-
odilatation or change in cardiac output. It is most often admin-
istered as an intravenous infusion, beginning at 3 to 5 mg/hour, to a maximum of 15 mg/hour, but it can also be given as 0.5-
to 1-mg boluses. 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 (86). It has compared favorably with NTP in clinical trials, with therapeutic targets achieved in a similar amount of time, fewer episodes of severe hypotension, and less frequent dose adjust-
ment (86,87). Nicardipine has been used in a variety of settings, including malignant hypertension, perioperative hypertension, pre- eclampsia, and acute heart failure. It is generally well toler-
ated, with few adverse effects when used with caution. Given
that nicardipine increases cerebral blood flow, one might ex-
pect that it would raise ICP. Although this has been reported, it
does not appear to be a major concern in most studies (86,88).

Fenoldopam. Fenoldopam is a selective dopamine-1 (DA-1) receptor agonist, which produces peripheral, renal, splanchic,
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 little effect
on cerebral blood flow and ICP. It is typically administered in
doses of 0.025 to 1 μg/kg/minute, and begins to lower blood
pressure after as little as 2 minutes, although the maximal ef-
ficacy 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, thought to be related to
activation of the baroreflex, may occur and can be attenuated
with concomitant use of a β-blocker (89). A theoretical advan-
tage of fenoldopam is improved renal blood flow, but despite
a slight increase in creatinine clearance, it remains unclear that
this will translate into clinically important prevention of renal
failure (90). Fenoldopam has been demonstrated to be effec-
tive at controlling blood pressure in hypertensive emergencies,
with similar efficacy to nitroprusside (91), but has shown no
clear improvement in outcomes; it is also considerably more ex-
pensive (92). Overall, fenoldopam seems to have few adverse
effects. It does raise intracranial pressure, and should therefore
probably be avoided in patients with a known history of glau-
coma (93).

Treatment for Specific Hypertensive Emergencies

Malignant Hypertension

Because of the shift in the autoregulatory curve that occurs
with prolonged hypertension, rapid reductions in blood pres-
sure may cause organ ischemia (94). With hypertensive urgen-
cies, the blood pressure should therefore be reduced carefully
and gradually with oral medications over the course of several
days. It is not certain how long it takes for the autoregulatory
curve to recover and shift back toward the left, such that the
initial goal should never be a 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 individu-
alized to ensure that the pressure is reduced sufficiently for
organ failure to resolve without compromising perfusion. To
facilitate keeping blood pressure in a narrow range, place-
ment of an arterial catheter and careful observation in the ICU
are recommended.

Neurologic

Acute Ischemic Stroke. Although acute hypertension is com-
mon in patients with ischemic stroke, optimal treatment re-
mains uncertain. The greatest priority in these patients is to
preserve as much of the ischemic penumbra as possible. Be-
cause autoregulation is usually impaired within the penumbra,
pressure reductions may cause blood flow to fall, which in turn
may increase infarct size (95). Accordingly, there are several
observational studies demonstrating that lowering blood pres-
sure may cause clinical deterioration (96). Preliminary studies
have even suggested that transcranial Doppler middle cerebral
artery (MCA) flow velocities, cerebral perfusion as determined
by MRI, and neurologic examination may improve with supra-
normal augmentation of blood pressure using a vasopressor
(97). The International Stroke Trial of more than 17,000 pa-
tients found a U-shaped relationship, where the best outcomes
occurred in patients with a presenting systolic blood pressure
of about 150 mm Hg (98). The American Stroke Association
guidelines currently recommend not treating hypertension un-
less the systolic pressure exceeds 220 mm Hg or the diastolic
pressure exceeds 120 mm Hg (99).

The exception to this rule is if the patient is a candidate for
intravenous, or possibly intra-arterial, thrombolysis. Of pa-
tients who receive intravenous rt-PA for treatment of acute
ischemic stroke, approximately 5% to 6% will develop ICH (100).
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 less than 185 mm Hg
and 110 mm Hg, respectively, were excluded from the definitive
clinical trial (101). Patients who did receive thrombolysis had
a goal blood pressure of less than 180/105 mm Hg. Approx-
imately 10% of patients require intravenous antihypertensive
therapy prior to receiving thrombolysis, while 25% to 30%
require treatment in the 24 hours after thrombolysis (24).

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 sev-
eral hours, with a significant proportion of patients having de-
tectable expansion even within the first few hours after pre-
sentation to the emergency department or ICU (102). 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 sug-
gested that patients with higher blood pressure at presentation
are more likely to develop hematoma expansion (103) and
have a higher mortality (104). However, a randomized con-
trolled trial of lowering blood pressure for acute ICH has not
yet been performed. At present, the American Heart Associa-
tion guidelines are conservative, and recommend the following
goals: MAP less than 130 mm Hg, SBP less than 180 mm Hg,
and DBP less than 105 mm Hg (105). The main reason for
concern 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, recent studies using positive emission
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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 AVMs, the sudden “represurization” 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, hypotension should be avoided in the immediate postoperative period. Conversely, the sacrifice of vascular branches during the procedure, or vasospasm from surgical manipulation and retraction, may also create areas of relative underperfusion, such that hypotension would also be deleterious (112).

Cardiovascular Hypertensive Emergencies

Aortic Dissection. The purpose of emergently lowering blood pressure in aortic dissection is to decrease shear stress in 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 calcium channel blocker 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 per minute, and the blood pressure reduced as much as can be tolerated, ideally below a systolic pressure of 120 mm Hg. 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 (86,113).

Acute 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 (39,114). 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/minute, may be required to significantly lower cardiac filling pressures and improve symptoms (115). 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 (116). 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. Another agent that has been proposed for use in acute heart failure is nevirapine (recombinant human brain natriuretic peptide). However, it has not been demonstrated to improve clinically important outcomes when compared with standard therapy (117), may worsen...
renal function (118), and has been linked to a possible increased risk of short-term death (119).

Acute Coronary Syndromes. Although definitive therapy for acute coronary syndromes (ACSs) involves revascularization, tachycardia, and increased myocardial oxygen requirements, and can potentially worsen ischemia and increase infarct size. β-blockers are recommended for all ACS patients without a contraindication. An intravenous β-blocker is therefore a good initial choice as an antihypertensive (42). 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 β-blockade in patients with STEMI has demonstrated an increased risk of cardiogenic shock (41). If the blood pressure remains significantly elevated, especially with ongoing chest pain or pulmonary edema, then nitroglycerin should be used. In addition to reducing preload and afterload, 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) (42).

Pre-eclampsia and Eclampsia

Although hypertensive encephalopathy and eclampsia have largely been considered separate entities, they have a similar pathophysiology and essentially the same MRI findings (123), and should be used to treat acute seizures to prevent the development of seizures in patients with severe pre-eclampsia, adverse effects on fetal heart rate, increased risk of cardiogenic shock (41). If the blood pressure remains significantly elevated, especially with ongoing chest pain or pulmonary edema, then nitroglycerin should be used. In addition to reducing preload and afterload, 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) (42).

SUMMARY

The occurrence of acute hypertension in critically ill patients is not uncommon and can have serious consequences with regard to outcome. Careful evaluation of the underlying causes is important in selecting the best treatment options. Furthermore, the severity of the condition is determined by the magnitude of the acute increase in blood pressure from baseline more than by the absolute blood pressure level. Thus, in the presence of primarily normotensive baseline values (such as those in pre-eclampsia), a minor increase of blood pressure may lead to a life-threatening condition. Organ manifestations in the course of a hypertensive emergency concern the cardiovascular system and brain, and greatly affect 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, all the while monitoring the cardiovascular and central nervous systems. The selection of the antihypertensive agent, therefore, depends on the existing organ failure as well as its reliable effectiveness.

References

16. Portman RJ, Judd J, Schmeler KM, et al. Captopril caused deterioration of renal function in the absence of organ dysfunction, but more rapid and tighter control is necessary for severe pre-eclampsia and eclampsia. Although there has been extensive experience with intravenous hydralazine (5–10 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 (122). Other intravenous agents that have been successfully and safely used include labetalol and nicardipine (84,86). In addition to the above, magnesium sulfate should be given to prevent the development of seizures in patients with severe pre-eclampsia (123), and should be used to treat acute seizures when eclampsia occurs (124).
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