

# Hypertensive Crisis: Hypertensive Emergencies and Urgencies

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Hypertension affects an estimated 50 million people in the United States, and it contributed to more than 250,000 deaths in the year 2000 because of end-organ damage [1]. Normal blood pressure is defined as a systolic blood pressure of less than 120 mm Hg and diastolic blood pressure of less than 80 mm Hg. Hypertension is defined as a systolic blood pressure of 140 mm Hg or higher or a diastolic blood pressure of 90 mm Hg or higher. A systolic blood pressure of 120 to 139 mm Hg or a diastolic blood pressure of 80 to 89 mm Hg is considered prehypertension, because people in this range of blood pressure have higher tendency to develop hypertension over time. There is a continuous, graded relationship between hypertension and cardiovascular risk; even a slightly elevated blood pressure increases risk for cardiovascular disease. The maximum blood pressure as well as the duration of elevated pressure determines the outcome [2,3]. Most patients who have chronically uncontrolled hypertension suffer end-organ damage over time. Patients with previously untreated or inadequately treated high blood pressures are most prone to acute rises in their blood pressures [4,5]. Patients with secondary causes of hypertension are at higher risk of acute rises of blood pressure than patients who have essential hypertension [6,7]. The terms “malignant hypertension,” “hypertensive emergency,” and “hypertensive urgency” were instituted to describe these acute rises in blood pressure and resulting end-organ damage.

Hypertensive crisis includes hypertensive emergencies and urgencies. Hypertensive emergency is

defined as severe hypertension with acute end-organ damage, such as aortic dissection, heart failure, papilledema, or stroke. Although there is no blood pressure threshold for the diagnosis of hypertensive emergency, most end-organ damage is noted with diastolic blood pressures exceeding 120 to 130 mm Hg. In these patients, immediate but monitored reduction, often accomplished with parenteral medications, is essential in preventing long-term damage. Hypertensive urgency, on the other hand, describes significantly elevated blood pressure but without evidence of acute end-organ damage. These patients also need reductions in their blood pressures; but these reductions can be achieved over a period of days, with oral medications and usually without an intensive monitoring setting.

## Historical perspective

Physicians have noticed the effects of hypertension and hypertensive crises for decades. Volhard and Fahr [8] were the first to notice the acute changes in blood pressure and the differences in pathophysiology of these changes from the chronically elevated blood pressure. They noted that patients who had severe hypertension had fundoscopic changes such as retinopathy and papilledema along with renal insufficiency and fibroid necrosis of the renal arterioles. Also, they noticed that patients who had acute elevations in blood pressure were more prone to papilledema and to acute changes in their kidneys. In 1914, they defined the term “malignant hypertension” as an elevation in blood pressure with the sign of acute end-organ damage. Subsequently, in 1921, Keith and Wagener [9] described a similar finding of

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papilledema and severe retinopathy in patients who had severe hypertension but who did not have renal insufficiency. They then realized that the end-organ eye and kidney damage were not mutually exclusive to acute hypertensive episodes and therefore broadened the definition of malignant hypertension by stating that renal insufficiency was not a necessary requirement for acute hypertensive damage. Keith and Wagener [9] also used the term “accelerated hypertension,” which they defined as a syndrome with severe elevations in blood pressure in the presence of retinal hemorrhages and exudates but without papilledema. Later studies have shown that retinal hemorrhages and exudates are important in malignant hypertension and are associated with decreased survival. Notably, however, the presence or absence of papilledema is not associated with decreased survival [10,11].

In 1928, Oppenheimer and Fishberg [12] were the first to use the term “hypertensive encephalopathy” when they noted malignant hypertension associated with headaches, convulsions, and neurologic deficits in a 19-year-old student. Currently, the terms “malignant hypertension” and “accelerated hypertension” are used infrequently and have been replaced by terms such as “hypertensive crisis,” “hypertensive emergency,” and “hypertensive urgency” (Table 1).

### Demographics

The prevalence of hypertension has increased, partially because of the stringent definition of hypertension. There are notable demographic trends in the prevalence of hypertension. Hypertension is more common in older age groups and is more common in men than in women [13]. It is 1.5 to two times more prevalent in black Americans. An analysis of data from the 1999 to 2000 National Health and Nutrition Examination Survey has shown that the combined prevalence of prehypertension and hypertension has increased to 60% of American adults (67% of men and 50% of women), and 27% of American adults have established hypertension. The combined prevalence of prehypertension and hypertension is 40% in the 18- to 39-years age group and is 88% in the greater-than-60-years age group [14]. This survey showed certain risk predictors of hypertension. Education level was a notable factor. The combined prevalence of prehypertension and hypertension increased from 54% in the high-school-educated group to 65% in the non-high-school-educated

Table 1  
Definitions

Term	Definition
Prehypertension	Systolic blood pressure 120–139 mm Hg and diastolic blood pressure 80–89 mm Hg
Hypertension	Systolic blood pressure > 140/90 mm Hg
Hypertensive crisis	Hypertensive urgency or emergency
Hypertensive urgency	Acute rise in blood pressure without acute end-organ damage; diastolic blood pressure usually > 120 mm Hg
Hypertensive emergency	Acute rise in blood pressure with acute end-organ damage; diastolic blood pressure usually > 120 mm Hg

group. Obesity was also an important risk predictor in this analysis; 75% of overweight individuals were prehypertensive or hypertensive, but only 47% of the non-overweight group qualified as such.

Patients who were noted to have prehypertension were also noted to have other risk factors for stroke and cardiovascular disease, such as hypercholesterolemia, obesity, and diabetes. These risk factors were less prevalent in people who had normal blood pressures. The percentage of people who had more than one risk factor for cardiovascular disease was higher in the prehypertensive group than in patients who had normal blood pressure [14]. This cross-sectional analysis also evaluated patients who, when made aware of their hypertension, followed dietary, lifestyle, and medication changes. It was noted that 7% of patients did not adopt any lifestyle changes, and 15% of patients would not take any antihypertensive medications. The problem was more notable in younger patients and in Mexican-American patients. Of the patients taking anti-hypertensive medications, 54% had their hypertension controlled. Men and patients with higher education were more likely to have their blood pressures well controlled.

Of the estimated 50 million Americans with hypertension, less than 1% will have a hypertensive crisis [15]. In a study by Zampaglione and associates [16], hypertensive crises were found to account for more than 25% of all patient visits to a medical section of an emergency department. One third of those patients were noted to have hypertensive emergencies. In the years when

treatment of hypertensive crises was difficult, because of inadequate monitoring and lack of parenteral medications, survival was only 20% at 1 year and 1% at 5 years [17]. Before antihypertensive agents became available, thoracolumbar sympathectomy prolonged survival to 40% at 6.5 years. With the advent of ganglionic blocking medications, the 5-year survival rates increased to 50% to 60% in 1960 [18]. During the past 2 decades, with the increased focus on blood pressure control and emphasis on compliance, the 10-year survival rates have approached 70% [19].

### Cause

Ninety-five per cent of patients who have hypertension have no obvious underlying cause. As such, hypertension without secondary causes is defined as essential hypertension. The remaining 5% of patients have an underlying cause for their elevated blood pressures, of which certain groups have higher chances of presenting with a hypertensive crisis (Box 1). Use of recreational drugs, such as cocaine, has become a frequent cause of hypertensive crisis. Cocaine amphetamines, phencyclidine hydrochloride, and diet pills are sympathomimetic and thus may cause severe acute hypertension. Patients taking monoamine oxidase inhibitors along with tricyclic antidepressants, antihistamines, or food with tyramine are prone to hypertensive crises. Withdrawal syndromes from drugs such as clonidine or beta-blockers may also precipitate hypertensive crises [20]. Pheochromocytoma is a rare cause of hypertensive crises. Patients with spinal cord disorders, such as Guillain Barré syndrome, are also at a higher risk for hypertensive crises. These patients are prone to autonomic overactivity syndrome manifested by severe hypertension, bradycardia, headache, and diaphoresis. The syndrome is triggered by stimulation of dermatomes or muscles innervated by nerves below the spinal cord lesions.

### Pathophysiology

#### *Normal mechanisms to regulate blood pressure*

Blood pressure regulation is a critical action that allows perfusion to vital organs of the body. This action is based on a balance between peripheral vascular resistance and cardiac output and is dependent on the integrated actions of the cardiovascular, renal, neural, and endocrine systems. This interdependence allows a back-up

### Box 1. Causes of secondary hypertension

#### Medications

- Oral contraceptive pills
- Cocaine hydrochloride
- Phencyclidine hydrochloride
- Monoamine oxidase inhibitors
- Sympathomimetic diet pills
- Nonsteroidal anti-inflammatory drugs
- Amphetamines
- Cyclosporin
- Steroids

#### Acute glomerulonephritis

- Renal parenchymal disease
- Renal artery stenosis
- Hyperaldosteronism
- Cushing disease
- Pheochromocytoma
- Pregnancy
- Sleep apnea
- Coarctation of aorta
- Spinal cord injuries

system so that the body can cope with internal and external stresses such as thirst, fear, infection, and trauma. Multiple intrinsic systems are activated in the body in response to external and internal stressors [21]. The renin-angiotensin-aldosterone system is thought to be critically responsible for blood pressure changes. Renin is released from the juxtaglomerular apparatus in response to low sodium intake, underperfusion of the kidney, and increased sympathetic activity. Renin is responsible for converting angiotensinogen to angiotensin, which is not metabolically active. The angiotensin is subsequently converted to angiotensin II in the lungs by the angiotensin-converting enzyme. Angiotensin II is a potent vasoconstrictor, which leads to increases in blood pressure. Besides its intrinsic vasoconstrictive effects, angiotensin II also causes aldosterone release, which further increases blood pressure by causing salt and water retention. Studies in rats support the role of the renin-angiotensin-aldosterone system in blood pressure elevation. When rats were given the Ren-2 gene, which activates the renin-angiotensin-aldosterone system, they developed severe hypertension [22]. Further support comes from therapeutic methods, such as using angiotensin-converting enzyme inhibitors or angiotensin receptor blockers or

surgical removal of an ischemic kidney, which can prevent blood pressure elevations [23].

The renin-angiotensin-aldosterone system is not considered solely responsible for changes in blood pressure. Black Americans, for instance, often have low renin, angiotensin II, and aldosterone levels and yet have a notably higher incidence of hypertension. Therefore, they are less responsive to medications blocking the renin-angiotensin-aldosterone system. Theoretically, patients who have low renin states might have noncirculatory local renin-angiotensin paracrine or epicrine systems. These systems have been found in the kidney, arterial tree, and the heart; and are probably responsible for local control of blood pressure [24].

The sympathetic nervous system also affects blood pressure, especially in times of stress and exercise. The sympathetic nervous system can cause arterial vasoconstriction and can raise cardiac output. It is thought that initially the sympathetic nervous system increases the cardiac output without affecting peripheral vascular resistance. The raised cardiac output increases flow to the vascular bed, and as the cardiac output increases, the autoregulatory response of the vascular bed is activated. This autoregulatory response results in constriction of the arterioles to prevent the pressure from reaching the capillaries and affecting cell hemostasis [21].

In addition, endothelial function plays a central role in blood pressure maintenance. The endothelium secretes nitric oxide, prostacyclin, and endothelin, which modulate vascular tone. Nitric oxide is released by endothelial agonists such as acetylcholine and norepinephrine and in response to shear stress [21]. Endothelin-1 has great vasoconstrictive activities and may cause a salt-sensitive rise in blood pressure and a rise in blood pressure by triggering the renin-angiotensin-aldosterone system [24]. Other vasoactive substances involved in blood pressure maintenance include bradykinin and natriuretic peptides. Bradykinin is a potent vasodilator that is inactivated by angiotensin-converting enzyme. Natriuretic peptides are secreted from the heart in response to increase in blood volume and cause an increase in sodium and water excretion.

#### *Altered mechanisms in hypertension and hypertensive crises*

The pathophysiology of hypertensive crisis is not well understood. It is thought that an abrupt rise in blood pressure, possibly secondary to

a known or unknown stimulus, may trigger the event. During this abrupt initial rise in blood pressure, the endothelium tries to compensate for the change in vasoreactivity by releasing nitric oxide. When the larger arteries and arterioles sense elevated blood pressures, they respond with vasoconstriction and subsequently with hypertrophy to limit pressure reaching the cellular level and affecting cellular activity. Prolonged smooth muscle contraction leads to endothelial dysfunction, loss of nitric oxide production, and irreversible rise in peripheral arterial resistance. Without the continuous release of nitric oxide, the hypertensive response becomes more severe, promoting further endothelial damage, and a vicious cycle continues. The endothelial dysfunction is further triggered by inflammation induced by mechanical stretch. The expression of inflammatory markers such as cytokines, endothelial adhesion molecules, and endothelin-1 is increased [25,26]. These molecular events probably increase the endothelial permeability, inhibit fibrinolysis, and, as a result, activate coagulation. Coagulation along with platelet adhesion and aggregation results in deposition of fibrinoid material, increased inflammation, and the vasoconstriction of the arteries, resulting in further endothelial dysfunction. The role of the renin-angiotensin-aldosterone system also seems to be important in hypertensive emergency. There seems to be an amplification of this system that contributes to vascular injury and tissue ischemia [27].

The blood pressure at which the acute end-organ damage starts occurring is different in each individual. Patients who are more chronically hypertensive have had more smooth muscle contraction and subsequent arterial hypertrophy, which lessens the effect of acute rise in blood pressure on the capillary circulation. Although malignant hypertension is defined as a diastolic blood pressure greater than 130 mm Hg, normotensive patients who have not had time to establish compensatory autoregulatory mechanisms are more sensitive to elevations in blood pressure and may suffer end-organ damage when diastolic blood pressure becomes greater than 100 mm Hg.

#### **Clinical manifestations**

Hypertensive crisis shares all of the pathologic mechanisms and end-organ complications of the milder forms of hypertension [27]. In one study of the prevalence of end-organ complications in

hypertensive crisis, central nervous system abnormalities were the most frequent. Cerebral infarctions were noted in 24%, encephalopathy in 16%, and intracerebral or subarachnoid hemorrhage in 4% of patients. Central nervous system abnormalities were followed in incidence by cardiovascular complications such as acute heart failure or pulmonary edema, which were seen in 36% of patients, and acute myocardial infarction or unstable angina in 12% of patients. Aortic dissection was noted in 2%, and eclampsia was noted in 4.5% of patients [16]. The end-organ damage is outlined in **Box 2**.

### *Acute neurologic syndromes*

The cerebral vasculature must maintain a constant cerebral perfusion despite changes in blood pressure. Cerebral autoregulation is the inherent ability of the cerebral vasculature to maintain this constant cerebral blood flow [28,29]. Normotensive people maintain a constant cerebral blood flow between mean arterial pressures of 60 mm Hg and 120 mm Hg. As the mean arterial pressure increases, there is disruption of the cerebral endothelium and interruption of the blood–brain barrier. Fibrinoid material deposits in the cerebral vasculature and causes narrowing of the vascular lumen. The cerebral vasculature, in turn, attempts to vasodilate around the narrowed lumen, which leads to cerebral edema and microhemorrhages [30]. The changes in cerebral vasculature and cerebral perfusion seem to affect primarily the white matter in the parieto-occipital areas of the brain [31]. The predilection toward the parieto-occipital

regions possibly results from decreased sympathetic innervation of the vessels in this region [32]. There are also reports of brainstem involvement, however [33].

Normotensive patients may develop endothelial dysfunction at lower mean arterial pressures, whereas chronically hypertensive patients can tolerate higher mean arterial pressures before they develop such a dysfunction. Chronically hypertensive patients have the capacity to autoregulate and have cerebral blood flow and oxygen consumption similar to those in normotensive persons [34]. Changes in the structure of the arterial wall cause increased stiffness and higher cerebrovascular resistance, however [35]. Although a higher threshold must be reached before they have disruption of their autoregulation system, hypertensive patients, because of the increased cerebrovascular resistance, are more prone to cerebral ischemia when flow decreases [30].

Hypertensive encephalopathy is one of the clinical manifestations of cerebral edema and microhemorrhages seen with dysfunction of cerebral autoregulation. It is defined as an acute organic brain syndrome or delirium in the setting of severe hypertension. Symptoms include severe headache, nausea, vomiting, visual disturbances, confusion, and focal or generalized weakness. Signs include disorientation, focal neurologic defects, focal or generalized seizures, and nystagmus. If not adequately treated, hypertensive encephalopathy can lead to cerebral hemorrhage, coma, and death, but with proper treatment it is completely reversible [36]. The diagnosis of hypertensive encephalopathy is a clinical diagnosis. Stroke, subarachnoid hemorrhage, mass lesions, seizure disorder, and vasculitides need to be ruled out.

Cerebral infarction, caused by an imbalance between supply and demand, is another neurologic sequela of severe acute rises in blood pressure [37]. Intracranial and subarachnoid hemorrhages are other possible neurologic complications of hypertensive crisis. The risk is increased in patients who have intracranial aneurysms and in those taking anticoagulant medications.

### *Myocardial ischemia*

Hypertension affects the structure and function of the coronary vasculature and left ventricle. Activation of the renin-angiotensin-aldosterone system in hypertension constricts systemic vasculature and, thereby, increases myocardial oxygen demand by increasing left ventricular wall tension.

#### **Box 2. End-organ damage in hypertension**

Acute neurologic syndromes  
Hypertensive encephalopathy  
Cerebral infarction  
Subarachnoid hemorrhage  
Intracranial hemorrhage

Myocardial ischemia and infarction  
Acute left ventricular dysfunction  
Acute pulmonary edema  
Aortic dissection  
Retinopathy  
Renal insufficiency  
Eclampsia

Increasing wall tension leads to hypertrophy of the left ventricular myocytes and to deposition of protein and collagen in the extracellular matrix of the ventricular wall. These actions increase ventricular mass, which further increases oxygen demand on the heart. A second effect of the hypertrophy is that the newly thickened ventricle can cause coronary compression and decreased luminal blood flow. Thirdly, hypertension can increase the epicardial coronary wall thickness, which increases the wall-to-lumen ratio and decreases coronary blood flow reserve. Concomitant atherosclerosis worsens the wall-to-lumen ratio, further decreases coronary flow reserve, and leads to coronary ischemia [38]. Acute rise in blood pressure also results in endothelial injury at the level of the coronary capillaries.

#### *Left ventricular failure*

Another effect of hypertensive crisis on the heart is left ventricular failure and acute pulmonary edema. In certain cases, despite increasing wall tension, the left ventricle cannot hypertrophy enough to overcome the acute rise in systemic vascular resistance. This inability to compensate leads to left ventricular failure and a backup of flow causing pulmonary edema. Secondly, neurohormonal activation of the renin-angiotensin-aldosterone system leads to increased sodium content and increased total body water. In addition, left ventricular hypertrophy leads to focal ischemia and subsequent inadequate diastolic filling, which can result in imbalance between left ventricular contraction and relaxation, leading to pulmonary edema [5]. Clinically, patients show signs of volume overload or signs of reduced tissue perfusion such as cool limbs.

#### *Aortic dissection*

Aortic dissection is the most rapidly fatal complication of hypertensive crises. Risk factors for dissection include untreated hypertension, advanced age, and diseases of the aortic wall. Dilation of the aorta caused by atherosclerosis and high blood pressures tear the intima of the vessel, allowing a surge of blood into the aortic wall. The blood driven by pulsatile pressure separates the arterial wall into two layers [39]. Clinically, patients complain of retrosternal or interscapular chest pain that migrates to the back. If dissection extends proximally, it can lead to aortic insufficiency or a pericardial effusion. Dissection can lead to compression or occlusion of a branch

of the aorta and subsequently lead to organ ischemia. Clinical signs that are notable with dissection include discrepancies between pulses, murmur of aortic insufficiency, and neurologic deficits [40]. Diagnosis of aortic dissection can be confirmed with transesophageal echocardiography, CT, or MRI [41].

#### *Hypertensive retinopathy*

Retinopathy was one of the first signs of hypertension, noted in 1914. In the early years fundoscopy was considered a definitive tool in diagnosing hypertensive encephalopathy. Papilledema was noted in patients who had hypertensive encephalopathy but was not necessary for diagnosis [42]. Retinal hemorrhages and exudates were considered indicative of malignant hypertension. Since 1914, multiple studies have looked at retinopathy in the setting of hypertension. In mild to moderate hypertension, the degree of focal narrowing of arterioles has been associated with the level of blood pressure rise. No relationship has been found between retinal changes and the end-organ damages such as ventricular hypertrophy or microalbuminuria, however [43]. Ophthalmoscopy may be useful in recognizing acute hypertensive target-organ damage such as hypertensive encephalopathy, but the absence of retinal exudates, hemorrhages, or papilledema does not exclude the diagnosis [11].

#### *Acute renal insufficiency*

Acute renal insufficiency may be a cause or result of rapidly progressive hypertension. Important causes of hypertension are parenchymal disease, such as acute glomerulonephritis or renal artery stenosis, or cyclosporine use in kidney transplant patients. Renal insufficiency could also be a result of hypertension and hypertensive crisis, however. Normal renal autoregulation enables the kidney to maintain a constant renal blood flow and glomerular filtration rate for mean arterial pressures between 80 and 160 mm Hg. Under normal conditions, autoregulatory vasodilation is maximal at a mean arterial pressure of about 80 mm Hg. In chronic hypertension, the small arteries of the kidney, including the afferent arteriole, undergo pathologic changes that alter renal autoregulation, showing signs of endothelial dysfunction and impaired vasodilation. Structural changes initially are probably protective of the kidney, but over time progressive narrowing of the preglomerular vessels results in ischemic injury, tubular atrophy,

and fibrosis. With the impairment of the renal autoregulatory system, the intraglomerular pressure begins to vary directly with systemic arterial pressure [44]. As such, the afferent vasculature becomes a passive conduit and cannot prevent the kidney from being affected by fluctuations in pressure and flow, leading to acute renal ischemia in cases of hypertensive crisis.

#### *Pregnancy-induced hypertension*

Pre-eclampsia is characterized as a syndrome of pregnancy-induced hypertension, edema, and proteinuria in a pregnant woman after the twentieth week of gestation [27]. Eclampsia is the end result of this spectrum and is associated with acute hypertension, edema, proteinuria, and concomitant seizures. Although the pathophysiologic mechanisms of pre-eclampsia and eclampsia are not well understood, blood pressure elevation is characterized by an increased responsiveness to vasoconstrictors, especially angiotensin II. There is also decreased sensitivity to endothelium-derived vasodilators [27]. Pregnancy-induced hypertension usually resolves spontaneously after delivery of baby.

#### *Postoperative hypertension*

The postoperative hypertensive crisis is classically an acute rise in blood pressure within the first 2 hours after surgery and is typically short in duration, with most patients requiring treatment for 6 hours or less [45]. Although postoperative hypertensive crises can occur with any surgery, they are more common with cardiothoracic, vascular, head, neck, and neurosurgical procedures [45]. In one study of patients undergoing radical neck dissection, the frequency of hypertensive crisis ranged from 9% to 25% [46]. A feared complication of postoperative hypertensive crisis is bleeding from operation site [47]. The pathophysiology of postoperative hypertensive crisis is probably related to stimulation of the sympathetic nervous system and catecholamine surge [48].

#### **Clinical evaluation**

History and detailed physical examination are important in all patients who present with severe hypertension. A thorough history is important to determine the time since diagnosis of hypertension, the severity, and the baseline blood pressures at home. Determining the presence of end-organ damage and other comorbidities is important, because both are crucial factors influencing the

choice of antihypertensive drugs. Knowledge of the patient's medications and compliance with these medications, including over-the-counter medications and recreational drugs, is essential, because both could contribute to an acute rise in blood pressure. Blood pressure should be checked in both arms and should be done in supine and standing positions, if possible, to determine volume status. Neurologic examination is important to determine the focal signs of an ischemic or hemorrhagic stroke. The presence of delirium, nausea, vomiting, and seizures suggests hypertensive encephalopathy. Fundoscopic examination could be of help, because the presence of exudates, hemorrhage, or papilledema supports the diagnosis of hypertensive encephalopathy. Cardiovascular examination includes listening for new murmurs of aortic insufficiency associated with dissection or of ischemic mitral regurgitation. A gallop or left ventricular heave could suggest heart failure. Crackles in the lung fields suggest pulmonary edema. Laboratory studies should include serum electrolytes, blood urea nitrogen, serum creatinine level, blood cell count, and peripheral smear. An ECG should be taken for myocardial ischemia and left ventricular hypertrophy, and a chest radiograph should be obtained for cardiac enlargement and widened mediastinum. Urine analysis is indicated for assessment of proteinuria and tubular casts. Plasma renin and aldosterone levels could be obtained if patient is not taking diuretics or other medications that could have affected these levels [22].

#### **Treatment**

Hypertensive urgency can be treated in a non-ICU setting with oral medications over 24 to 48 hours. Medications such as beta-blockers, diuretics, angiotensin-converting enzyme inhibitors, and calcium-channel blockers can be titrated initially as an inpatient; then the patient can be discharged with close follow-up. If there is acute end-organ damage, however, the patient should be admitted to the ICU and treated with intravenous medications. The goal of therapy is prompt but gradual reduction in blood pressure. The most reasonable goal is to lower the mean arterial pressure by about 25% or to reduce the diastolic blood pressure to 100 to 110 mm Hg.

#### *Medication options for treatment*

There have been no large clinical trials to determine the optimal pharmacologic therapy in hypertensive emergency patients, primarily

because of the heterogeneity among the patients and their end-organ damage. As such, management of hypertensive crisis should be dictated by individual presentation and should be specific to the end organ at risk (Tables 2, 3).

Sodium nitroprusside is the drug of choice for most hypertensive emergencies because it has an immediate onset of action and can be titrated quickly and accurately. The duration of effect is 1 to 2 minutes. The mechanism of action of this agent is probably similar to that of endogenous nitric oxide. Sodium nitroprusside is an endogenous arteriolar and venous dilator and has no effects on the autonomic or central nervous system [49]. The venous dilation decreases preload to the heart and subsequently decreases cardiac output, whereas the arterial dilation inhibits the reflex rise in blood pressure from the drop in cardiac output. Because sodium nitroprusside is a direct vasodilator, one might think that it increases cerebral blood flow and intracranial pressure. The fall in systemic pressure, however, seems to inhibit the rise in cerebral blood flow, and patients who have neurologic damage respond well to this agent [18]. Sodium nitroprusside must be administered as an infusion and thus requires continuous surveillance with intra-arterial monitoring. An end product of nitroprusside is thiocyanate, a precursor to cyanide that can cause nausea, vomiting, lactic acidosis, and altered mental status. Cyanide toxicity can be rapidly fatal. Sodium nitroprusside is broken down by the liver and cleared through the kidney, and thus thiocyanate levels must be followed in patients who have hepatic or renal insufficiency to ensure prevention of a toxic buildup [21].

Labetalol is another first-line agent for hypertensive emergency. It is a combined alpha- and beta-blocking agent; the beta-blocking activity of labetalol is five- to tenfold that of the alpha component [50]. The beta effects of labetalol are only about one fifth the activity of propranolol, however [18]. Its onset of action is within 5 to 10 minutes, and the duration of action is about 3 to 6 hours. Labetalol can be used safely in most patients, but caution should be exercised in patients who have severe bradycardia, congestive heart failure, or bronchospasm.

Fenoldopam is the first selective dopamine-1 receptor agonist approved for in-hospital shorter-term management of severe hypertension up to the first 48 hours of treatment [51–54]. The mechanism of action involves activating dopamine at the level of the kidney. Dopamine is a well-known vasoconstrictor and is sympathomimetic at intermediate to high doses. At low doses, however, dopamine lowers diastolic blood pressure and, importantly, increases renal perfusion and promotes diuresis. Fenoldopam is administered by parenteral continuous infusion and has 50% of its maximal effect within 15 minutes. Its duration of action is about 10 to 15 minutes; thus, it can be discontinued swiftly if the decrease in blood pressure is too rapid. The efficacy of fenoldopam in renal perfusion is equal to or possibly better than that of sodium nitroprusside. There are no toxic metabolites of fenoldopam; however, the onset of action is slower, and the duration of effect is longer than that of sodium nitroprusside. Patients develop tachyphylaxis to fenoldopam after 48 hours, and headache can be a side effect.

Table 2  
Medications used in hypertensive emergencies

Name	Dosing	Onset of Action	Duration of Action	Preload	Afterload	Cardiac Output	Renal perfusion
Sodium nitroprusside	IV 0.25–10 µg/kg/min	within seconds	1–2 min	decreased	decreased	no effect	decreased
Labetalol	IV (20- to 80-mg bolus/10 min)	5–10 min	2–6 hr	no effect	decreased	decreased	no effect
Fenoldopam	IV 0.1–0.6 µg/kg/min	10–15 min	10–15 min	no effect	decreased	increased	increased
Nicardipine	IV 2–10 mg/hr	5–10 min	2–4 hr	no effect	decreased	increased	no effect
Esmolol	IV 80-mg bolus over 30 seconds, followed by 150 µg/kg/min infusion	6–10 min	20 min	no effect	no effect	decreased	no effect
Methyldopa	IV (250-to 1000-mg bolus every 6 hr)	3–6 hr	up to 24 hr	no effect	decreased	decreased	no effect
Hydralazine	IV bolus (10–20 mg)	10 min	2–6 hr	no effect	decreased	increased	no effect

Abbreviation: IV, intravenous.

Table 3  
Major side effects of medications

Name	Comments	Major Side Effects
Sodium nitroprusside	Need to measure thiocyanate levels, caution in renal insufficiency	Cyanide toxicity: nausea, vomiting, altered mental status, lactic acidosis, death
Labetolol	Alpha and beta blocker, contraindicated in acute heart failure	Bradycardia, bronchospasm, nausea
Nicardipine	Safe in coronary bypass patients	Reflex tachycardia, flushing
Esmolol	Short-acting beta blocker, contraindicated in acute heart failure	Bradycardia, bronchospasm
Methyldopa	Safe in pregnancy, needs renal dosing	Drowsiness, fever, jaundice
Hydralazine	Safe in pregnancy	Reflex tachycardia, lupus-like syndrome

Nicardipine is a calcium-channel blocker administered parenterally by continuous infusion for hypertensive crises. The onset of action of this drug is 5 to 10 minutes, and the duration of action is 1 to 4 hours. Adverse reactions are reflex tachycardia and headache [55]. Nicardipine is contraindicated in patients who have heart failure.

Esmolol is a cardioselective beta-blocker with a short duration of action. It reduces the systolic blood pressure and mean arterial pressure as well as heart rate, cardiac output, and stroke volume. There is a notable decrease in myocardial oxygen consumption. Peak effects are generally seen within 6 to 10 minutes after a bolus dose. The effects resolve 20 minutes after discontinuation of infusion. The elimination half-life of esmolol is about 8 minutes.

#### *Choice of agent*

The choice of pharmacologic agent to treat hypertensive crisis should be tailored to each individual based on risks, comorbidities, and the end-organ damage. The lower limit of cerebral blood flow autoregulation is reached when blood pressure is reduced by 25%, and the cerebral ischemia can be precipitated with rapid reductions of blood pressure of greater than 50% [35]. Hence,

the goal of therapy in hypertensive encephalopathy is to reduce the mean arterial pressure gradually by no more than 25% or to a diastolic blood pressure of 100 mm Hg, whichever is higher, during the first hour. If neurologic function worsens, the therapy should be suspended, and blood pressure should be allowed to increase [20]. In intracerebral or subarachnoid hemorrhage, blood pressure reduction is necessary to stop the bleeding and can be facilitated by decreasing pressures by 25%. It is important to reduce blood pressure slowly to prevent cerebral hypoperfusion to the already ischemic areas [36]. Often after a stroke there is a loss of cerebral autoregulation in the infarct/ischemic region. This loss of cerebral autoregulation makes blood pressure reduction cautionary, because the ischemic region is more prone to hypoperfusion during blood pressure reduction. As such, blood pressure reduction is not recommended after stroke, except in cases of extreme blood pressure elevation (diastolic blood pressure > 130 mm Hg). If neurologic function deteriorates with reduction of blood pressure, therapy should be suspended, and blood pressure should be allowed to rise. Blood pressure usually declines spontaneously to prestroke levels within 4 days of an acute ischemic stroke without any antihypertensive treatments [37]. Sodium nitroprusside is the drug of choice for treatment of acute neurologic syndromes in hypertensive crisis. Labetolol is a good alternative unless there is evidence of severe bradycardia associated with the cerebral edema. Clonidine and methyldopa should not be used, because they can cause central nervous system depression and complicate the clinical picture.

Severe acute hypertension often results in myocardial ischemia even with patent coronary arteries. In this situation, intravenous nitroglycerin is effective in reducing systemic vascular resistance and improving coronary perfusion. Nitrates should be given until symptoms subside or until diastolic blood pressure is 100 mm Hg. Beta-blockers and calcium-channel blockers are also potential options; both can decrease blood pressure while improving myocardial oxygenation. Calcium-channel blockers should be used with caution in patients who have possible heart failure. Acute pulmonary edema that is precipitated by hypertension is best treated with sodium nitroprusside. The concomitant venous and arterial dilation improve forward flow and cardiac output. This agent should be used in conjunction with morphine, oxygen, and a loop diuretic [49].

Treatment of an aortic dissection depends on location of the injury [41]. Type A or proximal aortic dissections need immediate institution of antihypertensive medications and immediate surgery, but type B or distal aorta dissections can be controlled medically. The medical therapy of aortic dissection is aimed at reducing the shear stress on aortic wall. This reduction is achieved by lowering diastolic blood pressure to less than 100 to 110 mm Hg and by decreasing heart rate. This reduction is best achieved with a combination of an intravenous beta-blocker and sodium nitroprusside to decrease both the blood pressure and the heart rate. Another option is the use of labetalol, which has both alpha- and beta-blocking effects.

Renal insufficiency is a cause and a consequence of severe hypertension. These patients need reduction of systemic vascular resistance without compromising renal blood flow or glomerular filtration rate. Fenoldopam is a good choice in these patients because of the improvement in renal perfusion, diuresis, and lack of production of toxic metabolites. Tolerance does develop to fenoldopam after 48 hours [53]. Sodium nitroprusside can also be used, but there is a risk of thiocyanate toxicity, and the thiocyanate level needs to be closely monitored. Calcium-channel blockers are effective and well tolerated in renal transplant patients. Beta-blockers are also useful agents in hypertension in kidney disease. Calcium-channel blockers and beta-blockers have no clinically important effects on glomerular filtration or renal hemodynamics [44]. Patients who have renal insufficiency should not be treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

In pre-eclampsia and eclampsia, blood pressure control is essential. Many of the traditional antihypertensive medications are contraindicated in pregnancy because of their detrimental effects on the fetus. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers can adversely affect fetal development and increase fetal morbidity. Calcium-channel blockers reduce blood pressure but decrease uterine blood flow and can inhibit labor. Methyldopa is the mainstay of treatment of blood pressure in pregnant patients. It works centrally in reducing blood pressure and heart rate. Methyldopa can be administered orally or intravenously. With renal dysfunction the doses need to be adjusted. The side effects are drowsiness, fever, and jaundice. The medication does cross into the placenta but is considered class B in

pregnancy [2]. Hydralazine is another agent that is safe in pregnancy and can be administered safely parenterally. Hydralazine may cause reflex tachycardia and fluid retention because it activates the renin-angiotensin-aldosterone system [27]. Data show that labetalol is probably effective in reducing blood pressure in treatment of eclampsia without inducing fetal distress [56].

Pheochromocytoma is a rare cause of paroxysmal or sustained blood pressure and can induce hypertensive crisis. The treatment of choice in these patients is labetalol or phentolamine (an alpha-blocking agent). It is important not to use beta-blockers alone, because then there is an unopposed alpha activity that will worsen the vasoconstriction, resulting in a further increase in blood pressure. A reflex hypertensive crisis can develop in patients who have abruptly stopped taking antihypertensives, particularly clonidine or beta-blockers. The treatment in these cases is to restart previous medications after the initial reduction of blood pressure with labetalol or sodium nitroprusside. Postoperative hypertension is typically related to catecholamine surge from activation of the sympathetic nervous system. Therefore, the treatment of choice for postoperative hypertensive crisis is with a beta-blocker or labetalol.

## Summary

Hypertensive crisis is a serious condition that is associated with end-organ damage or may result in end-organ damage if left untreated. Causes of acute rises in blood pressure include medications, noncompliance, and poorly controlled chronic hypertension. Treatment of a hypertensive crisis should be tailored to each individual based on the extent of end-organ injury and comorbid conditions. Prompt and rapid reduction of blood pressure under continuous surveillance is essential in patients who have acute end-organ damage.

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