

# Hypertensive Crises

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**M**ost patients with hypertension remain asymptomatic for many years, until complications from atherosclerosis, cerebrovascular disease, or congestive heart failure supervene. In some patients, this so-called benign course is punctuated by a hypertensive crisis. *Hypertensive crisis* is defined as the turning point in the course of an illness at which acute management of the elevated blood pressure plays a decisive role in the eventual outcome [1]. The haste with which blood pressure must be controlled varies with the type of hypertensive crisis. If the patient's outcome is to be optimal, however, the crucial role of hypertension in the disease process must be identified and a plan for management of the blood pressure successfully implemented. The absolute level of the blood pressure clearly is not the most important factor in determining the existence of a hypertensive crisis. For example, in children, pregnant women, and other previously normotensive persons in whom mild to moderate hypertension develops suddenly, a hypertensive crisis can occur at a level of blood pressure that normally is well-tolerated by adults with chronic hypertension. Furthermore, a crisis can occur in adults with mild to moderate hypertension with the onset of acute end-organ dysfunction involving the heart or brain.

CHAPTER

8

### HYPERTENSIVE CRISES

Malignant hypertension  
(Hypertensive neuroretinopathy present)

Benign (nonmalignant) hypertension with acute complications  
(Acute organ system dysfunction without hypertensive neuroretinopathy)

Hypertensive encephalopathy (also common in malignant hypertension)

Acute hypertensive heart failure (also common in malignant hypertension)

Acute aortic dissection

Central nervous system catastrophe  
  Intracerebral hemorrhage  
  Subarachnoid hemorrhage  
  Severe head trauma

Acute myocardial infarction or unstable angina

Active bleeding, including postoperative bleeding

Uncontrolled hypertension in patients requiring surgery

Severe postoperative hypertension  
  Post–coronary artery bypass hypertension  
  Post–carotid endarterectomy hypertension

Catecholamine excess states  
  Pheochromocytoma  
  Monoamine oxidase inhibitor–tyramine interactions

Miscellaneous hypertensive crises  
  Preeclampsia and eclampsia  
  Scleroderma renal crisis  
  Autonomic hyperreflexia in quadriplegic patients

**FIGURE 8-1**

Malignant hypertension is a clinical syndrome characterized by marked elevation of blood pressure, with widespread acute arteriolar injury (hypertensive vasculopathy). Funduscopy reveals hypertensive neuroretinopathy with flame-shaped hemorrhages, cotton-wool spots (soft exudates), and sometimes papilledema. Regardless of the severity of blood pressure elevation, malignant hypertension cannot be diagnosed in the absence of hypertensive neuroretinopathy. Thus, hypertensive neuroretinopathy is an extremely important clinical finding, indicating the presence of a hypertension-induced arteriolitis that may involve the kidneys, heart, and central nervous system. In malignant hypertension, rapid and relentless progression to end-stage renal disease occurs if effective blood pressure control is not implemented. Mortality can result from acute hypertensive heart failure, intracerebral hemorrhage, hypertensive encephalopathy, or complications of uremia. Malignant hypertension represents a hypertensive crisis given that adequate control of blood pressure clearly prevents these morbid complications. Even in patients with so-called benign (nonmalignant) hypertension, in which hypertensive neuroretinopathy is absent, a hypertensive crisis may occur based on the development of concomitant acute end-organ dysfunction. Hypertensive crises caused by benign hypertension with acute complications include hypertension in the setting of hypertensive encephalopathy, acute hypertensive heart failure, acute aortic dissection, intracerebral hemorrhage, subarachnoid hemorrhage, severe head trauma, acute myocardial infarction or unstable angina, and active bleeding. Poorly controlled hypertension in patients requiring surgery increases the risk of intraoperative cerebral or myocardial ischemia and postoperative acute renal failure. Severe postoperative hypertension, including post–coronary artery bypass hypertension and post–carotid endarterectomy hypertension, increases the risk of postoperative bleeding, hypertensive encephalopathy, pulmonary edema, and myocardial ischemia. The various catecholamine excess states can cause a hypertensive crisis with hypertensive encephalopathy or acute hypertensive heart failure. Preeclampsia and eclampsia represent hypertensive crises unique to pregnancy. Scleroderma renal crisis is a hypertensive crisis because failure to adequately control blood pressure with a regimen that includes a converting enzyme inhibitor results in rapid irreversible loss of renal function. Hypertensive crises as a result of autonomic hyperreflexia induced by bowel or bladder distention also can occur in patients with quadriplegia. The sudden onset of hypertension in this setting can lead to hypertensive encephalopathy or acute pulmonary edema. Each hypertensive crisis is discussed in more detail in the figures that follow.

**HYPERTENSIVE SYNDROMES SOMETIMES MISDIAGNOSED AS HYPERTENSIVE CRISES**

## Severe uncomplicated hypertension

(Severe hypertension without hypertensive neuroretinopathy or acute end-organ dysfunction, formerly known as *urgent* hypertension)

## Benign hypertension with chronic end-organ complications

Chronic renal insufficiency from primary renal parenchymal disease

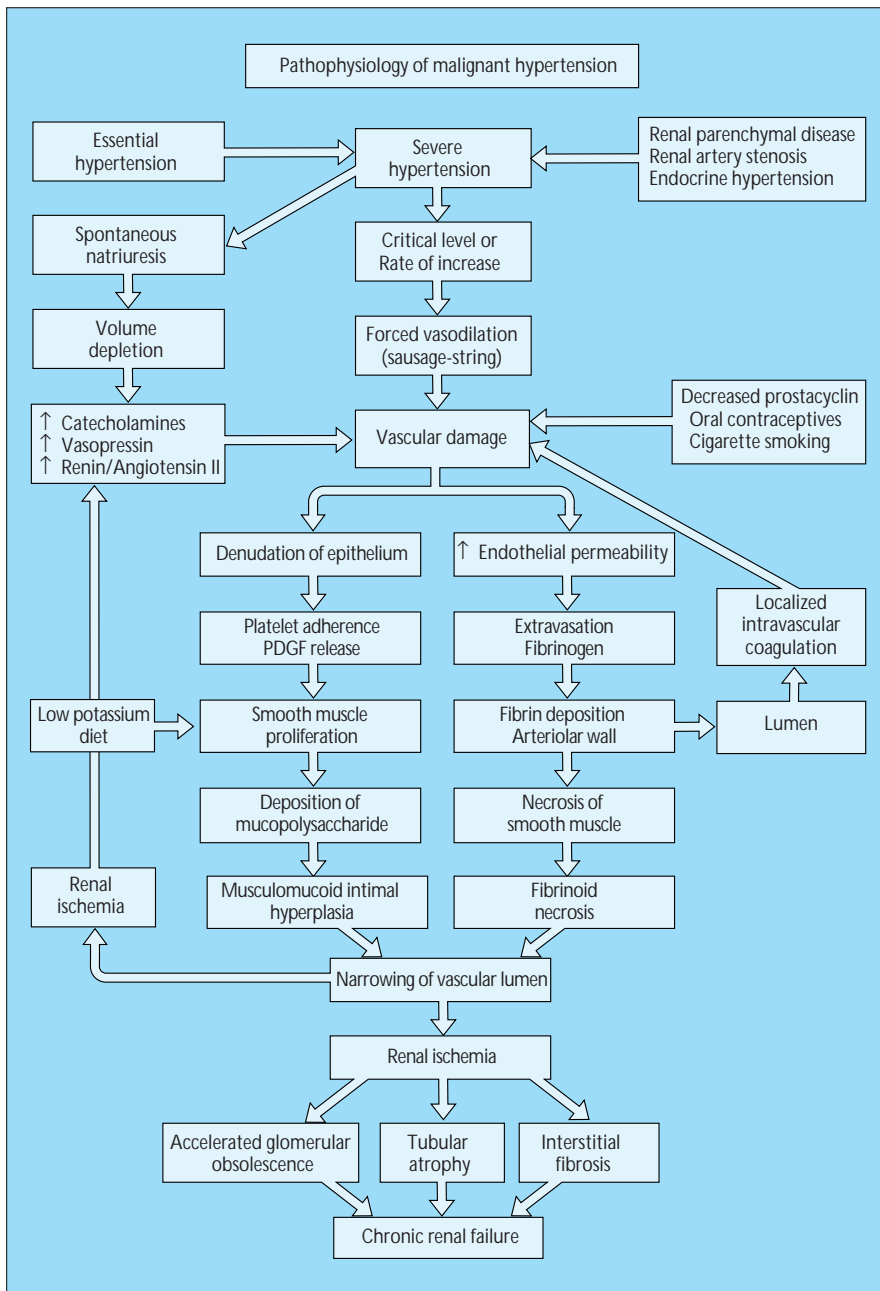
Chronic congestive heart failure from systolic or diastolic dysfunction

Atherosclerotic coronary vascular disease (previous myocardial infarction, stable angina)

Cerebrovascular disease (history of transient ischemic attack or cerebrovascular accident)

**FIGURE 8-2**

Hypertensive syndromes sometimes misdiagnosed as hypertensive crises. It should be noted that the finding of severe hypertension does not always imply the presence of a hypertensive crisis. In patients with *severe uncomplicated hypertension* (formally known as urgent hypertension) in which severe hypertension is not accompanied by evidence of malignant hypertension or acute end-organ dysfunction, eventual complications due to stroke, myocardial infarction, or congestive heart failure tend to occur over months to years, rather than hours to days. Long-term control of blood pressure can prevent these eventual complications. However, a hypertensive crisis cannot be diagnosed because no evidence exists that acute reduction of blood pressure results in improvement in short- or long-term prognosis. Moreover, the presence of chronic hypertensive end-organ complications in a patient with nonmalignant hypertension does not imply the existence of a hypertensive crisis requiring rapid control of blood pressure. The category of *benign hypertension with chronic complications* includes hypertensive patients with chronic renal insufficiency due to underlying primary renal parenchymal disease, chronic congestive heart failure as a result of either systolic or diastolic dysfunction, atherosclerotic coronary vascular disease (stable angina or previous myocardial infarction), or chronic cerebrovascular disease (previous transient ischemic attacks or cerebrovascular accident). Long-term inadequate blood pressure control increases the risk of further deterioration of end-organ function in each of these conditions. However, no evidence exists that rapid control of blood pressure is necessary to prevent further complications. Therefore, a true hypertensive crisis does not exist.



**FIGURE 8-3**

Pathophysiology of malignant hypertension. The vicious cycle of malignant hypertension is best demonstrated in the kidneys. This cycle also applies equally well to the vascular beds of the retina, pancreas, gastrointestinal tract, and brain [1]. In this scheme, severe hypertension is central. Hypertension may be either essential or secondary to any one of a variety of causes. Because not all patients develop malignant hypertension despite equally severe hypertension, the interaction between the level of blood pressure and the adaptive capacity of the vasculature may be important. In this regard, chronic hypertension results

in thickening and remodeling of arteriolar walls that may be an adaptive mechanism to prevent vascular damage from the mechanical stress of hypertension. However, when the blood pressure increases suddenly or increases to a critical level, these adaptive mechanisms may be overwhelmed, resulting in vascular damage. As a result of the mechanical stress of increased transmural pressure, focal segments of the arteriolar vasculature become dilated, producing a *sausage-string* pattern. Endothelial permeability increases in the dilated segments, leading to extravasation of fibrinogen, fibrin deposition in the media, and necrosis of smooth muscle cells (fibrinoid necrosis). Platelet adherence to damaged endothelium with release of platelet-derived growth factor induces migration of smooth muscle cells to the intima where they proliferate (neointimal proliferation) and produce mucopolysaccharide. These cells also produce collagen, resulting in proliferative endarteritis, musculomucoid hyperplasia, and eventually, fibrotic obliteration of the vessel lumen. Occlusion of arterioles leads to accelerated glomerular obsolescence and end-stage renal disease. Other factors may synergize with hypertension to damage the arterial vasculature. Renal ischemia leads to activation of the renin-angiotensin system that can cause further elevation of blood pressure and progressive vascular damage. Spontaneous natriuresis early in the course of malignant hypertension leads to volume depletion with activation of the renin-angiotensin system or catecholamines that further elevates blood pressure. It also is possible that angiotensin II may be directly vasculotoxic. Activation of the clotting cascade within the lumen of damaged vessels may lead to fibrin deposition with localized intravascular coagulation. Thus, microangiopathic hemolytic anemia is a common finding in malignant hypertension. Cigarette smoking and oral contraceptive use may contribute to development of malignant hypertension by decreasing prostacyclin production in the vessel wall and thereby inhibiting repair of hypertension-induced vascular injury. Low dietary intake of potassium may help promote vascular smooth muscle proliferation and therefore predisposes to the development of malignant hypertension in Blacks with severe essential hypertension. PDGF—platelet-derived growth factor.

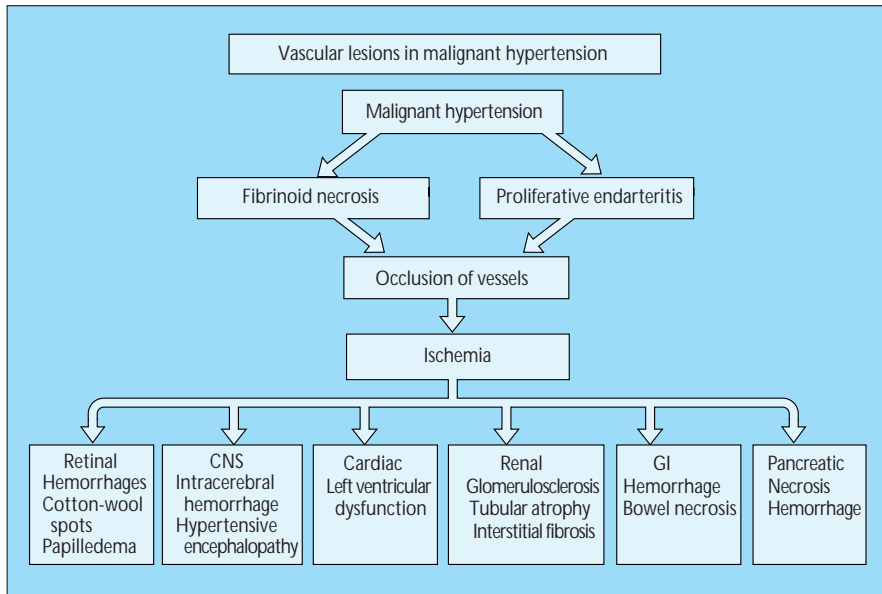


FIGURE 8-4

Distribution of vascular lesions in malignant hypertension. Malignant hypertension is essentially a systemic vasculopathy induced by severe hypertension. Fibrinoid necrosis and proliferative endarteritis occur throughout the body in numerous vascular beds, leading to ischemic changes. In the retina, striate hemorrhages and cotton-wool spots develop. The finding of hypertensive neuroretinopathy is the clinical *sine qua non* of malignant hypertension. Vascular lesions in the gastrointestinal tract (GI) can lead to hemorrhage or bowel necrosis. Hemorrhagic pancreatitis also can occur. Cerebrovascular lesions can lead to cerebral infarction or intracerebral hemorrhage. Hypertensive encephalopathy also can develop as a result of failure of autoregulation with cerebral overperfusion and edema (Fig. 8-22). Vascular lesions also can develop in the myocardium; however, acute hypertensive heart failure is largely the result of acute diastolic dysfunction induced by the marked increase in afterload that accompanies malignant hypertension (Figs. 8-24 and 8-25). CNS—central nervous system.

### COMMON CAUSES OF MALIGNANT HYPERTENSION

Primary (essential) malignant hypertension\*  
 Secondary malignant hypertension  
 Primary renal disease  
 Chronic glomerulonephritis\*  
 Chronic pyelonephritis\*  
 Analgesic nephropathy\*  
 Immunoglobulin A nephropathy\*  
 Acute glomerulonephritis  
 Radiation nephritis  
 Renovascular hypertension\*  
 Oral contraceptives  
 Atheroembolic renal disease (cholesterol embolism)  
 Scleroderma renal crisis  
 Antiphospholipid antibody syndromes  
 Chronic lead poisoning  
 Endocrine hypertension  
 Aldosterone-producing adenoma (Conn's syndrome)  
 Cushing's syndrome  
 Congenital adrenal hyperplasia  
 Pheochromocytoma

\*Most common causes of malignant hypertension.

FIGURE 8-5

Malignant hypertension is not a single disease entity but, rather, a syndrome in which the hypertension can be either primary (essential) or secondary to any one of a number of different causes [2]. Among Black patients the underlying cause is almost always essential hypertension that has entered a malignant phase. The most common secondary causes of malignant hypertension are primary renal parenchymal disorders. Chronic glomerulonephritis is thought to be the cause of malignant hypertension in up to 20% of cases. Unless a history of an acute nephritic episode or long-standing hematuria or proteinuria is available, the underlying glomerulonephritis may only

become apparent when a renal biopsy is performed. Recently, immunoglobulin A (IgA) nephropathy has been reported as an increasingly frequent cause of malignant hypertension. In one series of 66 patients with IgA nephropathy, 10% developed malignant hypertension [3]. Chronic atrophic pyelonephritis in children, often a result of underlying vesicoureteral reflux, is the most common cause of malignant hypertension [4]. In Australia, malignant hypertension complicates up to 7% of cases of analgesic nephropathy [5]. Transient malignant hypertension responsive to volume expansion has been reported in analgesic nephropathy. It has been suggested that interstitial disease with salt-wasting is important in the pathogenesis by causing profound volume depletion with activation of the renin-angiotensin axis. Malignant hypertension is both an early and late complication of radiation nephritis that can occur up to 11 years after radiotherapy. Renovascular hypertension from either fibromuscular dysplasia or atherosclerosis is a well-recognized cause of malignant hypertension. In a series of 123 patients with malignant hypertension, renovascular hypertension was found in 43% of Whites and 7% of Blacks [6]. Among women of childbearing age, oral contraceptives can cause malignant hypertension [7]. In the absence of underlying renal disease, with discontinuation of the drug, long-term prognosis is excellent. Severe hypertension that may become malignant is a common complication of atheroembolic renal disease. In patients presenting with malignant hypertension in the weeks to months after an arteriographic procedure, a careful history and physical should be performed to look for evidence of atheroembolism. Scleroderma renal crisis is the most life-threatening complication of progressive systemic sclerosis. Scleroderma renal crisis is characterized by hypertension that may enter the malignant phase. Even in the absence of hypertensive neuroretinopathy suggesting malignant hypertension, the renal lesion in scleroderma renal crisis is virtually indistinguishable from primary malignant nephrosclerosis [8]. Patients with antiphospholipid antibody syndrome, either primary or secondary to systemic lupus erythematosus, can develop malignant hypertension with renal insufficiency as a result of thrombotic microangiopathy [9]. The endocrine causes of hypertension only rarely lead to malignant hypertension. Pheochromocytoma can cause hypertensive crises owing to hypertensive encephalopathy or acute hypertensive heart failure in the absence of hypertensive neuroretinopathy (malignant hypertension).

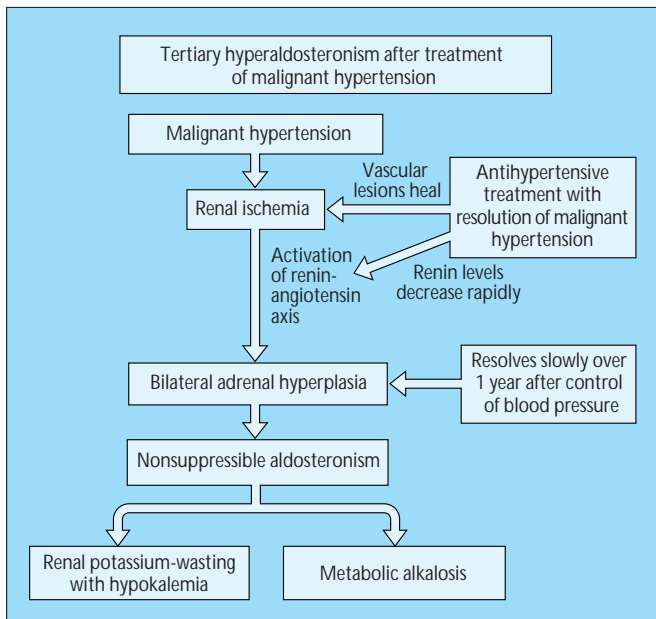


FIGURE 8-6

Tertiary hyperaldosteronism after treatment of malignant hypertension. The diagnosis of primary hyperaldosteronism must be made with caution in patients with a history of malignant hypertension. After successful treatment of malignant hypertension, plasma renin activity rapidly normalizes, whereas aldosterone secretion may remain elevated for up to a year. This phenomenon has been attributed to persistent adrenal hyperplasia induced by long-standing hyperreninemia during the malignant phase [10]. During this phase of tertiary hyperaldosteronism, despite suppressed renin activity, hypokalemia, metabolic alkalosis, and aldosterone levels that are not suppressible, mimic primary hyperaldosteronism. Adrenal imaging studies reveal bilateral nodular adrenal hyperplasia. With continued long-term control of blood pressure this hyperaldosteronism remits spontaneously.

### RENAL CHANGES IN HYPERTENSION

#### Retinal arteriosclerosis and arteriosclerotic retinopathy (benign hypertension)

- Focal or diffuse arteriolar narrowing
- Arteriovenous crossing changes
- Broadening of the light reflex
- Copper or silver wiring
- Perivasculitis (parallel white lines around the arteries)
- Solitary round hemorrhages
- Hard exudates
- Central or branch venous occlusion

#### Hypertensive neuroretinopathy (malignant hypertension)

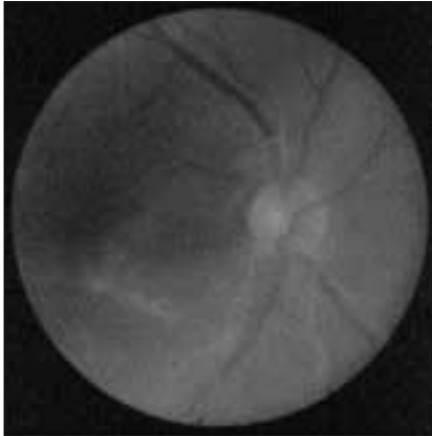
- Generalized arteriolar narrowing
- Striate (flame-shaped) hemorrhage\*
- Cotton-wool spots\*
- Papilledema\*
- Star figure at the macula

\*Features that distinguish hypertensive neuroretinopathy from retinal arteriosclerosis.

FIGURE 8-7

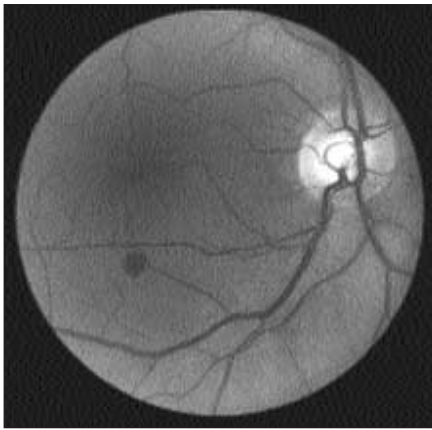
Funduscopy findings are pivotal in the diagnosis of malignant hypertension. Keith and Wagener [11] graded retinal findings in hypertensive patients as follows: grade I, arteriolar narrowing; grade II, arteriovenous crossing changes; grade III, hemorrhages and exudates; grade IV, the changes in grade III plus papilledema. Although this classification of hypertensive retinopathy is of great historical importance, its clinical utility has several limitations, *eg*, it is extremely difficult to quantify arteriolar narrowing. In this regard, a tendency exists for significant observer bias such that patients with mild hypertension and questionable narrowing are invariably assigned to grade I. More importantly, this classification does not distinguish the retinal changes of benign and malignant hypertension. For example, the clinical significance of a cotton-wool spot appearing in the fundus of a young man with severe

hypertension (diagnostic of malignant hypertension) is quite different from the clinical significance of a hard exudate in the fundus of a 60-year-old man with moderate hypertension. The prognostic and therapeutic implications of these two types of exudates clearly are different, although both would be classified as grade III. For this reason, the Keith and Wagener classification has been supplanted by the more clinically useful classification of hypertensive retinopathy shown here. This classification system draws a distinction between *retinal arteriosclerosis with arteriosclerotic retinopathy*, which is characteristic of benign hypertension, and *hypertensive neuroretinopathy*, which defines the existence of malignant hypertension [12,13]. Retinal arteriosclerosis, which is characterized histologically by the accumulation of hyaline material in arterioles, occurs in elderly normotensive persons or in the setting of long-standing benign hypertension. Funduscopy findings reflecting retinal arteriosclerosis include arteriolar narrowing, arteriovenous crossing changes, perivasculitis, and changes in the light reflex with copper or silver wiring. Arteriosclerotic retinopathy manifests as solitary round hemorrhages in the periphery of the fundus and hard exudates. The finding of retinal arteriosclerosis is of no prognostic significance with regard to the risk of coronary atherosclerosis or cerebrovascular disease. The arteries visualized with the ophthalmoscope are technically arterioles with a diameter of 0.1 mm. Hyaline arteriosclerosis of the retinal vessels is a process entirely distinct from the atherosclerotic process that affects larger muscular arteries. Thus, the finding of retinal arteriosclerosis cannot predict the presence of atherosclerosis of the coronary or cerebral vessels. This lack of clinical significance of retinal arteriosclerosis in hypertensive patients contrasts dramatically with the importance and prognostic significance of the finding of hypertensive neuroretinopathy. This finding is the clinical *sine qua non* of malignant hypertension. The appearance of striate hemorrhages or cotton-wool spots with or without papilledema closely parallels the development of fibrinoid necrosis and proliferative endarteritis in the kidney and other organs. Thus, the presence of hypertensive neuroretinopathy predicts the development of end-stage renal disease, or other life-threatening hypertensive complications, within a year if adequate control of the blood pressure is not achieved.



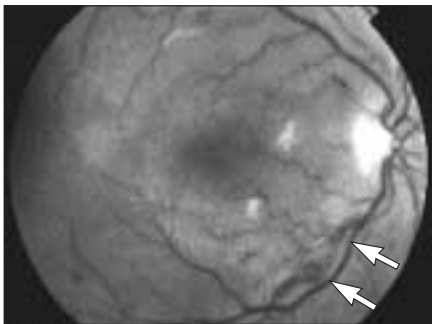
**FIGURE 8-8** (see Color Plate)

Fundus photography of retinal arteriosclerosis in benign hypertension. Funduscopy in a 60-year-old man reveals the characteristic changes of retinal arteriosclerosis, including arteriolar narrowing, mild arteriovenous crossing changes, copper wiring, and perivasculitis (parallel white lines around blood columns). The striate hemorrhages, cotton-wool spots, and papilledema characteristic of malignant hypertension are absent.



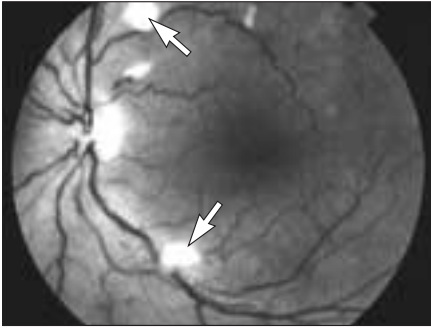
**FIGURE 8-9** (see Color Plate)

Fundus photography of arteriosclerotic retinopathy in benign hypertension. Funduscopy in a 52-year-old woman with benign hypertension demonstrates a solitary round hemorrhage characteristic of arteriosclerotic retinopathy.

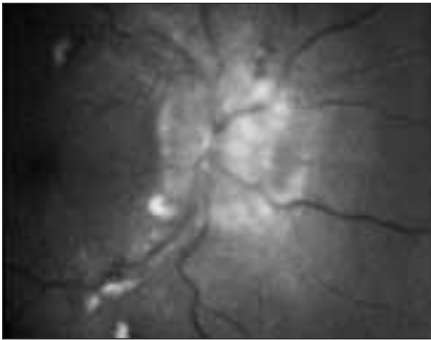


**FIGURE 8-10** (see Color Plate)

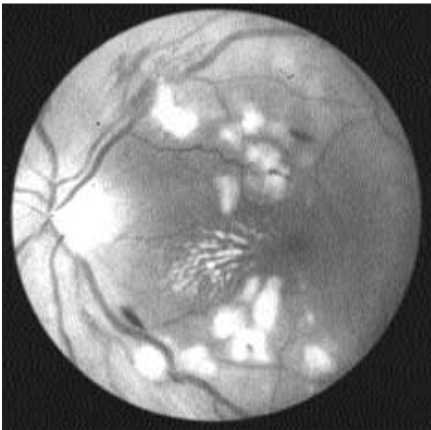
Fundus photography of striate hemorrhages in hypertensive neuroretinopathy. Fundoscopic findings in a 53-year-old woman with secondary malignant hypertension as a result of underlying immunoglobulin A nephropathy, demonstrating striate or flame-shaped hemorrhages (*arrows*). The appearance of small striate hemorrhages often is the first sign that malignant hypertension has developed. These hemorrhages are most commonly observed in a radial arrangement around the optic disc. The retinal circulation is under autoregulatory control such that under normal circumstances as blood pressure increases, arterioles constrict to maintain constant retinal blood flow. The appearance of striate hemorrhages implies that autoregulation has failed. Striate hemorrhages are a result of bleeding from superficial capillaries in the nerve fiber bundles near the optic disc. These capillaries originate directly from arterioles so that when autoregulation fails, the high systemic pressure is transmitted directly to the capillaries. This process leads to breaks in the continuity of the capillary endothelium. The resultant hemorrhages extend along nerve fiber bundles parallel to the retinal surface. The hemorrhages often have a frayed distal border owing to extravasation of blood between nerve fiber bundles.

**FIGURE 8-11** (see Color Plate)

Fundus photography of cotton-wool spots in hypertensive neuroretinopathy. Cotton-wool spots (*arrows*) are the most characteristic feature of malignant hypertension. They usually surround the optic disc and most commonly occur within three disc-diameters of the optic disc. Cotton-wool spots result from ischemic infarction of retinal nerve fiber bundles owing to arteriolar occlusion caused by proliferative arteriopathy in retinal vessels. Fluorescein angiography demonstrates that cotton-wool spots are areas of retinal nonperfusion. Embolization of pig retina with glass beads produces immediate neuronal cell edema followed by accumulation of mitochondria and other subcellular organelles in ischemic nerve fibers. It has been postulated that the normal axoplasmic flow of subcellular organelles is disrupted by retinal ischemia such that accumulation of organelles in ischemic nerve fiber bundles results in a visible white patch. Cotton-wool spots tend to distribute around the optic disc because nerve fiber bundles are most dense in this region. The detection of cotton-wool spots is a crucial clinical finding because they are the retinal manifestation of the malignant hypertension-induced systemic vasculopathy that also causes proliferative endarteritis and ischemia in the kidney and other organs. (This is the same patient as in Fig. 8-10.)

**FIGURE 8-12** (see Color Plate)

Fundus photography of papilledema in hypertensive neuroretinopathy. Funduscopic findings in a 23-year-old Black man noted incidentally to be severely hypertensive during a routine dental clinic visit. Papilledema of the optic disc is apparent, with surrounding cotton-wool spots and striated hemorrhages. The pathogenesis of papilledema in hypertensive neuroretinopathy is unclear. Intracranial pressure is not always increased in patients with malignant hypertension and papilledema. Papilledema has been produced experimentally in Rhesus monkeys by occlusion of the long posterior ciliary artery that supplies the optic nerve. As in cotton-wool spots, indeed papilledema may result from hypertensive vasculopathy-induced ischemia of nerve fiber bundles in the optic disc. Thus, in hypertensive neuroretinopathy, papilledema essentially may represent a giant cotton-wool spot resulting from ischemia of the optic nerve. When papilledema occurs in malignant hypertension, it almost always is accompanied by striated hemorrhages and cotton-wool spots. When papilledema occurs alone, the possibility of a primary intracranial process such as tumor or cerebrovascular accident should be considered.

**FIGURE 8-13** (see Color Plate)

Fundus photography of far-advanced hypertensive neuroretinopathy. Funduscopy in this 30-year-old man with malignant hypertension demonstrates all the characteristic features of hypertensive neuroretinopathy. These features include striate hemorrhages, cotton-wool spots, papilledema, and a star figure at the macula.

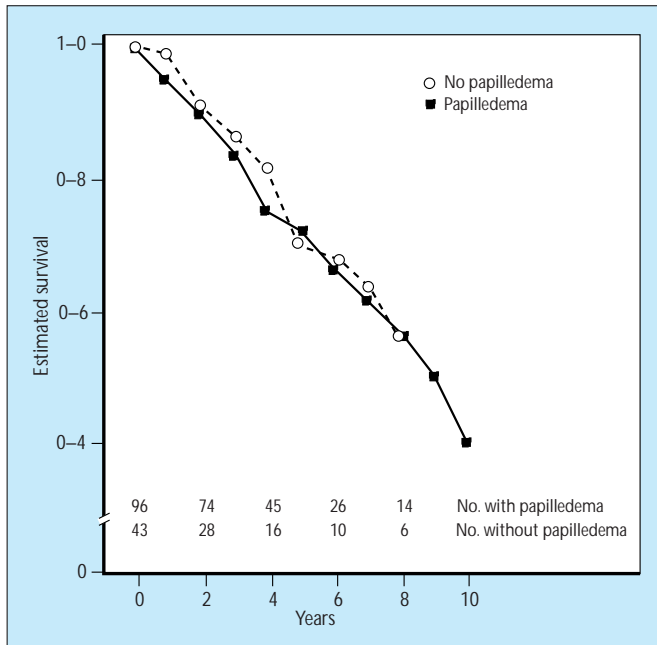


FIGURE 8-14

Prognosis in accelerated hypertension versus malignant hypertension. In the original Keith and Wagener [11] classification of hypertensive retinopathy, *malignant hypertension* (grade IV) was defined by the presence of papilledema, whereas the term *accelerated hypertension* (grade III) was used when hemorrhages and exudates occurred in the absence of papilledema. However, more recent studies indicate that the prognosis is the same in hypertensive patients with striate hemorrhages and cotton-wool spots whether or not papilledema is present. In this regard, the World Health Organization has recommended that accelerated hypertension and malignant hypertension be regarded as synonymous terms for the same disease. Demonstrated are the effects of the presence or absence of papilledema on survival among 139 hypertensive patients with hypertensive neuroretinopathy (striated hemorrhages and cotton-wool spots) [14]. By multivariate analysis, after controlling for age, gender, smoking habit, initial serum creatinine concentration, and initial and achieved blood pressure, the presence of papilledema did not influence prognosis. (From McGregor [14] *et al.*; with permission.)

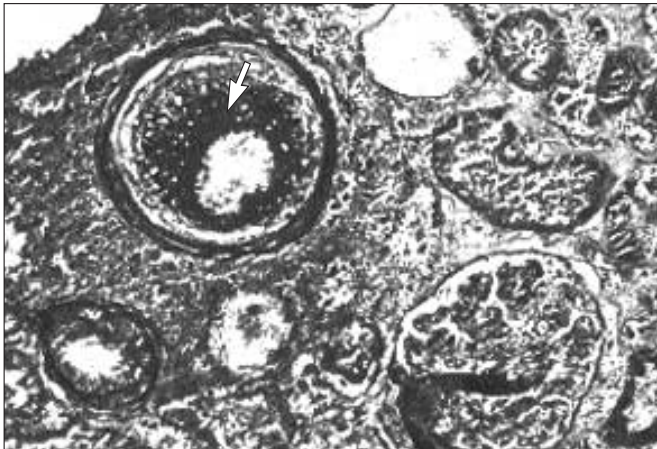
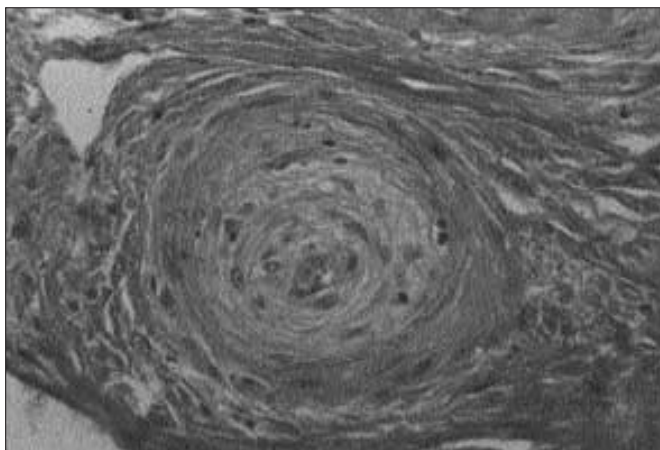


FIGURE 8-15 (see Color Plate)

Micrograph of fibrinoid necrosis in malignant hypertension. Fibrinoid necrosis of the afferent arterioles and interlobular arteries has traditionally been regarded as the hallmark of malignant hypertension. The characteristic finding is the deposition in the arteriolar wall of a granular material that is a bright-pink color on hematoxylin and eosin staining. On Masson trichrome staining, as illustrated, the granular fibrinoid material is bright red (arrow). The fibrinoid material usually is found in the media of the vessel; however, deposition in the intima also may occur. Whole or fragmented erythrocytes may be extravasated into the arteriolar wall. These hemorrhages account for the petechial hemorrhages that give rise to the peculiar flea-bitten appearance of the capsular surface of the kidney in malignant hypertension. Fibrinoid necrosis is thought to result from the mechanical stress placed on the vessel wall by severe hypertension. Forced vasodilation occurs when there is failure of autoregulation of renal blood flow, which leads to endothelial injury with seepage of plasma proteins into the vessel wall. Contact of plasma constituents with smooth muscle cells activates the coagulation cascade, and fibrin is deposited in the wall. Fibrin deposits then cause necrosis of smooth muscle cells (*fibrinoid necrosis*). (Masson trichrome stain, original magnification  $\times 100$ .)



**FIGURE 8-16** (see Color Plate)

Micrograph of proliferative endarteritis in malignant hypertension (*musculomucoid intimal hyperplasia*). In malignant nephrosclerosis, the interlobular (cortical radial) arteries reveal characteristic lesions. These lesions are variously referred to as proliferative endarteritis, endarteritis fibrosa, musculomucoid intimal hyperplasia, or the onionskin lesion. The typical finding is marked thickening of the intima that obstructs the vessel lumen. In severely affected vessels the luminal diameter may be reduced to the caliber of a single erythrocyte. Occasionally, complete obliteration of the lumen by a superimposed fibrin thrombus occurs.

Traditionally, three patterns of intimal thickening have been described [15]. (1) The onionskin pattern consists of pale layers of elongated concentrically arranged myointimal cells along with delicate connective tissue fibrils that give rise to a lamellar appearance. The media often appears as an attenuated layer stretched around the expanded intima. (2) In the mucinous pattern, intimal cells are sparse. Seen is an abundance of lucent, faintly basophilic-staining amorphous material. (3) In fibrous intimal thickening, seen are few cells with an abundance of hyaline deposits, reduplicated bands of elastica, and coarse layers of collagen. The renal histology in Blacks with malignant hypertension demonstrates a characteristic finding in the larger arterioles and interlobular arteries known as *musculomucoid intimal hyperplasia*, with an abundance of cells and a small amount of myxoid material (that is light blue in color on hematoxylin and eosin staining) between the cells [16, 17]. These various intimal findings may represent progression over time from an initially cellular lesion to fibrosis of the intima. Electron microscopy demonstrates that in each type of intimal thickening the most abundant cellular element is a modified smooth muscle cell. This cell is called a *myointimal cell*. Proliferative endarteritis is thought to occur as a result of phenotypic modulation of medial smooth muscle cells that dedifferentiate from the normal contractile phenotype to acquire a more embryologic proliferative-secretory phenotype. It has been proposed that the endothelial injury in malignant hypertension results in attachment of platelets with release of platelet-derived growth factor (PDGF) that may induce the phenotypic change in smooth muscle cells. PDGF stimulates chemotaxis of medial smooth muscles to the intima, where they proliferate and secrete mucopolysaccharide and later collagen and other extracellular matrix proteins, resulting in proliferative endarteritis, musculomucoid hyperplasia, and ultimately fibrous intimal thickening. (Hematoxylin and eosin stain, original magnification  $\times 100$ .)

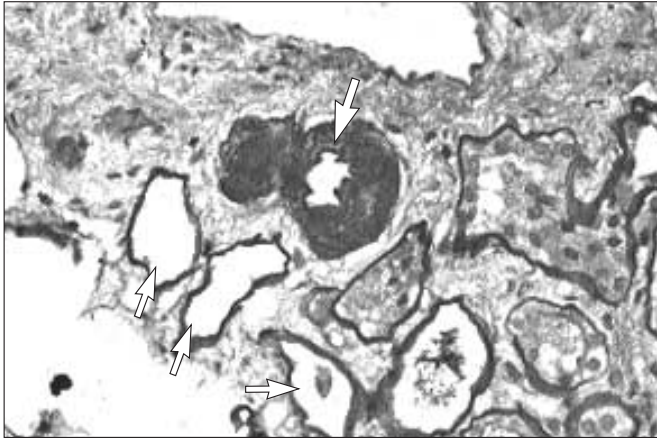
### SPECTRUM OF CLINICAL RENAL INVOLVEMENT IN MALIGNANT HYPERTENSION

Progressive subacute deterioration of renal function to end-stage renal disease  
 Transient deterioration of renal function with initial blood pressure control  
 Oliguric acute renal failure  
 Established renal failure

**FIGURE 8-17**

Malignant hypertension is a progressive systemic vasculopathy in which renal involvement is a relatively late finding. In this regard, patients with malignant hypertension can present with a spectrum of renal involvement ranging from normal renal function with minimal albuminuria to end-stage renal disease (ESRD) indistinguishable from that seen in primary renal parenchymal disease. In patients initially exhibiting preserved renal function, in the absence of adequate blood pressure control, it is common to observe subacute deterioration of renal function to ESRD over a period of weeks to months. Transient deterioration of renal function with initial control of blood pressure is a well-documented entity in patients initially exhibiting mild to moderate renal impairment. Occasionally, patients with malignant hypertension initially exhibit oliguric acute renal failure, necessitating initiation of dialysis within a few days of hospitalization. Because erythrocyte casts sometimes appear in the urine sediment, malignant nephrosclerosis initially may be misdiagnosed as a rapidly progressive glomerulonephritis or systemic vasculitis [18]. Careful examination of the fundus for evidence of hypertensive neuroretinopathy confirms the diagnosis of malignant hypertension.

Patients with malignant hypertension can also present with established renal failure. Often, it is impossible to determine clinically whether a patient initially exhibiting hypertensive neuroretinopathy and renal failure has primary malignant hypertension or secondary malignant hypertension with underlying primary renal parenchymal disease. The presence of normal-sized kidneys on ultrasonography supports a diagnosis of primary malignant nephrosclerosis that potentially is reversible with long-term blood pressure control. However, a renal biopsy may be required for definitive diagnosis. All patients with malignant hypertension should receive aggressive antihypertensive therapy to prevent further renal damage, regardless of the degree of renal impairment. Control of blood pressure in patients with malignant hypertension and renal insufficiency often causes further deterioration of renal function, especially when the initial glomerular filtration rate (GFR) is less than 20 mL/min. However, a fall in GFR is not a contraindication to intensive blood pressure control aimed at normalization of blood pressure. Control of hypertension protects other vital organs, such as the heart and brain, whose function cannot be replaced. Moreover, with rigid blood pressure control, renal function may eventually recover over the ensuing months, even in patients with apparent ESRD owing to primary malignant nephrosclerosis [19,20].



**FIGURE 8-18** (see Color Plate)

Micrograph of hyaline arteriolar nephrosclerosis in benign hypertension. It is important to draw a clear distinction between malignant hypertension and benign hypertension with regard to renal histology and clinical renal involvement. In benign arteriolar nephrosclerosis caused by benign hypertension, the characteristic histologic lesion is hyaline arteriosclerosis. In hyaline arteriosclerosis there is expansion of the intima of afferent arterioles with hyaline material that stains a pale-pink color on periodic acid-Schiff staining (*large arrow*). Patchy (focal) ischemic atrophy of the glomeruli usually is seen. Many glomeruli appear normal, whereas some are completely hyalinized. Atrophic tubules (*small arrows*), sometimes filled with amorphous material, may be seen in the vicinity of ischemic glomeruli. The severity of the glomerular and tubular changes generally reflect the extent of vascular involvement with hyaline arteriosclerosis. On gross examination, the kidneys are small with a granular-appearing capsular surface (contracted granular kidney). The loss of renal mass primarily is due to a thinning of the cortex. In untreated malignant hypertension, relentless progression to end-stage renal disease (ESRD) occurs within a year. In contrast, in benign hypertension, without underlying renal disease or superimposed malignant hypertension, despite well-established folklore to the contrary, ESRD seldom develops [21,22]. In benign hypertension, there is usually a long asymptomatic phase, with eventual complications resulting from cerebrovascular disease, atherosclerotic disease, or congestive heart failure, in the absence of significant renal impairment despite histologic evidence of benign nephrosclerosis. In this regard, patients classified as having ESRD owing to “hypertensive nephrosclerosis” typically exhibit advanced disease initially, making the original process that initiated the renal disease difficult to detect. Moreover, significant racial bias may occur in the clinical diagnosis of the cause of ESRD [23]. Nephrologists presented with identical case histories of hypothetical patients with ESRD and hypertension in which the race is arbitrarily stated to be Black or White, tend to diagnose hypertensive nephrosclerosis in Blacks and chronic glomerulonephritis in Whites. It has been proposed that many of the patients presumed clinically to have ESRD owing to benign hypertension, actually have occult intrinsic renal disease with chronic glomerulonephritis, unrecognized bilateral atherosclerotic renal artery stenosis with ischemic nephropathy, atheroembolic renal disease, or episodes of malignant hypertension that had gone undetected [21,22]. (Periodic acid-Schiff stain, original magnification  $\times 100$ .)

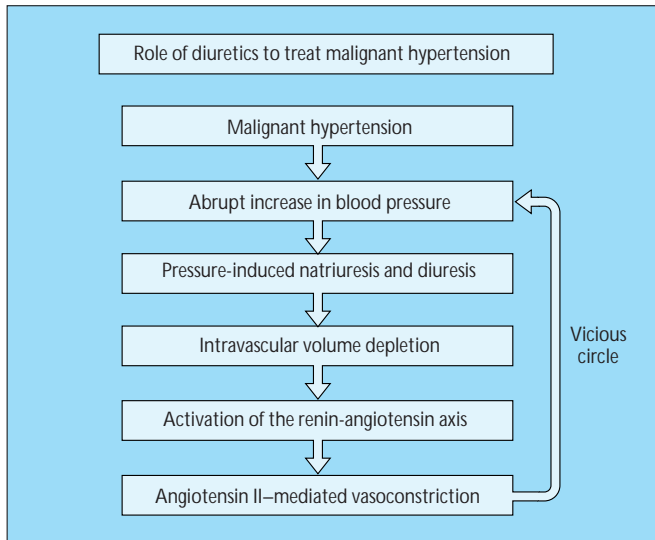
**INDICATIONS FOR PARENTERAL THERAPY  
IN MALIGNANT HYPERTENSION**

Hypertensive encephalopathy  
Rapidly failing vision  
Pulmonary edema  
Intracerebral hemorrhage  
Rapid deterioration of renal function  
Acute pancreatitis  
Gastrointestinal hemorrhage or acute abdomen from mesenteric vasculitis  
Patients unable to tolerate oral therapy because of intractable vomiting

**FIGURE 8-19**

Malignant hypertension must be treated expeditiously to prevent complications such as hypertensive encephalopathy, acute hypertensive heart failure, and renal failure. The traditional approach to patients with malignant hypertension has been the initiation of potent parenteral agents. Listed are the settings in which parenteral antihypertensive therapy is mandatory in the initial management of malignant hypertension. Parenteral therapy generally should be used in patients with evidence of acute end-organ dysfunction or those unable to tolerate oral medications. Nitroprusside is the treatment of choice for patients requiring parenteral therapy. Diazoxide, employed in minibolus fashion to avoid sustained overshoot hypotension, may be advantageous in patients for whom monitoring in an intensive care unit is not feasible. It generally is safe to reduce the mean arterial pressure by 20% or to a level of 160 to 170 mm Hg systolic over 100 to 110 mm Hg diastolic. The use of a short-acting agent such as nitroprusside has obvious advantages because blood pressure can be stabilized quickly at a higher level if complications develop during rapid blood pressure reduction. When no evidence of vital organ hypoperfusion is seen during this initial reduction, the diastolic blood pressure can be lowered gradually to 90 mm Hg over a period of 12 to 36 hours. Oral antihypertensive agents should be initiated as soon as possible to minimize the duration of parenteral therapy. The nitroprusside infusion can be weaned as the oral agents become effective. The cornerstone of initial oral therapy should be arteriolar vasodilators such as calcium channel blockers, hydralazine, or minoxidil. Usually,  $\beta$ -blockers are required to control reflex tachycardia, and a diuretic must be initiated within a few days to prevent salt and water retention, in response to vasodilator therapy, when the patient's dietary salt intake increases. Diuretics may not be necessary as a part of initial parenteral therapy because patients with malignant hypertension often present with volume depletion (Fig. 8-20).

Many patients with malignant hypertension definitely require initial parenteral therapy. However, some patients may not yet have evidence of cerebral or cardiac dysfunction or rapidly deteriorating renal function and therefore do not require instantaneous control of blood pressure. These patients often can be managed with an intensive oral regimen, often with a  $\beta$ -blocker and minoxidil, designed to bring the blood pressure under control within 12 to 24 hours. After the immediate crisis has resolved and the patient's blood pressure has been controlled with initial parenteral therapy, oral therapy, or both, lifelong surveillance of blood pressure is mandatory. If blood pressure control lapses, malignant hypertension can recur even after years of successful antihypertensive therapy. Triple therapy with a diuretic,  $\beta$ -blocker, and a vasodilator often is required to maintain satisfactory long-term blood pressure control.

**FIGURE 8-20**

Role of diuretics in the treatment of malignant hypertension. Traditionally, it had been taught that patients with malignant hypertension require potent parenteral diuretics in conjunction with potent vasodilator therapy during the initial phase of management of malignant hypertension. However, evidence now exists to suggest that parenteral diuretic therapy during the acute management phase actually may be deleterious. In experimental animals, spontaneous natriuresis appears to be the initiating event in the transition from benign to malignant hypertension, and treatment with volume expansion leads to resolution of the malignant phase [24]. Rapid weight loss often occurs in patients with malignant hypertension, which is consistent with a pressure-induced natriuresis. In analgesic nephropathy, profound volume depletion often accompanies malignant hypertension, perhaps owing to tubular dysfunction with salt-wasting [5]. In this setting, restoration of normal volume status actually lowers blood pressure and leads to resolution of the malignant phase. Thus, some patients with malignant hypertension may benefit from a cautious trial of volume expansion. Volume depletion should be suspected when there is exquisite sensitivity to vasodilator therapy with a precipitous decrease in blood pressure at relatively low infusion rates. Even patients with malignant hypertension complicated by pulmonary edema may not be total-body salt and water overloaded. Pulmonary congestion in this setting may result from acute hypertensive heart failure caused by an acute decrease in left ventricular (LV) compliance precipitated by severe hypertension. In this setting, pulmonary edema occurs owing to a high LV end-diastolic pressure with normal LV end-diastolic volume (Fig. 8-24). Thus, the need for diuretic therapy during the initial phases of management of malignant hypertension depends on a careful assessment of volume status. Unless obvious fluid overload is present, diuretics should not be given initially. Overdiuresis may result in deterioration of renal function owing to superimposed volume depletion. Moreover, volume depletion may further activate the renin-angiotensin system and other pressor hormone systems. Although vasodilator therapy will eventually result in salt and water retention by the kidneys, an increase in total body sodium content cannot occur unless the patient is given sodium. Eventually, during long-term treatment with oral vasodilators, the use of diuretics becomes imperative to prevent fluid retention and adequately control blood pressure.

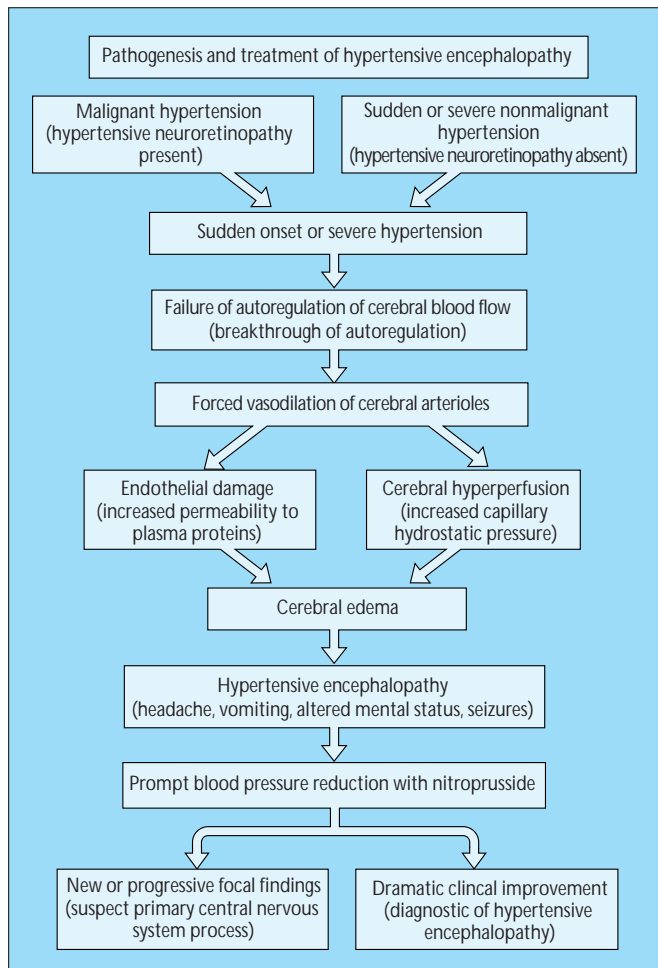


FIGURE 8-21

Pathogenesis and treatment of hypertensive encephalopathy. *Hypertensive encephalopathy* is a hypertensive crisis in which acute cerebral dysfunction is attributed to sudden or severe elevation of blood pressure [25–27]. Hypertensive encephalopathy is one of the most serious complications of malignant hypertension. However, malignant hypertension (hypertensive neuroretinopathy) need not be present for hypertensive encephalopathy to develop. Hypertensive encephalopathy also can occur in the setting of severe or sudden hypertension of any cause, especially if an acute elevation of blood pressure occurs in a previously normotensive person, *eg*, from postinfectious glomerulonephritis, catecholamine excess states, or eclampsia. Under normal circumstances, autoregulation of the cerebral microcirculation occurs, and therefore, cerebral blood flow remains constant over a wide range of perfusion pressures. However, in the setting of sudden severe hypertension, autoregulatory vasoconstriction fails and there is forced vasodilation of cerebral arterioles with endothelial damage, extravasation of plasma proteins, and cerebral hyperperfusion with the development of cerebral edema. This breakthrough of cerebral autoregulation underlies the development of hypertensive encephalopathy. In patients with chronic hypertension, structural changes occur in the cerebral arterioles that lead to a shift in the autoregulation curve such that much higher blood pressures can be tolerated without breakthrough. This phenomenon may explain the clinical observation that hypertensive encephalopathy occurs at much lower blood pressure in previously normotensive persons than it does in those with chronic hypertension. Clinical features of hypertensive encephalopathy include severe headache, blurred vision or occipital blindness, nausea, vomiting, and altered mental status. Focal neurologic findings can sometimes occur. If aggressive blood pressure reduction is not initiated, stupor, convulsions, and death can occur within hours. The *sine qua non* of hypertensive encephalopathy is the prompt and dramatic clinical improvement in response to antihypertensive drug therapy. When a diagnosis of hypertensive encephalopathy seems likely, antihypertensive therapy should be initiated promptly without waiting for the results of time-consuming radiographic examinations. The goal of therapy, especially in previously normotensive patients, should be reduction of blood pressure to normal or near-normal levels as quickly as possible. Theoretically, cerebral blood flow could be jeopardized by rapid reduction of blood pressure in patients with chronic hypertension in whom the lower limit of cerebral blood flow autoregulation is shifted to a higher blood pressure. However, clinical experience has shown that prompt blood pressure reduction with the avoidance of frank hypotension is beneficial in patients with hypertensive encephalopathy [25]. Of the conditions in the differential diagnosis of hypertension with acute cerebral dysfunction, only cerebral infarction might be adversely affected by the abrupt reduction of blood pressure. Pharmacologic agents that have rapid onset and short duration of action such as sodium nitroprusside should be used so that the blood pressure can be titrated carefully, with close monitoring of the patient's neurologic status. A prompt improvement in mental status with blood pressure reduction confirms the diagnosis of hypertensive encephalopathy. Conversely, when blood pressure reduction is associated with new or progressive focal neurologic deficits, the presence of a primary central nervous system event, such as cerebral infarction, should be considered.

### CAUSES OF HYPERTENSIVE ENCEPHALOPATHY

Malignant hypertension of any cause  
 Acute glomerulonephritis, especially postinfectious  
 Eclampsia  
 Catecholamine-induced hypertensive crises  
   Pheochromocytoma  
   Monoamine oxidase inhibitor–tyramine interactions  
   Abrupt withdrawal of centrally acting  $\alpha_2$ -agonists  
   Phenylpropranolamine overdose  
 Cocaine-hydrochloride or alkaloid (crack cocaine) intoxication  
 Phencyclidine (PCP) poisoning  
 Acute lead poisoning in children  
 High-dose cyclosporine for bone marrow transplantation in children  
 Femoral lengthening procedures  
 Scorpion envenomation in children  
 Acute renal artery occlusion from thrombosis or embolism  
 Atheroembolic renal disease (cholesterol embolization)  
 Recombinant erythropoietin therapy  
 Transplantation renal artery stenosis  
 Acute renal allograft rejection  
 Paroxysmal hypertension in acute or chronic spinal cord injuries  
 Post–coronary artery bypass or post–carotid endarterectomy hypertension

### FIGURE 8-22

Hypertensive encephalopathy can complicate malignant hypertension of any cause. However, not all patients with hypertensive encephalopathy have hypertensive neuroretinopathy, indicating the presence of malignant hypertension. In fact, hypertensive encephalopathy most commonly occurs in previously normotensive persons who experience a sudden onset or worsening of hypertension. In acute postinfectious glomerulonephritis, the abrupt onset of even moderate hypertension may cause breakthrough of autoregulation of cerebral blood flow, resulting in hypertensive encephalopathy. Eclampsia can be viewed as a variant of hypertensive encephalopathy that complicates preeclampsia. Moreover, hypertensive encephalopathy is a common complication of catecholamine-induced hypertensive crises such as pheochromocytoma, monoamine oxidase inhibitor–tyramine interactions, clonidine withdrawal, phencyclidine (PCP) poisoning, and phenylpropranolamine overdose. Cocaine use also can induce a sudden increase in blood pressure accompanied by hypertensive encephalopathy. In children, acute lead poisoning, high-dose cyclosporine for bone marrow transplantation, femoral lengthening procedures, and scorpion envenomation may be accompanied by the sudden onset of hypertension with hypertensive encephalopathy. Acute renal artery occlusion resulting from thrombosis or renal embolism can induce hypertensive encephalopathy. Likewise, atheroembolic renal disease (cholesterol embolization) can cause a sudden increase in blood pressure complicated by encephalopathy. Recombinant erythropoietin therapy occasionally results in encephalopathy and seizures. This complication is unrelated to the extent or rate of increase in hematocrit; however, it is associated with a rapid increase in blood pressure, especially if the patient was normotensive previously. Transplantation renal artery stenosis or acute renal allograft rejection may cause sudden severe hypertension with encephalopathy. Hypertensive encephalopathy may complicate acute or chronic spinal cord injury. Sudden elevation of blood pressure occurs owing to autonomic stimulation by bowel or bladder distention or noxious stimulation in a dermatome below the level of the injury. Hypertensive encephalopathy also may complicate the rebound hypertension that follows coronary artery bypass procedures or carotid endarterectomy.

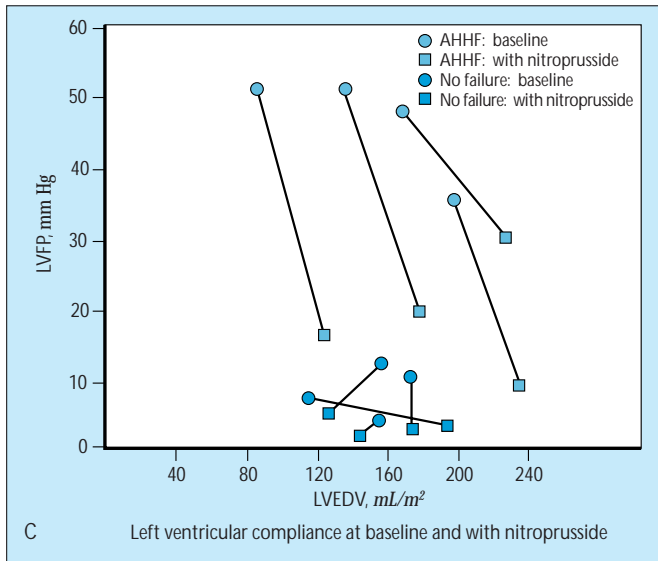
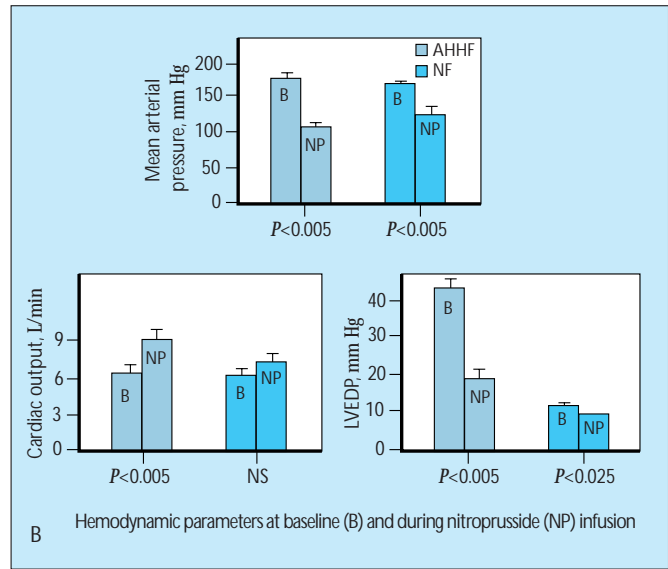
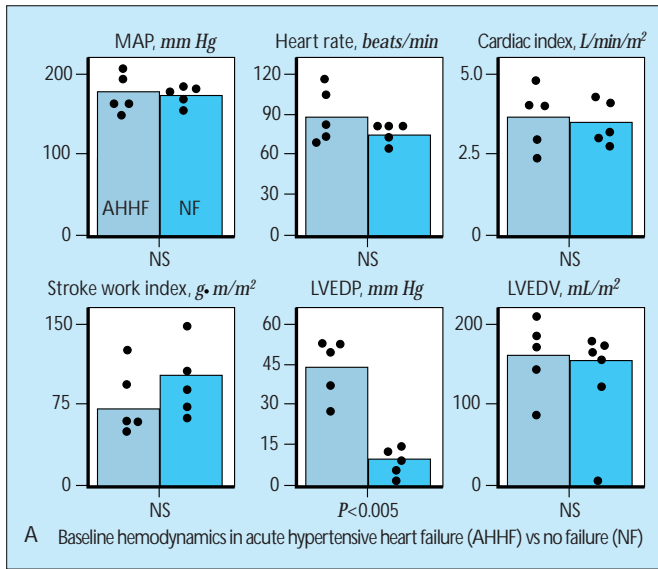
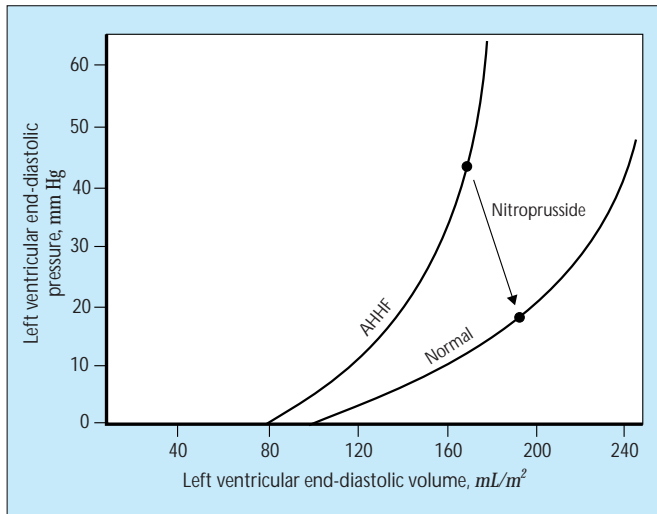


FIGURE 8-23

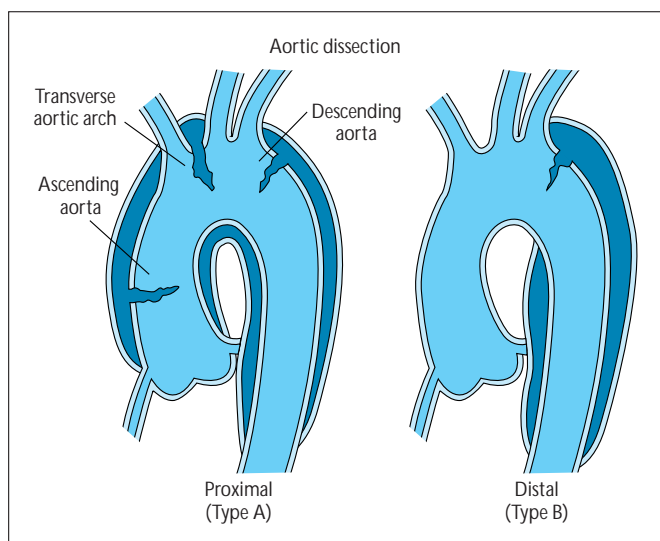
**Pathogenesis of acute hypertensive heart failure.** Both malignant hypertension and severe benign hypertension can be complicated by acute pulmonary edema caused by isolated diastolic dysfunction. In acute hypertensive heart failure the compromise of left ventricular (LV) diastolic function occurs as a result of a decrease in LV compliance caused by an increased workload imposed on the heart by the marked elevation in systemic vascular resistance. Illustrated are the hemodynamic derangements in acute hypertensive heart failure in a study that compared five patients with severe essential hypertension complicated by acute pulmonary edema with a control group of five patients with equally severe hypertension but no pulmonary edema [28]. Patients

in both groups had electrocardiographic evidence of LV hypertrophy caused by long-standing hypertension.

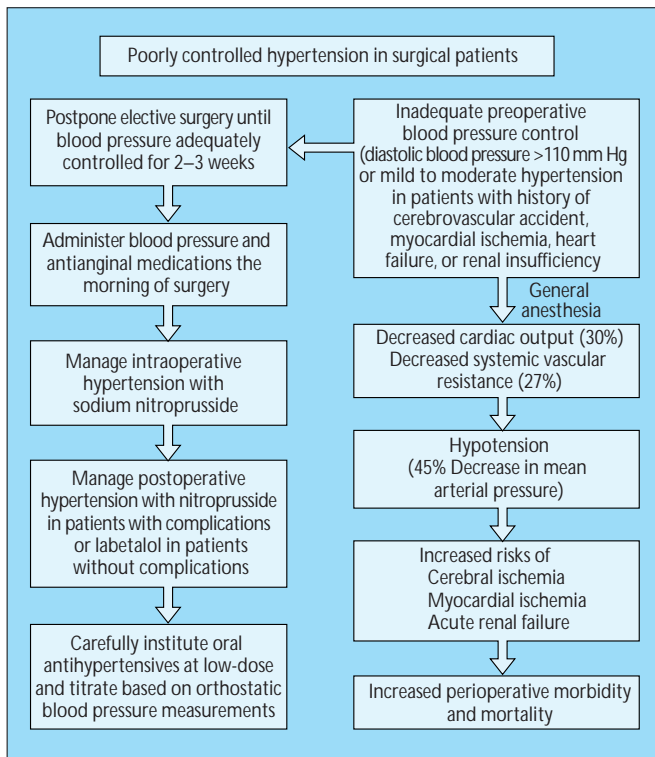
**A**, Baseline hemodynamic measurements before treatment revealed that the following measurements were the same in both groups: mean arterial pressure (MAP), heart rate, cardiac index, systemic vascular resistance, and stroke work index. Likewise, the LV end-diastolic volume (LVEDV) was similar in both groups. In fact, the only hemodynamic difference between the groups was a significant elevation of LV filling pressure (LVFP) (pulmonary capillary wedge pressure) in the group with pulmonary edema. In acute hypertensive heart failure the finding of elevated LV end-diastolic pressures (LVEDPs), despite normal ejection fraction and cardiac index, implies the presence of isolated diastolic dysfunction. The increased LV end-diastolic pressure (LVEDP), despite similar LVEDV, can only be explained by a decrease in LV compliance in patients with acute hypertensive heart failure. **B**, The importance of an acute decrease in LV compliance in the pathogenesis of acute hypertensive heart failure (AHHF) was confirmed in these patients by the hemodynamic response to vasodilator therapy. Sodium nitroprusside infusion resulted in prompt resolution of pulmonary edema in the group having AHHF, with the LVEDP decreasing from a mean of 43 to 18 mm Hg. **C**, The decrease in filling pressure during nitroprusside therapy in patients with AHHF was not caused by venodilation with decreased venous return because the LVEDV actually increased during nitroprusside infusion. Thus, the response to sodium nitroprusside therapy was mediated through a decrease in systemic vascular resistance that led to an immediate improvement in LV compliance and reduction in wedge pressure despite an increase in LVEDV. These findings suggest that the proximate cause of AHHF is an elevation of the systemic vascular resistance that precipitates acute diastolic dysfunction (decreased LV compliance) with elevated pulmonary capillary wedge pressure, resulting in pulmonary edema. NS— not significant. (Adapted from Cohn and coworkers [28]; with permission.)

**FIGURE 8-24**

Treatment of acute hypertensive heart failure. The left ventricular (LV) end-diastolic pressure-volume relationships (compliance curves) in acute hypertensive heart failure (AHHF) before and after treatment with sodium nitroprusside are represented schematically. In AHHF, the pressure-volume curve is shifted up and to the left, reflecting an acute decrease in LV compliance caused by severe systemic hypertension. In this setting, a higher than normal LV end-diastolic pressure (LVEDP) is required to achieve any given level of LV end-diastolic volume (LVEDV). Normal LV systolic function (ejection fraction and cardiac output) is maintained but at the expense of a very high wedge pressure that results in acute pulmonary edema. Treatment with sodium nitroprusside causes a reduction in the elevated systemic vascular resistance, with a concomitant decrease in impedance to LV ejection. As a result, LV compliance improves. Pulmonary edema resolves owing to a reduction in LVEDP, despite the fact that LVEDV actually increases during treatment. Sodium nitroprusside is the preferred drug for treatment of AHHF. There is no absolute blood pressure goal. The infusion should be titrated until signs and symptoms of pulmonary edema resolve or the blood pressure decreases to hypotensive levels. Rarely is it necessary to lower the blood pressure to this extent, however, because reduction to levels still within the hypertensive range is usually associated with dramatic clinical improvement. Although hemodynamic monitoring is not always required, it is essential in patients in whom concomitant myocardial ischemia or compromised cardiac output is suspected. After the hypertensive crisis has been controlled and pulmonary edema has resolved, oral antihypertensive therapy can be substituted as the patient is weaned from the nitroprusside infusion. As in the treatment of hypertensive patients with chronic congestive heart failure symptoms owing to isolated diastolic dysfunction, agents such as  $\beta$ -blockers, angiotension-converting enzyme inhibitors, or calcium channel blockers may represent logical first-line therapy. These agents directly improve diastolic function in addition to reducing systemic blood pressure. In patients with malignant hypertension or resistant hypertension, however, adequate control of blood pressure may require therapy with more than one drug. Potent direct-acting vasodilators such as hydralazine or minoxidil may be used in conjunction with a  $\beta$ -blocker to control reflex tachycardia and a diuretic to prevent reflex salt and water retention.

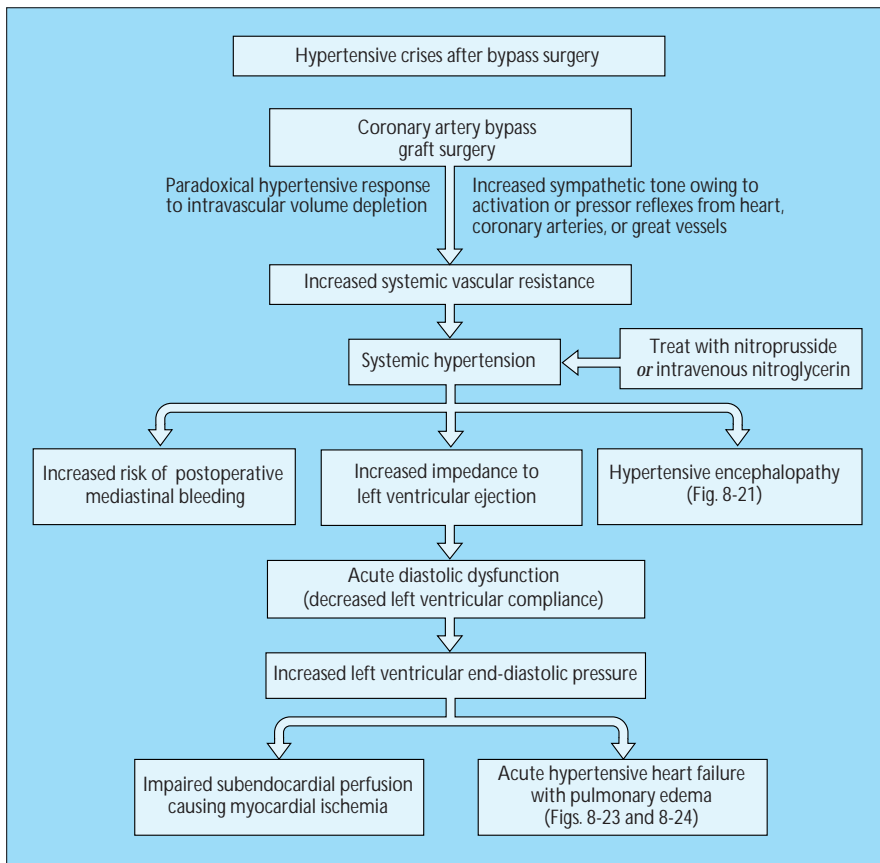
**FIGURE 8-25**

**Aortic dissection.** Classification of aortic dissection is based on the presence or absence of involvement of the ascending aorta [29]. The dissection is defined as proximal if there is involvement of the ascending aorta. The primary intimal tear in proximal dissection may arise in the ascending aorta, transverse aortic arch, or descending aorta. In distal dissections, the process is confined to the descending aorta without involvement of the ascending aorta, and the primary intimal tear occurs most commonly just distal to the origin of the left subclavian artery. Proximal dissections account for approximately 57% and distal dissections 43% of all acute aortic dissections. Acute aortic dissection is a hypertensive crisis requiring immediate antihypertensive treatment aimed at halting the progression of the dissecting hematoma. The three most frequent complications of aortic dissection are acute aortic insufficiency, occlusion of major arterial branches, and rupture of the aorta with fatal hemorrhage (location of rupture-hemorrhage: ascending aorta-hemopericardium with tamponade, aortic arch-mediastinum, descending thoracic aorta-left pleural space, abdominal aorta-retroperitoneum). Patients with acute dissection should be stabilized with intensive antihypertensive therapy to prevent life-threatening complications before diagnostic evaluation with angiography. The initial therapeutic goal is the elimination of pain that correlates with halting of the dissection, and reduction of the systolic pressure to the 100 to 120 mm Hg range or to the lowest level of blood pressure compatible with the maintenance of adequate renal, cardiac, and cerebral perfusion [30]. Even in the absence of systemic hypertension the blood pressure should be reduced. Antihypertensive therapy should be designed not only to lower the blood pressure but also to decrease the steepness of the pulse wave. The most commonly used treatment regimens consist of initial treatment with intravenous  $\beta$ -blockers such as propranolol, metoprolol, or esmolol followed by treatment with sodium nitroprusside. After control of the blood pressure, angiography or transesophageal echocardiography, or both, should be performed. The need for surgical intervention is determined based on involvement of the ascending aorta. In proximal dissections, surgical therapy is clearly superior to medical therapy alone (70% vs 26% survival, respectively). In contrast, in patients with distal dissection, intensive drug therapy alone leads to an 80% survival rate compared with only 50% in patients treated surgically. The explanation for the advantage of surgical therapy in proximal dissection is probably that the risks of complications such as cerebral ischemia, acute aortic insufficiency, and cardiac tamponade are higher and managed more effectively with surgery. Because these complications do not occur in distal dissection, in the absence of occlusion of a major arterial branch or development of a saccular aneurysm during long-term follow-up, medical therapy is preferred. Patients with distal dissection tend to be elderly with more advanced aortic atherosclerosis and therefore are at higher risk of complications from operative intervention. (*Adapted from Wheat [29]; with permission.*)

**FIGURE 8-26**

Poorly controlled hypertension in the patient requiring surgery. Hypertension in the preoperative patient is a common problem. Poor control of preoperative hypertension, with a diastolic blood pressure higher than 110 mm Hg, is a relative contraindication to elective surgery. In such patients, perioperative morbidity and mortality are increased because of a higher incidence of intraoperative hypotension accompanied by myocardial ischemia and a heightened risk of acute renal failure [31]. Malignant hypertension clearly represents an excessive surgical risk and all but lifesaving emergency surgery should be deferred until the blood pressure can be controlled and organ function stabilized. Mild to moderate uncomplicated hypertension with diastolic blood pressure less than 110 mm Hg does not appear to increase the risk of surgery significantly and therefore is not an absolute indication to postpone elective surgery. However, patients with mild to moderate hypertension and preexisting complications such as ischemic heart disease, cerebrovascular disease, congestive heart failure, or chronic renal insufficiency, represent a subgroup with significantly increased perioperative risk. In these patients, adequate preoperative control of blood pressure

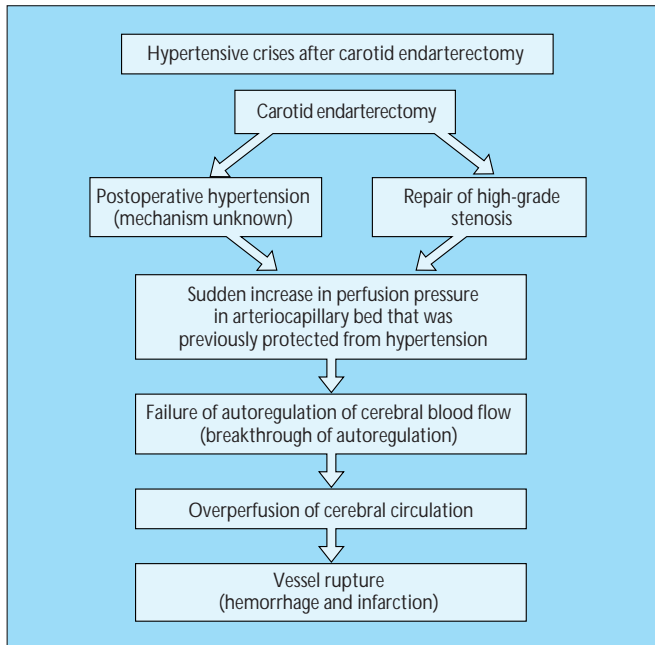
is imperative [32]. Even though the blood pressure in patients with severe or complicated hypertension usually can be controlled within hours using aggressive parenteral therapy, such precipitous control of blood pressure carries the risk of significant complications such as hypovolemia, electrolyte abnormalities, and marked intraoperative blood pressure lability. General anesthesia is accompanied by a 30% decrease in cardiac output. In normotensive persons and patients with adequately treated hypertension, anesthesia is not associated with a decrease in systemic vascular resistance. Therefore, the decrease in mean arterial pressure (MAP) is modest (25–30%). However, in patients with inadequate preoperative blood pressure control, anesthesia is associated with a concomitant decrease in systemic vascular resistance (SVR) of approximately 27%. The combined decrease in cardiac output and SVR leads to a profound decrease in MAP (45%) during anesthesia [33]. This intraoperative hypotension predisposes to myocardial ischemia, cerebrovascular accidents, and acute renal failure. Therefore, in patients with diastolic blood pressure over 110 mm Hg or these other high-risk groups, elective surgery should be postponed and blood pressure brought under control for a few weeks before surgery, if possible. Ideally, sustained adequate preoperative blood pressure control should be the goal in all hypertensive patients [34]. In patients with adequately treated hypertension, oral antihypertensive, and antianginal medications should be continued up to and including the morning of surgery, administered with small sips of water. Because hypovolemia increases the risk of intraoperative hypotension and postoperative acute renal failure, diuretics should be withheld for 1 to 2 days preoperatively except in patients with overt heart failure or fluid overload. Adequate potassium repletion should be given to correct hypokalemia well in advance of surgery. Continuation of  $\beta$ -blockers to within a few hours of surgery does not impair cardiac function and has been shown to decrease the risks of dysrhythmia and myocardial ischemia during surgery. In patients with complications and a history of cardiovascular disease or heart failure, or after coronary artery bypass surgery, postoperative hypertension should be managed with short-acting agents such as nitroglycerin or nitroprusside. In patients without complications, intermittent intravenous infusions of labetalol may be useful for management of mild to moderate postoperative hypertension until the preoperative oral antihypertensive agents can be resumed. Many patients with long-standing hypertension, even if severe, require much smaller doses of antihypertensive medications in the early postoperative course. Thus, the preoperative regimen should not be restarted automatically. Measurement of orthostatic blood pressures should be used as a guide to dosage adjustment during the postoperative recovery period. In most instances, the need for antihypertensive medications will gradually increase over a few days to weeks to eventually equal the preoperative requirement.



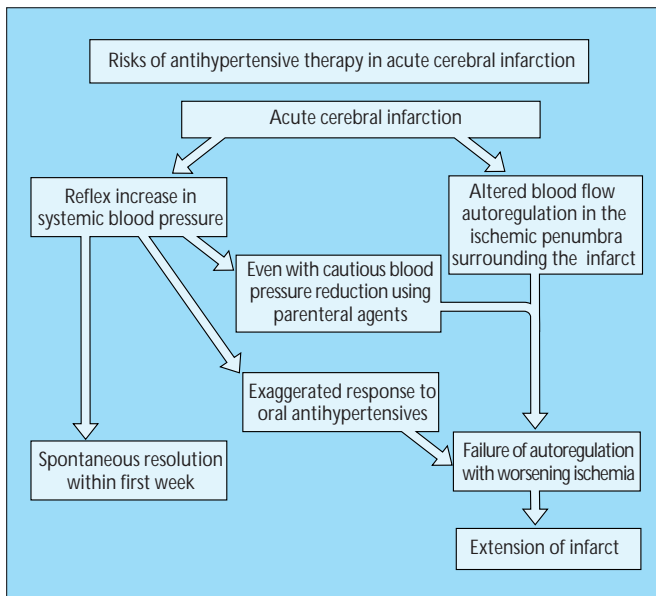
**FIGURE 8-27**

Hypertensive crisis after coronary artery bypass surgery. Paroxysmal hypertension in the immediate postoperative period is a frequent and serious complication of cardiac surgery [35,36]. Paroxysmal hypertension is the most frequent complication of coronary artery bypass surgery, occurring in 30% to 50% of patients. It occurs just as often in normotensive patients as it does in those with a history of chronic hypertension. The increase in blood pressure usually occurs during the first 4 hours after surgery. The hypertension results from a dramatic increase in systemic vascular resistance (SVR) without a change in the cardiac output and is most commonly mediated by an increase in sympathetic tone owing to activation of pressor reflexes from the heart, great vessels, or coronary arteries. Hypervolemia, although often cited as a potential mechanism of postoperative hypertension, is a rare cause of postbypass hypertension except in patients with renal failure. In fact, increased SVR owing to marked sympathetic overreaction to volume depletion is a common, often unrecognized, cause of severe postoperative hypertension [37]. Patients with this paradoxical hypertensive response to hypovolemia are exquisitely sensitive to vasodilator therapy and

may develop precipitous hypotension with even low-dose infusions of nitroglycerin or nitroprusside. Hypertension in this setting should be treated using careful volume expansion with crystalloid solutions or blood if required. Post-coronary artery bypass hypertension represents a hypertensive crisis because the heightened SVR increases the impedance to left ventricular (LV) ejection (afterload) that can result in an acute decrease in ventricular compliance with elevation of LV end-diastolic pressure (LVEDP) and acute hypertensive heart failure with pulmonary edema (Figs. 8-23 and 8-24). The increase in LVEDP also impairs subendocardial perfusion and can cause myocardial ischemia. Moreover, the elevated blood pressure increases the risk of mediastinal bleeding in these recently heparinized patients. The initial management of postbypass hypertension should focus on attempts to ameliorate reversible causes of sympathetic activation, including patient agitation on emergence from anesthesia, tracheal or nasopharyngeal irritation from the endotracheal tube, pain, hypothermia with shivering, ventilator asynchrony, hypoxia, hypercarbia, and volume depletion. If these general measures fail to control the blood pressure, further therapy should be guided by measurement of systemic hemodynamics. Intravenous nitroglycerin or nitroprusside is the drug of choice to provide a controlled decrease in SVR and blood pressure. Nitroglycerin may be the preferred drug because it dilates intracoronary collateral arteries [35,36]. Therapy with  $\beta$ -blockers is not indicated in this setting and may be detrimental because these drugs impair cardiac output and cause a further increase in SVR. Labetalol also has been shown to cause a significant reduction in cardiac output in postbypass hypertension. Postbypass hypertension is usually transient and resolves by 6 to 12 hours postoperatively, so that the vasodilatory therapy can be weaned. The hypertension usually does not recur after the initial episode in the immediate postoperative period.

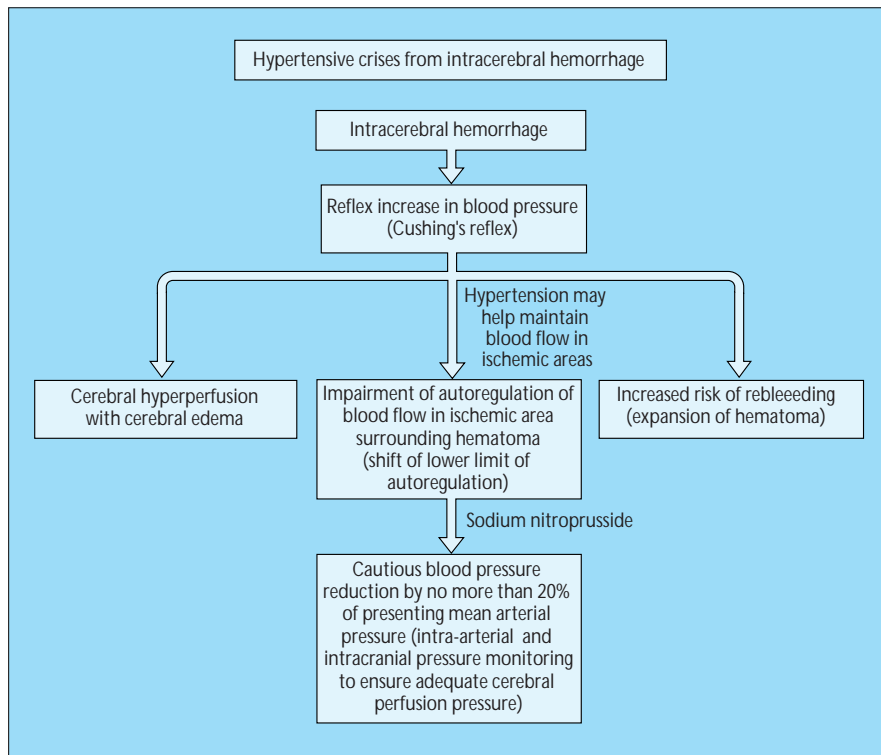
**FIGURE 8-28**

Hypertensive crisis after carotid endarterectomy. Hypertension in the immediate postoperative period occurs in up to 60% of patients after carotid endarterectomy [38]. A history of chronic hypertension, especially if the blood pressure is poorly controlled preoperatively, dramatically increases the risk of postoperative hypertension. The mechanism of post-endarterectomy hypertension is unknown. The incidence of hypertension is the same whether or not the carotid sinus nerve is preserved. Hypertension after endarterectomy is a hypertensive crisis because it is associated with increased risk of intracerebral hemorrhage and increases the postoperative mortality rate [39]. A mechanism for the development of post-carotid endarterectomy cerebral hemorrhage owing to postoperative hypertension has been proposed. In patients with high-grade carotid artery stenosis, the distal cerebral circulation has been relatively protected from systemic hypertension. In this regard, the autoregulatory curve may be shifted to a lower threshold to compensate for reduced perfusion pressure. After repair of the obstructing lesion, a relative increase in perfusion pressure occurs in the cerebral arteriocapillary bed. In the setting of systemic hypertension the increased blood flow and perfusion pressure may overwhelm the autoregulatory mechanisms. Overperfusion and rupture may then occur, resulting in hemorrhagic infarction. Because poor preoperative blood pressure control increases the risk of postoperative hypertension, strict blood pressure control is essential before elective carotid endarterectomy. Furthermore, intra-arterial pressure should be monitored in the operating room and in the immediate postoperative period. Ideally, the patient should be awake and extubated before reaching the recovery room so that serial neurologic examinations can be performed to assess for the development of focal deficits. When the systolic blood pressure exceeds 200 mm Hg, an intravenous infusion of sodium nitroprusside should be initiated to maintain the systolic blood pressure between 160 and 200 mm Hg. The use of a short-acting parenteral agent is imperative to avoid overshoot hypotension and cerebral hypoperfusion.

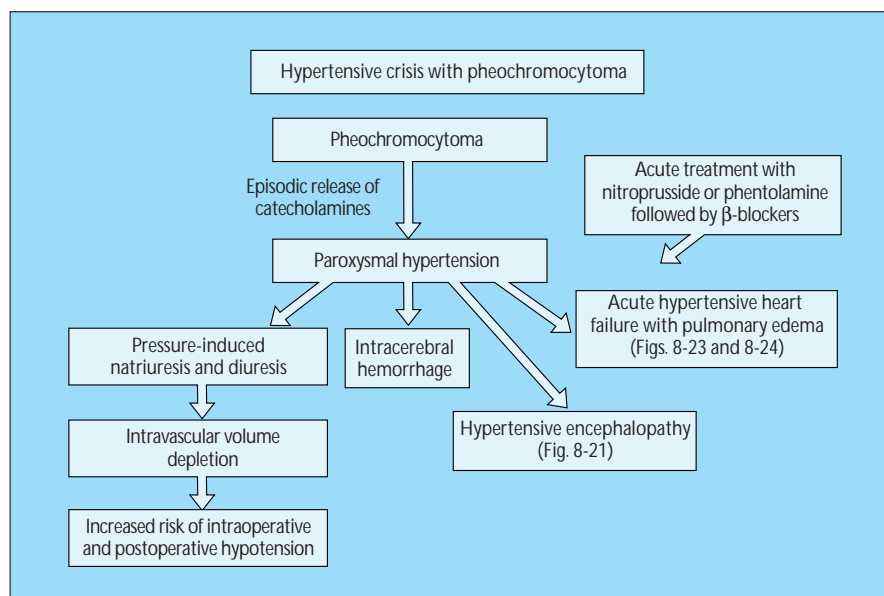
**FIGURE 8-29**

Risks of antihypertensive therapy in acute cerebral infarction. Cerebral infarction results from partial or complete occlusion of an artery by an atherosclerotic plaque or embolization of atherothrombotic debris from a more proximal plaque. These atherothrombotic infarcts typically involve the cerebral cortex, cerebellar cortex, or pons; these infarcts are to be contrasted with hypertension-induced lipohyalinosis of the small penetrating cerebral end-arteries that is the principal cause of the small lacunar infarcts occurring in the basal ganglia, pons, thalamus, cerebellum, and deep hemispheric white matter. Hypertension occurs in up to 85% of patients with acute cerebral infarction, even in previously normotensive persons [40]. This early elevation of blood pressure probably represents a physiologic response to brain ischemia. Because of the known benefits of antihypertensive therapy with regard to stroke prevention, it previously had been assumed that acute reduction of blood pressure would also be of benefit in acute cerebral infarction. However, no evidence exists to suggest that acute reduction of blood pressure is beneficial in this setting. In fact, reports exist of worsening neurologic status, apparently precipitated by emergency treatment of hypertension in patients with cerebral infarction [41]. In the setting of acute cerebral

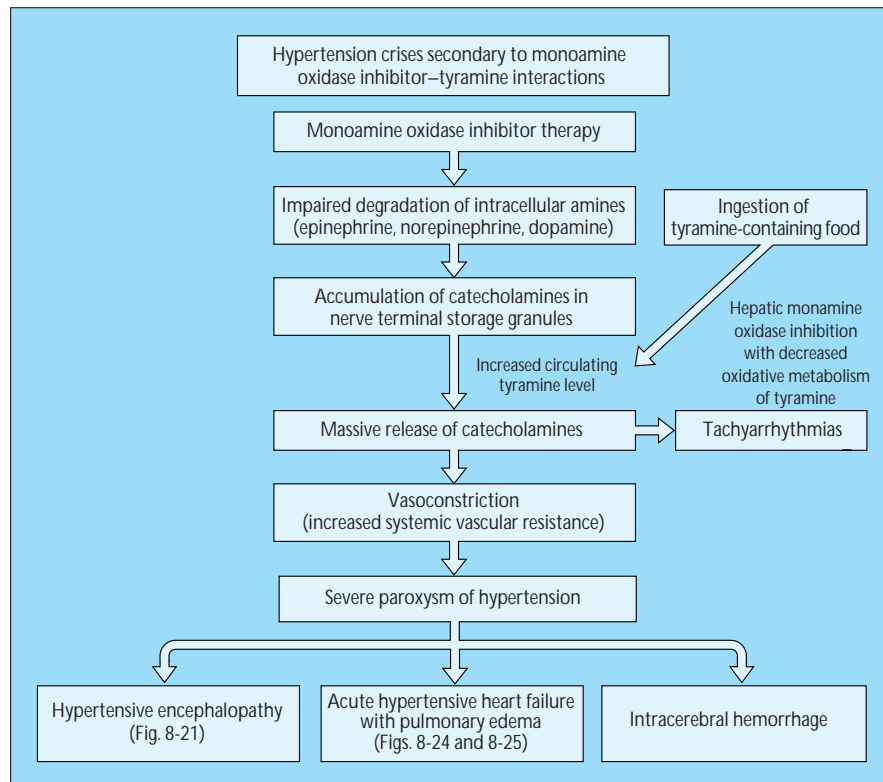
infarction, hypertension tends to be very labile and exquisitely sensitive to hypotensive therapy. Thus, even modest doses of oral antihypertensive agents can lead to profound and devastating overshoot hypotension with extension of the infarct [42]. An additional rationale for not treating hypertension in the acute setting is based on evidence that local autoregulation of cerebral blood flow is impaired in the so-called ischemic penumbra, which surrounds the area of acute infarction [43]. Without intact autoregulation, the regional blood flow in this marginal zone of ischemia becomes critically dependent on the perfusion pressure. Thus, the presence of mild to moderate systemic hypertension may actually be protective, and acute reduction of blood pressure may cause a regional reduction in blood flow with extension of the infarct. Thus, in most cases of cerebral infarction it is prudent to allow the blood pressure to seek its own level during the first few days to weeks after the event. In most cases the hypertension tends to resolve spontaneously, without any specific therapy, over the first week as brain function recovers. When hypertension persists for more than 3 weeks after a completed infarction, reduction of the blood pressure into the normal range with oral antihypertensives is appropriate. Although benign neglect of mild to moderate hypertension is prudent in acute cerebral infarction, there may be certain indications for active treatment of blood pressure. When the diastolic blood pressure is sustained at over 130 mm Hg, cautious reduction of blood pressure into the ranges of 160 to 170 mm Hg systolic and 100 to 110 mm Hg diastolic may be appropriate. In stroke patients requiring anticoagulation therapy, moderate control of severe hypertension also should be considered. Cautious blood pressure reduction is indicated when stroke is accompanied by other hypertensive crises such as acute myocardial ischemia or acute hypertensive heart failure. Stroke caused by carotid occlusion by a proximal aortic dissection mandates aggressive blood pressure reduction into the normal range to halt the dissection process. In the setting of sudden severe hypertension, it may be difficult to distinguish hypertensive encephalopathy with focal neurologic findings from cerebral infarction. Because rapid reduction of blood pressure is lifesaving in patients with hypertensive encephalopathy, a cautious diagnostic trial of blood pressure reduction may be warranted (Fig. 8-21). If blood pressure reduction is deemed necessary in patients with acute cerebral infarction, treatment should be initiated using small doses of a short-acting parenteral agent such as sodium nitroprusside. Use of oral or sublingual nifedipine is associated with excessive risk of prolonged overshoot hypotension. Oral clonidine loading also is contraindicated because of the risk of hypotension and because sedative side effects interfere with the assessment of mental status.

**FIGURE 8-30**

Hypertensive crises due to intracerebral hemorrhage. Chronic hypertension is the major risk factor for intracerebral hemorrhage. The most common sites of hemorrhage are the small-diameter penetrating cerebral end-arteries in the basal ganglia, pons, thalamus, cerebellum, and deep hemispheric white matter. Lacunar infarcts arise from the same vessels and are similarly distributed. Intracerebral hemorrhage characteristically begins abruptly with headache and vomiting followed by steadily increasing focal neurologic deficits and alteration of consciousness [44]. More than 90% of hemorrhages rupture through brain parenchyma into the ventricles, producing bloody cerebrospinal fluid. Patients presenting with intracerebral hemorrhage are invariably hypertensive. In contrast to cerebral infarction, the hypertension does not tend to decrease spontaneously during the first week. The patient's condition worsens steadily over a period of minutes to days until either the neurologic deficit stabilizes or the patient dies. When death occurs, most often it is due to herniation caused by the expanding hematoma and surrounding edema. Treatment of hypertension in the setting of intracerebral hemorrhage is controversial. An increase in intracranial pressure accompanied by a reflex increase in systemic blood pressure almost always occurs. Because cerebral perfusion pressure is a function of the difference between arterial pressure and intracranial pressure, reduction of blood pressure could compromise cerebral perfusion. Moreover, as in cerebral infarction, autoregulation is impaired in the area of marginal ischemia surrounding the hemorrhage. In contrast, cerebral vasogenic edema may be exacerbated by hypertension. Moreover, hypertension may increase the risk of rebleeding with expansion of the hematoma. Thus, in deciding to treat hypertension in the setting of intracerebral hemorrhage, a precarious balance must be struck between beneficial reduction in cerebral edema on the one hand, and deleterious reduction of cerebral blood flow on the other. Studies have shown that the lower limit of autoregulation after intracerebral hemorrhage is approximately 80% of the initial blood pressure; therefore, a 20% decrease in mean arterial pressure should be considered the maximal goal of blood pressure reduction during the acute stage [45]. Antihypertensive therapy should be undertaken only in conjunction with intracranial and intra-arterial pressure monitoring to allow for assessment of cerebral perfusion pressure. The short duration of action of nitroprusside makes its use preferable over other agents with a longer duration of action and the risk of sustained overshoot hypotension, despite the theoretic concern that nitroprusside treatment could lead to an increase in intracranial pressure by way of dilation of cerebral veins and arteries.

**FIGURE 8-31**

Hypertensive crisis with pheochromocytoma. In most patients, pheochromocytoma causes sustained hypertension that sometimes becomes malignant as evidenced by the presence of hypertensive neuroretinopathy. Paroxysmal hypertension is present in approximately 30% of patients. Spontaneous paroxysms consist of severe hypertension, headache, profuse diaphoresis, pallor, coldness of hands and feet, palpitations, and abdominal discomfort. Paroxysmal hypertension in pheochromocytoma represents a hypertensive crisis because it can lead to intracerebral hemorrhage, hypertensive encephalopathy, or acute hypertensive heart failure with pulmonary edema. Prompt control of the blood pressure is mandatory to prevent these life-threatening complications. Although the nonselective  $\alpha$ -blocker phentolamine often is cited as the treatment of choice for pheochromocytoma-related hypertensive crises, sodium nitroprusside is equally effective and easier to administer [46]. Only after blood pressure has been controlled with nitroprusside or phentolamine can intravenous  $\beta$ -blockers, such as esmolol, labetalol, or propranolol, be used to control tachycardia or arrhythmias. After resolution of the hypertensive crisis, oral antihypertensive agents should be instituted as the parenteral agents are weaned. The nonselective  $\alpha$ -blocker phentolamine usually is administered orally for 1 to 2 weeks before elective surgery. After adequate  $\alpha$ -blockade is achieved, based on the presence of moderate orthostatic hypotension, oral  $\beta$ -blocker therapy can be initiated as needed to control tachycardia. Oral or intravenous  $\beta$ -blockers should never be administered before adequate  $\alpha$ -blockade. Doing so can precipitate a hypertensive crisis as the result of intense  $\alpha$ -adrenergic vasoconstriction that is no longer opposed by  $\beta$ -adrenergic vasodilatory stimuli. Careful attention to volume status also is mandatory in the preoperative period. Catecholamine-induced hypertension induces a pressure natriuresis with volume depletion. Moreover, alleviation of the chronic state of vasoconstriction by  $\alpha$ -blockade results in increases in both arterial and venous capacitances. Preoperative volume expansion, guided by measurement of central venous pressure or wedge pressure often is advocated to reduce the risk of intraoperative hypotension [47]. During surgery, rapid and wide fluctuations in blood pressure should be anticipated. Careful intraoperative monitoring of intra-arterial pressure, cardiac output, wedge pressure, and systemic vascular resistance is mandatory to manage the rapid swings in blood pressure. Despite adequate preoperative  $\alpha$ -blockade with phenoxybenzamine, severe hypertension can occur during intubation or intraoperatively as a result of catecholamine release during tumor manipulation. Sodium nitroprusside is the treatment of choice for controlling acute hypertension owing to pheochromocytoma during surgery. At the opposite end of the spectrum, profound intraoperative hypotension can occur. Hypotension or even frank shock can supervene after isolation of tumor venous drainage from the circulation, with resultant abrupt decrease in circulating catecholamine levels. Volume expansion is the treatment of choice for intraoperative and postoperative hypotension [46]. Pressors only should be employed when hypotension is unresponsive to volume repletion.

**FIGURE 8-32**

Hypertensive crises secondary to monoamine oxidase inhibitor-tyramine interactions. Severe paroxysmal hypertension complicated by intracerebral or subarachnoid hemorrhage, hypertensive encephalopathy, or acute hypertensive heart failure can occur in patients treated with monoamine oxidase (MOA) inhibitors after ingestion of certain drugs or tyramine-containing foods [48,49]. Because MAO is required for degradation of intracellular amines, including epinephrine, norepinephrine, and dopamine, MAO inhibitors lead to accumulation of catecholamines within storage granules in nerve terminals. The amino acid tyramine is a potent inducer of neurotransmitter release from nerve terminals. As a result of inhibition of hepatic MAO, ingested tyramine escapes oxidative degradation in the liver. In addition, the high circulating levels of tyramine provoke massive catecholamine release from nerve terminals, resulting in vasoconstriction and a paroxysm of severe hypertension. A hyperadrenergic syndrome resembling pheochromocytoma then ensues. Symptoms include severe pounding headache, flushing or pallor, profuse diaphoresis, nausea, vomiting, and extreme prostration. The mean increase in blood pressure is 55 mm Hg systolic and 30 mm Hg diastolic [49]. The duration of the attacks varies from 10 minutes to 6 hours. Attacks can be provoked by the ingestion of foods known to be rich in tyramine: natural or aged cheeses, Chianti wines, certain imported beers, pickled herring, chicken liver, yeast, soy sauce, fermented sausage, coffee, avocado, banana, chocolate, and canned figs. Sympathomimetic amines in nonprescription cold remedies also can provoke neurotransmitter release in patients treated with an MAO inhibitor. Either sodium nitroprusside or phentolamine can be used to manage this type of hypertensive crisis. Because most patients are normotensive before onset of the crisis the goal of blood pressure treatment should be normalization of the blood pressure. After blood pressure control, intravenous  $\beta$ -blockers may also be required to control heart rate and tachyarrhythmias. Because the MAO inhibitor-tyramine hypertensive crisis is self-limited, parenteral antihypertensive agents can be weaned without institution of oral antihypertensive agents.

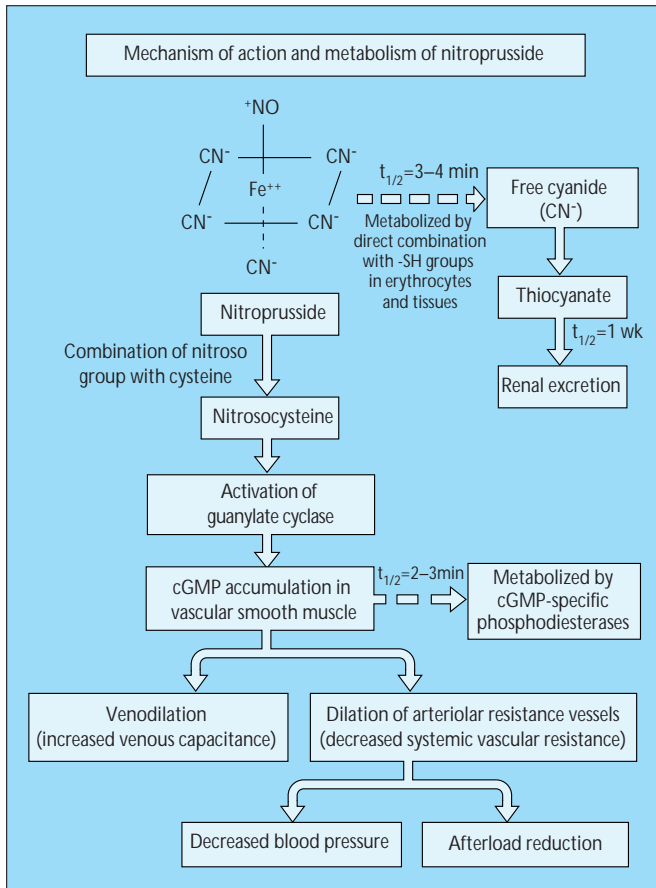


FIGURE 8-33

Mechanism of action and metabolism of nitroprusside. Sodium nitroprusside is the drug of choice for management of virtually all hypertensive crises, including malignant hypertension, hypertensive encephalopathy, acute hypertensive heart failure, intracerebral hemorrhage, perioperative hypertension, catecholamine-related hypertensive crises, and acute aortic dissection (in combination with a  $\beta$ -blocker) [1,50]. Sodium nitroprusside is a potent intravenous hypotensive agent with immediate onset and brief duration of action. The site of action is the vascular smooth muscle. Nitroprusside has no direct action on the myocardium, although it may affect cardiac performance indirectly through alterations in systemic hemodynamics. Nitroprusside is an iron (Fe) coordination complex with five cyanide moieties and a nitroso (NO) group. The nitroso group combines with cysteine to form nitrosocysteine and other short-acting *S*-nitrosothiols. Nitrosocysteine is a potent activator of guanylate cyclase, thereby causing cyclic guanosine monophosphate (cGMP) accumulation and relaxation of vascular smooth muscle [51,52]. Nitroprusside causes vasodilation of both arteriolar resistance vessels and venous capacitance vessels. Its hypotensive action is a result of a decrease in systemic vascular resistance. The combined decrease in preload and afterload reduces myocardial wall tension and myocardial oxygen demand. The net effect of nitroprusside on cardiac output and heart rate depends on the intrinsic state of the myocardium. In patients with left ventricular (LV) systolic dysfunction and elevated LV end-diastolic pressure, nitroprusside causes an increase in stroke volume and cardiac output as a result of afterload reduction and heart rate may actually decrease in response to improved cardiac performance. In contrast, in the absence of LV dysfunction, venodilation and preload reduction can result in a reflex increase in sympathetic tone and heart rate. For this reason, nitroprusside must be used in conjunction with a  $\beta$ -blocker in acute aortic dissection. The hypotensive action of nitroprusside appears within seconds and is immediately reversible when the infusion is stopped. The cGMP in vascular smooth muscle is rapidly degraded by cGMP-specific phosphodiesterases. Nitroprusside is rapidly metabolized with a half-life ( $t_{1/2}$ ) of 3 to 4 minutes. Cyanide is formed as a short-lived intermediate product by direct combination with sulfhydryl (SH) groups in erythrocytes and tissues. The cyanide groups are rapidly converted to thiocyanate by the liver in a reaction in which thiosulfate acts as a sulfur donor. Thiocyanate is excreted by the kidneys, with a half-life of 1 week in patients with normal renal function. Thiocyanate accumulation and toxicity can occur when a high-dose or prolonged infusion is required, especially in patients with renal insufficiency. When these risk factors are present, thiocyanate levels should be monitored and the infusion stopped if the level is over 10 mg/dL. Thiocyanate toxicity is rare in patients with normal renal function requiring less than 3  $\mu\text{g}/\text{kg}/\text{min}$  for less than 72 hours [50]. Cyanide poisoning is a very rare complication, unless hepatic clearance of cyanide is impaired by severe liver disease or massive doses of nitroprusside (over 10  $\mu\text{g}/\text{kg}/\text{min}$ ) are used to induce deliberate hypotension during surgery [50].

VARIOUS ANTIHYPERTENSIVE DRUGS FOR PARENTERAL USE IN THE MANAGEMENT OF MALIGNANT HYPERTENSION AND OTHER HYPERTENSIVE CRISES

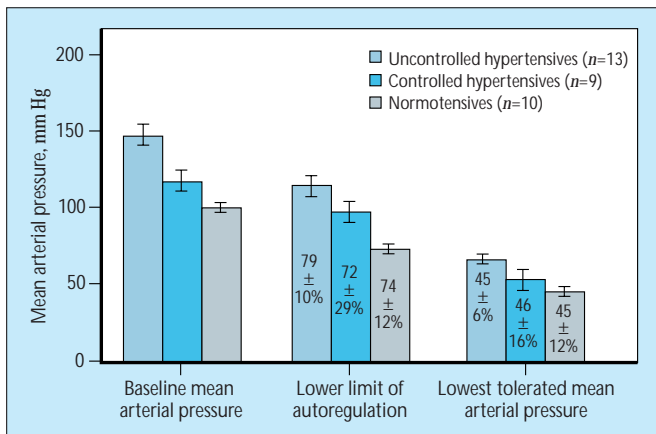
Drug	Mechanism of action	Onset of action	Peak effect	Duration of action	Method of administration	Advantages	Disadvantages	Side effects	Comments
Sodium nitroprusside	Direct arteriolar vasodilation and venodilation	Instantaneous	Immediate	2–3 min after infusion stopped	Continuous infusion: Initial, 0.5 µg/kg/min Average, 3 µg/kg/min Maximum, 10 µg/kg/min	Precise titration of BP. Consistently effective when other drugs fail. Parenteral agent of choice for hypertensive crises	Monitoring in ICU required	Nausea, vomiting, apprehension. Thiocyanate toxicity with prolonged infusion, renal insufficiency	Discontinue if thiocyanate level >10 mg/dL
Diazoxide	Direct arteriolar vasodilation	1–2 min	10–15 min	4–24 h	IV minibolus: 50–100 mg given rapidly over 5–10 min. Total dose, 150–600 mg	Long duration of action. Constant monitoring not required after initial titration	Sustained hypotension with CNS and myocardial ischemia can occur. Reflex sympathetic cardiac stimulation	Nausea, vomiting, hyperglycemia, myocardial ischemia, uterine atony	Contraindicated in aortic dissection, cerebrovascular disease, myocardial ischemia
Trimethaphan camsylate	Ganglionic blockade with venodilation and arteriolar vasodilation	Minutes	Minutes	5–10 min after infusion stopped	Continuous infusion: Initial, 0.5 mg/min Maximum, 5.0 mg/min	Blocks baroreceptor-mediated sympathetic cardiac stimulation	Parasympathetic blockade	Dry mouth, blurred vision, urinary retention, paralytic ileus, respiratory arrest	Tilt-bed enhances effect; tachyphylaxis after 24–48 h; contraindicated in respiratory insufficiency and glaucoma; potentiates succinylcholine
Nitroglycerin	Direct venodilation at low doses; combined venodilation and arteriolar dilation at higher doses	Minutes	Minutes	1–5 min after infusion stopped	Continuous infusion: Initially, 5 µg/min Increase by 5 µg/min over 3–5 min	Theoretic advantages over nitroprusside in setting of myocardial ischemia	Fails to control BP in some patients	Headache, nausea, vomiting, palpitations, abdominal pain	Contraindicated in pheochromocytoma, heart failure, asthma, heart block >1 degree, after coronary artery bypass graft surgery
Labetalol	Selective α <sub>1</sub> - and noncardioselective β-blocker; arteriolar and venous dilation	Minutes	5–50 min	16–18 h	IV minibolus: Initial, 20 mg over 2 min then, 40–80 mg over 10 min. Maximum, 300 mg	Continuous monitoring not required	β-blockage can worsen congestive heart failure, bronchospasm, heart block	Nausea, vomiting, paresthesias, headache, bradycardia	Nitroprusside: equally efficacious in catecholamine-related crises
Phentolamine	Nonselective α-blocker	2–3 min	5 min	15–30 min	IV bolus: 1–5 mg over 5 min	Useful in catecholamine-related crises	Short duration of action	Tachycardia, arrhythmias, nausea, vomiting, diarrhea, exacerbation of peptic ulcer disease	Contraindicated in aortic dissection, atherosclerotic, coronary vascular disease
Hydralazine	Direct arteriolar vasodilation	10–30 min	30–60 min	3–9 h	IV bolus: 5–10 mg over 20–30 min or continuous infusion: 400 µg/mL solution. Loading dose: 200–300 µg/min for 30–60 min. Maintenance infusion: 50–150 µg/min over 6–8 h	Proven efficacy and safety in hypertensive crises of pregnancy	Delayed onset of action, unpredictable hypotensive effect	Headache, angina	Contraindicated in hypertensive encephalopathy, CNS catastrophe
Methyldopa	Decrease sympathetic nervous system activity via CNS α <sub>2</sub> stimulation; decrease systemic vascular resistance	2–4 h	4–6 h	4–6 h	IV of 250–500 mg over 6–8 h	None—not recommended for use in hypertensive crises	Delayed onset of action, unpredictable hypotensive effect	Sedation	Contraindicated in hypertensive encephalopathy, CNS catastrophe
Reserpine	Sympathetic dysfunction owing to central and peripheral catecholamine dysfunction; decreased SVR, decreased CO	2–4 h	2–4 h	2–8 h	Intramuscular: Initial, 0.5–1.0 mg 2–4 mg over 3 h 2–4 mg over 3–12 h	None—not recommended for use in hypertensive crises	Delayed onset of action, unpredictable hypotensive effect	Nasal congestion, CNS sedation, bradycardia, exacerbates peptic ulcer disease, depression	Contraindicated in hypertensive encephalopathy, CNS catastrophe, cumulative hypotensive response

BP—blood pressure; CNS—central nervous system; CO—cardiac output; ICU—intensive care unit; IV—intravenous; SVR—systemic vascular resistance.

FIGURE 8-34

Sodium nitroprusside remains the treatment of choice in virtually all hypertensive crises requiring rapid blood pressure control with

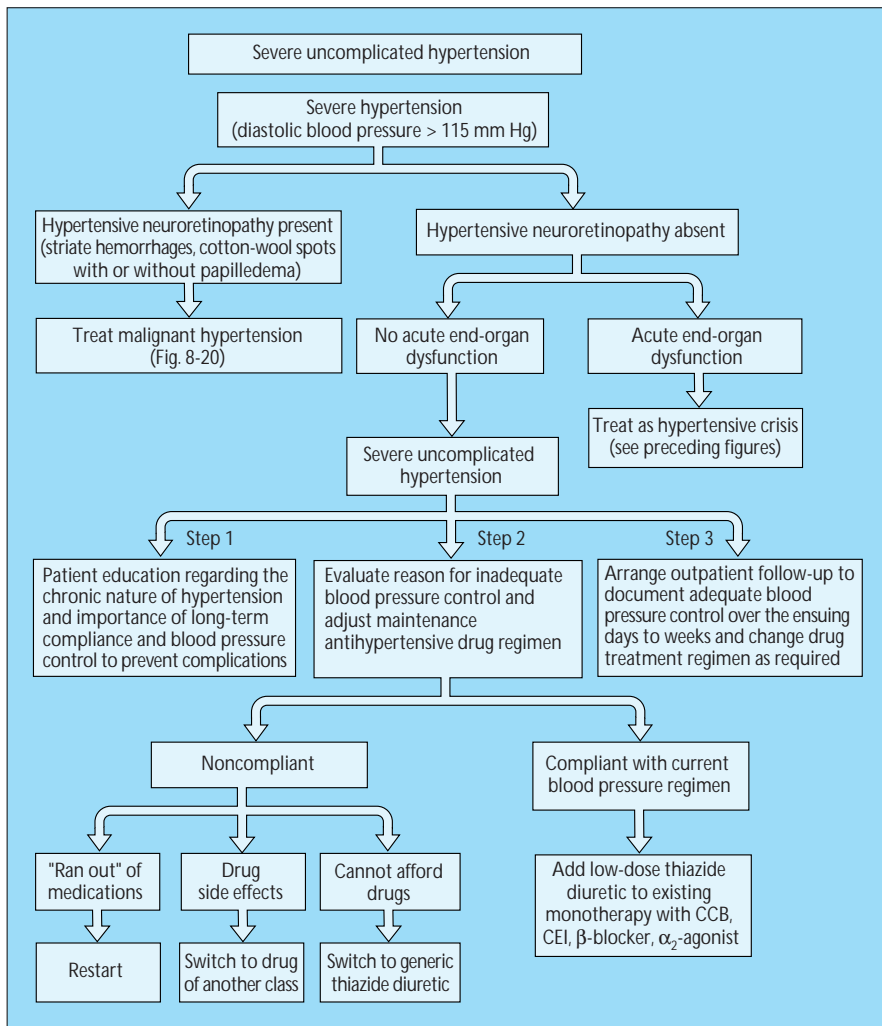
parenteral therapy. However, other parenteral antihypertensive agents may be useful in certain circumstances.



**FIGURE 8-35**

Risks of rapid blood pressure reduction in hypertensive crises. It has been argued over the years that rapid reduction of blood pressure in the setting of hypertensive crises may have a detrimental effect on cerebral perfusion because the autoregulatory curve of cerebral blood flow is shifted upward in patients with chronic hypertension. Conversely, this upward shift protects the brain from hypertensive encephalopathy in the face of severe hypertension. However, this autoregulatory shift could be deleterious when the blood pressure is reduced acutely because the lower limit of autoregulation is shifted to a higher level of blood pressure. Theoretically, aggressive reduction of the blood pressure in chronically hypertensive patients could induce cerebral ischemia. Nonetheless, in clinical practice, moderately controlled reduction of blood pressure in patients with hypertensive crises rarely causes cerebral ischemia. This clinical observation may be explained by the fact that even though the cerebral autoregulatory curve is shifted in patients with chronic hypertension, a considerable difference still exists between the initial blood pressure at presentation and the lower limit of autoregulation. Illustrated are the differences in the lower autoregulatory threshold during blood pressure reduction with trimethaphan in patients with uncontrolled hypertension and treated hypertension, and those in the control group [53]. At least eight of the 13 patients with uncontrolled hypertension had hypertensive neuroretinopathy consistent with malignant hypertension. The control groups included nine patients with a history of severe hypertension in the past whose blood pressure was effectively controlled at the time of study and a group of 10 normotensive persons. Baseline mean arterial pressures (MAPs) in the three groups were  $145 \pm 17$  mm Hg,  $116 \pm 18$  mm Hg, and  $96 \pm 17$  mm Hg, respectively. The lower limit of blood pressure at which autoregulation failed was  $113 \pm 17$  mm Hg in persons with uncontrolled hypertension,  $96 \pm 17$  mm Hg in persons with treated hypertension, and  $73 \pm 9$  mm Hg in normotensive persons. Although the absolute level at which autoregulation failed was substantially higher in patients with uncontrolled hypertension, the percentage reduction in blood pressure from the baseline level required to reach the autoregulatory threshold was similar in each group. The numbers on the bars indicate the percentage reduction from the baseline

blood pressure required to reach the autoregulatory limit. Thus, a reduction in MAP of approximately 20% to 25% was required in each group to reach the threshold. This result indicates that a considerable safety margin exists for blood pressure reduction before cerebral autoregulation of blood flow fails, even in patients with severe untreated hypertension. Moreover, symptoms of cerebral ischemia did not develop until the blood pressure was reduced substantially below the autoregulatory threshold because even in the face of reduced blood flow, cerebral metabolism can be maintained and ischemia prevented by an increase in oxygen extraction by the tissues. The lowest tolerated MAP, defined as the level at which mild symptoms of brain hypoperfusion developed (*ie*, yawning, nausea, and hyperventilation), was  $65 \pm 10$  mm Hg in patients with uncontrolled hypertension,  $53 \pm 18$  mm Hg in persons with treated hypertension, and  $43 \pm 8$  mm Hg in normotensive persons. The numbers on the bars illustrate that these MAP values were approximately 45% of the baseline blood pressure level in each group. Thus, symptoms of cerebral hypoperfusion did not occur until the MAP was reduced by an average of 55% from the presenting level. In the reported cases of neurologic sequelae sustained during rapid reduction of blood pressure in patients with hypertensive crises, the MAP was reduced by more than 55% of the presenting blood pressure. This frank hypotension was sustained for a period of hours to days, mostly as a result of treatment with bolus diazoxide, which has long duration of action [54]. The general guideline for acute blood pressure reduction in the treatment of hypertensive crises is reduction of systolic blood pressure to 160 to 170 mm Hg and diastolic pressure to 100 to 110 mm Hg, which equates to MAPs of 120 to 130 mm Hg. Alternatively, the initial goal of antihypertensive therapy can be a 20% reduction of the MAP from the patient's initial level at presentation. This level should be above the predicted autoregulatory threshold. Once this goal is obtained the patient should be evaluated carefully for evidence of cerebral hypoperfusion. Further reduction of blood pressure can then be undertaken in a controlled fashion based on the overall clinical status of the patient. Of course, in previously normotensive persons in whom hypertensive crises develop, such as patients with acute glomerulonephritis complicated by hypertensive encephalopathy, the autoregulatory curve should not yet be shifted. Therefore, the initial goal of therapy should be normalization of blood pressure. In terms of avoiding sustained overshoot hypotension in the treatment of hypertensive crises, the use of potent parenteral agents with short duration of action, such as sodium nitroprusside or intravenous nitroglycerin, has obvious advantages. If neurologic sequelae develop during blood pressure reduction with these agents, these sequelae can be reversed quickly by tapering the infusion and allowing the blood pressure to stabilize at a higher level. Agents with a long duration of action have an inherent disadvantage in that excessive reduction of blood pressure cannot be reversed easily. Thus, bolus diazoxide, labetalol, minoxidil, hydralazine, converting enzyme inhibitors, calcium channel blockers, and central  $\alpha_2$ -agonists should be used with extreme caution in patients requiring rapid but controlled blood pressure reduction in the setting of hypertensive crises. (*Adapted from Strandgaard [53]; with permission.*)



**FIGURE 8-36**

Severe uncomplicated hypertension. The benefits of acute reduction in blood pressure in the setting of true hypertensive crises are obvious. Fortunately, true hypertensive crises are relatively rare events that almost never affect hypertensive patients. Another type of presentation that is much more common than are true hypertensive crises is that of the patient who initially exhibits severe hypertension (diastolic blood pressure  $> 115$  mm Hg) in the absence of hypertensive neuroretinopathy or acute end-organ damage that would signify a true crisis. This entity, known as *severe uncomplicated hypertension*, is very commonly seen in the emergency department or other acute-care settings. Of patients with severe uncomplicated hypertension, 60% are entirely asymptomatic and present for prescription refills or routine blood pressure checks, or are found to have elevated pressure during routine physical examinations. The other 40% of patients initially exhibit nonspecific findings such as headache, dizziness, or weakness in the absence of evidence of acute end-organ dysfunction. In the past, this entity was referred to as *urgent hypertension*, reflecting the erroneous notion that acute reduction of blood pressure, over a few hours before discharge from the acute-care facility, was essential to minimize the risk of short-term complications from severe hypertension. Commonly employed treatment regimens included oral clonidine loading or sublingual nifedipine. However, in recent years the practice of acute blood pressure reduction in severe uncomplicated hypertension has been questioned [55,56]. In the Veterans Administration Cooperative Study of patients with severe hypertension, there were 70 placebo-treated patients who had an average diastolic blood pressure of 121 mm Hg at entry. Among these untreated patients, 27 experienced morbid events at a mean of  $11 \pm 8$  months of follow-up. However, the earliest morbid event occurred only after 2 months [57]. These data suggest that in patients with *severe uncomplicated hypertension* in which severe hypertension is not accompanied by evidence of malignant hypertension or acute end-organ dysfunction, eventual complications from stroke, myocardial infarction, or congestive

heart failure tend to occur over months to years, rather than hours to days. Although long-term control of blood pressure clearly can prevent these eventual complications, a hypertensive crisis cannot be diagnosed because no evidence exists that acute reduction of blood pressure results in an improvement in short- or long-term prognosis. Acute reduction of blood pressure in patients with severe uncomplicated hypertension with sublingual nifedipine or oral clonidine loading was once the *de facto* standard of care. This practice, however, often was an emotional response on the part of the treating physician to the dramatic elevation of blood pressure or motivated by the fear of medico-legal repercussions in the unlikely event of a hypertensive complication occurring within hours to days [55]. Although observing and documenting the dramatic decrease in blood pressure is a satisfying therapeutic maneuver, there is no scientific basis for this approach. At present, no literature exists to support the notion that some goal level of blood pressure reduction must be achieved before the patient with severe uncomplicated hypertension leaves the acute-care setting [58]. In fact, acute reduction of blood pressure often is counterproductive because it can produce untoward side effects that render the patient less likely to comply with long-term drug therapy. Instead, the therapeutic intervention should focus on tailoring an effective well-tolerated maintenance antihypertensive regimen with patient education regarding the chronic nature of the disease process and the importance of long-term compliance and medical follow-up. If the patient has simply run out of medicines, reinstatement of the previously effective drug regimen should suffice. If the patient is thought to be compliant with an existing drug regimen, a sensible change in the regimen is appropriate, such as an increase in a suboptimal dosage of an existing drug or the addition of a drug of another class. In this regard, addition of a low dose of a thiazide diuretic as a second-step agent to existing monotherapy with converting enzyme inhibitor (CEI), angiotensin II receptor blocker, calcium channel blocker (CCB),  $\beta$ -blocker, or central  $\alpha_2$ -agonist often is remarkably effective. Another essential goal of the acute intervention should be to arrange suitable outpatient follow-up within a few days. Gradual reduction of blood pressure to normotensive levels over the next few days to a week should be accomplished in conjunction with frequent outpatient visits to modify the drug regimen and reinforce the importance of lifelong compliance with therapy. Although less dramatic than acute reduction of blood pressure in the acute-care setting, this type of approach to the treatment of chronic hypertension is more likely to prevent long-term hypertensive complications and recurrent episodes of severe uncomplicated hypertension.

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